Recent advances in vertebrate and invertebrate trans-generational immunity in the light of ecology and evolution

Olivia Roth[1,*], Anne Beemelmanns[1,2], Seth M. Barribeau[3] & Ben M. Sadd[4]

[1] GEOMAR Helmholtz Centre for Ocean Research Kiel, Marine Ecology, Düsternbrookerweg 20, 24105 Kiel, Germany

[2] Memorial University of Newfoundland, Department of Ocean Sciences, 0 Marine Lab Rd, St. John's, NL, Canada

[3] Institute of Integrative Biology, University of Liverpool, Crown Street, Liverpool, L69 7ZB, United Kingdom

[4] School of Biological Sciences, Illinois State University, Normal, IL, 61790-4120, USA

- corresponding author: Olivia Roth, GEOMAR Helmholtz Centre for Ocean Research Kiel, Düsternbrookerweg 20, 24105 Kiel, Germany, email: oroth@geomar.de, phone: ++494316004557

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Abstract

Parental experience with parasites and pathogens can lead to increased offspring resistance to infection, through a process known as trans-generational immune priming (TGIP). Broadly defined, TGIP occurs across a wide range of taxa, and can be viewed as a type of phenotypic plasticity, with hosts responding to the pressures of relevant local infection risk by altering their offspring's immune defenses. There are ever increasing examples of both invertebrate and vertebrate TGIP, which go beyond classical examples of maternal antibody transfer. Here we critically summarise the current evidence for TGIP in both invertebrates and vertebrates. Mechanisms underlying TGIP remain elusive in many systems, but while it is unlikely that they are conserved across the range of organisms with TGIP, recent insight into epigenetic modulation may challenge this view. We place TGIP into a framework of evolutionary ecology, discussing costs and relevant environmental variation. We highlight how the ecology of species or populations should affect if, where, when, and how TGIP is realised. We propose that the field can progress by incorporating evolutionary ecology focused designs to the study of the so far well chronicled, but mostly descriptive TGIP, and how rapidly developing -omic methods can be employed to further understand TGIP across taxa.

Keywords: maternal and paternal effects, phenotypic plasticity, immune defence, trans-generational effect, maternal antibodies, epigenetics

1. Parental effects and trans-generational immune priming

The genotype of an offspring is determined by the merging of maternal and paternal DNA, but the offspring's phenotype is influenced by a plethora of environmental factors, which provide enormous plasticity (Bonduriansky and Day, 2009; Bonduriansky, 2012; Scheiner, 2014). Parental effects represent one form of phenotypic plasticity across generations, where inherited environmental effects can be transferred to offspring from mothers and fathers (Kirkpatrick and Lande, 1989; Rossiter, 1996; Mousseau and Fox, 1998). Traditionally, paternal effects were thought to be rare due to both evolutionary and mechanistic constraints (Kokko and Jennions, 2008; Crean and Bonduriansky). However, a number of recent examples suggested they might be more prevalent (Heijmans *et al*, 2008; Carone *et al*, 2010; Rando, 2012; Roth *et al*, 2012; Crean *et al*, 2013; Jiang *et al*, 2013; Crean and Bonduriansky, 2014; Eggert *et al*, 2014; Kaufmann *et al*, 2014; Stein and Bell, 2014). Thus, while mechanistic constraints may exist, in sexually reproducing species both maternal and paternal effects have the potential to mediate offspring phenotype.

Parental effects are responsible for a broad range of plastic responses across generations, e.g. predator defenses (Agrawal *et al*, 1999), acclimation to abiotic environmental changes (Donelson *et al*, 2012; Sunday *et al*, 2012; Shama and Wegner, 2014; Roth and Landis, 2017), and disease resistance (Mitchell and Read, 2005; Goellner and Conrath, 2008). Trans-generational immune priming (TGIP), where parents enhance offspring immune defense based on their own immunological experience, can thus be viewed as a case of phenotypic plasticity achieved through parental effects (Grindstaff *et al*, 2003; Moret, 2006; Hasselquist and Nilsson, 2009; Moreau *et al*, 2012; Roth *et al*, 2012).

Here we present and discuss current evidence for TGIP in vertebrate and invertebrate systems. This focus does not exclude the possibility of TGIP in other systems, e.g. plants (for example see Luna and Ton, 2012; Henry *et al*, 2013). Within vertebrates and invertebrates, we address the potential mechanisms by which the phenotypic plasticity can be achieved across generational boundaries. We discuss the ecological conditions where TGIP is expected to evolve, and finish by considering future directions in TGIP research to address outstanding gaps in our knowledge of this fundamental and widespread phenomenon.

Based on its use in the field of ecological and evolutionary immunology, we use a broad definition of TGIP that constitutes any transfer of parental immunological experience to offspring, which can also include examples where the parental immunological experience takes place when developing offspring cells are already present. Under a strict mechanistic definition, this could include both inter- and trans-generational epigenetic inheritance (Heard and Martienssen, 2014), but can fit with a broad definition of transgenerational epigenetics (Burggren, 2016) where, in this case, a modified immunological phenotype is inherited due to experiences of parents, without changes in gene sequences. This broad classification of TGIP also includes different phenomena with distinct mechanistic underpinnings. Two broad categories can be characterised: 1) the provisioning of active immune components to offspring, for example maternal antibody transfer in mammals or deposition of antimicrobial peptides in insect eggs, and 2) heightened endogenous immune function of offspring, for example through altered offspring gene expression. The merit of viewing mechanistically distinct phenomena under the same umbrella definition is that we can

generally assess the causes and consequences of parental derived modifications to offspring immunological phenotypes. We also note that it is important to compare and contrast these differentiated phenomena when assessing TGIP from an adaptive evolution standpoint.

