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Invasion of the four kingdoms: the parasite journey across plant and non-plant hosts

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ABSTRACT

Parasites have a rich and long natural history among biological entities, and it has been suggested that parasites are one of the most significant factors in the evolution of their hosts. However, it has been emphasized less frequently how co-evolution has undoubtedly also shaped the paths of parasites. It may seem safe to assume that specific differences among the array of potential hosts for particular parasites have restricted and diversified their evolutionary pathways and strategies for survival. Nevertheless, if one looks closely enough at host and parasite, one finds commonalities, both in terms of host defences and parasite strategies to out-manoeuvre them. While such analyses have been the source of numerous reviews, they are generally limited to interactions between, at most, one kingdom of parasite with two kingdoms of host (e.g. similarities in animal and plant host responses against fungi). With the aim of extending this view, we herein critically evaluate the similarities and differences across all four eukaryotic host kingdoms (plants, animals, fungi, and protists) and their parasites. In doing so, we show that hosts tend to share common strategies for defence, including both physical and behavioural barriers, and highly evolved immune responses, in particular innate immunity. Parasites have, similarly, evolved convergent strategies to counter these defences, including mechanisms of active penetration, and evading the host's innate and/or adaptive immune responses. Moreover, just as hosts have evolved behaviours to avoid parasites, many parasites have adaptations to manipulate host phenotype, physiologically, reproductively, and in terms of behaviour. Many of these strategies overlap in the host and parasite, even across wide phylogenetic expanses. That said, specific differences in host physiology and immune responses often necessitate different adaptations for parasites exploiting fundamentally different hosts. Taken together, this review facilitates hypothesis-driven investigations of parasite–host interactions that transcend the traditional kingdom-based research fields.

Key words: parasites, innate immunity, adaptive immunity, parasite effectors, behavioural modification of hosts.

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I. INTRODUCTION

"The empire, long divided, must unite; long united, must divide. Thus it has ever been." Opening line to *The Romance of the Three Kingdoms* (Lo, 2002).

The historical novel, *The Romance of the Three Kingdoms*, is considered one of the four great classical novels of Chinese literature (Luo, 1991). At 800,000 words, divided into 120 chapters, and with roughly 1000 characters, it is an epic description of the struggles, political, military, and personal, during the years after the Han dynasty broke into three kingdoms. The lengthy, detailed story highlights the battles among these three separate entities either to replace the Han dynasty or restore it.

In biology, the study and discussion of certain specific phenomena has historically been subdivided into separate subgroups, often obscuring important parallels that could provide a more enriched, clearer picture. The case of parasites provides a compelling and instructive example. Here, we define "parasites" as organisms or entities that utilize host species for nutrients, as well as for their reproduction and dissemination, while providing no benefit and often leading to large costs for their hosts. Under this umbrella, we include parasitoids, organisms that are parasitic during part of their life cycle, often leading to the death of the host. The parasitic lifestyle has numerous distinct phylogenetic origins across the tree of life. For example, in the animal kingdom alone parasitism of animal hosts has arisen independently >200 times across many phyla (Weinstein & Kuris, 2016). And yet these vastly different lineages of parasites have converged, at least in terms of how they exploit the host, to a small number of strategies (Poulin, 2011). It can even be argued that plants parasitic on other plants have adopted strategies similar to those used by fungal or animal parasites to exploit their hosts (Poulin, 2011). For example, parasitic plants often employ haustoria: root-like organs produced at the site of attachment that develop inside the host plant to absorb nutrients (Wilson & Calvin, 2006; Jhu & Sinha, 2022). Similarly, haustoria are a common feature of fungi that infect plants. Moreover, fungi that parasitize other fungi have also been suggested to use haustoria-like structures (Zhao, Liu & Bai, 2019).

This example demonstrates that, as in the quote above, the kingdoms of life, long studied separately, must be examined together to reveal what unites and what divides them in their battles against parasites. The study of parasites according to host taxa has revealed commonalities to infection strategies, making a comparative approach insightful. That said, distinct parasite strategies obviously have evolved in the context of their respective host species, likely due to differences in host responses to parasite exposure, as well as to differences in host physiology and metabolic processes.

Just as *The Romance of the Three Kingdoms* is an epic saga with countless characters, our discussion of parasites and the hosts that harbour them is one of many taxa. We provide a detailed examination of the interactions between and among these warring factions in the biological world. We explore parasites of eukaryotic hosts in the plant, animal, fungal, and protist kingdoms by examining and comparing strategies for parasite success in plants with those used by parasites of non-plant hosts (Table 1). While we refer to some examples of prokaryotic parasites, we focus mainly on eukaryotic endoparasites. Thus, we exclude discussion of multicellular ectoparasites (or "micropredators"), such as arthropods (e.g. mosquitoes, ticks, fleas, mites, bedbugs, etc.) or annelids (i.e. leeches) that attack more than one host type, other than when these ectoparasites are themselves intermediate hosts for parasites that use them as vectors for spread to the definitive host and between infected and naïve hosts. We also do not include parasites that are primarily opportunists, nor organisms that primarily kill their host species or that are necrotrophic in nature. From the host perspective, we compare host defence mechanisms and how differences in host strategies necessitate alternative strategies for establishment and persistence by their parasites. Finally, we explore alternative dispersal and transmission strategies and why many parasites have evolved mechanisms to control or alter host phenotypes, ranging from physiology and metabolism/energetics to effects on various host behaviours (e.g. host defences, mate responses, predator avoidance/attraction) and, for animals, their neurobiological correlates.

In this review, we examine, in chronological order, the steps followed by all parasites: encountering potential hosts, establishing an association, persisting, and spreading their offspring to new hosts of the same or different species. We use this framework to identify strategies used by parasites of host taxa from the four kingdoms, and compare and contrast these strategies, and those of their hosts in attempting to avoid or contain the parasites. Figure 1 provides an overview of these interactions between the host and parasite, using a fungal parasite and plant host as an example.

Table 1. Cross-kingdom comparisons of parasite strategies and host responses. The table is not meant to be exhaustive, but to provide a summary of examples used in the main text; empty boxes generally mean that the particular parasite and/or host do not interact.

Aspect of parasitism	Type of parasite	Host			
		Animals	Plants	Fungi	Protists
Finding a host/ association	Cryptomycota/ aphelids			Contact/fusion with parasite cells on the surface of host cells	In aphelids, both flagellated and amoeboid zoospore forms can attach to algae and encyst
	Fungus	For insect hosts, association of fungal spores ma-y be random; germination occurs upon contact and attachment. Haustoria may be used for penetration of cuticle in some cases, for example *Arthrorhynchus nycteribiae* on *Penicillidia conspicua*, a bat fly Mammal hosts tend to have commensal associations on skin that require lipids provided there. Disruption of normal skin conditions may cause dimorphic transition to mycelia (e.g. *Malassezia furur*) leading to severe dandruff, atopic dermatitis, psoriasis	Random association *via* wind/rain Location of hosts using volatiles and directed hyphal growth Attachment: adhesion by fungal hydrophobins, integrins and mucilages Vector-mediated transmission, for example Scolytinae for Ascomycetes; Apidae, Noctuidae for *Ustilago*	Attachment of parasitic fungus to outer surface of host hyphae	In aphelids, both flagellated and amoeboid zoospore forms can attach to algae and encyst
	Protist	Protozoan attachment to animal cells/ tissues: *Trypanosoma brucei*, attachment to host tissues *via* flagellar proteins; others may find host through ingestion of parasite-contaminated water or through vector-mediated introduction into vertebrate hosts			
	Worm	Use of arthropod or annelid vectors involves very little host choice Trophic transmission also involves very little host choice, although exploitation of strongest trophic link can increase likelihood of predation by definitive hosts Transmission *via* mobile stages can involve environmental cues that bring parasite into close proximity with the host, followed by chemotaxis Trematode miracidia have chemoreceptors that respond to glycoproteins on host Hookworms use cues, such as CO_2 and temperature to locate their warm-blooded hosts	Components of host exudate [both volatile organic compounds (VOCs) and aqueous compounds] are evaluated by nematode and direct its migration to infection site Other VOCs can attract nematodes to plants, and plant damage by insects releases VOCs that attract entomophagous nematodes Stem and bulb nematodes (e.g. *Bursaphelenchus*, J4 stage) vectored by insects (Mamiya, 1983).		

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Table 1. *(Cont.)*

Aspect of parasitism	Type of parasite	Host			
		Animals	Plants	Fungi	Protists
Entry	Cryptomycota/ aphelids				In aphelids, after germination, a penetration tube is used to penetrate the host cell wall In intracellular parasites a thallus or hypha is used
	Fungus	Natural openings or wounds Also have adaptations to penetrate the skin or cuticle, for example using cutinases and proteases	Natural openings or wounds Penetrate tissues using specialized structures, for example appressoria, which may employ turgor pressure and/or cutinases and xylanases		
	Protist	Ingestion by host Transmission by arthropod vectors			
	Worm	Natural openings or wounds Adaptations to penetrate skin or cuticle	Burrowing worms use stylets to penetrate plant cell wall and to deliver secretions (enzymes and other effectors) to induce cell wall degradation, and suppress plant immune responses		
Host response	Cryptomycota/ aphelids				
	Fungus	Avoidance (physical barrier) Innate immunity (barrier; humoral/cellular responses), including pattern recognition receptors (PRRs), and recognition of pathogen-associated molecular patterns (PAMPs), microbe-associated molecular patterns (MAMPs), microbe-induced molecular patterns (MIMPs), damage-associated molecular patterns (DAMPs) and effector-triggered immunity (ETI); production of antimicrobial peptides (AMPs) Adaptive immunity (humoral/cellular) in vertebrates only, but possible adaptive innate immunity in some invertebrates: antimicrobial compounds (AMPs), with antifungal activity (Section IV.2)	Innate immunity (barrier; humoral/ cellular responses), including PRRs and recognition of PAMPs, MAMPs, MIMPs, DAMPs for pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) for recognition of effectors Priming in plants: metabolite- or small molecule-based responses in plants that can detect self *versus* non-self; epigenetic changes contribute to sustained plant establishment of pre-conditioned or primed state	Barrier; some evidence for components or progenitors of PRRs, for example *het/vic* systems of vegetative incompatibility	

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Table 1. *(Cont.)*

Aspect of parasitism	Type of parasite	Host			
		Animals	Plants	Fungi	Protists
	Protist	Innate and adaptive immunity Non-specific mechanism(s) or factor(s), for example presence of non-specific serum component lethal to the parasite; specific mechanism(s) involving the immune system In malaria and trypanosome infections, antibodies have a major role in immunity Cellular immunity may be the most important defence mechanism in leishmaniasis and toxoplasmosis		Barrier; some evidence of components or progenitors of PRRs, for example *het*/*vic* systems of vegetative incompatibility	Barrier; some evidence of components or progenitors of PRRs from BLASTp searches
	Worm	Barriers Innate and adaptive immunity	Barriers Innate immunity: plants recognize a chemical signal from the worm and initiate immune responses; production of VOCs with anti-nematode activity		
Parasite responses to host defences	Cryptomycota/ aphelids				
	Fungus	Use of extracellular vesicles (EVs), secreted molecules; effectors Overwhelm complement system	Effectors used to block host innate immune responses (e.g. PTI) EVs in some filamentous plant pathogenic/parasitic species		
	Protist	Penetration of barriers using a blood-sucking or other skin-piercing vector EVs used to modify host immune response (e.g. *Leishmania donovani*)			
	Worm	Animal-parasitic nematodes use glutathione transferases (GSTs) to detoxify a wide range of endogenous and xenobiotic compounds (Campbell *et al.*, 2001) EVs used to deliver microRNAs (miRNAs) to modulate host immune response	GSTs important in successful parasitism by nematodes (Dubreuil *et al.*, 2011).		

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Table 1. *(Cont.)*

Aspect of parasitism	Type of parasite	Host			
		Animals	Plants	Fungi	Protists
Persistence	Cryptomycota/ aphelids				
	Fungus	*Candida albicans* utilizes three-pronged approach: secretion of effectors to degrade AMPs, efflux pumps to remove AMPs, and regulation of signalling pathways *Malassezia* spp. synthesize aryl hydrocarbon receptors (AhRs), indolic proteins, whose ligands potentially down-regulate host immune response	Various effectors used during different parasite developmental stages Modifications of host physiology/ development		
	Protist	Secreted molecules Shifting antigenic variation (in trypanosomes)			
	Worm	Upregulation of protective proteins, for example hydatid tapeworm *E. granulosus* upregulates expression of different Kunitz multigene proteins at different stages of its life cycle in mammalian hosts for protection against host proteases	Shifting use of effectors during different parasite developmental stages Additional modifications of host physiology/development		
Nutrient acquisition/ utilization	Cryptomycota/ aphelids				Feed by attaching to, engulfing, or living inside other cells
	Fungus	Secreted enzymes	Fungal haustoria		
	Protist	Malaria uses Plasmodium translocon of exported proteins (PTEX) membrane-spanning pore exported protein 2 (EXP2), for waste efflux, effector protein export, and uptake of host cell cytosol *Cryptosporidium* spp. reside in host-produced parasitophorus sac, and cause rearrangements to host Actin, thereby hiding from host immune system, while regulating transport and acquisition of nutrients			
	Worm	Some have piercing mouthparts Tapeworms and acanthocephalans have lost their mouth and digestive tract, and feed by absorbing nutrients through their tegument	Stylet for nutrient acquisition		

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Table 1. *(Cont.)*

Aspect of parasitism	Type of parasite	Host			
		Animals	Plants	Fungi	Protists
Reproduction	Cryptomycota/ aphelids				Reproductive cells (zoospores) that swim with a motile cilium or crawl like an amoeba
	Fungus	Growth and development on skin/nail surface as yeast-like forms; dimorphic switch to mycelial stage if skin environment changes or host becomes immunocompromised	Often obligatory completion of sexual cycle in host		
	Protist	Development may require different hosts for different stages of development as a life history/developmental adaptation			
	Worm	Can reproduce sexually (dioecious or as hermaphrodites, depending on the taxon) or *via* parthenogenesis	Three types observed: amphimictic; parthenogenesis with variations; and obligatory mitotic (apomictic) parthenogenesis		
Dispersal/host behaviour modifications	Cryptomycota/ aphelids				
	Fungus	Alter host behaviour to increase parasite transmission (e.g. *Ophiocordyceps*) Common behavioural modifications include circadian clock manipulations, light perception, summiting	Strategies to increase spore availability (e.g. increasing numbers of anthers in flowers where fungal spores develop) Altering host volatile profile may alter pollinator visitation behaviour		
	Protist	Alterations of intermediate host behaviour to reach definitive host (*Toxoplasma gondii*)			
	Worm	Faecal spread Use of arthropod or annelid vector Alteration of intermediate host phenotype to achieve trophic transmission (e.g. *Leucochloridium*/snail interaction) Environmental light cues associated with summiting			

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Table 1. *(Cont.)*

Aspect of parasitism	Type of parasite	Host			
		Animals	Plants	Fungi	Protists
Co-infection with other organisms	Cryptomycota/ aphelids				
	Fungus	Other skin flora may impede or benefit the fungal parasite	Co-infection with endophytes or other symbionts can be protective against fungal parasites: for example *Fusarium* endophytes of maize can be protective against *Ustilago maydis*		
	Protist	Microbiomes of arthropod intermediate host/vectors can affect spread of the protist host; such effects may be cooperative or competitive			
	Worm	Infection by the worm (e.g. infestation of three-spined stickleback, *Gasterosteus aculeatus*, with *Schistocephalus solidus*) lowers immunity of this intermediate host, leading to co-infection with other parasites	Co-infection with endophytes, other symbionts, or other parasites, for example bacteria or fungi, can inhibit growth of the nematode parasite		

II. FINDING A HOST/ASSOCIATION

(1) Recognizing a suitable host

How does a parasite recognize a suitable host, do all parasites use similar strategies, and if not, why not? The answers to these questions will partly depend on how contact is established and whether such contact requires a particular transmission mode. Transmission that requires direct contact between the parasite and host is generally associated with specialists, that is parasites that are limited to infecting one or a few host species, or, even more restrictively, to only a limited number of genotypes within a particular species.

