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Integrating the Study of Polyploidy Across Organisms, Tissues, and Disease

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Abstract

Polyploidy is a cellular state containing more than two complete chromosome sets. It has largely been studied as a discrete phenomenon in either organismal, tissue, or disease contexts. Increasingly, however, investigation of polyploidy across disciplines is coalescing around common principles. For example, the recent Polyploidy Across the Tree of Life meeting considered the contribution of polyploidy both in organismal evolution over millions of years and in tumorigenesis across much shorter timescales. Here, we build on this newfound integration with a unified discussion of polyploidy in organisms, cells, and disease. We highlight how common polyploidy is at

multiple biological scales, thus eliminating the outdated mindset of its specialization. Additionally, we discuss rules that are likely common to all instances of polyploidy. With increasing appreciation that polyploidy is pervasive in nature and displays fascinating commonalities across diverse contexts, inquiry related to this important topic is rapidly becoming unified.

1. OVERVIEW OF POLYPLOID FORMATION AND DYNAMICS

The number of chromosome sets in a cell defines ploidy, with more than two chromosome sets considered polyploid. Ploidy terminology is not uniform across the literature (43). However, one consistent convention is the C value, where 1C refers to one haploid genome (15). Somatic cells in G1 phase of the cell cycle have 2C DNA content, while cells in G2 phase have 4C content. Any cell with greater than 4C DNA content is considered polyploid. Further, if a 4C cell resets its cell cycle to G1, this cell becomes polyploid. Quantitative flow cytometry and microscopy approaches are commonly used to measure C. Other frequent terms used in describing ploidy are the *n* value and *x* value, which have generally been used to describe numbers of chromosome sets or chromatids (15), respectively. However, such counting can be confounded when chromosomes are closely aligned (e.g., polytene chromosomes) (121). Furthermore, in plants, *n* can refer to a life cycle stage (43).

Polyploidy can be present in a subset of an organism's cells (i.e., endopolyploidy; see **Figure 1*a***) or in every somatic cell (i.e., organismal polyploidy; see **Figure 1*a***). Polyploidy arises by several whole-genome duplication (WGD) mechanisms (89). Organismal polyploidy results from maintaining ploidy during meiosis. Specifically, aborted meiosis I chromosome segregation yields diploid unreduced gametes instead of haploid gametes (i.e., unreduced gamete fusion; see **Figure 1*b***). Fusion of two unreduced diploid gametes yields a tetraploid organism, whereas triploid organisms arise through fusion of a reduced, haploid gamete and an unreduced, diploid gamete, with further organismal ploidy alterations (e.g., hexaploid) resulting from variations on this theme. Inter- and intraspecies fusion of unreduced gametes can lead to allopolyploidy and autopolyploidy, respectively. The prevalence of polyploid organisms in nature is discussed in Section 2.1.

Endopolyploidy arises by cell cycle–dependent and –independent mechanisms. Successive S phases without complete mitosis or cytokinesis increase somatic cell ploidy. Such cell cycles go by many names, all involving the prefix endo-, and their mechanistic regulation is reviewed elsewhere (89). As many diploid organisms develop, subsets of cells undergo endo-cell cycles and become endopolyploid. Endo-cell cycles generate either mononucleate polyploid cells if karyokinesis does not occur or multinucleate polyploid cells if karyokinesis but not cytokinesis occurs (**Figure 1*b***). In addition to endo-cell cycles, endopolyploidy can arise through cell fusion, which generates multinucleate cells (**Figure 1*b***). Importantly, mechanisms of tissue endopolyploidy can be heterogeneous; tissues can exhibit a wide range of cellular ploidies and nuclear numbers (95). Heterogeneous tissue polyploidy is widely observed in both normal organ development (see Section 2.2) and disease (see Section 2.3). As discussed in Sections 2 and 3.1, all WGD mechanisms can increase size, at both cellular and organismal scales.

Ploidy can be stable or dynamic. This principle is true in both an organism over its lifespan and a population of organisms over evolutionary time. Programmed somatic polyploidy often coincides with a permanent mitotic cell cycle exit and terminal tissue differentiation (89). However, some endopolyploid cells can reenter the cell cycle during normal tissue development or regeneration. In these cases, polyploid mitosis may not be as faithful as diploid mitosis and can result in chromosome missegregation. Such unfaithful somatic cell divisions result in an unbalanced

C value: a measure of DNA content, with 1C = 1 haploid genome

***n* value:** a measure of the number of chromosome sets per cell; in plants, this term is also used to distinguish the gametophyte and sporophyte stages

***x* value:** a measure of the number of chromatids per cell

Polytene chromosome: a structure where chromatids of the same chromosome type are closely aligned in a polyploid cell nucleus

Polyploidy: more than two sets of chromosomes per cell

Endopolyploidy: polyploidy that is present in a subset of cells in an organism

Organismal polyploidy: polyploidy in every cell of an organism

Whole-genome duplication (WGD): a process that produces polyploidy or the state of being polyploid