2. Evidence for TGIP in vertebrates

Studies of trans-generational immunity have a long history in vertebrate systems, but what constitutes vertebrate TGIP remains a developing field. Recent studies have demonstrated novel instances of TGIP that relate to both innate and adaptive immune components. Innate immunity is evolutionary conserved and is present in both invertebrates and vertebrates. Due to its immediate activation, it constitutes a rapid reaction against infection. Although recent studies have shown the innate immune system is capable of specificity and can provide lasting protection (Chambers and Schneider, 2012; Netea *et al*, 2016), in general it is considered to be comparatively unspecific. In vertebrates, it acts as the first line of defence, with the highly targeted and specific vertebrate adaptive immune response developing later.

Paul Ehrlich first described the passive transfer of components of the maternal adaptive immune response in 1892, with antibodies being transferred from mothers to offspring via the placenta, milk or eggs (Brambell, 1958; Brambell, 1969; Silverstein, 2001). This can boost offspring survival against pathogens isolated from the maternal environment. As the antibody-mediated adaptive immune system of vertebrates requires time to mature (Grindstaff *et al*, 2006; Boulinier and Staszewski, 2008; Hasselquist and Nilsson, 2009), TGIP is considered beneficial for early life stages when mortality selection is highest (Rossiter, 1996). Selection from parasites is

considered to have resulted in the independent evolution of TGIP across vertebrates (Patterson *et al*, 1962; Hasselquist and Nilsson, 2009; Swain and Nayak, 2009; de Oya *et al*, 2011).

In a common aquaculture application, TGIP of teleost fish is taken advantage of to improve offspring survival by boosting parental immunity (Mulero *et al*, 2007). Effects of TGIP are seen on both innate and adaptive immune responses of fish (Bly *et al*, 1986; Fuda *et al*, 1992; Takemura and Takano, 1997). Teleost fish mothers deposit antibodies directly into eggs, with primed offspring having increased body weight, lysozyme activity, complement system efficiency, and anti-protease activity (Hanif *et al*, 2004). Fish are interesting vertebrate model systems to investigate TGIP in an evolutionary ecology framework, as large scale breeding can permit laboratory manipulation experiments, and novel routes to achieve TGIP may be facilitated by differential parental investment strategies in teleosts (Clutton-Brock, 1991; Wourms and Lombardi, 1992; Blackburn, 2015). For example, in mouthbrooding cichlids active immune substances can be transferred via the oral mucosa to boost offspring immune defence (Sin *et al*, 1994; Keller *et al*, 2017) Similarly, in species with paternal care, fathers can provide eggs or fry with antimicrobial immune components in a thick mucus layer, facilitating biparental protection of their offspring (Giacomello *et al*, 2006; Buckley *et al*, 2010; Pizzolon *et al*, 2010). Biparental TGIP influences offspring lymphocyte proliferation and immune gene expression in syngnathids (i.e. seahorses and pipefishes), with their unique male pregnancy (Roth *et al*, 2012; Beemelmanns and Roth, 2016a; Beemelmanns and Roth, 2016b; Beemelmanns and Roth, 2017). In vertebrates, these are currently the only examples for a paternal involvement in TGIP, including the potential involvement of epigenetic mechanisms leading to changes in

endogenous offspring immunity, in addition to the transfer of active immune components.

Studies in amphibians and reptiles are limited, but there is some evidence of TGIP in these taxonomic groups. The transfer of maternal antigen-specific antibodies to eggs has been shown in African clawed frogs (*Xenopus laevis*), potentially protecting eggs prior to the development of the offspring immune system (Poorten and Kuhn, 2009). Active innate immune components have also been shown to be transferred to embryos from adult glass frogs, *Hyalinobatrachium colymbiphyllum* (Walke *et al*, 2011. A study of desert tortoises (*Gopherus agassizri*) suggested higher Immunoglobulin (Ig) G and IgM antibody concentrations in offspring from infected parents (Schunlacher *et al*, 1999). These examples show transfer of active innate and adaptive immune components, but studies are yet to investigate epigenetic changes leading to altered immune responses of the offspring themselves.

In birds, the antibody quantity transferred to offspring via maternal deposition into the eggs corresponds to the maternal antibody titer in the blood during the pre-laying period (Gasparini *et al*, 2002). Most studies of TGIP in birds have induced parental immunity via the injection of sheep red blood cells or other benign antigens. Specific TGIP has only rarely been experimentally investigated in natural host-parasite systems, e.g. Lyme disease *Borrelia burgdorferi* (Gasparini *et al*, 2002) and Newcastle disease virus (Rehmani and Firdous, 1995). TGIP in birds enhances offspring defence by elevating offspring immune responsiveness, and maternally transferred antibodies may persist for several weeks up to years after hatching (Ramos *et al*, 2014). In addition to eggs as a route of maternal antibody transmission, transfer by crop milk

feeding has been shown in the pigeon *Columba livia* (Jacquin *et al*, 2012). Hence, maternal antibody provisioning via milk-feeding (breast or crop) seems to have independently evolved in mammals and birds.

In mammals, maternal vaccination or disease exposure can enhance offspring survival. Most studies, however, have focused on the impact of TGIP on early life stages (Watanaveeradej *et al*, 2003; Leuridan and Van Damme, 2007; Leuridan *et al*, 2011), while the question of persistent effects of TGIP was largely ignored. Only more recently, it has been demonstrated that maternal vaccination of mice (*Mus musculus*) with mousepox (VACV WR) increased not only survival of offspring upon a usually lethal infection early in life, but also that this positive impact of TGIP persisted beyond the maturation of the offspring adaptive immune system and into adulthood (Navarini *et al*, 2010). Studies of wild populations suggest a similar effect, e.g. in a wild sheep population (*Ovis aries*), maternal antibody concentration was positively correlated with lamb survival (Graham *et al*, 2010).

Examples from amphibians, reptiles, and mammals have demonstrated the transfer of active innate and adaptive immune components, but studies are yet to explicitly investigate and show evidence for epigenetic changes leading to altered immune responses of the offspring themselves in any of these taxonomic groups. However, given studies in fish showing changes to offspring and even grand-offspring immune gene expression (Beemelmanns and Roth, 2017), there is a precedent for TGIP to also be achieved in vertebrates through this route.