Successful host recognition and subsequent invasion (and, thus, host range) are attributed to the presence of a compatible "lock" (i.e. host recognition site) and "key" mechanism (i.e. a parasite's ability to attach to and make use of that recognition site). We can explain this principle by considering the methods employed by bacteriophage parasites of prokaryotes. Bacteriophages provide an example where encounter with a potential host is essentially random. Once an encounter occurs, the phage must identify specific host receptors on the host bacterial surface. Proper recognition and binding by phage components to the bacterial receptor leads to adsorption of the phage, a prerequisite for subsequent downstream events in phage reproduction. In the competition between phage and potential host bacteria, evolution has favoured several bacterial strategies to prevent phage adsorption. These include blocking receptors used by phages on the bacterial cell surface, production of inhibitors that compete for attachment to those receptors, or covering the receptors with extracellular matrices (Labrie, Samson & Moineau, 2010).

An analogous approach for recognition/attachment is used by single-celled parasites attaching to other single-celled hosts, for example in Chlamydiota encountering and attachment to protists or fungi (Horn, 2008), parasitic infections of algae and in interactions of parasitic fungi with host fungi (mycoparasitism) (Table 1). Algae and microalgae can be infected by a rather wide array of potential parasites, including fungi, slime molds, oomycetes, vampyrellids (amoebae), and alveolates (Carney & Lane, 2014). Aphelids are endoparasitoids of algae and diatoms that belong to the fungal kingdom. They have both flagellated and amoeboid zoospores that can attach to the host alga, and encyst; after germination, the cyst penetrates the host cell wall with a penetration tube (Karpov *et al.*, 2014; see Section III). Some biotrophic mycoparasites (e.g. *Sphaerodes quadrangularis*, a facultative contact parasite of *Fusarium avenaceum*; Goh & Vujanovic, 2010) absorb nutrients from the host *via* contact/fusion with the surface of host cells, rather than by internalization of the parasite. While the mechanism of zoospore or cyst encounter and attachment remains unresolved, microscopic labelling techniques have suggested that cell surface sugars act as a recognition component used to discriminate between hosts and non-hosts in at least some mycoparasites (Manocha, Chen & Rao, 1990). The latter study compared attachment of the

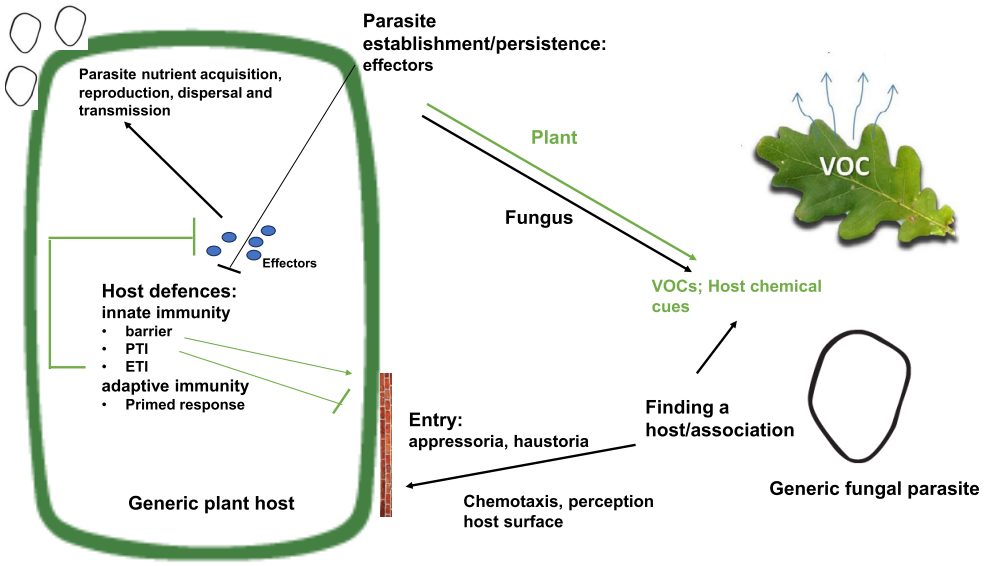

Fig. 1. Summary of host/parasite interactions. Overview of generic parasite life cycle, using plant–fungal interactions as a model. For host defence responses, counter-measures by the parasite are illustrated. ETI, effector-triggered immunity; PTI, pattern-triggered immunity; VOCs, volatile organic compounds.

mycoparasite *Piptocephalis virginiana* to compatible (*Choanephora cucurbitarum* and *Mortierella pusilla*) and incompatible hosts (*Phascolomyces articulosus*). The cell wall of the compatible and incompatible hosts displayed key differences in sugar content, and both recognition and attachment were associated with specific sugar residues (Manocha *et al.*, 1990).

How a parasite is spread also may dictate how it locates its potential hosts. Some parasites spread *via* direct contact between an infected and a naïve host of the same species (Boldin & Kisdi, 2012; Fenner, Godfrey & Bull, 2011; Grear, Luong & Hudson, 2013). For example, transmission of parasites of animals with direct faecal–oral life cycles, such as some nematode (i.e. roundworm) species, is dependent on the degree to which hosts encounter and interact with one another (Grear *et al.*, 2013). This type of transmission is different from a random environmental encounter of the free parasite by a host. Both types of transmission are expected to have a different evolutionary trajectory compared to infection with parasites with trophic life cycles (*via* mobile intermediate hosts; see Section II.3) that spatially decouple transmission from host contact (Grear *et al.*, 2013).

(2) Encounter and attachment to plant hosts

Parasites often require cues from potential plant hosts to guide them towards their target. Some fungi may reach potential hosts *via* directed hyphal growth towards a chemical stimulus, that is chemotaxis. Such directed growth in fungi takes place in response to nutrient sources or mating factors secreted by potential mates, but can also include movement towards potential hosts (Sridhar, Sharma & Loewen, 2023). In parasitic fungi, chemotaxis is mostly mediated by G-protein-coupled receptors and allows for close contact between the parasite and host to facilitate infection. Recently, a pheromone-sensing receptor FgSte2, also involved in fungal mating, was implicated in chemotaxis by *Fusarium graminearum*, the causal agent of head blight of wheat (Sridhar *et al.*, 2023). This receptor was shown to be essential for sensing a wheat peroxidase-derived chemoattractant, and its deletion significantly reduced fungal pathogenicity. A variety of molecules can serve in communication between hosts and potential parasites. Volatile organic compounds (VOCs) are produced by a wide array of organisms in which they may function in communication (Dudareva & Pichersky, 2006). For example, they can act as alarm signals and elicit plant defences against potential parasites. Belowground, such compounds can serve as attractants for both parasitic and beneficial fungi (Duc *et al.*, 2022). Hundreds of VOCs produced by plant roots have been identified. Most often these tend to repel parasitic fungi and attract beneficial microbes such as mycorrhizal fungi (Duc *et al.*, 2022). Fungal VOCs produced by several soil-borne parasitic fungi (*R. solani*, *F. oxysporum*, *Ulocladium atrum*, and *P. leveillei*) can provide below- and aboveground protection for the plant against herbivores (e.g. cabbage root fly, *Delia radicum*; large cabbage white butterfly, *Pieris brassicae*) (Moisan *et al.*, 2019).

Fungal parasites of plants also may be spread to potential hosts *via* intermediate vectors (e.g. insects, pollinators, etc.) (Eigenbrode, Bosque-Pérez & Davis, 2018; Wielkopolan, Jakubowska & Obrępalska-Stęplowska, 2021; Alsudani & Al-Awsi, 2022; Chandra & Huff, 2014) or *via* wind, rain, or other environmental factors. The anther smuts and other fungi that parasitize reproductive organs and/or flowers provide well-studied examples of pollinator-transmitted parasites (Antonovics *et al.*, 2023; Schäfer *et al.*, 2010; Ngugi & Sherm, 2006). Fungi transmitted to plants *via* pollinators or

other insect vectors may still require additional cues or signals from the potential host. Rarely, the cue may be purely topographical, as for *Uromyces appendiculatus*, in which infection structures (e.g. appressoria; see Section III) are induced following perception of an approximately 0.5 μm high ridge of stomatal guard cells (Hoch *et al.*, 1987). Both smut and rust fungi filament and produce appressoria only on suitable host plants with a hydrophobic surface whose perception by the fungal cells provides a trigger for development (de la Torre, Castanheira & Pérez-Martín, 2020; Freitag *et al.*, 2011; Castanheira & Pérez-Martín, 2015; Lanver *et al.*, 2010). Certain host-produced compounds, for example lipids, corn oils, or tocopherols, stimulate developmental switches in potentially parasitic fungi (Klose, de Sá & Kronstad, 2004; Kokontis & Ruddat, 1986, 1989; Castle & Day, 1984). Such developmental switches include transition from mating of haploid yeast-like cells to stable filamentous cells capable of entering the parasitic pathway (Klose *et al.*, 2004).

Attachment to plant surfaces by fungi often involves surface-acting proteins such as fungal hydrophobins and integrins (for a review, see Tucker & Talbot, 2001). Spores and other cell types may employ different mechanisms for adhesion to plant surfaces and interaction between molecules of the parasite and those of potential host plant surfaces can provide a mechanism for host recognition and subsequent stages of fungal development. In some ways, such attachment, for example by adhesins, is analogous to attachment by bacterial parasites such as *Agrobacterium tumefaciens* to plant surfaces such as roots and root hairs (Matthysse, 2014). The adhesion of fungal spores to plant surfaces often utilizes appendages that emerge from the spore (Jones & Epstein, 1990; Tucker & Talbot, 2001). While initial attachment to surfaces can involve entrapment on a surface or substrate, active attachment occurs when production of adhesive mucilages is stimulated (Jones & Epstein, 1990).

Nematode parasites of plants can be attracted to potential hosts *via* perception of plant-produced cues. In particular, root-knot nematodes (RKN; *Meloidogyne* spp.) are considered to be the most damaging group of plant-parasitic nematodes. Such worm species can parasitize over 2000 plant species worldwide (Čepulytė *et al.*, 2018). Infective juveniles (J2) are non-feeding and must locate and invade a host before their reserves are depleted. A key factor in their identification of host roots lies in compounds present in root tip exudates from susceptible host plants (Čepulytė *et al.*, 2018).

To summarize, parasites may find potential plant hosts *via* chemotaxis or perception of volatiles produced by the host. Additionally, attachment to algal cells and plants is accomplished using recognition of specific cell surface topology, proteins, or sugars, and may involve parasite-produced mucilages.

(3) Encounter and attachment to animal hosts

Fungal attachment to arthropods can involve both non-penetrative and penetrative interactions. Laboulbeniales fungi are found on the external cuticle of arthropod hosts with certain characteristics in common: large and stable populations; overlap of generations; and inhabiting moist environments (Reboleira *et al.*, 2021). Copulation is the usual mode of transmission. Some parasitic fungal species remain exclusively on the cuticle surface (e.g. *Rickia gigas* on its millipede host), whereas others (e.g. *Arthrorhynchus nycteribiae* on *Penicillidia conspicua*, a bat fly), utilize an haustorial structure (see Section III) to penetrate the host cuticle after attachment (Reboleira *et al.*, 2021).

Entomopathogenic fungi often have a high degree of host specificity. For example, *Ophiocordyceps unilateralis sensu lato* infects ants, and each species in this complex seems to infect only a single ant species (Araújo *et al.*, 2015, 2018, 2020). On the other hand, some fungi are broad generalists that can infect both plants and vertebrates (e.g. species of the genus *Metarhizium*; St. Leger & Wang, 2020). In some cases, specialized strains (and eventually species) with a smaller host range appear to have radiated from a generalist ancestor in response to selective pressures imposed by insect host adaptive defences against spores of the generalists (St. Leger & Wang, 2020). Compared to fungal plant parasites, less is known regarding how potential insect hosts are targeted. In the case of *O. unilateralis s.l.*, release of sexual spores appears to be controlled in a seemingly circadian manner to coincide with its ant host's peak foraging time (de Bekker & Das, 2022). This strategy could maximize spore attachment to hosts immediately upon their release, thereby increasing transmission. There is no evidence to suggest that *Ophiocordyceps* spores or host cadavers release VOCs to attract new hosts. By contrast, spores of *Entomopthora muscae* found in cadavers of females of the house fly (*Musca domestica*) generate a blend of volatile sesquiterpenes that alter the profile of natural host cuticular hydrocarbons. This aromatic blend entices male flies to copulate with the cadaver, enabling spore attachment to a new host (Naundrup *et al.*, 2022).

Trypanosoma brucei, the protozoan parasite responsible for sleeping sickness in humans and additional diseases in livestock in sub-Saharan Africa, utilizes its flagellum for attachment to host tissues, with flagellar proteins mediating this attachment. In addition to allowing motility of the parasite within the host, including penetration of the blood/brain barrier, the flagellum also is involved in nutrient acquisition. Its antigenic diversity also provides a means to evade the host immune response (Langousis & Hill, 2014) (see Section VI).

For helminth parasites of animal hosts, the ability to locate and recognize a suitable host depends on their mode of transmission. Where transmission is achieved by free-living infective stages with some mobility, directed movement can allow the parasite to reach potential hosts. For example, the cercariae of marine trematode species respond differentially to various environmental cues such as light intensity or gravity, with the consequence that they select the appropriate water depth to encounter their target host (Combes *et al.*, 1994). At close range, free-living infective stages rely mostly on chemotaxis to orient their movements along chemical gradients to reach a suitable host, or to recognize that host upon contact (Haas, 1994, 2003). Trematode miracidia possess

chemoreceptors that respond specifically to glycoprotein molecules from their target host and allow them to avoid unsuitable snail species (Haas, 2003; Allan *et al.*, 2009). Hookworm larvae initiate crawling towards sources of vibration, heat, humidity and CO_2, stimuli usually associated with their warm-blooded hosts (Haas, 2003; Haas *et al.*, 2005).