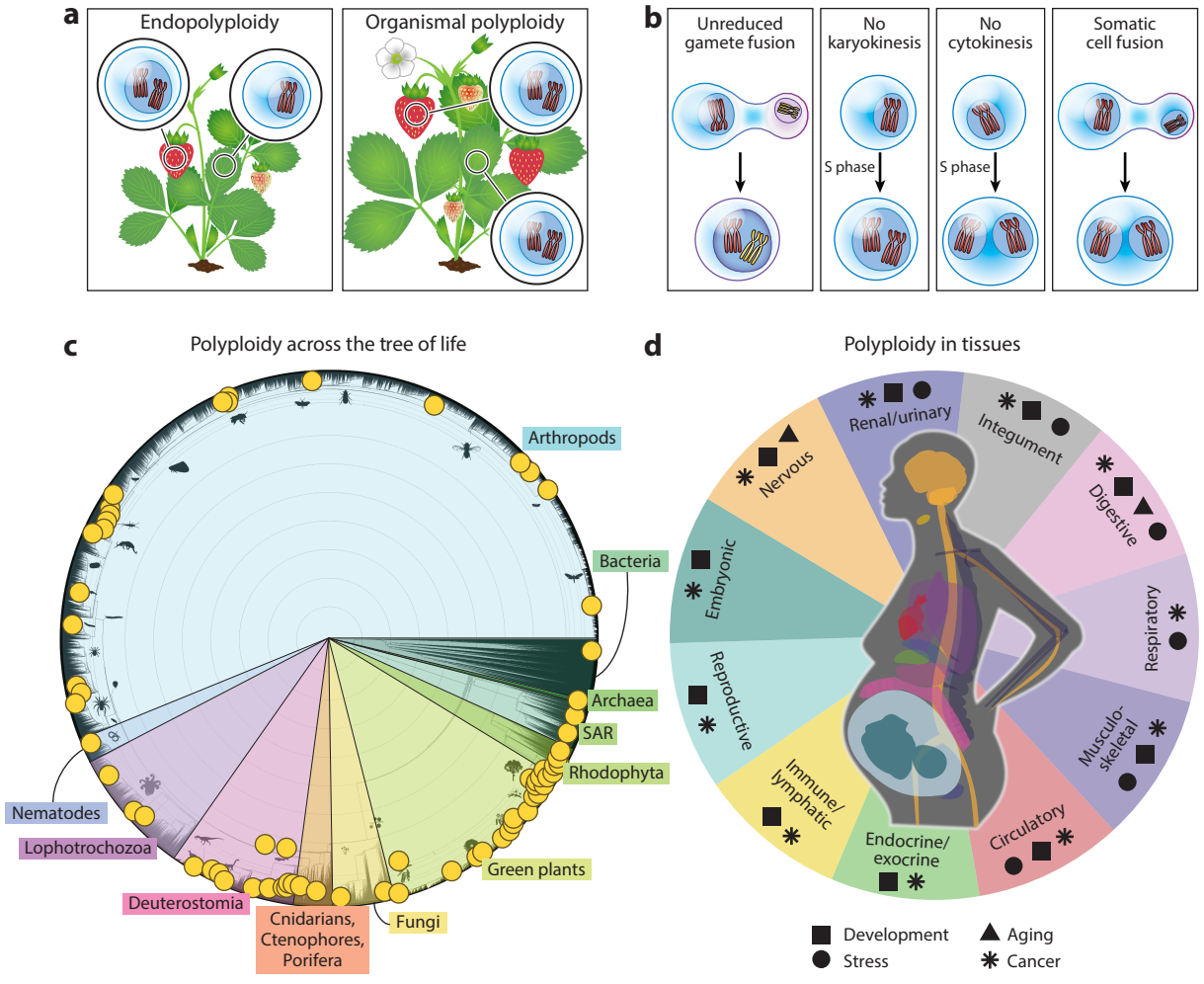

Figure 1

Terminology, generation, and occurrence of polyploidy. (*a*) The contrast between endopolyploidy and organismal polyploidy. A cell with one set of homologous chromosomes, drawn here with each having two sister chromatids, indicates diploid, while a cell with two sets of homologous chromosomes indicates tetraploid (a proxy for all polyploidy). (*b*) Mechanisms leading to polyploidy. Chromosomes denote diploid/polyploid as in panel *a*, while darkened circles indicate the presence of one or more nuclei in a cell. For unreduced gamete fusion, note that the illustration shows the union of two gametes, both of which are unreduced. (*c*) Organismal polyploidy across the tree of life. Shown are approximate occurrences of WGD events (*yellow dots*). This is by no means a comprehensive compilation of WGD across the tree of life, nor do the dots correspond to a point in time. Panel adapted from Reference 47 with modifications by Stephen Smith. (*d*) Tissue polyploidy across animal organ systems. A pregnant human female is used to represent the prevalence of tissue polyploidy. Symbols (see key) indicate polyploidy arising during development, aging, stress, and in cancer. Although a human is used in the diagram, the symbols indicate polyploidy in the indicated organ system for at least one animal species. Abbreviations: SAR, clade of eukaryotes including stramenopiles, alveolates, and rhizarians; WGD, whole-genome duplication.

complement of chromosomes (aneuploidy). Similarly, organismal polyploidy enhances genomic alteration and adaptation, particularly during meiosis. At both cellular and organismal scales, this polyploid genome dynamism is biologically functional, suggesting roles in adaptive and evolutionary processes as routes to cellular and organismal fitness in speciation and disease (see Section 3.2).

This review comes at a time of unprecedented integration in the field of polyploidy (93). Recently, researchers studying polyploidy from single cells to entire ecosystems and from settings as divergent as agriculture to cancer biology came together in a single meeting (Polyploidy Across the Tree of Life). Building on this new, much-needed emphasis on cross-system study, here we present an overview of polyploidy across biological scales. We focus on two key points. First, in Section 2, we explain that polyploidy is not rare but incredibly common. This is the case in organisms, tissues, and diseases. Second, in Section 3, we discuss the common rules of polyploidy that are emerging across these varied contexts. As our focus is on integrating the study of polyploidy across organismal, tissue, and disease settings, many other topics could not be covered. We refer readers to other excellent reviews for complementary discussion (7, 13, 42, 60, 88, 89, 132).

Unreduced gametes: germ cells containing the same number of chromosomes after meiosis as before meiosis

Allopolyploidy: whole-organism polyploidy resulting from hybridization between two different species

Autopolyploidy: whole-organism polyploidy resulting from genome doubling within a single species

Endo-cell cycle: a truncated cell cycle that produces a polyploid somatic cell

Mononucleate: one nucleus

Multinucleate: many nuclei

Cell fusion: a process involving a plasma membrane breach that produces a multinucleate polyploid cell

Aneuploidy: possessing an imbalanced complement of chromosomes, with gains and/or losses of specific chromosomes

2. POLYPLOID ORGANISMS AND CELLS ARE WIDESPREAD

While polyploidy has been documented in cells and organisms since the early 1900s (64, 139), a common misconception is that it is a rare state. However, the evolution of technologies and their application to the study of organisms and tissues across the tree of life are revealing an ever-increasing incidence of the phenomenon. For example, multicolor fluorescent reporters have revealed many new polyploid cell types in flies and mice (75, 81, 96), while next-generation sequencing and modeling have reconstructed a great number of ancient WGD events in organismal phylogenies. This section highlights the incredible prevalence of polyploidy in organisms, tissues, and disease. We also note contexts in which a function of WGD has been ascribed.

2.1. Polyploid Organisms Are Seemingly Everywhere

Organismal polyploidy is widespread across the tree of life (**Figure 1*c***), yet its significance is overlooked and underappreciated. This is likely due to fragmentary knowledge regarding its incidence, with only a small fraction of Earth's species examined for chromosome number and ploidy. We anticipate a deluge of reports in the coming years consequent to a renewed interest in the field. Here, we share a current compilation across the tree of life that is most certainly the tip of the genomic iceberg.

2.1.1. No lineage left behind? Organismal polyploidy is found in all major clades of life.

A generalization is often made that polyploidy is common only in plants. This generalization is rooted in reasoning related to the prevalence of sex chromosomes and greater developmental/structural complexity of animals, especially mammals, compared to plants (65, 88). However, when traced phylogenetically, one finds polyploidy in all major lineages of the tree of life, including vertebrate and invertebrate animals (103). In addition, when traced even further in time, polyploidy is found in the ancestors of all multicellular life: prokaryotes and protists (103).

Polyploidy in prokaryotes, the quintessential single circular chromosome–bearing haploids, was reported in 1948 (16) in the well-studied bacterium *Escherichia coli*. Polyploidy has since been described in many other prokaryotic lineages, including *Bacillus subtilis*, another well-studied system (71, 117). In some cases, polyploidy in prokaryotes involves more than 10,000 genome copies [*Epulopiscium* spp. type B (4)]. Regardless of the underlying evolutionary advantages of the phenomenon, polyploidy is proposed to have played a critical role in the origin of eukaryotes via frequent genetic exchange between polyploid proto-eukaryote protists (71) and remains present in contemporary protist species. Ciliates, members of a clade of ~8,000 species, provide a particularly intriguing example of organismal polyploidy; they possess two types of nuclei within the cell: a diploid germ cell known as a micronucleus and a polyploid macronucleus that has thousands of

genome copies and is highly transcribed (21). New technologies such as single-cell sequencing are revealing considerable genomic diversity in ciliates, with extensive WGD associated with speciation and environmental adaptation (21). Polyploidy is also reported in Amoebozoa (27). While uncertainty regarding the evolutionary drivers of prokaryotic polyploidy and its relationship with eukaryotic emergence remain, polyploidy is proposed to mask deleterious mutations, improve DNA break repair, increase protein synthesis, and promote survival in stressful environments (71, 117), topics for which experimental evidence is emerging.