3. Evidence for TGIP in invertebrates

Despite lacking the characteristic antibody-mediated immune memory achieved by the adaptive immune system in vertebrates, invertebrates have been shown to exhibit functionally analogous responses to immune memory, which provides increased protection on secondary pathogen/parasite exposures. The breadth of taxa with some form of this immune memory-like response is impressive, from comb jellies (Bolte *et al*, 2013), sea anemones (Brown and Rodriguez-Lanetty, 2015) and bivalves, through a variety of crustaceans (Rowley and Pope, 2012) and insects (Sadd and Schmid-Hempel, 2006; Roth *et al*, 2009), spanning >900 millions years of divergence. For within generational immune priming in diverse invertebrates we refer readers to a recent and thorough review of the topic (Milutinović and Kurtz, 2016). While evidence for TGIP is less abundant than within generational priming, it has been described for a number of these taxa (Sadd *et al*, 2005; Watson *et al*, 2005; Freitak *et al*, 2009; Roth *et al*, 2010; Freitak *et al*, 2014).

While much earlier work hinted at TGIP in invertebrates, with increased survival of greater wax moth *Galleria mellanoella* against bacteria following exposures three generations prior (Ishimori and Metalnikov, 1924), there has been a more recent revival of studies into invertebrate TGIP. This began with work in the waterflea *Daphnia magna*, where it was found that when mothers were exposed to particular strain of the bacterial pathogen *Pasteuria ramosa*, clonal offspring were better protected to that strain over a heterologous strain (Little *et al*, 2003). Subsequently, work in the bumblebee *Bombus terrestris* and the mealworm beetle *Tenebrio molitor* found priming of anti-bacterial responses in offspring of mothers exposed to immune eliciting bacterial components (Sadd *et al*, 2005; Moret, 2006). This general pattern of elevated immunity or qualitatively better survival against pathogens in offspring

following maternal pathogen exposure has been described in a range of host taxa (various insects, crustaceans, nematodes).

Demonstrations of increased offspring survival to pathogens following prior parental exposure do not require the involvement of immunity. However, other studies have directly measured immune parameters in offspring. Recent gene expression studies have shown that even within insects the routes to the realization of TGIP may be highly diverse. TGIP may elevate baseline expression of immune effectors in offspring (Barribeau *et al*, 2016), prime offspring to induce immune-related genes when required (Trauer-Kizilelma and Hilker, 2015), or have diverse effects beyond our understanding of classical innate immunity and resistance (Tate *et al*, 2017). In addition, depending on the system, only specific types of pathogens may trigger TGIP. For example, in mealworm beetles priming against gram-positive bacteria was shown to be more efficient than against gram-negative bacteria (Dhinaut *et al*, 2018), although in the moth *Manduca sexta*, TGIP was shown upon inoculation with gram-negative *Serratia marcescens* (Rosengaus *et al*, 2017). Concerning the afforded protection, highly specific protection on a strain level (Roth *et al*, 2010) and cross-reactivity (Dhinaut *et al*, 2018) have both been shown in related flour beetle systems, indicating that the specificity of protection given by TGIP may also vary greatly among pathogen types and hosts. The work on flour beetles is especially noteworthy, because it has been shown that both mothers and fathers can confer resistance to offspring following immune challenges (Roth *et al*, 2010; Zanchi *et al*, 2011). Of relevance for potential mechanisms behind TGIP, an elegant comparison of contemporary step and genetic offspring of the same mother but different fathers showed TGIP only in genetic offspring (Eggert *et al*, 2014). Other invertebrate systems have been used to

demonstrate the persistence of TGIP, which has been shown to cross multiple generational boundaries. Priming of antiviral immunity in the nematode *Caenorhabditis elegans* can last to F4 progeny (Rechavi *et al*, 2011). There is suggestive evidence for elevated resistance over multiple generations in the aquatic invertebrate *Artemia franciscana* following exposure to the pathogen *Vibrio campbellii* (Norouzitallab *et al*, 2015; Norouzitallab *et al*, 2016), although this is based on an experimental design with unaccounted for pseudo-replicated.

In invertebrates, both mechanistically distinct routes of achieving TGIP, transfer of active components or induced changes in endogenous offspring immunity, have been demonstrated, including in the same species. For example, in bumblebees, eggs from immune challenged mothers have greater antibacterial activity (Sadd and Schmid-Hempel, 2007), but in addition, adult offspring show increased immune gene expression (Barribeau *et al*, 2016). The studies that demonstrate TGIP across multiple generations in invertebrates are really indicative of underlying epigenetic mechanisms regulating offspring gene expression and phenotypes.

4. Established and potential mechanisms of TGIP: the unique and the shared

Comparing the mechanistic underpinnings of TGIP between and within vertebrates and invertebrates provides a great deal of information on convergent evolutionary strategies to adaptively adjust offspring immunity based on the prevailing pathogen environment. Particularly promising is a comparative approach that investigates TGIP contingent on innate immunity, which is relatively conserved between vertebrates and invertebrates. Yet, aside from a few specific cases, e.g. maternal antibody transfer in vertebrates, mechanisms underlying TGIP are relatively poorly understood, and filling

this void will require considerable further research effort. However, based on existing knowledge of other plastic physiological traits and immunity, we can suggest potential pathways leading to the realization of TGIP.

4.1. Transfer of active immune components

For decades, the mechanistic basis of TGIP in vertebrates focused on the acquired immune system, and, specifically the transfer of maternal Ig. The transfer of maternal antibodies to offspring has been well documented and reviewed substantially elsewhere (Hasselquist and Nilsson, 2009; Swain and Nayak, 2009). Data further suggest that the degree of transfer and persistence varies among species and individuals (Boulinier and Staszewski, 2008; Garnier *et al*, 2013). More recent evidence from vertebrates has demonstrated that components of the innate immune system could also be transferred to offspring (Hanif *et al*, 2004; Beemelmanns and Roth, 2016b; Beemelmanns and Roth, 2017).