By contrast, when there is trophic transmission from an intermediate to a definitive host, or *via* the ingestion of eggs, there is very little possibility of active choice by the parasite (Lafferty, 1999; Kuris, 2005). The consumption of juvenile helminths by unsuitable hosts as a result of ingestion of their intermediate host(s), a phenomenon referred to as concomitant predation, is extremely common in nature (Thieltges *et al.*, 2013). The same is probably true for the consumption of helminth eggs by unsuitable hosts. Instead, such parasites may have evolved preferences for intermediate hosts that maximize their chances of reaching the target definitive host, for example by preferentially infecting intermediate hosts that are prominent in the diet of the definitive host. Exploitation of the strongest trophic links within a food web could therefore be seen as an indirect host-finding mechanism (Cirtwill *et al.*, 2017). Vector-borne parasites, from *Plasmodium* to filarial nematodes, have no direct control over host finding, but instead rely on the sophisticated host-location mechanisms of their vectors, a feature they share with vector-borne plant parasites. Mosquitoes, for instance, integrate multiple cues ranging from exhaled CO_2 to skin chemicals to locate and identify their next blood meal (Cardé, 2015), thereby locating a suitable host for the parasites they transmit.

In sum, encounter, transmission, and evaluation of host suitability are challenges in common for all parasites, whether the host is prokaryotic, a single-celled eukaryote, or a multicellular plant or animal. The limited number of options for finding a host means that there are potentially similar evolutionary trajectories among this wide array of parasites. Random/stochastic encounters remove the agency of a parasite to seek out a host directly. Similarly, trophic transmission limits the possibility for the parasite to choose a suitable host, although such parasites have evolved preferences for intermediate hosts that are more likely to be eaten by the definitive host. By contrast, many parasites seek out hosts *via* directed host cues, and we are increasingly understanding the molecular mechanisms involved.

III. ENTRY

Once a potential host has been identified and the parasite has made contact, the next step for endoparasites is to make their way inside (Table 1). As will be discussed later (see Section IV.1), cellular organisms have some sort of barrier that separates their internal biology from the outside world. Such barriers tend to be selective, allowing entry of essential nutrients, either by diffusion or *via* facilitated transport, while excluding potential toxins, pathogens, or parasites. So, a first necessary step for an endoparasite is to breach this barrier. Many parasites take advantage of natural openings such as pores or stomata. For example, some fungi and nematodes that parasitize plants enter through open stomata – pores in the epidermis of leaves, stems, and other organs that allow gas exchange (Melotto *et al.*, 2006; Edwards & Bowling, 1986; Solanki *et al.*, 2019; Wallace, 1960). Similarly, open wounds are an easy access route for parasites of both plants and animals. In humans and other animals, portals of entry (Atlas, 1997) include skin, mucus membranes, respiratory and gastrointestinal tracts, and the placenta. Oral ingestion is common for a variety of parasites, including bacteria, fungi, protozoa, and worms, often from contaminated water.

If natural openings are unavailable, a successful parasite needs to have other means to gain entry into their host. While bacteriophages and some bacterial pathogens inject biological macromolecules into their hosts (Deng *et al.*, 2017; Labrie *et al.*, 2010), many parasites directly penetrate host physical barriers. Among parasites of single-celled eukaryotes, Cryptomycota species such as *Rozella allomycis*, an obligate endoparasite of the water mold *Allomyces*, have a chitinous spore cell wall that generates turgor pressure *via* the polarized movement of its protoplasm. This is initiated *via* uptake of water into the cyst or spore, followed by the formation of a posterior vacuole, and then forward injection of protoplasm into the host (James *et al.*, 2013). Once *R. allomysis* is inside the host it grows as a naked protoplast without a cell wall that uses phagocytosis to devour the host's cytoplasm (Powell, 1984; James *et al.*, 2013). For chytrids, the penetration mechanism differs among host species. Diatom-infecting chytrids utilize a germ tube, entering the host cell *via* the frustule [the girdle region (Van Donk & Ringelberg, 1983; Beakes, Canter & Jaworski, 1992)]. In other algal hosts the germ tube penetrates the host cell through the mucilage covering the host or directly through the cell wall if no mucilage is present (Canter & Lund, 1951; Karpov *et al.*, 2014; Lepelletier *et al.*, 2014). For aphelids, the amoeboid body penetrates into the host cell through an appressorium penetration tube (Karpov & Paskerova, 2020), or a cyst stalk (Letcher & Powell, 2019). All these entry strategies involve the generation of turgor pressure to facilitate penetration.

In penetration of multicellular hosts, turgor pressure again can play a role. Fungal plant pathogens and biotrophic parasites of plants often employ appressoria to penetrate the host cuticle (for reviews, see Howard & Valent, 1996; Demoor, Silar & Brun, 2019; Chethana *et al.*, 2021; Ryder *et al.*, 2022). An appressorium is usually a flattened structure at the end of a hypha, used to generate a path for hyphae to enter the plant. Examples include, *Magnaporthe oryzae* (Howard & Valent, 1996), *Hyaloperonospora parasitica*, whose spores produce an appressorium, which in turn produces a penetration peg (Coates & Beynon, 2010), and the parasitic biotrophic smut and rust species, for example *Ustilago maydis* (Lanver *et al.*, 2014) and *U. appendiculatus* (Hoch *et al.*, 1987; Acevedo, Steadman & Rosas, 2013). Such structures may develop after spore germination or after transition, for a dimorphic fungus, from a yeast-like mating pair to a

filamentous dikaryotic hypha (Lanver *et al.*, 2014). Analogous to the Cryptomycota species *R. allomycis* described above, some of the best understood examples mechanistically are of appressoria that generate high turgor pressures (as high as 8 MPa), enabling them to puncture the plant cuticle (Howard *et al.*, 1991). In germinating spores, the germ tube may detect physical and/or chemical cues from the host plant surface, including both surface hardness and hydrophobicity, as well as the presence of plant cutin monomers like hexadecanoic acid, the plant hormone ethylene, or exogenous cyclic AMP (cAMP), that trigger formation of the appressorium (Howard & Valent, 1996). Rust fungi, such as *U. appendiculatus*, *Uromyces uiciae-fabae*, and *Puccinia graminis* f. sp. *tritici* only produce appressoria at plant stomata, their required site of entry (Edwards & Bowling, 1986; Solanki *et al.*, 2019). Appressoria of other fungi, for example powdery mildew pathogen, *Blumeria graminis*, or maize smut, *Ustilago maydis*, are not restricted to stomata and do not generate turgor pressure. Instead, they utilize less-melanized or melanin-free appressoria (Lanver *et al.*, 2014) that secrete plant cell-wall degrading enzymes such as cutinases and xylanases (Schirawski *et al.*, 2005; Moreno-Sánchez *et al.*, 2021). Interestingly, appressoria may also allow for secretion of specific fungal effector proteins used to evade the host immune response or to alter host metabolism, physiology, or behaviour (see Sections V and IX). Moreover, appressoria are also found in fungi that infect insects [e.g. *Beauveria* and *Metarhizium* species (Wang & Wang, 2017; St. Leger & Wang, 2020)]. Here again, the initial event is spore germination on the insect cuticle, followed by appressorium development, although in this case lipid droplets are translocated from the mother conidium to the appressorium for hydrolysis, generating high glycerol concentrations and hence high turgor pressure (Wang & Wang, 2017). Insect-penetrating appressoria also secrete proteases and cutinases.

Besides facilitating host entry by themselves, endoparasites can also enter multicellular hosts *via* use of an ectoparasite vector. Ectoparasites, often arthropods or annelids, attach to the host's outer surface and acquire nutrients/blood by inserting their mouthparts into the skin or by piercing the skin with a hollow proboscis. Such ectoparasites can serve as a vector or intermediate host for parasites whose entry into the definitive host relies on the feeding mechanism(s) employed by the ectoparasite. Arthropods are possibly the best-known vectors, including mosquitoes, fleas, ticks, and biting flies (e.g. tsetse flies) on vertebrate animal hosts, and sucking insects, such as aphids, on plants. Aphids are primarily known for transmission of phloem-limited viruses to their host plants (Jimenez *et al.*, 2020; van Munster, 2020). Mosquitoes are well-known vectors of parasites (Dahmana & Mediannikov, 2020) ranging from viruses (e.g. Dengue Fever, West Nile Virus, Japanese Encephalitis Virus), and bacteria (Tularemia/*Francisella tularesnsis*), to protozoans (malaria), and worms (i.e. filariasis: *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*). At least for the protozoan and filarial parasites, the mosquito serves not only as a vector of transmission and penetration of the vertebrate host, but also as a host itself, in which obligate developmental phases of the parasite life cycle take place (Beier, 1998; Nuss *et al.*, 2018). In the case of *Plasmodium*, the mosquito is the host where sexual reproduction takes place. The mosquito proboscis, characterized as an "elegant biomicroelectromechanical system" (Kong & Wu, 2010) is an essential component for transmission. Female mosquitoes have a proboscis that can penetrate animal skin without causing pain and is used to suck blood from the host. In the process of acquiring a blood meal, the mosquito provides an elegant means of parasite transmission. Other arthropod vectors bite their hosts and, in the process, introduce anticoagulants for the consumption of blood meals, during which they may transmit viruses (Flaviviruses, Nairoviruses), bacteria [e.g. bubonic plague (Bitam *et al.*, 2010), Borrelia species, *Anaplasma phagocytophilum*], Rickettsia (e.g. Rocky Mountain Spotted Fever); babesioses (*Babesia divergens*, *B. microti*, *B. venatorum*; Boulanger *et al.*, 2019); and trypanosomes (Abdeta, Deresa & Haile, 2022). After being introduced into the bloodstream, some parasites have mechanisms to enter specific cell types in their multicellular hosts, although we do not consider these further in this review.

While trophically transmitted and vector-borne metazoan parasites of animal hosts need no particular adaptations to get inside their host, direct transmission *via* free-living infective stages does require active penetration. This is usually achieved using mechanical and/or chemical means. For example, trematode cercariae combine vigorous movements with secretions from their acetabular glands, which soften the host tegument (Ligasová *et al.*, 2011). Cercariae of some species, including members of the family Microphallidae, which have crustacean intermediate hosts, even possess stylets to help breach the thinner parts of the cuticle of their host (Saville & Irwin, 2005). By contrast, hookworm larvae use existing entry points on their host's skin. After hookworms contact their target host, skin extracts trigger the onset of penetration behaviour, which is involves vigorous burrowing through the orifices of sweat glands on moist skin (Haas *et al.*, 2005).

As with the previous examples of active penetration, whether through the aid of an arthropod intermediate, or mechanical/chemical means for free-living parasites, structures have evolved to facilitate entry that are reminiscent of the appressoria used by fungal parasites of both plants and animals.

IV. HOST RESPONSE

Potential host organisms are not passive spectators, but can employ a range of defences including avoidance, physical barriers, innate immunity involving recognition of foreign biological molecules, and adaptive immunity that may involve specialized cells for both recognition and subsequent action against future exposure. These defence strategies share commonalities across the four kingdoms, although

members of each kingdom likely have evolved defence specializations against specific types of parasite. For recent reviews of comparative immunology, particularly comparing plant and animal immune responses, see Menezes & Jared (2002), Hunter (2005), and Jones, Vance & Dangl (2016). Here, we expand this comparison across the four kingdoms, and include a discussion of adaptive immunity.

For motile creatures, the first line of defence may be behavioural (Sarabian, Curtis & McMullan, 2018), that is (*i*) take the animal away from sources of infection, (*ii*) prevent the parasite from making contact with the skin or entering the body, or (*iii*) physical removal of the parasite from the skin or even from inside the body [e.g. use of herbal medicine by chimpanzees, behavioural fever in ectotherms (Hart, 2011), or allogrooming in social insects (Hughes, Eilenberg & Boomsma, 2002; Walker & Hughes, 2009; Yanagawa, Yokohari & Shimizu, 2008)]. An additional defence response at the group level involves recognition of self/non-self based on odour and attacking or expelling diseased individuals (Kavaliers *et al.*, 2004). Studies on the biology of disgust suggest that it may function to avoid pathogens and parasites (Curtis & de Barra, 2018; Curtis, 2013).

However, many organisms are relatively sessile (e.g. vascular plants, bryophytes, fungi) and thus lack the ability to move away from potential parasites. Interestingly, plants too, although they are sessile, have in some cases evolved mechanisms of avoiding attachment by at least some parasites. For example, some plants constitutively produce VOCs that block the activity of nematode parasites and may prevent infection (Desmedt *et al.*, 2020).

All cellular organisms possess outer barriers that separate their internal structures from the outside environment and these layers provide protection from abiotic conditions, such as osmotic stress, pH, water loss, toxins, etc., while also providing the ability to block and/or facilitate entry of molecules or other organisms. Whether this barrier takes the form of a semi-permeable membrane, a cell wall, a surface mucous layer, or, for multicellular organisms, skin, cuticle, or bark, these structures help in delineating self from non-self. Such barriers usually form a critical first step in innate immunity for most organisms from single-celled microbes to multicellular fungi, plants, or animals, and whether they are sessile or mobile.

(1) Types of barriers

Among the simplest single-celled organisms are the Mycoplasma and other Mollicutes – prokaryotes with a cytoplasmic membrane but lacking a cell wall, and therefore, peptidoglycans. They are thereby resistant to antibiotics that target bacterial cell wall synthesis. Nevertheless, the cytoplasmic membrane alone provides a semi-permeable barrier that regulates molecule uptake and release. Prokaryotes with a cell wall have added protection provided by this structural feature that enables osmotic stability. A further innovation in bacteria is the polysaccharide capsule or coat, found on the outer surface of the outer membrane in both Gram-negative and Gram-positive bacteria.

All known eukaryotic cells have plasma/cytoplasmic membranes. Single-celled eukaryotes, including fungi and protists, have these membranes as barriers, but often also have cell walls that differ in composition from those of bacteria and archaea, which contain peptidoglycans or pseudopeptidoglycans, respectively. Fungal cell walls lie outside the cell membrane, and are composed of chitin, glucans, and glycosidic linkages with proteins. As for prokaryotic cell walls, fungal cell walls provide rigidity, protection against osmotic stress, and water loss, and serve as a barrier against potential pathogens or parasites. While older texts refer to some "fungi" without cell walls (cellular slime molds; Bonner, 1967) these are no longer considered as such and have been re-classified as protists. Although some protists have cell walls, this is not always the case. Plant-like protists (i.e. algae), and fungi-like protists (i.e. molds) both have cell walls, but animal-like protists (protozoa) do not.

Multicellular plants, including bryophytes and vascular plants, all have cell walls composed of cellulose surrounding the plasma membrane. In addition to the functions described above for other organisms, the plant cell wall provides features underlying the success of multicellular land plants, including tensile strength and the extensibility necessary for growth (Höfte & Voxeur, 2017). While animal cells do not possess cell walls, multicellular animals have evolved protective outer coverings. The cuticle of arthropods, the external mucosal layer of amphibians and fish (Guardiola, Cuesta & Esteban, 2022), and the skin of both invertebrates and vertebrates, all provide a measure of protection against internal tissue injury and a barrier against parasite association and/or entry (Guardiola *et al.*, 2022; Harris-Tryon & Grice, 2022). Another important feature is the skin microbiota, which can bolster the barrier function of skin by providing protection against parasites, tuning immune responses, fortifying the epithelium (Harris-Tryon & Grice, 2022), and improving wound healing.