As in prokaryotes, fungal life cycles are often dominated by the haploid state. Regardless, polyploidy has been detected across all major fungal groups (3, 104) and importantly inferred as ancient (3), producing well-balanced genomes that behave like diploids at meiosis (104). Furthermore, recent whole-genome sequencing and associated methods are revealing new examples of fungal polyploidy (124). As in many other organisms, fungal polyploidy is widespread and associated with stress tolerance (3, 124). Finally, in parallel with crop plants, several domesticated fungi are polyploids (18).

Across photosynthetic organisms, polyploidy is also widespread. In chromists, polyploidy in the brown alga *Fucus* associates with a shift from rocky shoreline habitats to brackish marshes (24). Polyploidy is also present in diatoms (56) and *Phytophthora*, a related nonphotosynthetic oomycete (i.e., water molds, once considered fungi) and pathogen that caused the potato blight of the Great Irish Famine (51). Archaeplastida comprise glaucophytes, red algae, and Viridiplantae (green plants). Polyploidy is unknown in glaucophytes but common in red algae and Viridiplantae. In the latter, WGD is frequent in chlorophytes, ferns, and angiosperms—in which organismal polyploidy is perhaps best studied—but rarer in conifers and liverworts (84, 87).

Traditionally, polyploidy has erroneously been thought of as absent in animals, which is perhaps one cause of its limited study. However, in invertebrates, polyploidy occurs in many species and is particularly well documented in annelids, cnidarians, crustaceans, insects, and turbellarian flatworms (42). Within annelids, polyploidy is widespread in Oligochaeta (i.e., earthworms and relatives) (72), with polyploidy as common as diploidy in earthworms themselves (Lumbricidae). Importantly, and as in many other lineages, earthworm polyploidy is associated with cryptic speciation (5, 94), with further evidence for allopolyploidy recently noted in apomictic *Meloidogyne* species (103, 122). Ancient polyploidy was detected in rotifers (phylum Rotifera) (49, 103) and cnidarians and in the latter linked to diversification, namely in reef-building corals (*Acropora*, Cnidaria) (68). However, nonhydrozoan cnidarians (i.e., jellyfish) and echinoderms (e.g., sea urchins) appear to have stable chromosome numbers and genome sizes (1). The rarity of polyploidy in hexapods (i.e., insects and relatives), except where it co-occurs with parthenogenesis, was noted decades ago (63), with the caveat that the clade is large and chromosome counts were sparse. A more recent survey (26) suggests that insect polyploidy is scattered across diverse families, including walking sticks (Bacillidae), black flies (Simuliidae), moths (Psychidae), and leaf beetles (Chrysomelidae). At a molecular level, transcriptome and genome studies provide evidence for 18 ancient WGD events (61), suggesting that polyploidy has occurred throughout hexapod evolution and may be more common than previously thought.

Two WGD events early in vertebrate evolution are considered foundational to innovations in this clade (85, 113). All vertebrates share the first WGD; the second is shared only by jawed vertebrates (including humans). In addition, numerous additional WGDs are evident in teleost fish (59), amphibians (108), squamate reptiles [e.g., snakes and lizards (42, 78)], some birds (e.g., chickens and parrots), and a few mammals [e.g., pikas (78)]. All ray-finned fishes (Actinopteri; 22,000 species, 50% of all living vertebrates) share an ancient WGD (123). Polyploidy occurred in the ancestor of paddlefish and sturgeon (99) and also occurs in perch, carps, and minnows, and an ancient event characterizes salmon and trout (66). Furthermore, within Cypriniformes (>4,000 species,

including carps, minnows, and loaches), recent data suggest 13 separate WGD events (145); consequently, WGD has played a major, yet often underappreciated, role in fish evolution (59). As within many other lineages, polyploidy is associated with large body size, fast growth rate, long life, and ecological adaptability (59, 110). Polyploidy is widespread in Anura (frogs) and Urodela (salamanders) and played an important role in speciation and evolution. Amphibia are unusual among vertebrates in having related diploid and polyploid bisexual species or populations (108). Recurrent origins of the same polyploid amphibian species are documented (108), a phenomenon also reported commonly in plants (116).

Further exploration of ploidy across the tree of life will undoubtedly uncover new examples of polyploid organisms. Examination of where and when polyploid organisms emerged phylogenetically can illuminate constraints and advantages of organismal WGD.

2.1.2. The distribution of polyploid organisms across geographic space. Global biogeographic surveys for flowering plants (angiosperms) (100) and several animal clades (amphibians, fish, and insects) (26) reveal strikingly similar global latitudinal gradients and patterns across these diverse lineages. WGD correlates with extreme environments, with glaciation as one potential driver (128). Polyploidy therefore appears to both trigger and confer a fitness advantage under certain stressful environmental conditions.

2.2. Tissue Polyploidy Is Found in All Organ Systems

As in organisms, tissue polyploidy is similarly widespread. In animal tissues, polyploidy is now documented in every organ system, including in mammals. In this section, we survey tissue polyploidy during development, aging, and tissue stress, organized by mammalian organ systems, with examples from numerous animal and plant species. For a more comprehensive survey, see the Polyploid Atlas (82). Here, we focus on physiological polyploidy, whereas in Section 2.3, we discuss aberrant tissue polyploidy in disease.

2.2.1. Tissue polyploidy that emerges during development and aging. As diploid organisms develop or age, many cell types undergo endo-cell cycles or cell–cell fusion to produce endopolyploid cells and tissues. In animals, the phenomenon begins prenatally, in embryonic supporting structures where polyploid cells play a critical barrier role. The mammalian placenta has multiple polyploid cell types, which can be mono- or multinucleated (114). The addition of hundreds to thousands of new genomes in a single cytoplasm may facilitate growth without compromising barriers to infection, as endo-cell cycles do not transiently disrupt cell junctions in the same way as cell division. Endosperm, the placental analog in plants, is also polyploid (11). In the developing endosperm of flowering plants, endopolyploidy plays a prominent role in several economically important grasses, where it facilitates the accumulation of storage compounds that nourish the developing embryo (105). The embryo suspensor of flowering plants pushes the developing embryo into the nutritive endosperm; endopolyploidy enables very large suspensors that facilitate the thrust of the embryo into the endosperm (25). Further, endopolyploid tapetal cells supply necessary materials for enzyme secretion and pollen wall (exine) formation in developing angiosperm pollen grains (25, 52).