In teleost fish, the formation of lymphoid tissue, B-cells and T-cells takes time, and thus there is a lag before offspring adaptive immunity becomes effective (Magnadóttir *et al*, 2005; Swain and Nayak, 2009). To overcome this period of high vulnerability, females provide their eggs with adaptive and innate immune components such as complement factors, serine protease-like molecules, lectins, macroglobulin, and antimicrobial peptides (Magnadóttir, 2006; Magnadóttir *et al*, 2005; Swain *et al*, 2006; Zhang *et al*, 2013). While fish rely on a combination of both innate and adaptive immune effectors for the transfer of immunity to their offspring, it remains unknown whether similar modes of transfer are at work in other vertebrate clades.

Elevated antibacterial activity has been demonstrated in eggs from immune challenged mothers in insects (Sadd and Schmid-Hempel, 2007; Dubuffet *et al*, 2015). In the snail *Biomphalaria glabrata*, parental immune protection of eggs takes place through the loading of eggs with an antimicrobial protein (Baron *et al*, 2013). However, immune activity of eggs may not solely derive from passive transfer, and early stage invertebrate eggs may be capable of producing robust immune responses (Gorman *et al*, 2004), which result from endogenous immune gene expression (Jacobs *et al*, 2017).

4.2. Transfer of PAMPs to offspring

Aside from the direct transfer of immune components between parents and offspring, it is possible that transfer of pathogen associated molecular patterns (PAMPs) to offspring will ready their own endogenous immune responses for the prevailing environment of potential infections. Early transfer of microbes between generations may be much more pronounced than previously thought in animals (Funkhouser and Bordenstein, 2013). In insects, mothers exposed to bacterial immune challenge can transfer bacterial fragments to their eggs (Freitak *et al*, 2014). In honey bees this may be achieved by the nutrition protein vitellogenin acting in a novel role as a potential carrier of an immune priming signal to offspring by binding to PAMPs and transporting bacteria fragments into eggs (Salmela *et al*, 2015). However, it remains to be investigated if this transfer alone is sufficient to elicit the substantial TGIP responses seen in several insects, and no transfer of bacterial fragments was shown to be associated with TGIP against bacteria in *M. sexta* moths (Rosengaus *et al*, 2017).

4.3. Epigenetic inheritance influencing offspring gene expression

Environmental influences can induce epigenetic changes in an organism leading to an altered phenotype that might be maintained across generations (Clutton-Brock, 1991; Campos *et al*, 2014; Jablonka and Lamb, 2015; Ragunathan *et al*, 2015; Rassoulzadegan and Cuzin, 2015; Szyf, 2015). The contemporary term epigenetics or epigenetic inheritance refers to all non-genetic heritable changes apart from DNA-based changes (mutations) that may lead to altered gene expression and could create phenotypic differences among individuals (Berger *et al*, 2009; Jablonka and Lamb, 2015). Recent studies focusing on impact of environmental stress on both vertebrates and invertebrates have confirmed that maternal and paternal experience induces epigenetic changes, such as DNA-methylation and histone modifications, which might be transferred over the generational boundary (Heijmans *et al*, 2008; Szyf, 2015; Youngson and Whitelaw, 2008; Curley *et al*, 2011). In humans and mice, epigenetic modifications may play a role in maintaining pools of memory CD8 T cells following viral infection (Youngblood *et al*, 2015). In pipefish, parental and grand-parental immune challenge leads to the differential expression of 15 genes responsible for epigenetic regulation (DNA-methylation and histone de/methylation and de/acetylation) in subsequent generations (Beemelmanns and Roth, 2016b; Beemelmanns and Roth, 2017). Epigenetic modification could thus represent a mechanism for TGIP and the transfer of parental and grandparental immunological experience, with the potential of mediating long-term protection.

4.3.1. DNA methylation

DNA methylation adds a methyl group (CH_3) to the 5' carbon of cytosine bases and generally occurs where a cytosine meets a guanine, at CpG sites (Bird, 2002; Jaenisch and Bird, 2003). These sites tend to accumulate in promoter regions forming “CpG islands” (Craig and Bickmore, 1994). Hypermethylation of CpG islands located within

or adjacent to promotor regions initiates packing of chromatin structure or heterochromatin remodeling, resulting in gene silencing (Grewal and Moazed, 2003). DNA methylation negatively regulates gene expression and is necessary for all cell differentiation processes, such as stem cell differentiation during embryogenesis (Monk *et al*, 1987; Razin and Shemer, 1995; Lee *et al*, 2015). The chemical reaction of DNA methylation is mediated by enzymatic action of several evolutionarily-conserved DNA methyltransferases (DNMTs) involved in either maintaining methylation marks or *de novo* methylation on previously unmethylated sequences (Okano *et al*, 1999; Bestor, 2000). *De novo* methylation can thus play an essential role in maternal and paternal imprinting (Kaneda *et al*, 2004), and is potentially a crucial factor for epigenetic changes based on environmental stress. In contrast to mutations, DNA methylation patterns are reversible, highly dynamic, and can change several times throughout the life of an organism (Monk *et al*, 1987; Bird, 2002; Lee *et al*, 2015). Recent studies have shown that methylation marks are transferred during meiosis, and are thus heritable across generations (Szyf, 2015). It was initially thought that trans-generational epigenetic inheritance through DNA methylation marks was impossible due to embryonic demethylation (Reik *et al*, 2001), however, other evidence suggests that certain elements escape demethylation, and may represent inherited epimutations (Lane *et al*, 2003). While derived from a pseudoreplicated experimental design, stochastic methylation patterns have been found across generations of *Artemia* primed against *Vibrio campbellii* (Norouzitallab *et al*, 2016). In addition, DNA methylation genes are differentially expressed in offspring and grand-offspring of immune challenged pipefish individuals exhibiting TGIP (Beemelmanns and Roth, 2016a; Beemelmanns and Roth, 2016b; Beemelmanns and Roth, 2017; Roth and Landis, 2017). These findings could in principle be suggestive evidence for

a role for DNA methylation in TGIP. While methylation is an attractive mechanism for TGIP, recent work on *Tenebrio molitor* beetles found no evidence of changes in either DNA or RNA methylation during TGIP but did detect lower proportion of RNA methylation under within generational immune priming (Castro-Vargas *et al*, 2017). However, this work only quantified global patterns of methylation, leaving open the possibility of altered specific methylation profiles leading to TGIP phenotypes in this system.