(2) Innate immunity

Once a parasite has breached the outer surface, hosts have additional lines of defence in their repertoire of innate immunity (see online Supporting Information, Tables S1–S5). These may include biomolecular and cellular strategies. A feature common to almost all taxa is the ability to recognize self *versus* non-self.

Eukaryotes have evolved extensive ways to recognize foreign entities (Tables S1–S5). Across all four kingdoms, taxa have acquired a varied inventory of pattern recognition receptors (PRRs). These nearly ubiquitous proteins recognize patterns associated with various threats. These include pathogen-associated molecular patterns (PAMPs), microbe-associated molecular patterns (MAMPs), microbe-induced molecular patterns (MIMPs), nematode-associated molecular patterns (NAMPs), and damage-associated molecular patterns (DAMPs) (Ipcho *et al.*, 2016). Recognition of these

signals of potential risk may be focused on particular types of pattern in different hosts (Table 1), however the overall outcome is pattern-triggered immunity in plants, animals, fungi, and possibly also in single-celled eukaryotes. Recognition by PRRs is associated with activation of signalling pathways that ultimately function to kill or contain the invader. Innate immunity is found among potential hosts from all four kingdoms (de Jonge *et al.*, 2010).

Plants display innate immunity, although they lack a direct cellular response. Unlike animals, plants lack mobile defence cells and a somatic adaptive immune system. As shown in Table S4, they instead rely on the innate immunity of each cell and on systemic signals arising from sites of infection (Głowacki, Macioszek & Kononowicz, 2011). Plants utilize a variety of membrane-bound and cytosolic receptors. These include toll-like receptors (TLRs), evolutionarily conserved proteins also found in animal innate immune responses, where they are localized at barriers such as the skin or intestinal tract mucosa. In plants, TLRs are found in both gymnosperms and angiosperms and are typically proteins containing leucine-rich repeat (LRR) motifs. The LRR group of proteins also includes receptor-like kinases (RLKs) and recognition of MAMPs and PAMPs is often associated with such proteins (Głowacki *et al.*, 2011). Since plants are exposed to parasitic fungi, insects, and nematodes, all of which contain chitin components, plants have evolved innate defences that recognize chitin. These chitin-recognition systems often employ receptors that contain a lysin motif (LysM), an approximately 40-amino-acid globular domain that can bind bacterial peptidoglycan and eukaryotic chitin (Jamieson, Shan & He, 2018). An additional class of receptors, found both in membranes and within the cytosol/nucleus are the nucleotide-binding leucine-rich repeat (NB-LRR) proteins, ubiquitous in angiosperms, gymnosperms, bryophytes, and algae (Zhang *et al.*, 2016). These are part of a larger class of proteins known as nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), which act as intracellular sensors of (*i*) PAMPs that enter the cell *via* phagocytosis or pores, and (*ii*) DAMPs associated with cell stress (Jamieson *et al.*, 2018). Plant NB-LRRs have a central nucleotide-binding domain and a C-terminal LRR domain, and thus are structurally similar to animal NLRs. Unpublished analyses of several protozoan genomes (*Toxoplasma gondii*, *Plasmodium falciparum*, and *Leishmania brasiliensis*) also have identified putative NLR homologues (M.H. Perlin, unpublished observations) in protists. Whereas NLRs in animals exhibit a range of N-terminal domains, the variation in N-terminal domain of most plant NB-LRRs is restricted to either a coiled-coil domain or a Toll/interleukin-1 receptor (TIR) domain (Meng & Zhang, 2013). There is some evidence that the NLR protein family may have originated in green algae (Ortiz & Dodds, 2018). In addition, a recent report (Uehling, Deveau & Paoletti, 2017) proposed that the NLRs (i.e. *het* or *vic* locus) involved in vegetative incompatibility of filamentous fungi may represent an evolutionary precursor to NLRs used in innate defence. Like animals, plants also utilize mitogen-activated protein kinase (MAPK) signalling to mount a defence against insect herbivores (Hettenhausen, Schuman & Wu, 2015), for example in guard cells to close stomata after pathogen recognition.

The innate immunity of animals functions through both humoral and cellular components, with optimal immunity provided when these responses are coordinated (Pinaud *et al.*, 2019). Cells conferring innate immunity are varied and depend on the type of organism considered. Invertebrate cells involved in the innate immune response (see Table S2) include hemocytes – professional phagocytic cells that can be found in tissues or circulating within the hemolymph. Hemocytes can encapsulate parasites, eliminating them through the use of lysozymes and the production of reactive oxygen species (ROS) (Kinoshita *et al.*, 2022). They are present in various forms, across all invertebrate taxa.

In flies, epithelial tissues of the epidermis, gut, and trachea not only act as a physical barrier against entry of parasites, but also are a source of antimicrobial peptides (AMPs), lysozymes, and ROS (Kinoshita *et al.*, 2022). In mosquitoes some of these AMPs, which are a broad class of molecules produced as part of innate immunity, exhibit antifungal activity (Ramirez *et al.*, 2023). In response to fungal infection, cecropin, defensin, diptericin, holotricin, and lysozyme are all expressed, and act in concert against the fungal invader. Other AMPs target bacteria. For example, house flies produce AMPs when exposed to bacteria, which are ubiquitous in their environments (Pei *et al.*, 2014). One such peptide is the product of the *MDAP-2* gene and this peptide showed antibacterial activity against a variety of clinical isolates, including *E. coli*, *Salmonella pullorum*, and *Pasteurella multocida* (Pei *et al.*, 2014). The open vascular system of insects means that parasites passing through the epithelial barrier will encounter both humoral and cellular innate defence responses in the hemolymph (Kurata, 2010).

A variety of specialized hemocytes are found in different invertebrates. Depending on species, molluscs may have one or several functional categories of hemocytes, each originating from different connective tissues or organs, for example the amoebocyte-producing organ in gastropods (Souza & Andrade, 2012) and the white body organ in cephalopods (Claes, 1996). Lectins, which function as part of the humoral response, may also be found on the outer surface of hemocytes and participate in self- *versus* non-self recognition, triggering signalling and acting as PRRs. Additional components of the humoral response in invertebrates include PRRs such as lipopolysaccharide binding proteins and β-glucan binding proteins (βGBPs). These proteins bind to components of bacterial and fungal cell walls, leading to activation of the prophenoloxidase cascade, which results in parasite melanization, an important defence mechanism in arthropods (Kurata, 2010). These proteins are evolutionarily conserved across insects (e.g. *Drosophila*, *Anopheles*) and mammals (e.g. mouse, humans). Another critical component of hemocyte defence against bacterial pathogens is the immunoglobin-superfamily receptor, Down Syndrome cell adhesion molecule (DSCAM), which is required for phagocytosis by hemocytes. The high diversity of this class of molecule, generated by alternative splicing of

the *Dscam* transcript, suggests a function in discrimination between different bacterial threats (Kurata, 2010).

Cellular innate immune responses, especially in vertebrates, often involve the action of specialized cell types, such as hemocytes, macrophages, and neutrophils (Ten Hoeve *et al.*, 2022; Hakimi, Olias & Sibley, 2017). Humoral responses of the innate immune system include lectins, secreted antimicrobial compounds, naturally occurring antibodies, pentraxins, and the complement cascade. Interestingly, fibrinogen-related proteins (FREPs), originally discovered and characterized from trematode (fluke)-carrying *Biomphalaria* snails, have combined immunoglobulin-like and fibrinogen domains; they share similarity with vertebrate ficolins, lectins that activate the complement system and act as opsonins (Cerenius & Söderhäll, 2013). Moreover, conserved signalling pathways [especially MAPK and nuclear factor kappa B (NF-kB)] are found in both vertebrate and invertebrate immune responses, including initiation of innate immunity, activation of adaptive immunity, and cell death.

Table S1 includes a comparison of primary and secondary lymphoid tissues across the major groups of vertebrates, together with the types of cells with roles in innate immunity. As can be observed, with the exception of the agnathan (jawless) fishes, all vertebrates have a thymus as primary lymphoid tissue and, except for the fishes, all have bone marrow. In all vertebrates, the spleen functions as secondary lymphoid tissue, and all have gut-associated lymphoid tissue (GALT). For each vertebrate group, cells involved in innate immunity have been identified (e.g. dendritic cells, granulocytes, macrophages, natural killer cells). In addition, a variety of molecules are involved in the humoral response, including TLRs, NLRs, cytokines, complement, insulin-like receptors, and transforming growth factor β (TGFβ) receptors. Calcium-dependent lectins (C-type lectins) are found in both vertebrate and invertebrate innate immune responses (Table S5). Collectins are collagen-containing C-type lectins in mammals, where they are found in serum and a range of tissues at the mucosal surface (Murugaiah, Tsolaki & Kishore, 2020). Some are involved in activating the complement system, but they can also act as a link between the innate and adaptive immune responses, since they intensify the adaptive response initiated by macrophages and dendritic cells by modulating chemokines and cytokines (Murugaiah *et al.*, 2020).

Figure 2 and Table S5 summarize similarities and differences in innate immunity across the four kingdoms, although we note that details for fungi and protists have only recently begun to emerge. Membrane-bound receptors have been identified in animals (TLRs), fungi (LRRs), and plants [LRRs, RLKs and receptor-like proteins (RLPs)]. Cytosolic immune receptors also have been identified in these three kingdoms and are suggested *via* homology searches to be present in protists as well. Additional cytosolic factors (e.g. MAPKs, acharins, and tamavidins) have been found in all kingdoms but the protists.

(3) Adaptive immunity

Adaptive immunity traditionally has been considered limited to animals, and with a few exceptions, specifically to vertebrates. Molluscs, for example, have no lymphocytic defences, that is no T-cells, B cells or genes that drive generation of antigen-specific receptors (Warr, 1997). Neither are such cell types or responses found in insects. Vertebrate adaptive immunity has been extensively studied and reviewed (Litman, Rast & Fugmann, 2010; Hirano, 2015; Flajnik, 2018), and therefore only the critical aspects from the perspective of host responses to parasites are discussed below.

Ubiquitous in almost all vertebrates is the conserved structure and function of immunoglobulin M (IgM), as well as the presence of a thymus, spleen, conventional αβ T cell receptors and major histocompatibility complex (MHC) class II molecules (Table S1). Other components tend to vary in gene number, domain organization, and function across vertebrates. These include IgD, the γδ T cell receptor, natural killer (NK) receptors, non-classical MHC molecule, and Ig classes limited to particular taxa (see Table S1). Two different types of lymphocytes are involved in the adaptive immune response. T cells are produced in bone marrow (except in fishes) from hematopoietic stem cells and then mature in the thymus. They are distinguished from other lymphocytes in that they contain specific types of T cell receptor on their cell surface. T cells are required for cell-mediated adaptive immune responses. These lymphocytes are further divided into: (*i*) helper T cells, which assist B cells in antibody production (i.e. Th2 cells) and T helper cells that assist other T cells and macrophages by secreting certain cytokines (i.e. Th1 cells); and (*ii*) T regulatory cells, which regulate the immune response. The other type of lymphocyte is B cells, which are responsible for antibody responses, including the production and secretion of antibodies. B cells are activated by antigens presented by MHC and co-stimulatory [Cluster of differentiation 40, CD40(CD40)–CD40L (CD40 ligand) receptor–ligand pairs] signals from Th2 cells. After activation they develop into populations of high-affinity memory cells and plasma cells, the latter of which secrete antibodies, that is antigen-specific receptors. While both T cell and B cell populations are generated *via* hypermutation of somatic cells, B cells also undergo isotype switching, yielding different functional classes of antibodies (i.e. IgM and IgG) that all have the same antigen specificity. These antibodies bind to extracellular pathogens/toxins either to neutralize them directly or, to elicit effector-cell mediated phagocytosis (Litman *et al.*, 2010; Flajnik, 2018).

While still controversial in comparisons with vertebrates, there is growing evidence that exposure to foreign entities bearing specific patterns may result in some degree of priming memory of innate responses in invertebrates (Arala-Chaves, Sequeira & Salazar, 2000; Pinaud *et al.*, 2019, 2021). The snail *Biomphalaria glabrata*, intermediate host of the trematode *Schistosoma mansoni*, appears to exhibit a primed response specific to exposure to this parasite, yielding expression of apparently horizontally acquired prokaryotic