In the circulatory system, polyploidy and large cell size are widely prevalent in animal cardiomyocytes, including in fruit flies, and are particularly common in endothermic organisms (19, 48). It is worth speculating that larger polyploid cells adapt to a greater mechanical load in the constantly contracting myocardium. Vertebrate megakaryocytes can also be polyploid (34), possibly to enable the fragmentation of large amounts of platelets (118).

In the digestive/excretory system, polyploidy may defend against genotoxic insults. Hepatocytes of specific liver zones are commonly polyploid in mammals, and hepatocyte ploidy increases with aging (54, 136). The liver is a genotoxic environment, and, as a possible adaptation, polyploid mammalian hepatocytes tolerate chromosome number alterations during cell division (32). Similarly, divisions of insect polyploid intestinal papillar cells are remarkably tolerant of DNA breakage (14). Higher tolerance for genomic instability is also a common feature of cancer cells (see Section 2.3).

In the endocrine and exocrine systems, polyploidy commonly fuels rapid tissue growth. Mitosis and cytokinesis are energetically demanding (106), and endo-cell cycles may be an energetically favorable means of rapidly increasing tissue mass. For example, mammalian pancreatic acinar cells adjacent to islets undergo hypertrophic growth driven by polyploidy. Such ploidy increases drive rapid postnatal organ growth but decrease lifespan in these species (6). Similar ploidy-based hypertrophic growth occurs in human and mouse pancreatic β-cells (33, 150). During mouse lactation, all mammary tissue growth is driven by polyploidization (101).

Work in plants highlights a role for polyploidy in achieving specific functions in integumentary systems. Plant integument includes the epidermis, or outermost layer of cells covering most structures, as well as secretory glands and trichomes, which are hairs that grow out of the epidermis of aboveground structures. The sepal is a leaf-derived epidermal organ that protects the developing flower bud. In the model plant *Arabidopsis*, optimal sepal curvature requires the correct amount of polyploidy in specialized giant epidermal cells (77). Similarly, angiosperm leaf trichome development is also associated with high degrees of endopolyploidy (134). In multicellular trichomes, tip and basal cells show higher endopolyploidy than intermediate cells. Tip cells often secrete compounds stored in large vacuoles, and basal cell endopolyploidy may have structural benefits (8). Integumentary polyploidy is also found in insects and nematodes (22, 53). Polyploidy is documented in the human epidermis, although its role and conditions that favor its emergence are unclear (126).

In the immune and lymphatic systems, multinucleate polyploidy plays important roles. Mammalian osteoclasts that resorb bone are commonly polyploid (9), as are granulomas, aggregates of lymphatic cells that appear after infection (46).

In the musculoskeletal system, multinucleate polyploidy in muscle fibers is the norm throughout evolution and likely coordinates muscle action over long distances in the body (28, 97). Multinucleate skeletal muscle polyploidy is produced by cell fusion, whereas cardiac muscle polyploidy results from endo-cell cycles and can lead to either mononucleate or multinucleate (typically 2–8 nuclei per myocyte) states.

In the nervous system, polyploidy occurs in both neurons and glia. Gastropod brains exhibit neuronal giantism driven by polyploidy in the central ganglia (40). Large neurons may enhance presynaptic function by synthesis and transport of crucial molecules. Tetraploidy is reported in chick retinal ganglion cells and highly branched Purkinje neurons (36). Polyploidy plays a protective role against oxidative damage in the aging fly (*Drosophila*) brain, suggesting that polyploidy preserves brain function (81). Also in *Drosophila*, the developing blood–brain barrier is protected by polyploid glial cells, which expand in ploidy and size by endo-cell cycles (127). As in the placenta, endo-cell cycle–based growth may preserve the blood–brain barrier, as the tissue grows in a way that mitotic proliferation may not achieve.

Finally, in the reproductive system, transient multinucleate polyploidy is common in germline cysts, which are highly conserved in male and female gamete development. Such transient polyploid cells share nutrients between developing germ cells, coordinate gamete production, and balance out deleterious genetic events that are more harmful to haploid cells (95). As the above

survey illustrates, polyploidy features in the development of nearly every organ system in diverse organisms (**Figure 1*c***).

2.2.2. Tissue polyploidy that emerges from acute stress. Many of the aforementioned tissues acquire further polyploidy following acute injury. Such polyploidy rapidly restores lost tissue mass during organ regeneration in tissues such as the mammalian liver and skeletal muscle, as well as *Drosophila* integument and intestinal enterocytes (7). Injury-induced polyploidy is restorative to most animal tissues, though injury-induced polyploidy appears maladaptive in the mammalian heart (29).

Similarly, environmental stress amplifies endopolyploidy in plants, with presumed benefits including increased cell volume, redundancy in the face of DNA damage, and enhanced gene expression and metabolic rates (60, 109). Stress-induced [e.g., cold, water, salt, soil chemistry, low and high light, ultraviolet B (UV-B) radiation, chemical pollutants, herbivores, and competitors] endopolyploidy frequently affects leaf epidermal cells. In particular, leaf endopolyploidy offsets potential impacts of stress and DNA damage from UV-B radiation (144). Stress-induced endopolyploidy also occurs in root cells under chemical stress, in stem tissues in response to herbivory, and in multiple tissues and cell types in response to temperature and salt stresses. Given that endopolyploidy occurs in response to a broad range of stresses and in a phylogenetically and ecologically broad range of plants, it may be a generalized stress response (109). How this adaptive, yet plastic, response evolved remains unknown.

In animals, tissues less associated with developmental endopolyploidy nevertheless activate polyploidy to repair/regenerate injured tissues. In the renal/urinary system, acute injury activates regeneration by polyploidy in the mammalian kidney epithelium and bladder superficial layer (58, 135). In the respiratory system, subsets of mammalian alveolar cells increase in ploidy to repair the airway (137).

There are likely many more types of polyploid cells to be found, and new approaches (75) will facilitate their identification. Future studies should also expand beyond the study of traditional model organisms and examine tissues under different experimental conditions. For example, intermittent fasting can impact polyploidy in the mouse liver (107). New identification of cell types and growth conditions that generate polyploidy will further illuminate roles of tissue WGD. Already, as one considers the above examples, the notion that tissue polyploidy is rare becomes rather absurd.

2.3. Polyploidy Is a Cellular Feature of Most Human Disease Deaths

Polyploidy is pervasive across diseases, including the two most lethal human afflictions—heart disease and cancer (12, 55). In this section, we discuss the relationship between polyploidy and disease in two pathological categories: diseases where organs fail and cancer. In both cases, the frequency, distribution, and organization of polyploid cells are altered compared to their physiological settings. In diseases of organ dysfunction, polyploid cells resemble those observed in the healthy state, whereas in cancer, polyploid cells acquire properties of malignant cells. Cancer-associated polyploidy most commonly occurs in the context of genomic instability and evolutionary selection, which facilitates genetic innovation (see Section 3). Mechanistic understanding of polyploidy in disease and strategies that take it into consideration for treatment remain unmet goals but fertile avenues for discovery.