4.3.2. Histone modifications

Chromatin in its condensed form consists of linked nucleosomes, while the DNA is wrapped tightly around an octamer of core histones (Berger, 2002). Accessibility of the DNA for transcription is regulated by addition (acetylation) or removal (deacetylation) of acetyl groups to histone tails, which changes the charge of the histones and the affinity to negatively charged DNA (Wade *et al*, 1997; Zhang and Reinberg, 2001; Berger, 2002). Chromatin structure is loose with acetylated histones, and thus is more accessible for transcription, while DNA is bound more tightly by deacetylated histones and transcription is silenced (Perry and Chalkley, 1982; Berger, 2002). Histone acetyltransferase (HAT) and histone deacetylase enzymes (HDAC) acetylate and deacetylate, respectively (Holbert and Marmorstein, 2005), with the balance between their activity significantly impacting gene regulation throughout development and influencing human diseases (Mukherjee *et al*, 2015). Additionally, histone N-terminal tails are modified by methylation, phosphorylation, and ubiquitination, which are all necessary to accomplish specific functions during the transcription (Zhang and Reinberg, 2001; Berger, 2002; Holbert and Marmorstein, 2005). Histone methylation is catalyzed specifically by histone methyltransferases (HKMT) (Peters and Schübeler, 2005) or removed by histone demethylases (Kooistra

and Helin, 2012). Chromatin modifying processes have been shown to be essential regulators of the activity of many inflammatory genes (Foster and Medzhitov, 2009), and studies suggest methylation and acetylation patterns are heritable and that histones pass on epigenetic signals across generations (Campos *et al*, 2014; Gaydos *et al*, 2014; Jones, 2014). Thus, there is potential for a role of histone modification in TGIP.

TGIP in pipefish is potentially mediated via histone modifications, with offspring and grand-offspring of bacterially immune challenged males exhibiting differential gene expression patterns of genes involved in histone methylation, demethylation, acetylation, and deacetylation (Beemelmanns and Roth, 2017). Consistent patterns of paternal and grand-paternal influences on histone modification genes suggest regulation of patrilineal TGIP might be mediated by heritable histone modifications (Beemelmanns and Roth, 2017). However, it remains unclear at which exact sites histone modifications might be stably maintained in the gametes of vertebrates, and which mechanisms are responsible for heritable changes mediated by histones.

4.3.3. Small RNAs

Small RNAs are molecules that are often involved in the regulation of the activity of specific mRNA targets, which may affect a diversity of physiological processes (Kim *et al*, 2009). As such, small RNAs have been indicated to be involved in controlling immunological reactions (Xiao and Rajewsky, 2009; O'Connell *et al*, 2010; Lawless *et al*, 2014). Recent data suggested the transfer of one type of maternal small RNA, microRNAs (miRNAs), via breast-milk in humans could boost offspring immune responses (Kosaka *et al*, 2010; Munch *et al*, 2013). In invertebrates, another small

RNA type, small interfering RNAs (siRNAs) have been linked to TGIP. In *C. elegans*, priming of the antiviral response through siRNAs protects against viruses across multiple generations (Rechavi *et al*, 2011; Sterken *et al*, 2014; Gammon *et al*, 2017), although protective siRNA inheritance has not been confirmed in all cases (Ashe *et al*, 2015). The importance of small RNAs in TGIP more widely, including the breadth of taxa that employ this mechanism, is currently unclear. However, the involvement of small RNAs, which can be transmitted stably through meiosis, in other epigenetic phenomena (Richards, 2006) makes them a promising candidate for future studies of the mechanistic underpinnings of TGIP.

5. TGIP will not always be the rule: adaptive hypotheses and predicted ecological conditions for TGIP

Vertebrates and invertebrates have multiple pathways by which offspring immunity may be primed based on parental experience of pathogen and parasite exposures. There are two potential adaptive evolutionary hypotheses for the two distinct mechanistic types of TGIP (parental transfer or heightened endogenous offspring immunity) that have been discussed above. Transfer to offspring of active immune components may be beneficial in providing protection to offspring during an otherwise vulnerable period, when the offspring is not yet able to mount its own effective responses. Mechanisms leading to heightened endogenous responses by offspring that are based on parental immune experience will be selected for as they ready offspring for the prevailing parasite and pathogen environment. These hypotheses are not mutually exclusive. For example, transfer of antibodies in vertebrates will protect offspring before they can produce their own antibodies, but in addition, the diversity and quantity of antibodies can mirror the antecedent experienced parasite and

pathogen environment of the mother (Grindstaff *et al*, 2003). It should be noted, however, that a correlation between the levels of an active immune component in mothers and the quantity transferred to offspring does not require an adaptive explanation. A parsimonious explanation could be that this is a simple passive mechanistic consequence of an increased titre of the component in the mother, which requires no link to its effect on offspring fitness. The subsequent discussion of the evolution of TGIP assumes the hypothesis that TGIP will ready offspring for the infection risk of the current environment.