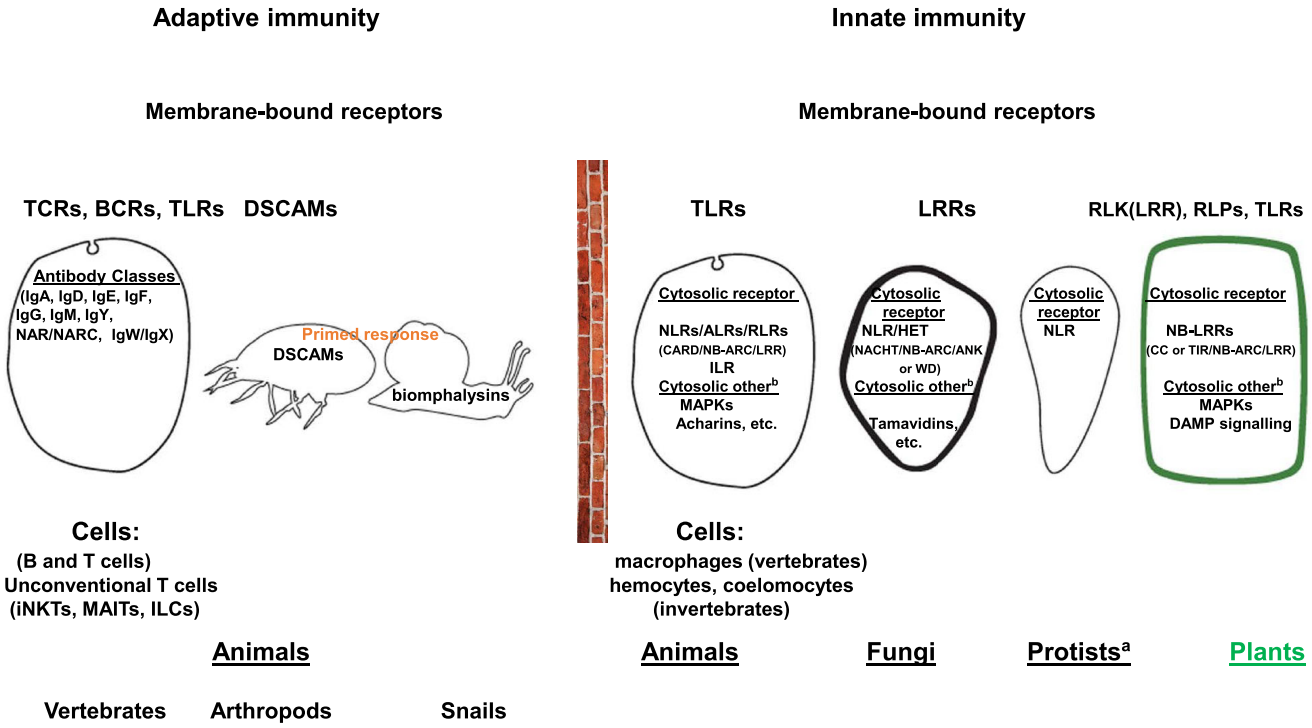

Fig. 2. Overview of comparative immune responses across kingdoms for different cell types, adaptive immunity and innate immunity. While there is possible evidence for innate immunity across all four kingdoms, adaptive immunity is traditionally thought to be present only in vertebrates. However, some controversial evidence may be consistent with adaptive immunity in invertebrates [e.g. primed response involving biomphalysins (part of a large family of aerolysins) in snails, and DSCAM in arthropods). "Priming" in plants also may be thought of as adaptive immunity (e.g. against hypovirulent fungi and endophytes). [a]In protists, evidence for NLR orthologues found in recent Delta BLASTp analysis (M. Perlin, unpublished results). [b]Additional "cytosolic other" components include: AMPs (in echinoderms), achacins and LBP/BPIs (in snails); and cysteine-stabilized α-helix/β-sheet motif (Csαβ)-defensins and glycoside hydrolase 24 (GH24)-type lysozymes (in fungi). Abbreviations: ALR, AIM2-like receptor; AMP, antimicrobial peptide; ANK, ankyrin; BCR, B cell receptor; BPI, bactericidal/permeability-increasing protein; CARD, caspase recruitment domain; CC, coiled coil; Csαβ, cysteine-stabilized α-helix/β-sheet motif; DAMP, damage-associated molecular pattern; DSCAM, Down Syndrome cell adhesion molecule; GH, glycoside hydrolase; HET, heterokaryon incompatibility; Ig, immunoglobulin; ILC, innate lymphoid cell; ILR, interleukin-1 receptor; iNKT, invariant NK T cell; LBP, lipopolysaccharide binding protein; LRR, leucine-rich repeat; MAIT, mucosal-associated invariant T cell; MAPK, mitogen-activated protein kinase; NACHT, specific domain used in the NB–LRR-containing protein (NLR) family; NAR/NARC, new antigen receptor, an IgX class antibody; NB-ARC, APAF-1 (apoptotic protease-activating factor-1), R proteins and CED-4 (*Caenorhabditis elegans* death-4 protein) domain containing protein, often associated with a nucleotide-binding domain; NB-LRR, nucleotide binding leucine-rich repeat; NLR, NOD-like receptor; RLK, receptor-like kinase; RLP, receptor-like protein; RLR, retinoic acid-induced gene-I like receptor; TCR, T cell receptor; TIR, Toll/intereukin-1 receptor; TLR, Toll-like receptor; WD, short structural motif, approximately 40 amino acids long, often terminating in a tryptophan-aspartic acid dipeptide. Original artwork by T. Hank Knight. Information used to construct this figure derived from Ipcho *et al.* (2016), Roudaire *et al.* (2020), Rauta *et al.* (2012), Schulenberg *et al.* (2008) and Uehling *et al.* (2017).

toxin genes that encode biomphalysins, part of a large family of aerolysins. These proteins are pore-forming toxins and the diverse family identified in *B. glabrata* is thought to be toxic to *S. mansoni* (Pinaud *et al.*, 2019, 2021). There is also a suggestion that DSCAM genes of arthropods, which can produce over 10,000 alternatively spliced variants, may represent a reservoir sufficient to recognize and bind to a large variety of potential pathogens/parasites (Li, 2021).

There is increasing evidence for the priming of immune responses, suggestive of adaptive immunity, in plants (Jung *et al.*, 2009; Tugizimana *et al.*, 2018; Leibman-Markus *et al.*, 2023) which may be analogous to the examples cited above for invertebrates. There are known examples of metabolite- or small molecule-based responses in plants that can detect self *versus* non-self. In some cases, epigenetic changes contribute to a sustained plant response, leading to establishment of a pre-conditioned or primed state (Tugizimana *et al.*, 2018). Such responses to environmental stimuli can sensitize or enhance aspects of innate immunity for faster and stronger responses. Such defence priming can involve either systemic acquired resistance or induced systemic resistance (Leibman-Markus *et al.*, 2023).

For example, defence priming can promote plant development in tomato, with a cytokinin response being activated during induced resistance. Such activation was required for the observed growth and disease resistance resulting from induced systemic resistance activation and was found to have a stronger effect on plant development than systemic acquired resistance (Leibman-Markus *et al.*, 2023).

Figure 2 summarizes components of adaptive immunity strategies in vertebrates and examples from invertebrates where immune systems display something akin to adaptation/learning. Importantly, relaxation of the criteria for adaptive immunity may allow inclusion of examples from invertebrates and plants where their innate immunity may be primed sufficiently to provide adaptation.

V. PARASITE RESPONSES TO HOST DEFENCES

Given the strategies described above used by potential host organisms to resist infection, parasites have developed ways to avoid or neutralize such host defences to allow them to establish and persist in prospective hosts. Effectors are molecules secreted by a pathogen or parasite that are used in the acquisition of nutrients from the host, to evade or modulate host defences or immune responses, or to manipulate host development or behaviour, so as to optimize parasite reproduction and/or dispersal. Effectors include, among others, secondary metabolites, antimicrobials, small RNAs, and small proteins. Antimicrobials tend to be used by endophytes as a mechanism to reduce potential competitors.

There is a vast and ever-growing literature describing fungal effectors, especially for plant pathogenic and parasitic fungi (see reviews by Lo Presti *et al.*, 2015; Kombrink & Thomma, 2013; Pradhan *et al.*, 2021; Rocafort, Fudal & Mesarich, 2020; Arroyo-Velez *et al.*, 2020), and recently for endophytic fungi (Stone, Paadilla-Guerrero & Bidochka, 2022). In the context of parasitic (usually biotrophic) or endophytic fungi, such effectors have a conserved set of characteristics, but rarely share conserved amino acid sequences or domains. Although larger secreted proteins with enzymatic function can be considered as effectors (Ma *et al.*, 2015), fungal effectors are usually defined as small (<250 amino acids), secreted, and possibly, cysteine-rich proteins. Moreover, their expression is usually up-regulated during infection or residence in the host. Finally, while some proteins labelled as effectors can be used for nutrient acquisition or breakdown of host tissues (e.g. glycosyl hydrolases, pectinases, etc.; Bradley *et al.*, 2022), for the most part they lack PFAM (protein family database) domains or homology/similarity to other known proteins (Lo Presti *et al.*, 2015). This suggests that at least a subset of effectors are specialized to the particular host(s) of a fungus and may be key components of host specificity (Lo Presti *et al.*, 2015). Importantly, some effectors in the fungal toolkit allow the fungus to optimize its interaction with different host tissue types. For instance, while *U. maydis* can infect all aerial parts of maize plants, resulting in galls (or tumours), different sets of effectors are required for optimal growth and reproduction of the fungus in leaves *versus* stem or tassel (Skibbe *et al.*, 2010; Villajuana-Bonequi *et al.*, 2019).

In addition to the traditionally studied bacterial and fungal effectors employed by plant parasites, details are now beginning to emerge for protist parasites of plants. Many phytopathogenic protists are biotrophs with complex polyphasic life cycles, making them difficult or impossible to culture. Nevertheless, improved genomics and bioinformatics tools, including, for example Alphafold (Jumper *et al.*, 2021), have enabled predictive characterization of some protist effectors. Interestingly, a well-studied effector type in plant pathogenic oomycetes, RxLR-DEER amino acid motif-containing proteins (where R = arginine, x = any amino acid, L = leucine, D = aspartic acid, and E = glutamic acid), is rarely found in non-filamentous protist pathogens of plants or algae (Mukhopadhyay *et al.*, 2024). The secretome of clubroot pathogen *Phytomyxea brassicae*, consisting of 553 proteins with a predicted signal peptide, is enriched with ankyrin binding domains, carbohydrate binding domains, and LRRs; a pattern also observed in other closely related rhizarian parasites (Mukhopadhyay *et al.*, 2024). Phytomyxea develop intracellularly, thereby reducing the need for cell wall-degrading enzymes. Instead, they manipulate host hormones to disrupt development and secure access to nutrients (Bürger & Chory, 2019). The impact of *P. brassicae* on the hormone balance of their hosts has been extensively studied; it causes prominent changes in host root phenotype (Malinowski, Truman & Blicharz, 2019), likely manipulating host development by changing auxin distribution and signalling in the infected tissue (Ciaghi, Schwelm & Neuhauser, 2019).

Whereas detailed research has centred on effectors of plant parasites, much less is known about effectors in animal systems, likely due to the necessity for alternative strategies by the parasite due to the different physiology and immune systems of their animal hosts. Table 1 provides a summary of available information on the strategies of parasites of hosts of the four kingdoms in response to the defences of their hosts. It is known that bacteria infecting animals produce secreted molecules to manipulate their hosts (e.g. in infection of humans by *Salmonella enterica*, or by *Yersinia pestis*, the causative agent of bubonic plague; Ke, Chen & Yang, 2013). Additionally, common protein domains have been identified in bacterial effectors from plants and animals that allow binding to host phosphoinositides (Salomon *et al.*, 2013), such as the *Vibrio parahaemolyticus* Type III secretion effector VopR. By contrast, much less is known about effectors of fungi that infect animals. In part, this may be due to the relative paucity of fungi that are true parasites of warm-blooded hosts. Most fungal infections of warm-blooded animals are opportunistic infections of immunocompetent or immunocompromised individuals (e.g. *Candida* spp., *Cryptococcus neoformans* spp., *Aspergillus* spp., *Mucor* spp., *Histoplasma capsulatum*). It therefore seems likely that differences in the immune systems of vertebrates compared with that of plants (see Tables S1, S4, and S5) could explain the relative paucity of fungal parasites in vertebrates. In addition, many fungi are unable to survive and persist at the higher temperatures associated with

mammalian hosts, and evolution of this ability is frequently a virulence factor in opportunistic species (Köhler *et al.*, 2017). Below, we first focus on fungal parasites of invertebrates, especially arthropod species. An examination of skin-associated fungal infections of warm-blooded animals follows thereafter.

Fungal parasites of insects are rather understudied compared to their plant counterparts, with the specific effectors that mediate fungus–arthropod interactions still in need of functional investigation to determine their precise roles. The generalist species *Metarhizium* and *Beauveria*, which have a more necrotrophic lifestyle, secrete small molecules (destruxins and beauverolides, respectively) thought to function as toxic killing compounds (Wang *et al.*, 2021; Wang *et al.*, 2023*a*). Fungi with a more parasitoid or hemibiotrophic lifestyle, some of which adaptively manipulate host behaviour, are thought to produce molecules with more diverse functions. Transcriptomic investigations of *Ophiocordyceps*–ant interactions demonstrate that a significant number of putative effector genes are upregulated during the host-manipulation stage, which takes place after prolonged infection. These often unique small secreted proteins share orthology and comparable gene expression patterns across ant-infecting *Ophiocordyceps* species (de Bekker *et al.*, 2015; Will *et al.*, 2020). Bioinformatic approaches can reveal potential effector functions by predicting *Ophiocordyceps*–ant protein–protein interactions. These predictions suggest that a significant subset of these fungal effectors bind to ant G-protein coupled receptors that are involved in various functions, including light perception and binding of neuromodulatory molecules such as dopamine (Will, Beckerson & de Bekker, 2023*b*). This is in agreement with metabolomics profiling that indicated altered dopamine levels in *Ophiocordyceps*-manipulated ants as compared to healthy conspecifics (Will, Attardo & de Bekker, 2023*a*). Thus, certain fungal effectors are involved in the manipulation of host physiological processes and behaviour rather than host killing.

In addition to small secreted proteins, the expression patterns of several secondary metabolite clusters suggest that their products also play a role in host manipulation by *Ophiocordyceps* species (de Bekker *et al.*, 2015; Will *et al.*, 2020). In addition, a range of larger secreted proteins that contain an enterotoxin alpha domain is dynamically expressed during *Ophiocordyceps* infection and manipulation. Proteins with such domains play a substantial role in the pathogenicity of *E. coli* and *Vibrio cholerae* bacteria (Lin *et al.*, 2010). So far, mostly insect- and nematode-infecting fungi are known to produce enterotoxin-domain containing proteins, with a few exceptions among plant pathogens (e.g. *M. grisea*). While generalist entomopathogens such as *Beauveria* and *Metarhizium* have only a few enterotoxin-encoding genes in their genomes, specialist fungi, such as those infecting nematodes and *Ophiocordyceps* species, have at least 20–30 genes (de Bekker *et al.*, 2017). Their exact function is currently largely uncharacterized. However, some initial molecular studies on enterotoxins from nematode-infecting fungi and *Beauveria bassiana* suggest that their functions are diverse and contribute to fungus–host interaction mechanisms (Zhang *et al.*, 2021; Ding *et al.*, 2023).

Fungal parasites of warm-blooded animals include those that infect the exterior parts of the animal body, including skin or nails. Such fungi are primarily dermatophytes and do not normally lead to lethal conditions in their host. Such infections can be contagious, spreading from infected to naïve hosts. The most common fungi responsible are *Malassezia* spp., associated with seborrheic dermatitis (dandruff) or atopic dermatitis (eczema), as well as species associated with toenail infections, athlete's foot (species of *Trichophyton*, *Epidermophyton*, and *Microsporum*), and jock itch (Burmester *et al.*, 2011). Secreted proteins from these fungal species are part of the parasitic process, contributing to their virulence. *Malassezia* spp. are probably the most abundant fungi associated with human skin (Goh *et al.*, 2022). Comparisons of individuals suffering with seborrheic dermatitis or atopic dermatitis with healthy individuals revealed differential expression of secreted proteases, lipases, phospholipases, and sphingomyelinases of *M. globosa*. One of the upregulated genes encoded a secreted aspartyl protease, Mgsap1. The role of this enzyme was explored in a genetically tractable system using *M. furfur*, where the corresponding orthologue, Mfsap1, was found to be necessary for proper adhesion and dispersal in human cell models, as well as inflammation in a mouse model of colonization (Goh *et al.*, 2022). In addition, another group of proteins, the AhR indolic proteins, appear to be involved in down-regulation of the host immune response, in particular, *via* their AhR ligands (Velegraki *et al.*, 2015). For infections with other dermatophytes (*Trichophyton*, *Epidermophyton*, and *Microsporum*), as with fungal pathogens, attachment utilizes varied types of adhesins. Interestingly, at least for *M. canis*, a secreted protease of the subtilisin family (Sub3) is involved in adhesion. After attachment, sensing of the host milieu involves the fungal transcription factors PacC and Hfs1, as well as heat shock proteins. These participate in sensing and adapting to the acidic pH of the skin in the early stages of fungus–host interaction (Martinez-Rossi, Peres & Rossi, 2017). As these fungi rely almost exclusively on keratin as a carbon source, the upregulation of secreted keratinolytic proteases provides them with nutrient sources for persistence (Martinez-Rossi *et al.*, 2017).