2.3.1. Polyploidy and organ dysfunction. Polyploidy is broadly observed in organ dysfunction, but whether such polyploidy is a cause or consequence of tissue damage and impaired homeostasis remains poorly understood. Functional experiments where polyploidy is increased or decreased

during development or tissue damage have revealed a role for context dependency. In cardiac tissue, for example, polyploidy impedes regeneration, leading to cardiac failure. Indeed, human cardiomyopathies exhibit high levels of polyploidy (76, 133). In mice, the frequency of mononucleate diploid cardiomyocytes predicts heart regeneration in a strain-dependent fashion, and genetic interventions that increase postnatal ploidy decrease proliferation after cardiac damage (44, 92). In zebrafish, diploid cardiomyocytes outcompete polyploid cardiomyocytes, and increasing cardiac polyploidy by interfering with RhoA signaling impairs regeneration (41). Thus, while developmental endopolyploidy plays a role in the adult heart of many species, the balance of diploid versus polyploid cardiomyocytes impacts regeneration.

In other organs, the relationship between regulated ploidy and organ maintenance is less clear. This ambiguous relationship is highlighted in liver hepatocytes, which, as discussed above, display frequent postnatal endopolyploidy but also can increase in ploidy following injury. Mononucleate hepatocyte polyploidy increases in response to both chronic [e.g., nonalcoholic fatty liver disease, steatohepatitis (39), and viral infection (125)] and acute [hepatectomy (80)] liver insults. Genetically reducing rodent hepatocyte ploidy does not impact liver development or regeneration (138), suggesting that ploidy is not required for liver formation. However, increasing hepatocyte polyploidy can block regeneration and compromise liver function in some contexts. Skewing hepatocytes toward endopolyploidy by inactivating the cytokinesis regulator Anillin (Anln) does not impair liver regeneration in response to acute or chronic liver toxins (148). By contrast, inactivating the *Plk4* and *Ankrd26* genes involved in centriole regulation causes extensive hepatocyte polyploidization and impaired regeneration during chronic liver stress (115). This stress-specific relationship between polyploidy and disease is also observed in the endocrine pancreas. Genetically enforced polyploidy reduction (via elimination of the *E2F7/E2F8* transcription factors during pancreatic development) neither prevents normal endocrine or exocrine development nor associates with diabetes (74). By contrast, eliminating *E2F1/E2F2* transcription factors during pancreatic development causes dramatic polyploidization, disorganization of both exocrine and endocrine compartments, and severe diabetes (50).

Mechanisms connecting inappropriate polyploidy to organ failure remain unclear. A possible model is that acute injury leads to regenerative levels of polyploidy, but excessive tissue damage leads to aberrant polyploidy. This model is consistent with extensive cell death observed in the liver and pancreas caused by extreme polyploidy upon *E2F1/E2F2* loss (50) versus modest ploidy changes observed by *E2F7/E2F8* loss (74). Furthermore, organ function and structure may dictate the role of polyploidy in organ homeostasis. For example, a notable distinction is seen between the highly regenerative liver and pancreas and the much less regenerative heart.

Comparing and contrasting polyploidy regulation in distinct organ settings may reveal mechanisms underlying these context-dependent outcomes. Such studies are important in not only understanding how polyploidy impacts organ regeneration and function but also developing molecular strategies to manipulate ploidy for therapy. Examples of important molecular ploidy regulators for further study include cell cycle regulators such as cyclin-dependent kinases and *E2F* transcription factors, nuclear structure proteins such as Anln and lamins, and centriole components (44). Better understanding of how these regulatory programs dictate ploidy and how they can be altered and/or reversed in disease may permit therapeutic increases in regenerative cells in diseases of chronic damage. Of note, ploidy reversal is observed in the liver, where polyploid hepatocytes produce cells of lower ploidy (32). Fluorescent lineage tracing approaches that report ploidy to precise timescales can facilitate future study (75). Similarly, spatial genomics and transcription profiling can link polyploidy to cellular and organ phenotypes. With these new approaches in hand, future work can discern the difference between productive polyploidy and the maladaptive polyploidy found in diseases of organ dysfunction.

2.3.2. Polyploidy and cancer. Polyploidy is a common feature across cancers (**Figure 1*d***). In terms of common cancer genetic events, endopolyploidy as a result of WGD is second only to mutations in the tumor suppressor gene p53 (12). Accordingly, most cancer WGD associates with p53 inactivation (12, 57). Polyploidy is also observed in tumors without p53 inactivation, for example, in renal cell carcinoma and certain colorectal cancer subtypes, where it corresponds with BAP1 deubiquitinase mutations and E2F pathway deregulation, respectively (12). In p53 mutant tumors, polyploidy predicts poor prognosis and increased metastasis across a number of hard-to-treat tumor types (10, 73, 83). Conversely, polyploidy is also a defining feature of relatively rare germ cell and embryonal tumors where, unlike p53 mutant solid tumors, it is associated with favorable prognosis (86, 112). Thus, while pervasive, cancer polyploidy displays remarkable genetic, lineage, and biological context dependencies. For example, polyploidy associated with p53 mutation is enriched in the gastrointestinal tract, notably in esophageal and pancreatic cancers (20, 23), whereas in hematological malignancies, p53 mutant cells are rarely polyploid, as observed in myeloid leukemias. Such heterogeneity is also apparent within tumor subtypes as is the case in breast cancer where polyploidy is more common in hormone receptor–negative, that is, basal or triple-negative, disease, versus hormone receptor–positive disease. These patterns may be governed by cell type– or cancer stage–specific regulation of polyploidy.

Genomically, there is a clear distinction between cancer-associated polyploidy and polyploidy observed in development and even organ dysfunction. Developmental and regenerative polyploidy manifests discretely as even sets of chromosomal material in cell nuclei (e.g., 4N and 8N, etc.). Cancer-associated polyploidy, by contrast, is spectral, presenting on a continuum of aberrant ploidy states in tumors (e.g., pseudotriploid or pseudotetraploid). This is because cancer polyploidy occurs in the setting of structural genome and chromosome number changes that manifest in aneuploidy and chromosomal copy number alterations, which quantitatively alter the ploidy of cancer genomes (30). Thus, in addition to the unique biology that the polyploid state may impart on cancer cells, polyploidy also confers a distinct genetic contribution to cancer by expanding the genomic configurations that evolved cells can sample as a conduit toward acquiring malignant fitness (see Section 3).

In sum, polyploidy in cancer presents uniquely compared to organisms and tissues and is associated with progression, prognosis, and specific genotypes. Cancer polyploidy is a highly selected evolutionary route to emergent, innovative, malignant phenotypes. Yet, how WGD directly impacts cancer cell biology remains poorly understood; thus, strategies to exploit it for diagnosis and therapy are lacking. However, recent efforts to further understand the phenomenon have begun to bear fruit. For example, WGD was recently linked with gene expression programs that impact therapeutic responses, such as immune evasion (98), potentially providing information for future immunotherapy approaches. Furthermore, recent evidence suggests that polyploid-specific susceptibilities may be druggable (98). Given its cancer prevalence, as in chronic diseases of organ dysfunction, further mechanistic understanding of polyploidy in cancer development and progression is an important goal.