While the literature abounds with evidence of TGIP in vertebrate and invertebrate systems, its existence is not universal. For example in invertebrates, several studies have not found evidence for TGIP (Voordouw *et al*, 2008; Vorburger *et al*, 2008; Linder and Promislow, 2009; Pigeault *et al*, 2015), and in some cases even reversed patterns of negative effects of parental immune stimulation on offspring resistance have been shown (Vantaux *et al*, 2014; Littlefair *et al*, 2017). Such cases may also be more common than the literature suggests as a consequence of publication bias against negative results (Møller and Jennions, 2001). The absence of TGIP in these systems may be due to mechanistic constraints preventing TGIP, or that specific assays may miss the relevant immune parameter. For example, the observation of a TGIP phenotype can depend on the physiological immune pathway assayed (Sadd *et al*, 2005; Trauer-Kizilelma and Hilker, 2015). However, the presence or absence of TGIP may have deeper routes pertaining to the evolutionary history of an organism, with the evolution and maintenance of TGIP being dependent on the predictability of parasite and pathogen environments across generations and the fitness-related costs of TGIP to both parents and offspring. In the following section, we discuss these aspects that

may influence the evolution of TGIP. Exceptions might exist to these broad generalizations of the underlying ecological determinants relating to the selective advantage of TGIP, and we highlight these where appropriate.

The evolution of TGIP, the degree of specificity or cross-reactivity it shows across parasite and pathogen types, and extent of protection it confers to offspring will fundamentally depend on the ecology of the organism in question and the parasites and pathogens that it encounters (Figure 1). The risks of parasites and pathogen infection are often spatially patchy. When environmental barriers limit parasite dispersal and assemblages of parasite genotypes are stable over generations, it is highly probable that hosts and their offspring will encounter the same parasite genotypes repeatedly (Little and Kraaijeveld, 2004). In this case, long lasting and specific TGIP will be beneficial by facilitating a faster reaction towards the current parasite or pathogen assemblage that is based on the immunological experience of parents (Lui, 2000). Hence, ecological conditions where pathogenic communities are stable may select for persistent and multigenerational TGIP (Lemke *et al*, 1994; Norouzitallab *et al*, 2015; Beemelmanns and Roth, 2017). Likewise, when host dispersal is low the likelihood of similar parasite pressures being encountered across generations increases. Such scenarios will promote the evolution of TGIP (Pigeault *et al*, 2016). For similar reasons, models predict that when investment into TGIP is a plastic trait, in species with philopatric and dispersing individuals, TGIP will be found only in philopatric individuals (Pigeault *et al*, 2016). While TGIP is intuitively expected to be present when offspring are more likely to encounter the same parasites and pathogens as their parents, there are exceptions. For instance, TGIP has been described in marine invertebrates like scallops that are broadcast spawn (Yue *et al*,

2013), where parental experience is unlikely to predict offspring pathogen environment. However, in these cases there is at least a conceivable benefit if TGIP protects against vertically transmitted pathogens, and thus offspring will, by the nature of this transmission route, be exposed to the same pathogens as their parents.

The assumption is that the benefits of increased protection afforded by TGIP will be weighed against costs. If parasite and pathogen pressures fluctuate over generations, TGIP may come at a net cost (von Schantz *et al*, 1999). Parental effects are shaped by selection on both parents and offspring (Kirkpatrick and Lande, 1989; Mousseau and Fox, 1998). These levels of selection may frequently oppose each other (Kirkpatrick and Lande, 1989; Wolf and Brodie, 1998), resulting in costs that can either be inflicted upon the parents, the offspring, or both (Gallizzi *et al*, 2008). The offspring may suffer as TGIP stimulates the young to mount a costly immune response (Carlier and Truyens, 1995). Mounting an immune response carries energetic costs, necessitating that resources are allocated away from development, maturation, reproduction, and growth (Sheldon and Verhulst, 1996; Lochmiller and Deerenberg, 2000; Schmid-Hempel, 2005; Ardia *et al*, 2011; Ardia *et al*, 2012). When considering whether TGIP is to be expected, costs of its implementation are important to take into account. By its very nature as an inducible phenotype, it is predicted that TGIP will carry costs. If this were not the case, the expectation would be for offspring immunity to be maintained at primed levels constantly. Experiments that manipulate the environment encountered by primed offspring have elucidated some of the underlying costs of TGIP. For instance, in bumblebees where a mismatch between maternal immunological experience (bacterial based immune challenge) and offspring parasite environment (trypanosome parasite) was created, costs were seen in that offspring

primed to bacteria were more susceptible to the distinct trypanosome parasite than naive offspring (Sadd and Schmid-Hempel, 2009). Further costs relating to offspring life-history traits have been highlighted in cases of TGIP in beetles (Roth *et al*, 2010; Zanchi *et al*, 2011). In mosquitoes, TGIP has been shown to be negatively correlated with offspring reproduction in the absence of infection (Contreras-Garduño *et al*, 2014). In vertebrates transfer of antibodies to offspring can hinder the development of an offspring's own immune response (Siegrist, 2003), as in the case of antibodies against Newcastle Disease virus in birds (Staszewski and Siitari, 2010). In mammals, the transfer of immunity via the placenta can result in a costly inflammation by inducing the complement system and phagocytes (Hanson, 2004). There can also be costs associated with TGIP as sexual hormones are depleted, decreasing nestling development and secondary sexual ornaments (Eising *et al*, 2001; Gil *et al*, 2006). Theoretical studies predicted that TGIP, especially when costly to reproduction, might increase parasite prevalence and destabilize population dynamics on the long-term (Tidbury *et al*, 2012). Thus, further experimental and theoretical work is required to understand the complex interplay between costs and benefits of TGIP.