Like parasitic fungi, biotrophic nematodes that infect plants secrete effectors that allow them successfully to invade and manipulate host plants (Vieira & Gleason, 2019). The inventory of such effector molecules is extensive, with varied types of effectors found in sedentary/endoparasitic worms, such as root-knot and cyst nematodes, compared with large, expanded families of effectors identified *via* comparative genomics for nematodes of more diverse lifestyles (Vieira & Gleason, 2019). Until recently, the best-studied effectors were the plant cell wall degrading enzymes of nematodes, believed to have been acquired from bacteria or fungi by horizontal gene transfer (Haegeman *et al.*, 2012). Other effectors lead to evasion of host plant immunity, while still others lead to formation of nematode feeding sites *via* interaction with signalling pathways or hormonal modifications

(Haegeman *et al.*, 2012). The sessile nematodes must induce a feeding site in the host plant and only one site can be produced by each worm, so its destruction is lethal for the parasite. Thus, it is essential that the parasite blocks host defences throughout the duration of the feeding structure. Mobile nematode species are not similarly constrained, as they leave a path of destruction as they move through the plant tissues. These different lifestyles are reflected in the respective secretion profiles of these nematode parasites of plants (Haegeman *et al.*, 2012). Most secreted molecules are produced by the pharyngeal glands of the nematode and are secreted into the host *via* the stylet. Other potential effectors are secreted on the cuticle surface of the parasite. As one example, *Meloidogyne incognita* has several glutathione-S-transferases (GSTs), at least one of which is expressed in the pharyngeal gland cells from where it is thought to be secreted into the host (Dubreuil *et al.*, 2007). Gene silencing studies suggest that these GSTs are important in successful parasitism by the nematode (Dubreuil *et al.*, 2007). Interestingly, animal-parasitic nematodes also use GSTs, in this case to detoxify a wide range of endogenous and xenobiotic compounds (Campbell *et al.*, 2001). An additional 83 candidate effectors from *M. incognita* have been identified as genes upregulated in dorsal gland-enriched samples from adult females (Rocha *et al.*, 2023).

Cestodes, that is flatworms that infect animal species, secrete proteins that appear to function analogously to effectors of plant parasites (Fló *et al.*, 2017). *Echinococcus granulosis*, the causative agent of cystic hydatid disease, secretes a monodomain family of Kunitz proteins, subsets of which inhibit the host serine peptidases chymotrypsin and trypsin, while others block cation channels (Fló *et al.*, 2017). Different members of this multigene family are differentially expressed, with upregulation during different stages of the parasite life cycle. Moreover, these appear to be important in medically relevant cestode infections, but not in trematodes. Transcriptome analyses of other cestodes have provided insights into possible parasite products that may exert an influence over hosts (Hébert *et al.*, 2016; Grecias *et al.*, 2020).

It is now emerging that a common strategy among several types of parasitic worms is the use of microRNAs (miRNAs), delivered *via* extracellular vesicles (EVs) once the parasite is inside its animal host. miRNAs are a group of regulatory RNA molecules that control gene expression; many miRNAs employed by worm species share high similarity to host miRNAs, likely a result of extended coevolution with their hosts (Wu *et al.*, 2022). For example, some tapeworms (*Cysticercus cellulosae*, *Echinococcus multilocularis*, and *Taenia solium*), and trematodes (e.g. *Schistosoma japonicum*), and, interestingly, the flagellated protozoan, *Leishmania donovani* (which causes debilitating visceral leishmaniasis or black fever) all utilize EVs that carry a cargo of different miRNAs that alter host immune responses (Wu *et al.*, 2022). For instance, *S. japonicum* eggs in infested host liver can inhibit liver fibrosis and *L. donovani* can alter the host macrophage response, promoting an anti-inflammatory outcome necessary for its survival. Specific targets of such immune response regulation include polarization of macrophages by inhibiting the expression of their inflammatory factors and decreasing levels of key components of the immune signalling pathway in cells (Wu *et al.*, 2022).

Trichinella spiralis is a nematode species that infects a variety of mammals and is commonly associated with infection of muscle tissue, especially in pigs, from where it can infect humans *via* consumption of undercooked pork (Saracino *et al.*, 2020). While adult worms reside in the intestinal track, the live larvae of the parasite, produced in the intestine, invade the intestinal mucosa and migrate to muscle tissue, where they encyst. These are then consumed by humans or other carnivores. In human skeletal muscle tissue, nurse cell formation is mediated by the hypoxic environment surrounding new vessel formation, leading to signalling to increase angiogenesis (see Section VII). The use of EVs by *T. spiralis* in host immunity has recently been investigated and found to be involved in parasite stage-specific modulation of the host microenvironment. This allows optimization of conditions for the parasite (Khueangchiangkhwang *et al.*, 2023), with adult-specific and muscle-specific EVs repressing host mucin-related genes or inducing myoblast differentiation in nurse cells, respectively. Additionally, an aspect of both types of EV, acting *via* the miRNA tsp-miR-1, was suppression of interleukin 6 (IL-6), an interleukin with both pro-inflammatory cytokine and anti-inflammatory myokine activities (Khueangchiangkhwang *et al.*, 2023).

Effectors are therefore a common approach utilized by parasites for evasion of host defences, as well as for host manipulation. The best-studied effectors, for example plant cell wall degrading enzymes of nematodes, are believed to have been acquired from bacteria or fungi by horizontal gene transfer (Haegeman *et al.*, 2012). Whether injected into host cells, secreted into plant apoplasts, taken into host cells *via* endocytosis, or delivered to target cells *via* EVs, the effector molecules [proteins, metabolites, messenger RNAs (mRNAs), or miRNAs] are now recognized usually to block, control, or rewire aspects of host defences. In some cases, they are used directly in nutrient acquisition, but more often, they provide a degree of host specificity and/or lead to behavioural changes in the host, ranging from physiological to developmental. Some of these, for example those that modulate host plant signalling, are conserved strategies across fungal, protist, and nematode parasites.

VI. PERSISTENCE

Once a parasite has entered the host and evaded host defences in order to establish infection, it must successfully persist in the host, using the host as a source of nutrients. It must also complete its reproductive cycle and release its progeny into the environment in order to start the process anew. Such persistence may include production of additional effectors, tailored for the next phases of infection [e.g. *U. maydis* produces different effectors at different stages of development

(Depotter *et al.*, 2020, Depotter & Doehlemann, 2020); *E. granulosis* upregulates different members of the Kunitz multigene family during different stages of its life cycle (Fló *et al.*, 2017)].

After establishing infection in plants, fungal parasites use effectors to continue to evade host defences and/or manipulate the host. The *Cladosporium fulvum* effector Ecp6 sequesters chitin molecules released from the cell walls of invading fungal hyphae to make chitin unavailable for host immune components such as PRRs. In this way, pattern-triggered immunity is suppressed (de Jonge *et al.*, 2010). Chitin-binding genes of *C. fulvum*, such as *Avr4*, therefore have been proposed to be involved in protection against host chitinases. By contrast, LysM effectors in *C. fulvum* compete with the chitin-recognizing PRRs to bind to chitin with high specificify (de Jonge *et al.*, 2010; Gong, Wang & Li, 2020; Kombrink & Thomma, 2013; Sánchez-Vallet *et al.*, 2013; Sánchez-Vallet, Mesters & Thomma, 2015). Persistence requires surviving the host effector-triggered immune defence pathway mounted after the initial infection. As a consequence, some effectors do not target the recognition process but, instead, the downstream signalling events. Necrosis-inducing secreted protein 1 (NIS1) is a conserved core effector present in filamentous fungi (present in most Ascomycota and Basidiomycota), that targets host immune signalling-associated kinases bri1-associated receptor kinase 1 (BAK1) and Botrytis-induced kinase 1 (BIK1) responsible for transmitting the host PRR signal upon PAMP perception. Phosphorylation of BIK1 by BAK1 normally is used in positive regulation of plant immunity. The NIS1 effector targets PRR-associated kinases to interfere with immune signalling pathways in various pathosystems (Depotter & Doehlemann, 2020).

Additional types of effectors are continually being identified. EVs have been identified in animal, plant, and fungal contexts (Wang *et al.*, 2023*b*). They have been observed in the human pathogenic yeast, *C. neoformans*, but also in filamentous plant-pathogenic fungi (e.g. *Zymoseptoria tritici* which causes *Septoria tritici* blotch in wheat), *F. oxysporum* (fusarium wilt in Brassicaceae), *F. graminearum* (fusarium head blight in wheat and other grains), *Colletotrichum higginsianum* (anthracnose disease in Brassicaceae), and in the biotrophic parasite, *U. maydis*, discussed above. The roles of EVs in host–pathogen interactions of filamentous fungi remain relatively unexplored. One recently investigated strategy involves the production of small non-coding RNAs (sncRNAs) by the fungus that are secreted in vesicles and subsequently taken up by the host plant *via* endocytosis. In some instances, the target RNAs for these molecules are the mRNAs of the host plant that express components of the host immune response pathway(s) (He *et al.*, 2023).

Plants and animals often produce secondary metabolites as defence molecules, for example AMPs (see Section IV.2) that may constrain fungal growth. Therefore, parasite persistence requires that the parasite evolves ways to evade the actions of such products. *Candida albicans* utilizes a three-pronged approach: secretion of effectors that degrade AMPs, efflux pumps that remove AMPs, and regulation of signalling pathways (Ernst & Swidergall, 2017). Examples of similar strategies used by fungal parasites include detoxification, repression of biosynthetic genes involved in biocontrol, and efflux pumps actively to expel the antifungal compounds produced by hosts or provided clinically (Duffy, Schouten & Raaijmakers, 2003). Parasitic fungi, bacteria and protozoans all display similar enzymatic activities to escape host oxidative defences during the immune response against infection; where the host produces potentially damaging ROS, these defences include superoxide dismutases, catalases, glutathione or thioredoxin systems, peroxidase systems, flavohemoglobins and nitrate or nitrite reductases (Staerck *et al.*, 2017). Finally, as described above, the hydatid tapeworm *E. granulosus* is able to survive in the gut of mammalian hosts for many years without being digested by host-produced proteases. To achieve this, *E. granulosis* upregulates expression of different Kunitz multigene proteins during different stages of its life cycle (Gonzalez *et al.*, 2009). Such proteins are members of the serine protease inhibitor family and inhibit proteases such as chymotrypsin, in addition to a separate function as ion channel blockers.

A completely different strategy is used by trypanosomes, unicellular protozoan parasites of vertebrates, with perhaps the best-known being *Trypanosoma cruzi*, *T. brucei*, which cause Chagas disease in humans, dourine and surra in horses, and a brucellosis-like disease in cattle. The flagellated parasite *T. cruzi* is spread by Triatominae (kissing bugs or vampire bugs), while species the genus *Glossina* (tsetse fly) are vectors for *T. brucei*. Inside the dipteran tsetse fly vector, parasite development occurs prior to infection of the human host. In this stage, metacyclic forms of the parasite, which develop in the vector salivary glands, begin to express and are covered by variant surface glycoprotein (VSG) (Ponte-Sucre, 2016). Once inside the human host the bloodstream form develops from the invading metacyclic parasites. The VSG triggers a humoral immune response from the host, that must be countered if the parasite is to survive in the bloodstream. It achieves this by periodically changing the VSG molecules on its surface, through a genetically controlled process reminiscent of that used to generate a highly diverse pool of antibodies (Stijlemans *et al.*, 2016). Concurrently, the parasites eliminate/remove surface-bound IgG as well as complement through a rapid VSG recycling system and thereby prevent elimination by the host (Stijlemans *et al.*, 2016). Furthermore, trypanosomes release vast amounts of soluble VSG (sVSG), mainly during the peak of parasitemia; this scavenges complement factors and results in a state of hypocomplementemia (Stijlemans *et al.*, 2016). The shedding of its existing VSG molecules into the bloodstream, combined with the altered antigenic properties of constantly changing coat proteins, allows the parasite to evade the human immune system.

Toxoplasma gondii, another protozoan parasite of warm-blooded animals, has adopted strategies to facilitate pseudo-asymptomatic persistence in hosts, thereby increasing its transmission success to new hosts. Several *T. gondii* effectors drive this strategy. For example, *Toxoplasma*

E2F4-associated EZH2-inducing gene regulator (TEEGR) is an effector that promotes parasite persistence by modulating NF-κB signalling *via* Enhancer of zeste homolog 2 (EZH2) (Braun *et al.*, 2019). After escaping destruction by the host immune response, a small group of surviving *T. gondii* cells are able to occupy tissues that are normally free from immune system surveillance (i.e. eyes, placenta and fetus, testicles, and central nervous system). In these tissues, the parasite differentiates into a slow-replicating stage. This process requires regulation/repression of the IL-12–interferon-γ (IFN-γ) axis of the host immune system (Braun *et al.*, 2019). The *T. gondii* effector, TEEGR counteracts the NF-κB signalling pathway of the host defence system. Originally characterized as an intrinsically disordered protein, containing a protein export signal peptide, TEEGR thus bears characteristics associated with effectors in a variety of organisms. Once exported into the host cell, TEEGR complexes with the host transcription factors E2F3 and E2F4 in the nucleus, inducing gene expression and epigenetic chromatin remodelling leading to EZH2 transcription. EZH2 subsequently causes epigenetic silencing of a subset of NF-κB-regulated cytokines. Additional *T. gondii* effectors are involved in parasite dissemination. The parasite's effector dense granule protein, GRA28, first induces dendritic cell-like migratory properties in infected macrophages (ten Hoeve *et al.*, 2022; Hakimi *et al.*, 2017). The intracellular phase of the life cycle is followed by active egress from the host cell and then rapid reentry into a different cell, since the parasite does not divide when it is extracellular. Interestingly, there are similarities between this process in *T. gondii* and the process that drives sporozoite and merozoite invasion by *Plasmodium*, possibly because they are both members of the large apicomplexan phylum of mainly parasitic alveolates (Seeber & Steinfelder, 2016).

As part of their persistence strategies, parasites can modify host phenotype in a range of other ways. For instance, the nematode *Trichinella spiralis* invades mammalian muscle tissue where it transforms a host's striated muscle cell into a "nurse cell" (Wu *et al.*, 2008). The parasite reprograms the cell and its surroundings to enlarge it, surround it with a fibrous wall, and increase vascularization to the cell. Within this structure, the parasite can obtain all the nutrition it requires and is protected from host defence mechanisms. The process requires co-opting multiple host genes, including some involved in cell division, differentiation and apoptosis (Wu, Nagano & Takahashi, 2013). Among genes identified as differentially expressed in this modification of normal muscle cell development are those associated with satellite cell activation, proliferation, and differentiation; dedifferentiation and misdifferentiation; pro-apoptosis and anti-apoptosis; and cell signalling. Thus, a variety of genes that control host cell physiology and that specifically block cell defence mechanisms are targeted as part of the strategy of this parasite to persist during infection.

Clearly, parasite effectors not only play important roles in evasion of initial host immune responses, thus facilitating establishment, but are also often required for persistence. As they are present in fungi, protist, and nematode parasites, the importance of these effectors in persistence cannot be overstated. Additionally, diverse parasites can stimulate the development of protective structures (e.g. plant galls; *Trichinella* nurse cells; encystment stages of some animal parasites) that permit persistence within the host.