3. COMMON RULES OF POLYPLOIDY ARE EMERGING ACROSS ORGANISMAL, TISSUE, AND DISEASE STATES

As the preceding sections illustrate, polyploidy is seemingly everywhere in nature. Yet, in some contexts, diploidy is dominant. This diversity of ploidal states in nature raises the question of how WGD alters cell and organismal biology. While answers to this question are frequently context dependent, common rules to polyploidy are beginning to emerge.

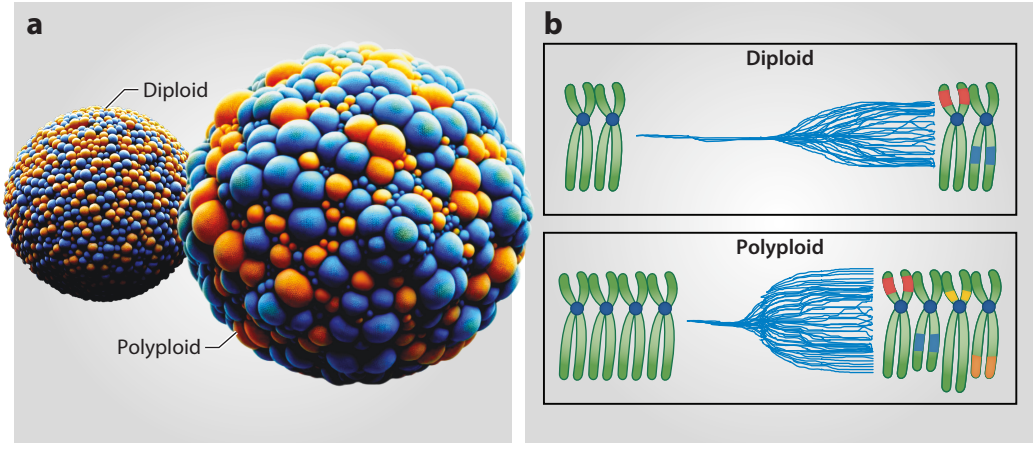

Figure 2

Emerging rules of polyploidy. (*a*) Polyploidy alters geometry and biological scaling. Pictured are two cells or organisms depicted as spheres: (*left*) one small diploid and (*right*) one large polyploid. Distinctly colored bumps on the sphere indicate changes in the distribution of molecules (in the case of a cell) or cells (in the case of an organism) on the surface of a cell or organism. (*b*) Polyploidy facilitates the exploration of genomic space. Simulated evolution of (*upper*) a diploid and (*lower*) a polyploid cell or organism over time. Colored bars on chromosomes indicate a genetic change of any kind (mutation, copy number change, etc.) to illustrate that polyploidy increases genetic change over time. Large focal changes (such as large duplications or deletions) are shown by changes in overall chromatid length.

3.1. Rule 1: Polyploidy Is Fundamentally Different from the Diploid State, and Size Plays an Important Role

At the most fundamental level, WGD duplicates gene copy number. There is a well-established connection between increased genome copy number and increased cell/organism size. These two principles—more genomes and a larger size—set up the null hypothesis that one WGD results in a cell with exactly twice the size and transcriptional output per gene. However, polyploidy can alter organisms and cells in nonlinear ways. In this section, we highlight ways in which polyploidy does more than make a big diploid cell/organism: The emerging picture of the effects of polyploidy is a lack of geometric scaling as the genome doubles (**Figure 2*a***), which enables polyploid cells and organisms to function in distinctive ways compared to their smaller diploid counterparts.

3.1.1. Building tissues and organisms with polyploid cells. WGD increases the genome content per cell, enabling cells and organisms to increase in size. With increased size comes altered geometry, as larger cells have a decreased surface area–to-volume ratio (45). This altered geometry profoundly impacts processes at single-cell, tissue, and organism scales (**Figure 2*a***). At the cellular scale, reduced surface area decreases the amount of plasma membrane and cell wall per cell. Successive WGDs in budding yeast lead to less plasma membrane uptake of several essential amino acids (45). Cells of triploid *Xenopus* frog species consume oxygen more slowly than in diploid species, likely due to decreased plasma membrane components (e.g., Na^+/K^+-ATPase) (17). The decreased plasma membrane demand associated with polyploidy reduces mitochondrial metabolism and lipid synthesis in mouse liver hepatocytes (79). Together, this evidence demonstrates how ploidy-driven size alterations can transform fundamental cellular processes such as metabolism.

At the tissue scale, building structures such as leaves with fewer large polyploid cells compared to many small diploid cells means that the same tissue space will have fewer intervening

membranes and cell walls between nuclei as ploidy increases. Studies of *Arabidopsis* found that the extra space not occupied by membranes in tetraploid plants increases storage capacity in leaves and higher water content in shoots (90). Another emerging theme is that the positioning of cells of different ploidies can impact tissue form and function. *Arabidopsis* sepals contain dispersed polyploid giant cells. Experimentally altering giant cell ploidy or density perturbs sepal curvature, which is important for flower opening (77). In *Drosophila* larvae and human organ donors, heart chambers have distinct ploidies. Perturbing this ploidy asymmetry in *Drosophila* decreases heart function in a way that resembles systemic heart failure (19). In addition to careful control of genomes per cell, nuclear number per cell may also be important. Inhibiting binucleation of *Caenorhabditis elegans* intestinal cells without changing cellular genome content decreases the production of yolk proteins that support reproduction (130). These studies underscore the need to understand how numbers of genomes and nuclei per cell are regulated throughout a tissue area to achieve biological functions.

At the organism scale, polyploidy typically generates larger organisms, a property exploited for agricultural purposes to generate larger fruits, for example. But there may be an upper limit to ploidy-driven organism size increases. In *Arabidopsis*, flower organ area increases only modestly in tetraploids compared to diploids due to reduced total cell number in tetraploids (102). Similarly, triploid *Xenopus* have fewer but larger cells than diploids (17). Such results suggest that there may be an optimal ploidy for an organism in a biological niche. For example, while tetraploid *Arabidopsis* plants have a larger biomass than diploids, octoploidy does not further increase biomass (90). In addition to promoting fewer, bigger cells, whole-organism polyploidy may carefully limit the pace of tissue growth by lessening the degree of endopolyploidy. In wild populations of *Arabidopsis arenosa*, tetraploids have less endopolyploidy in leaves than diploids (141). As with tissue-level studies, these organism-level studies suggest that larger polyploid size is carefully regulated to optimize organismal fitness.

3.1.2. Doubling the genome does not simply double gene expression. In addition to altering cellular geometry, WGD also causes fundamental molecular changes (**Figure 2*a***). Based on studies examining gene and protein expression in a ploidy series, genome doubling does not appear to equal transcriptome or proteome doubling. In tetraploid *Arabidopsis*, the overall increase in expression per sepal gene from diploids to tetraploids was only 1.69 as opposed to 2.0. Further, many genes were enriched beyond twofold in tetraploid versus diploid *Arabidopsis*, and these genes fit a signature found in yeast for increased cellular size (102, 142). In fission yeast, the increased DNA caused by WGD is thought to downregulate the activity of the cyclin-dependent kinase that controls cell size (91), meaning that doubling DNA alters a molecular regulator of cellular geometry. In addition to changes driven by altered cell size, mechanisms that generate endopolyploidy can also drive new gene expression. *Drosophila* cells undergoing endo-cell cycles dampen expression of conserved transcription factors *E2F1* and *Myb-MuvB* compared to cells in mitotic cycles (69). This transcriptional programming change also leads to epigenetic reprogramming, including silencing of apoptotic gene expression (147). Such silencing may accommodate the increased genome instability of polyploid cells discussed in Section 3.2.2.