Given the balance of costs and benefits based on the predictability of the parasite and pathogen environment, only under certain conditions will TGIP be favoured and have an adaptive benefit (Figure 1). If these conditions of environment, costs and benefits, and relationship between parents and offspring are not met, then we expect that TGIP will be absent or non-specific. If an environment is heterogenous with regard to the probability of infection, but parasite and pathogen types are not stable over time, then it could be expected that priming of a general immune response will be favoured (Figure 1). Furthermore, the existence of TGIP could be mechanistically constrained,

and thus particular immune pathways may not show immune priming or certain pathogens and parasites may not elicit it. The wider community of parasites and pathogens may even dictate constraints on the expression of TGIP phenotypes, as demonstrated in flour beetles where parental co-infection with a gut protozoan curtailed the normally observed TGIP against bacteria (Tate and Graham, 2015).

While many prerequisites need to be fulfilled for TGIP to evolve, spread and be maintained, it only requires one factor to be absent or the relative costs of TGIP to be too high for its evolution to be obstructed. In some examples of studies failing to demonstrate TGIP there are logical grounds for its absence. For example, in mosquitoes (*Aedes aegypti*) no effects in offspring following the stimulation of the maternal melanisation response were detected (Voordouw *et al*, 2008). However, eggs of *A. aegypti* are usually laid in ephemeral pools of water that are unlikely to be shared across generations. Thus, the parasite environment experienced by a mother may not be tightly correlated with the offspring environment, and as such, it is perhaps unsurprising that costly TGIP is predominantly absent. Interestingly, recent work in invertebrates has demonstrated that offspring may be primed to differing stages of the immune response, with recognition, signaling, or effectors being more readily induced, or that offspring exhibit heightened levels of constitutive immune expression (Trauer-Kizilelma and Hilker, 2015; Barribeau *et al*, 2016; Tate *et al*, 2017). It is plausible that these various levels of priming, from a readied state to elevated production of effector molecules are a consequence of the predictability of the parasite environment between generations. In systems where the likelihood of offspring encountering the same parasite and pathogen pressures as parents is high, it may pay for offspring to invest fully into heightened constitutive immunity, whereas in cases where the

likelihood is lower, just being ready, with sensitised recognition or signaling, may be beneficial.

Sex role reversed vertebrate species may further inform on the ecological conditions that can support TGIP evolution. TGIP was traditionally thought to be exclusively maternal in vertebrates, mediated by the maternal antibody transfer (Gasparini *et al*, 2002; Reid *et al*, 2006; Swain and Nayak, 2009), being supported by findings showing unchanged antibody titers in vertebrates when fathers, but not mothers, were immune challenged (Gasparini *et al*, 2002; Reid *et al*, 2006). Males may be considered unable to transfer immunity because sperm are simply too small to transfer much more than just DNA (Wassarman *et al*, 2001; Arnqvist and Rowe, 2005), but there is also an evolutionary benefit argument that offspring are more likely to encounter a similar parasite and pathogen environment to their mothers than their fathers. However, these limitations may not hold in animals with extreme paternal care. For instance, the sex-role reversed pipefish *Syngnathus typhle* has bi-parental TGIP (Roth *et al*, 2012; Beemelmanns and Roth, 2016a; Beemelmanns and Roth, 2016b; Beemelmanns and Roth, 2017; Roth and Landis, 2017). In *S. typhle*, males have evolved a unique placenta-like structure in the male brood pouch for nutrient and oxygen transfer (Wilson *et al*, 2001; Dzyuba *et al*, 2006; Harlin-Cognato *et al*, 2006; Stölting and Wilson, 2007; Ripley and Foran, 2009), but it may also facilitate TGIP. In Syngnathids with their male pregnancy, selection for bi-parental immune priming is likely due to the intimate connection of the father with the offspring both from an ultimate and a proximate view. Offspring are born in the environment of the father, and are hence exposed to the paternal parasite pressure (Roth *et al*, 2012).

From an evolutionary perspective, it is clear that the existence of TGIP will not be the ubiquitous default, and will depend on the presence of a suite of factors favouring its evolution and maintenance. Examples contradicting the predictions of the benefits of TGIP will be enormously informative to understanding the generality of this system of defense, but may be underrepresented in the published literature.

6. Future outlook

Although the term trans-generational immunity was originally coined for the transfer of maternal antibodies to offspring in vertebrates, it has become apparent that the concept has considerably broader consequences, taxonomically, immunologically, and in terms of mechanisms underlying trans-generationally primed phenotypes. Simplistically speaking, however, the existence of similar functional outcomes across vertebrate and invertebrate groups suggests common selective pressures from parasites and pathogens leading to the priming of offspring immunity dependent on parental experience. Yet, there remains a great deal that is unknown about the mechanistic causes and ecological and evolutionary consequences of TGIP.

To substantially add to our understanding of TGIP, studies need to step away from only measuring classical routes and immune parameters. For example, it is now apparent that TGIP in vertebrates is much more than maternal antibody transfer, and endogenous immune-related gene expression of offspring can be significantly altered (Roth *et al*, 2012; Beemelmanns and Roth, 2016a; Beemelmanns and Roth, 2016b; Beemelmanns and Roth, 2017; Roth and Landis, 2017). Rapid advancements in sequencing technologies now allow for the TGIP phenotype to be tied to genome-wide transcriptomic patterns, and this has been informative in invertebrate systems (Trauer-

Kizilelma and Hilker, 2015; Barribeau *et al*, 2016; Tate *et al*, 2017). Where study systems permit, future work should aim to assess temporal changes in gene expression and how these are linked to infection dynamics, as has been performed in the flour beetle-bacteria system (Tate *et al*, 2017).

More comparative studies should also be undertaken. While it is expected that the particulars of TGIP phenotypes may be host and parasite system specific, such approaches have the potential to reveal broader commonalities. Furthermore, comparative studies are necessary to directly test some of the hypotheses that relate to the existence and extent of TGIP in relation to the ecological setting within which organisms have evolved. Much of the discussion about the ecological conditions surrounding the evolution of TGIP remains speculative. We require extensive comparative studies that compare the existence of TGIP across categories of organisms that are predicted to differ, e.g. with different philopatric tendencies.