VII. NUTRIENT ACQUISITION/UTILIZATION

Some parasites develop specialized structures for nutrient acquisition inside the host. Cryptomycota species like *R. allomysis* grow in their host as a naked protoplast that steals ATP and devours host cytoplasm (James *et al.*, 2013). By contrast, some other parasites have specialized structures, such as the haustorium. Haustoria are common among the many and diverse species of parasitic angiosperms in which parasitism has evolved independently at least 12 times (Yoshida *et al.*, 2016). Such root-like structures develop after the parasite senses factors from the host that induce their development; these haustoria penetrate the root or stem of the host plant and become intimately associated with the host vasculature, enabling the exchange of water, nutrients (including amino acids, proteins, nucleotides, other carbon sources) and even of material from other parasites already infecting the host, including retrotransposons (Yoshida *et al.*, 2016). While haustoria are also used for penetration by some fungal parasites of insects (Reboleira *et al.*, 2021), by contrast, haustoria in plant parasitic fungi are not used for penetration, but develop later, once the hyphae have entered host cells. They tend to be a hallmark of obligate biotrophic fungi, such as powdery mildews, rusts, and some smuts, as well as oomycetes, like *Phytophthora* species. After initial penetration of the plant epidermis, smut fungi grow intra- and intercellularly, without disrupting the plant plasma membrane. Haustoria-like structures have been observed in some (e.g. *Ustilago hordei*, a parasite of barley and oats; Ökmen *et al.*, 2018), but not all smut fungi (notably, not in the maize parasites, *U. maydis* and *Sporisorium reilianum*; van der Linde & Göhre, 2021). Interestingly, there is evidence for conserved molecular mechanisms of nutrient acquisition. *Puccinia striiformis* f. sp. *tritici*, the causative agent of wheat stripe, produces haustoria and genes encoding members of the oligopeptide transporter (OPT) family are highly up-regulated in these structures; similarly, in *U. maydis*, several *opt* genes are highly expressed during biotrophic growth (Lanver *et al.*, 2018).

In the case of fungal parasites of insects, little is known about nutrient acquisition. For example, for *Ophiocordyceps*, all that is known is that the fungus is present in the insect body as yeast cells floating in the nutrient-rich haemolymph, where it causes minimal mechanical damage until it produces a stalk at the end of its life cycle (Fredericksen *et al.*, 2017; Li *et al.*, 2020). In comparison, malarial parasites have evolved specialized transporter systems at the interface of their cells and the intracellular vacuole of the host cells in which they reside (Beck & Ho, 2021). These transporters are involved

in a variety of processes, including nutrient acquisition [e.g. *via* small molecule transport by the Plasmodium translocon of exported proteins (PTEX) membrane-spanning pore exported protein 2 (EXP2)], waste efflux, effector protein export, and uptake of host cell cytosol (Beck & Ho, 2021). By contrast, another protozoan parasite, the epicellular *Cryptosporidium* spp., reside in a host-produced parasitophorus sac, where they cause rearrangements to host actin, and are concealed from the host immune system, while regulating transport and acquisition of nutrients, and being prevented from penetrating host cytoplasm (Kolářová & Valigurová, 2021). This last property allows the parasite to evade host cell repair and defence mechanisms, including ROS.

Metazoan parasites of animals display a range of adaptations for nutrient acquisition. These include specialized mouthparts for piercing the host tegument and feeding on blood, as seen in ectoparasites such as fleas, and endoparasites such as hookworms. Oher parasite taxa have evolved sophisticated feeding mechanisms.

Ectoparasitic monogeneans generally rely on chemical rather than mechanical means to acquire food. For instance, *Entobdella soleae* and *Gyrodactylus gasterostei* have no teeth, and feed on the superficial epidermis of their fish host by everting their glandular pharynx through their mouth and onto the host skin, where secretions loosen host cells and allow the worm to suck them up (Cable, Tinsley & Harris, 2002; Kearn, 2004). All species within two large taxa of intestinal helminths, the phylum Acanthocephala and the platyhelminth class Cestoda, have entirely lost their mouth and digestive tract. These worms feed on the contents of the host intestine and not on host tissues. In acanthocephalans, food is absorbed through the worm's tegument, which consists of a syncytial epithelium lined with "crypts" where nutrient assimilation takes place. The presence of enzymes on the acanthocephalan tegument suggests it may also have digestive capabilities (Starling, 1985). Cestodes also absorb nutrients from the host intestine directly through their tegument, whose surface area available for nutrient uptake is increased many-fold by finger-like projections, or microtriches (Dalton, Skelly & Halton, 2004). Active nutrient transport across the tegument is achieved by several carrier molecules.

One of the most striking feeding adaptations among metazoan parasites of animals is that seen in Rhizocephala, a highly derived group of barnacles that parasitize crustaceans. In parallel with the haustorium of parasitic angiosperms, rhizocephalans extend a branching root system, or interna, throughout their host's body through which nutrients are absorbed (Noever, Keiler & Glenner, 2016). A comparable root-like feeding apparatus has evolved independently in other lineages of parasitic barnacles (e.g. Sabadel *et al.*, 2022).

For *Trichinella* nematode larvae, development of the nurse cell provides not only a protection from the host defence system, but also a means of utilizing the host cells' metabolic processes to derive nutrients (Wu *et al.*, 2013). For the developing larva, this structure is both a source of nutrients required for rapid growth, as well as a means of removing waste products. During this time, the parasite directs increased blood supply to the nurse cell as it develops into a cyst, leading to increased angiogenesis (Capó, Despommier & Polvere, 1998). The larvae encourage this angiogenesis *via* vascular endothelial growth factor and thymosin 4, a peptide normally involved in wound healing (Kang *et al.*, 2011). *Trichinella* also utilizes the host insulin pathway to increase glucose uptake into nurse cells (Wu *et al.*, 2009). Evidence for this stems from transcriptome analyses that indicate upregulation of key genes with involvement in insulin production.

While some structures we identified in previous sections (plant galls; *Trichinella* nurse cells; other encystment stages of some animal parasites), may play a role in parasite protection against host defences, they also show parallels for nutrient acquisition strategies that demonstrate cross-kingdom links.

VIII. REPRODUCTION

Reproduction of parasites within a host can pose challenges, their population is subdivided into small groups of individuals, physically trapped within a host. This may be exacerbated if the parasite has a life cycle divided between multiple hosts or a series of intermediate hosts.

Thus, different parasites have evolved different strategies to accommodate their respective relationships with the host. For instance, the mycoparasite *R. allomycis* appears to stimulate the host cell (water mold, *Allomyces*) to make a cell wall around the developing zoosporangia containing motile zoospores or, alternatively, a chitin/cellulose thick-walled resting spore is generated (James & Berbee, 2012). Such resting spores are protected against host defences.

Obligate parasites, such as biotrophic fungi that parasitize plants are often unable to complete their life cycle outside their host plant. These fungi complete sexual reproduction inside the host, and this may also be a requirement for species with asexual reproduction (Steins *et al.*, 2023; Fei & Liu, 2023). For biotrophic, sexually reproducing fungi, plant-produced signals/cues determine when, within the plant, nuclear fusion/karyogamy occurs, followed by formation of diploid spores, ending its sexual reproductive phase. At this point, the fungus requires a dispersal mechanism. This may involve wind, rain, or pollinator species, for example. Spore germination to begin the infection/reproductive cycle again, can require additional cues or may depend on regulators produced by the parent fungus. For instance, *Uromyces phaseoli* produces methyl 3,4-dimethoxycinnamate, a "self-inhibitor" of spore germination that is effective at nanomolar concentrations and is only overcome when there is reduced competition as a result of spore dispersal (Hogan, 2006).

Parasitic plants may employ different reproductive strategies in different hosts (Yule & Bronstein, 2018), including variable pollinator rewards according to their host's niche. Endoparasitic plants, the most reduced of the flowering species, spend most of their lives as filaments within host tissues (Thorogood *et al.*, 2021). Recent investigations of members of the Rafflesiaceae identified similarities across four lineages

of parasitic plants, including total loss of the plastome, reduction of the vegetative phase to a proembryonic stage, and elevated information exchange between host and parasite (Thorogood *et al.*, 2021). Of note, there appears to have been convergent evolution between parasitic plants and some fungi; specifically, in their pollen–pistil and graft incompatibility interactions and associations with various fungi (Thorogood *et al.*, 2021).

Infection by *T. gondii*, a protozoan capable of infecting virtually all warm-blooded animals (Martorelli Di Genova *et al.*, 2019) has been extensively studied in cats. The cat is the only definitive host, that is where sexual reproduction of the parasite can occur. In felines the ingested parasite cysts pass through the stomach and into the small intestine. There, they infect epithelial cells and sexual reproduction occurs, leading to the massive production of oocysts bearing zygotes. This developmental stage requires high concentrations of linoleic acid; such concentrations are present since cats do not express the enzyme delta 6-desaturase (D6D) in their intestines, thus making cats the only definitive hosts (Martorelli Di Genova *et al.*, 2019). Eventually the epithelial cells rupture, releasing oocysts into the gut, from where they leave the cat in faeces. Other warm-blooded animals can be infected, but in these incidental hosts, the parasite cannot complete sexual development.

Root-knot sedentary nematode parasites of plants (*Meloidogyne* spp.) have three different modes of reproduction: amphimictic, producing cross-fertilized eggs after copulation; variations of parthenogenesis; and obligatory mitotic (apomictic) parthenogenesis (Castagnone-Sereno, 2006). Variations in parthenogenesis include reproduction by both crossfertilization and meiotic (automictic) parthenogenesis. For such species, when males are present, mating occurs, and reproduction is by crossfertilization. When males are absent, meiosis reduces the chromosome number in the egg, and the somatic chromosome number is re-established after fusion of the second polar nucleus with the egg pronucleus (Castagnone-Sereno, 2006).

Most parasitic platyhelminths, that is trematodes, cestodes and monogeneans, are hermaphroditic. This makes finding a mate easier, because any conspecific will suffice, or unnecessary if self-fertilization (selfing) is possible. In the cestode *Schistocephalus solidus*, selfing occurs even when partners are available (Lüscher & Milinski, 2003). Although outcrossing produces offspring that perform slightly better in terms of infection success and within-host growth (Christen, Kurtz & Milinski, 2002), selfing seems to be a reliable insurance strategy if mates are unavailable. Lifetime or long-term monogamy represents another adaptation to low probability of mate encounter. Schistosome trematodes are dioecious, with males being much larger than females. Although there are several exceptions, typically individual schistosomes of different sexes mate for a long time, sometimes for life: the female fits within a ventral groove on the male's body where she remains permanently with all her eggs fertilized by that male (Beltran & Boissier, 2008). Another more extreme form of monogamy has evolved in several taxa of ectoparasitic copepods, where the tiny males physically fuse with the body of the first female they encounter on a fish host (Raibaut & Trilles, 1993). Similarly, hermaphrodite monogeneans in the Diplozooidae family also fuse with a partner and the two members of a pair reciprocally outcross for life (Kearn, 2004).

Parthenogenesis is an alternative strategy against low mate-encounter probability. In the nematode *Strongyloides ratti*, adult worms in the intestine of rat hosts are always parthenogenetic females, which produce diploid eggs without the need for fertilization. Larvae hatching from eggs may give rise to a generation of sexually reproducing, dioecious adults outside the host, or directly infect a new host and develop into parthenogenetic females. The proportion of larvae adopting these alternative developmental routes depends on host immune and non-immune stresses experienced by their mother (Gemmill, Viney & Read, 1997; West *et al.*, 2001; Crook & Viney, 2005). Monogeneans in the genus *Gyrodactylus* combine hermaphroditism and parthenogenesis. These ectoparasites of fish are hermaphrodites and capable of sexual reproduction, however at least the first clutch of offspring produced by an adult worm come from automictic parthenogenesis (Cable & Harris, 2002). *Gyrodactylus* worms are hyper-viviparous: they give birth to full-grown progeny which are already "pregnant" with their own offspring, a "Russian doll" scenario that allows rapid population growth from a single worm (Cable & Harris, 2002).

Despite the variation in reproductive strategies of parasites, similarities are also apparent, especially when the parasite requires an intermediate host in order to complete some portion of its life cycle. Parallels can be seen between rust fungi that require one or more obligate intermediate hosts and protists, like malaria, where intermediate stages of the parasite develop in mosquitoes, or *T. gondii*, which requires a rodent intermediate host. Similarly, for parasitic worms, parthenogenesis and hermaphroditism have evolved convergently in parasites of both plant and animal hosts to solve the challenges of mate finding.

IX. DISPERSAL AND TRANSMISSION

Infectious propagules or spores can be dispersed *via* abiotic means, such as wind or rain, or may require the participation of other organisms. For instance, pollinator species may transfer parasite spores between flowers. There is evidence that pollinators can be influenced by plant host infection (Shykoff & Bucheli, 1995; Gupta *et al.*, 2012), including parasite-directed modification of host reproductive structures, for example increasing the number of male flowers produced (in *Microbotryum* infection of wildflower species in Caryophyllaceae) or increasing the number of female inflorescences (i.e. cobs in *S. reilianum* infection of maize) (Ghareeb *et al.*, 2015). These modifications likely provide more sites for parasite spore development and availability for dispersal. Similarly, among parasites of animal hosts,

modification of host physiology and behaviours induced by the parasite can improve dissemination of the parasite, for example diarrhoea elicited by an intestinal parasite that increases likelihood of contamination of water or food sources.

Vector-borne parasites can modify the smell of their vertebrate host to attract more vectors. For instance, mice infected with *Plasmodium chabaudi* release a different blend of volatiles and attract more mosquitoes compared to uninfected mice (De Moraes *et al.*, 2014). *Entomophthora* fungi employ odours to attract male flies to mate with sporulating cadavers of previous female fly hosts, thereby facilitating contact-mediated spore dispersal (Naundrup *et al.*, 2022). Hosts may adopt countermeasures to these strategies, with perceived changes in host odour leading to social adaptations to either dilute spore numbers [e.g. *via* social grooming (Pull *et al.*, 2018; Stock *et al.*, 2023)] or aggressive attack and/or removal of infected nest mates (Pull *et al.*, 2018; Malagocka, Eilenberg & Jensen, 2019; Will *et al.*, 2020; Trinh, Ouellette & de Bekker, 2021). *Ophiocordyceps*-infected ants show wandering behaviours, increased locomotory activity and reduced communication with nestmates, which could potentially represent parasite-adaptive behaviours that disconnect the host from the social context of the colony, increasing the parasite's chances of avoiding social immunity behaviours (Trinh *et al.*, 2021). Infected ants eventually perform summiting behaviour in which they climb vegetation to reach an elevated position that promotes fruiting body development (Will *et al.*, 2022) and spore spread *via* the wind. Similar summiting behaviours are induced by fungi of other genera, as well as certain worms (e.g. trematodes) and baculoviruses (Guler *et al.*, 2015; Liu *et al.*, 2022; Gasque & Fredensborg, 2023) to facilitate dispersal.