WGD also does not double the proteome. In budding yeast (*Saccharomyces cerevisiae*) strains, tetraploids roughly triple the amount of total protein relative to haploids. This sublinear scaling is driven by decreased ribosome abundance, messenger RNA (mRNA) translation, and activity of the translation-promoting target of rapamycin (TOR) pathway. A similar decrease in TOR activity was also found in human tetraploid cells (143). This study highlights another likely fundamental change brought on by WGD: a lack of organelle scaling, which drives further expression changes.

Recent work found that organellar transcripts (chloroplast and mitochondria) are highly dominant in the mRNA pool of diverse flowering plants across diploids and polyploids (35). Nuclear

genes encoding proteins that interact with counterpart chloroplast or mitochondrion gene products have much lower mRNA levels (over tenfold lower) than counterparts from the two organellar types. Interestingly, based on a comparison of diploids and related polyploids, these cytonuclear RNA ratios are maintained following WGD, indicating that any potentially negative impact of WGD on these nuclear–organellar gene interactions must be buffered at the level of the transcriptome in polyploids. Buffering could result from increasing the number and/or size of the two organelle types in concert with cell size increase upon WGD (35).

In polyploid-associated diseases, the relationship between scaling of the genome, transcriptome, and proteome remains an important unanswered question. Gene expression studies in diploid versus polyploid cardiomyocytes point to differences in metabolic regulators that correspond with hypertrophic heart maturation and transcription factors that may act as gatekeepers for regulated cytokinesis or endo-cell cycles. In the liver, however, genetic perturbations resulting in an organ-wide increase in polyploidy do not notably shift liver gene expression (62), whereas single-cell analysis of isolated diploid and polyploid hepatocytes reveals differences in genes defining liver zonation (54). The liver also represents a tissue type where polyploidy and its relationship to gene dosage may result in stage-dependent roles in cancer initiation versus progression. Hepatocellular carcinoma frequently displays WGD associated with p53 inactivation and poor prognosis (83). However, both lineage tracing in mouse models of liver cancer and genetic interventions that increase hepatocyte polyploidy suggest that diploid cells, in some contexts, are more sensitive to cancer initiation (75, 148). This context-dependent cancer resistance may be due to an increased dosage of tumor suppressor genes in normal polyploid cells (149).

Understanding causative roles for polyploidy in diseases will hinge on determining if negative impacts of aberrant polyploidy result from an imbalance of intrinsic differences between ploidy or additional differences between diseased versus normal polyploid cells. As polyploidy is implicated in immune recognition, such studies must also consider the role played by both inflammation and remodeling of tissue microenvironments, often hallmarks of diseased tissues.

The above discussion illustrates numerous emerging commonalities conferred by WGD in cellular, organismal, and disease states. It is clear that further integrative study is needed to uncover molecules and scaling rules that may be universal to the polyploid state.

3.2. Rule 2: Polyploidy Facilitates the Exploration of Genomic Space

Polyploidy increases chromosome copy number. Consequences of having more of each chromosome, or parts of chromosomes, have been studied at multiple scales, from single cells to tumors to populations of organisms in the wild. A common thread is that extra copies of chromosomes provide a substate for genetic innovation (**Figure 2*b***) and, subsequently, natural selection. In this section, we discuss evidence for this innovation in organisms, cells, and cancer, as well as mechanisms contributing to this phenomenon.

3.2.1. Recurrent selection for polyploidy in cellular, organismal, and tumor evolution. Evidence for the contribution of polyploidy to organismal evolution and speciation is stamped in the fossil record, most notably in plants but also across diverse clades of animals, including the ancestor of all vertebrates (113). Within plants, an ancient polyploidy event is associated with the origins of the vast majority of fern species (70), while another ancient WGD maps to the ancestor of all living angiosperms, a clade of ~350,000 species (2). Additional ancient polyploidy events are associated with many major clades of angiosperms, including core eudicots (70% of all flowering plant species); monocots (22%); and many major families, including the grass and sunflower families (87, 129). Conservatively, 15% of all angiosperms and 31% of all fern speciation events have involved polyploidy (140). Importantly, polyploidy events appear to be intricately linked to

adaptation, for example, the dramatic global change associated with the Cretaceous-Paleogene boundary (131). Thus, the imprint of polyploidy is clear across the tree of life, where it has been repeatedly selected for during evolution, including during stressful conditions.

Homoeologous chromosomes: chromosomes originating from different species in an allopolyploid

At the cellular and organism level, perhaps the clearest experimental evidence that polyploidy drives genome evolution comes from the budding yeast *S. cerevisiae*, which is simultaneously a single cell and an organism. Using in vitro evolution experiments, tetraploid yeasts were shown to evolve faster than haploid or diploid yeasts due to higher rates of chromosome instability (see Section 3.2.2). Selmecki et al. (111) provide direct evidence that WGD can accelerate evolutionary adaptation (**Figure 2*b***).

Polyploidy is a powerful driver of cancer evolution. While polyploidy is universal in only one cancer type (e.g., embryonal and germ cell tumors), selection for polyploidy is evidenced in histories of virtually every cancer type (57, 83). As with organismal evolution and the emergence of polyploidy as an adaptive mechanism, polyploidy is increasingly linked to cancers' most lethal and heterogeneous features: metastasis and therapeutic relapse/resistance, features associated with significant evolutionary pressures. Numerous studies associate polyploidy with metastatic dissemination, particularly in pancreas, prostate, kidney, and other tumors (12, 73, 83). Importantly, this association between polyploidy and metastasis is further linked by experimental evidence to the generation of structural variation and copy number events, particularly in pancreatic cancer, establishing more causal relationships (67). Similarly, polyploidy is linked to cancer therapy resistance, including in genotoxic and targeted therapies and immunotherapies (37, 73).

While thematically disparate, a common link from polyploidy to the genetic/genomic evolution of organisms, cells, and cancers can be proposed: the facilitation of genomic innovation (**Figure 2*b***).

3.2.2. Polyploidy and the role of genomic (in)stability. A sudden doubling of the genome results in an unstable state. Such genomic instability fuels further genetic change. Fundamentally, WGD impacts how chromosomes are structured and partitioned during gametogenesis and somatic tissue development.

The formation of new polyploid organisms causes chromosome instability. During meiosis in allopolyploids, where interactions between the parental genomes are required, the two distinct genomes (designated as distinct sets of homoeologous chromosomes) create challenges. Compared to homologous chromosomes, homoeologous chromosomes in new allopolyploid species may exhibit reduced meiotic pairing and recombination as well as problems in chromosome segregation (13). These challenges drive genetic novelty.