Further work is required to uncover the underlying mechanisms of TGIP. While many candidate mechanisms exist, which could be responsible in both vertebrates and invertebrates, stringent tests of these mechanisms have yet to be carried out. Epigenetic markers in offspring or the presence of apparently sampled antigens from the parental environment is, however, not enough. Causal links must be established that associate these potential mechanistic routes and the actual offspring phenotypes. Little knowledge exists about epigenetic mechanisms that could potentially regulate host-pathogen interactions and the development of host immune defense strategies (Gómez-Díaz *et al*, 2012). Numerous studies indicate that epigenetic mechanisms fulfill a crucial role in regulating the transcription of immune-related genes upon

infections (Huang and Wells, 2014; Marr *et al*, 2014; Okamoto *et al*, 2014; Smale *et al*, 2014). Pathogen exposure of the parental generation might mediate epigenetic marks that could be passed on as protective cues to the offspring and subsequent generations. How epigenetic effects are involved in TGIP is still unresolved, and empirical data that follow parental and filial phenotypes through time in controlled experiments are needed. Non-DNA based inheritance as one form of multi-generational plasticity might be more widespread than previously thought, leading to claims for a more wide-ranging view of inheritance and adaptation (Danchin *et al*, 2011). To what extent these epigenetic effects are adaptively beneficial and play a role in driving phenotypic variation of traits across generations is so far poorly understood. TGIP, particularly in systems amenable to high-throughput study, offers a conceptual framework within which generalizations about epigenetic effects and their ecological and evolutionary consequences may be interpreted.

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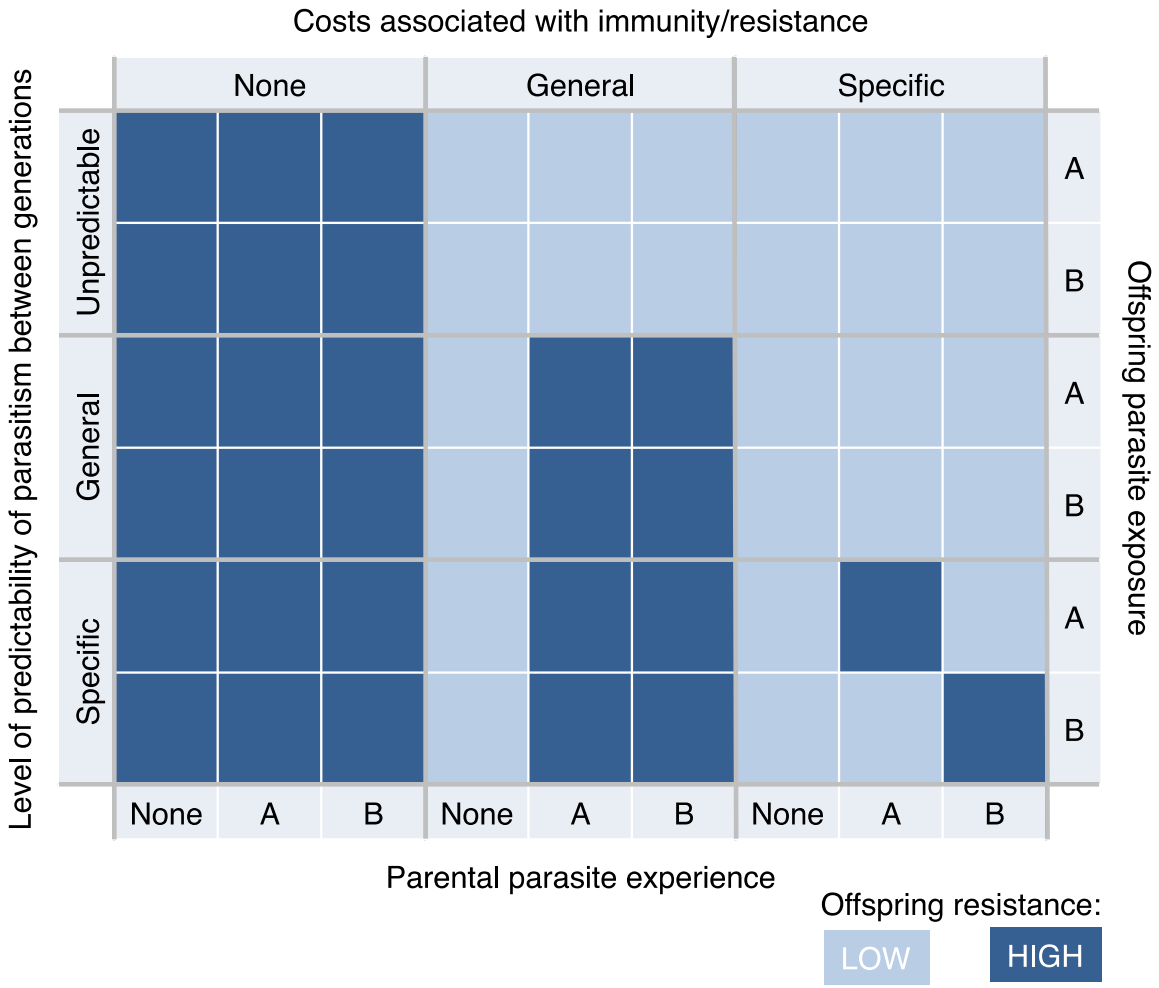

Figure 1. A simple schematic representing the base expectations of the existence of TGIP when accounting for the predictability of the parasite environment between generations and the costs associated with elevated immunity. In the absence of associated costs, all offspring will be expected to display increased resistance, irrespective of parental experience with parasites and the predictability of the environment across generations. When costs for increased resistance are present, increased resistance is only predicted when the parental environment predicts the parasite environment of offspring, and when parents are exposed to infection (TGIP). Under a framework of specific costs of resistance, parasite-specific TGIP is only expected to evolve when the predictability of the environment across generations is also specific to the parasite types.