Interestingly, many parasites have evolved host behaviour-modification strategies for more efficient transmission, whether by enhancing chances of abiotic transmission, increasing the likelihood of direct contact with a new host, or through increased probability of intermediate host ingestion by a new primary host. Mechanisms to alter various aspects of host phenotype have evolved repeatedly and independently across all types of parasites, sometimes with striking convergence (Poulin, 2010, 2011). As mentioned in Section VIII, parasites often change the physiology and even the reproductive processes of hosts. The anther smuts (*Microbotryum violaceum* fungal complex; https://www.fungusfactfriday.com/132-microbotryum-spp/; Lutz *et al.*, 2008; Shykoff & Bucheli, 1995; Gupta *et al.*, 2012; Perlin *et al.*, 2015) are one such example. These fungi "reprogram" their host plants so that fungal spores develop in the anther of the plant instead of pollen, in essence castrating the plant. In other cases the developing flowers are infected. In *Microbotryum lychnidis-dioicae* infection of the female white campion (*Silene latifolia*), the ovary is aborted and a pseudoanther develops, releasing fungal spores to complete the parasite life cycle (Toh *et al.*, 2017; Kawamoto *et al.*, 2019). In addition, infected male plants increase production of flowers (Uchida *et al.*, 2003).

In analogous ways, parasites of animals can modify host behaviour to increase the likelihood of parasite dispersal to intermediate or definitive hosts. One example is the fungus *Massospora cicadina*, which alters mating behaviour to facilitate dispersal and again castrates its cicada host. As *M. cicadina* infects periodical cicadas, its spores remain dormant in the soil to attach to immature hosts as they make their way to the surface to emerge after 13 to 17 years (depending on species). After the host moults into an adult, the male's abdominal plates detach to reveal that their genitals have been replaced by a plug of fungal spores. The infected cicada then displays hyperactive behaviour, singing to attract females and flicking its wings to entice other males to mate with it and become infected (Cooley, Marshall & Hill, 2018). Modifications in host behaviour by a parasite may also be found in arthropod intermediate hosts. A direct association has been found between tick endosymbionts and the spread of parasites or pathogens (e.g. Rickettsia-infected ticks show greater motility and thus are more likely to spread this parasite; Seppälä & Jokela, 2016). Evidence suggests that *Wolbachia* infection of red poultry mites may direct reproduction of the mite to improve transmission (Nishide *et al.*, 2022).

Other convergently evolved parasite-adaptive traits are being revealed. One is the apparent role of environmental light cues in acanthocephalans and baculoviruses that cause tree top disease in caterpillars (Bethel & Holmes, 1973; Han *et al.*, 2018). Field data on *Ophiocordyceps* infections provide evidence that summiting ants position themselves on vegetation relative to both the amount and direction of incident light (Chung *et al.*, 2017; Andriolli *et al.*, 2019; Will *et al.*, 2022). These specific light levels are likely paired with a suitable microclimate (temperature and humidity) for fungal development and fruiting body growth (Andersen *et al.*, 2012; Will *et al.*, 2022), as fruiting body development ceases when an ant cadaver is removed and placed under different conditions (Hughes *et al.*, 2011; Loreto *et al.*, 2014). The importance of circadian rhythms of both parasite and host in behavioural modifications that optimize dispersal of the parasite, especially for summiting behaviour, have been reviewed previously (Borrmann & Rijo-Ferreira, 2024; Hunter, Butler & Gibbs, 2022 Westwood *et al.*, 2019; Carvalho Cabral, Olivier & Cermakian, 2019). Altering daily rhythms in the host is likely to have evolved convergently in multiple taxa, for example in baculovirus-infected caterpillars (Han *et al.*, 2018), ants infected with *Ophiocordyceps* (de Bekker & Das, 2022), and flies and beetles infected with Entomophthorales fungi (Elya *et al.*, 2018, 2023; Krasnoff *et al.*, 1995; Steinkraus, Hajek & Liebherr, 2017). Another striking convergence can be found in molecular mechanisms employed by parasites, for example in the putative role of protein tyrosine phosphatases (PTPs). Together with protein kinases, these proteins regulate various physiological processes. In baculovirus-infected caterpillars these enzymes have been demonstrated to have a direct effect on the hyperactive locomotory activity that is displayed by hosts (Kamita *et al.*, 2005). Comparable hyperactivity is also displayed by *Ophiocordyceps*-infected ants, in which there is upregulation

of fungal-secreted PTPs (de Bekker *et al.*, 2015; Will *et al.*, 2020). While a direct functional link between fungal PTP and heightened locomotion in ants has yet to be established, this does suggest yet another mechanism that has repeatedly evolved.

Other behavioural modifications are found in parasites that require intermediate hosts for a portion of their life cycles. These include the well-known case of behaviour modification associated with infection by *T. gondii*. In intermediate rodent hosts (mice, rats), altered behaviour is directed by the parasite by epigenetic remodelling of neurons that control the rodent behaviours. Specifically, the parasite directs hypomethylation of genes in the amygdala associated with fear of predators. The result is that infected mice are more exploratory, have less anxiety, and generally are less averse to predators; infected rats show decreased aversion to cat urine (Hari Dass & Vyas, 2014; Flegr & Markoš, 2014). These manipulations of host behaviour increase the likelihood that it will be encounter and be eaten by a cat definitive host.

An altered phenotype due to parasite infection may alone make the host more attractive for consumption by the definitive host. Berry ants, specifically *Cephalotes atratus* ants infected with the nematode, *Myrmeconema neotropicum*, display a swollen red gaster, which resembles the red berries present in the canopies of tropical rainforests (Yanoviak *et al.*, 2008). Although not yet observed directly, these phenotypic modifications may make the ants more attractive to frugivorous birds, in which the parasite develops and produces eggs. The parasite eggs are released into the bird faeces, from which they are retrieved by the ants and fed to their offspring. Acanthocephalans are notorious for their manipulative abilities, inducing changes in body coloration, phototaxis or responses to other cues, or interfering in other ways with the anti-predator adaptations of their arthropod intermediate hosts (Fayard *et al.*, 2020). A striking example is the trematode *Leucochloridium paradoxum* which infests, as intermediate hosts, land snails (often in the genus *Succinea*). The eye stalks of the snail become filled with pulsating green broodsacs of the flatworm, imitating caterpillars, a desirable prey for the avian definitive host (Usmanova *et al.*, 2023).

Many parasites must either fully emerge from their host or release their propagules in habitats different from the one the host occupies. In such cases, some parasites alter host behaviour to move to more suitable habitat. For example, nematomorphs cause their terrestrial insect host to enter water when the parasites have completed their development and are ready to emerge (Thomas *et al.*, 2002; Hanelt, Thomas & Schmidt-Rhaesa, 2005), and trematodes induce their snail hosts to move to tidal levels or a water depth that are optimal for the release of the parasites' infective stages (Curtis, 1987; Lowenberger & Rau, 1994). Parasitoid insects within Diptera and Hymenoptera induce their hosts to move to microhabitats suitable for the parasitoid to emerge and pupate, and even to remain to protect their pupae (Grosman *et al.*, 2008; Maure *et al.*, 2013).

Vector-borne parasites also can alter the feeding behaviour of their vector, for instance by causing it to take smaller blood meals but visit more hosts, thus increasing transmission opportunities for the parasite. A range of vector-borne protozoans (e.g. genera *Plasmodium* and *Leishmania*) as well as filarial nematodes are capable of such behavioural manipulation (Hurd, 2003; Rogers & Bates, 2007; Beaulieu, 2019).

Transmission strategies involving behavioural changes elicited in hosts by parasites thus converge across several general categories. Mechanisms of dispersal often exploit manipulation of host reproduction (e.g. fungal co-opting of plant sexual reproduction *via* replacement of pollen, generating hypersexual behaviour in infected insects, producing volatiles attractive to uninfected mates). Summiting behaviour of insects parasitized by fungi and nematodes exploits circadian/light-responsive pathways. Similarly, parasites that require intermediate hosts to complete their life cycle have evolved mechanisms that make such hosts more likely to be eaten by the definitive host, whether by making the former more attractive or by advertising their presence.

X. CO-INFECTION WITH OTHER ORGANISMS

There is a growing body of evidence that, at least for parasite interactions with animal and plant hosts, co-infection with other microbes or even multicellular organisms can alter the parasite's success, either benefiting the host or the parasite depending on the example. There is emerging evidence for similar factors in parasite infections of both fungi and protist hosts.

Several studies have explored the extent to which facilitation among parasites can have significant impacts on infection outcome [Bruno, Stachowicz & Bertness, 2003; Hellard *et al.*, 2015; Seppälä & Jokela, 2016; see Zélé *et al.* (2018) for a review; Feng *et al.* (2023) on coinfection *via* tick vectors]. In animal hosts, co-infections with multiple parasites, whether from the same species, different species, or different kingdoms, can result in potential cooperation or competition between these different parasites (Kalbe *et al.*, 2016; Hafer & Milinski, 2016; Rodgers & Bolnick, 2023). Rodgers & Bolnick (2023) found some evidence that co-infection with other parasites was facilitated by infestation of three-spined stickleback *Gasterosteus aculeatus* fish, with *S. solidus*, a cestode that lowers the immunity of this intermediate host. Other studies (Cutler *et al.*, 2021; Feng *et al.*, 2023), have emphasized the prevalence of transmission of multiple parasites by the same species of ticks. Recent extensive analyses of the endosymbionts of blood-sucking arthropods potentially provide a resource to test hypotheses about their roles in parasite fitness and virulence, as well as providing possible targets for therapeutics (Sonenshine & Stewart, 2021; Fukatsu *et al.*, 2023). A comprehensive collection (Fukatsu *et al.*, 2023) includes articles on the endosymbionts of lice, ticks, fleas, leeches, bed bugs, mites, and tsetse flies. Such comparisons could be instructive for inferring the selective advantages of particular microbiomes. Infected arthropod intermediate hosts/vectors can show altered

behaviour associated with parasite spread (Fukatsu *et al.*, 2023) and such effects can change if the arthropod is co-infected with other microbes. Investigation of the role of co-infection of mosquitoes on susceptibility or resistance has provided some interesting results in terms of our understanding of the evolution of such processes (Ramirez *et al.*, 2014). For example, the presence of *Chromibacterium Csp_P* led to resistance of mosquitoes to both dengue fever (*Anopheles gambiae* host, virus) and malaria (*Aedes aegypti* host, protozoan) (Ramirez *et al.*, 2014).

A growing body of evidence is also finding protective effects of endophytic microbes on plant health and survival from nematode (Schouten, 2016) and fungal infections (Rodriguez Estrada *et al.*, 2011; Redman, Dunigan & Rodrigues, 2001; Redman *et al.*, 1999). Redman *et al.* (1999) identified a mutant of *Colletotrichum magna*, a pathogen of melons, that was not pathogenic to the host plants, but instead grew within the plant as an endophyte. Importantly, the presence of this mutant protected the melon plants from infection by virulent wildtype strains of the fungus and *C. orbiculare* and *Fusarium oxysporum* (Redman *et al.*, 1999). Similarly, *Fusarium verticillioides* is endophytic in maize (Rodriguez Estrada *et al.*, 2011, 2012). The presence of *F. verticillioides* strains protected the host plant from infection by the biotrophic plant parasite, *U. maydis* (Rodriguez Estrada *et al.*, 2011, 2012), a phenomenon examined at both the metabolomic and transcriptome levels (Jonkers *et al.*, 2012; Rodriguez Estrada *et al.*, 2012).

The occurrence of microbiome effects may not be limited to just plant and animal hosts, with recent work demonstrating a role of the microbiome of the parasitic aphelid, *Amoeboaphelidium protococcarum* in opportunistic changes in lifestyle from commensal to predatory on its microalgal host, *Scenedesmus vacuolatus* as infection proceeds (Hoeger *et al.*, 2022). Mycoparasites of the fungal gardens of attine ants can be combated, in some cases, by protective assemblages of microbes (especially Actinobacteria) within ants, for example the highly specialized *Escovopsis weberi* (Batey *et al.*, 2020). Thus, co-infections can moderate the outcome of parasitism for hosts in all four kingdoms.

XI. CONCLUSIONS

(1) Hosts across the four kingdoms share similarities in their use of innate responses as a defence strategy (see Fig. 2).
(2) To overcome initial host barriers, parasites take advantage of natural openings or wounds, or alternatively use mechanisms for active penetration, with a common feature being structures that generate turgor pressure for penetration.
(3) Behavioural or other phenotypic modification of hosts across the four kingdoms is common for parasites of highly diverse taxa, often mediated by proteins and other small molecules produced by the parasite.
(4) Host targets for different parasite-produced effectors may converge across different host taxa.
(5) Different types of parasites may use similar delivery mechanisms and similar effectors to manipulate host immune responses (e.g. extracellular vesicles of protists, worms, and fungi, on animal and plant hosts; microRNAs).
(6) Parasites of the same class (e.g. nematodes) often utilize the same type of effector molecules, but with different effects in their respective host species (e.g. in animals *versus* plants).
(7) There are limitations when proposing a unified parasite strategy across the four kingdoms to overcome host defences and to maximize parasite fitness. For example, differences in host physiology, immune systems, and environmental conditions will dictate differences in strategies used by parasites and will tend to restrict the options available to parasites. For example, there are relatively few fungal parasites of mammals, with the most important fungal infections tending to be due to opportunists, who primarily affect immunocompromised hosts.
(8) This examination of parasites and hosts across the four kingdoms provides a more complete picture of this evolutionary landscape. Many strategies overlap in both hosts and parasites, even across wide phylogenetic expanses. Either due to evolutionary convergence or *via* direct evolutionarily conserved mechanisms, parasites continue to find ways to survive and reproduce within greatly divergent host species. We hope that this review facilitates hypothesis-driven investigations of parasite–host interaction that transcend the traditional kingdom-based research fields.

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XIII. AUTHOR CONTRIBUTIONS

The authors declare no known conflicts of interest. M.H.P. conceived the overall idea and together with R.P. developed and refined the approach. M.H.P. organized the writing and conceived initial drafts of several parts of the manuscript. All authors contributed substantially to all parts of the final version. M.H.P. conceived and developed all supporting information tables; R.P. conceived and edited Table 1. C. de B. provided extensive expertise on fungal parasites of insects and in editing successive drafts of the manuscript.

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XV. SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Main features of vertebrate immune systems (Banerjee *et al.*, 2021; Rauta *et al.*, 2012; Sia *et al.*, 2022).
Table S2. Main features of invertebrate immune systems (Hauton, 2012; Parisi *et al.*, 2020; Schulenburg *et al.*, 2008; Smith *et al.*, 2010).
Table S3. Main features of the immune systems of insect and arachnid ectoparasitic vectors (Hillyer, 2010; Kurata, 2010; Kopáček, *et al.*, 2010).
Table S4. Main features of plant immune systems (Meng & Zhang, 2013; Van Ghelder *et al.*, 2018).
Table S5. Cross-kingdom comparisons (Roudaire *et al.*, 2020; Rauta *et al.*, 2012; Schulenberg *et al.*, 2008; Uehling *et al.*, 2017).

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