In somatic cell propagation and mitosis, polyploidy disrupts the scaling of intracellular structures (discussed in Section 3.1.1). This altered scaling can include the mitotic spindle, a microtubule-based structure responsible for attaching to each sister chromatid pair and generating the force required to segregate exactly half of each pair into a daughter cell. Sudden WGD in both yeast and cancer cells can alter spindle geometry (98, 119). In cancer cells, such spindle alterations lead to a greater dependence on the microtubule motor protein KIF18A, as depletion of this motor preferentially impacts tetraploid (not diploid) cancer cells (98). In addition, doubling the chromosome number also suddenly creates many more microtubule attachment sites (kinetochores) that must be properly regulated to ensure faithful sister chromatid separation. A challenge related to kinetochores arises when endo-cell cycles generate somatic polyploidy. If the genome is replicated twice without karyokinesis, the resulting tetraploid cell can have four chromatids conjoined together (i.e., a diplochromosome). The presence of both more kinetochores and more diplochromosomes after sudden WGD requires additional time for the spindle to properly interact with kinetochores. The mitotic spindle assembly checkpoint ensures this greater time at

metaphase, and depletion of spindle checkpoint proteins is preferentially lethal to polyploid cells in both *Drosophila* tissue and human cancer cells (98, 120).

Animal endopolyploidy also presents a problem related to the microtubule organizing center, known as the centrosome. In animal cells, centrosomes reside at the end of the mitotic spindle opposite of the attachment to chromosomes. These microtubule-organizing centers are carefully duplicated when the genome is duplicated. Therefore, endo-cell cycles can lead to greater numbers of centrosomes. If a cell undergoes endo-cell cycles to become polyploid and then reenters mitosis, it will contain more than two centrosomes and therefore may generate more than two spindle poles. Such multipolar spindles can wreak havoc on chromosome segregation (31). To prevent this, cells with aberrant polyploidy and amplified centrosome number can be prevented from further division. Supernumerary centrosomes trigger a protein complex known as the PIDDosome that stabilizes the tumor suppressor gene p53, which then promotes cell cycle arrest. Recently, the centrosome protein Ankrd26 was found to activate the PIDDosome in excess centrosome cells. Mice lacking ankrd26 exhibit excess polyploidy in the liver and accumulate liver damage under chronic injury conditions (115).

Fundamentally, DNA replication is an obligate requirement for polyploidy. Interestingly, replication can further influence the polyploid state in a genotype-specific manner. While p53 can restrain the division of polyploid cells in many eukaryotes, it paradoxically can also promote further polyploid genome instability. One gene induced by p53 is the progenome replication cyclin, Cyclin E. Excess Cyclin E expression in human tumor cells with wild-type levels of p53 can cause aberrant endo-cell cycles and polyploidy. Genome replication in such aberrant polyploid cells is not uniform across the genome, which creates a genome-destabilizing condition known as replicative stress (146). In the first round of aberrant WGD, a second source of replicative stress is the shortage of proteins required for a normal G1/S cell cycle transition. If a human cell is unable to complete M phase, the subsequent G1/S transition that generates tetraploidy is dysregulated, and the resulting polyploid cells exhibit high levels of replicative stress (38).

The processes described above—meiosis, mitosis, and replication—coupled with recombination and independent assortment generate genomic novelty at multiple scales. Whether the same drivers of genomic change apply to polyploidy at the cellular, tissue, and disease scales requires further study, but the association of chromosomal instability with polyploidy in cancer suggests the possibility of shared mechanisms between organismal, developing tissue, and cancer polyploidy.

3.2.3. Novelty from instability. Following initial genomic instability, polyploid organisms and cells appear remarkably adaptable. Fascinating similarities can be seen when comparing the evolution of polyploid organisms and tumors.

In allopolyploid organisms, selection resolves intergenomic conflicts in allopolyploid species, while duplicated chromosomes and/or nuclei facilitate genetic change in autopolyploids. In allopolyploids, homoeologous chromosome sets representing the parental genomes rarely stay intact; instead, genomic instability quickly arises, with intergenomic translocations (between parental subgenomes), homoeologous recombination, physical loss of homoeologous genes, and shifts in homoeologous gene expression all altering the null expectation of perfectly additive genomes. Moreover, activation of transposable elements may accompany allopolyploidy, yielding rapid transposition with potential impacts on chromosomal stability and gene expression. All of these processes may act simultaneously to generate novelty at genetic, chromosomal, and gene expression levels such that all individuals of a polyploid population may differ, providing expansive raw material for selection and evolutionary novelty.

In cancer, polyploidy predicts not only phenotypic heterogeneity, as described above for polyploid organisms, but also genomic diversification. Polyploid cancer genomes acquire more copy

number variations (CNVs) in the form of genomic deletions and gains than aneuploid, diploid genomes. While WGD often represents a point of clonal sweep during tumorigenesis, such polyploid lineages also display greater subclonal heterogeneity (i.e., more genetic novelty, as seen in polyploid organisms) than observed in diploid phylogenies. This heterogeneity may reflect the ability of higher-dimension polyploid genomes to accommodate novel allelic configurations that are inaccessible in a diploid state (**Figure 2*b***). For example, tetraploid configurations can permit sampling of wider gene dosage imbalances between putative tumor suppressor and oncogene loci by buffering the effects of potentially deleterious structural events. Thus, whereas diploid genomes are limited to heterozygous deletions of tumor suppressors linked with essential genes in the setting of two copies of a progrowth locus, polyploid genomes could accommodate a single copy of an essential linked tumor suppressor locus in combination with four copies of an oncogene. Iterations of copy number imbalance across polyploid genomes may result in emerging gene expression patterns related to tumor progression. The parallels between polyploid tumors and organisms are a powerful argument for future integrative studies.

4. CONCLUSIONS AND FUTURE DIRECTIONS

Polyploidy is ubiquitous not only across organismal diversity as encompassed by the tree of life but also across cells and tissues within organisms. Yet despite its widespread occurrence, the roles of polyploidy in evolution, cellular and tissue function, and disease response are all grossly underappreciated. Polyploidy is perhaps the single most important evolutionary, developmental, and functional force in biological systems, yet it remains poorly studied and understood at all levels. Research conducted to date has been siloed, hindering progress. Importantly, recent efforts have begun to develop linkages across disciplines, affording new opportunities for synthesis. Certain rules to polyploidy are emerging, including its role as an important response to stress at cellular, tissue, and organismal scales. Future research should include an integrated appraisal of polyploidy in the search for further commonalities. For example, we still know very little about the functional roles of polyploid cells and tissues. Furthermore, although polyploidy is widespread at the organismal level, what we know is only the tip of the iceberg: Most lineages remain uninvestigated for ploidy, with chromosome numbers for the vast majority of species across the tree of life unknown. Ecologically, polyploidy clearly increases with latitude in many plant and animal lineages, but little is actually known about the relationship between polyploidy and ecological amplitude. Polyploidy also remains grossly untapped from an economic standpoint, with many opportunities for innovations in treating cancer and in bioengineering cells and tissues to produce diverse products from synthetic molecules to medicines to crops. Finally, the importance of polyploidy needs to be better appreciated not only by the scientific community but also by the public; outreach efforts at all educational levels are needed. As the field unifies after decades of fractured investigation, this is an exciting time for the study of polyploidy.

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