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Opinion

Polyploidy: A Biological Force From Cells to Ecosystems

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Polyploidy, resulting from the duplication of the entire genome of an organism or cell, greatly affects genes and genomes, cells and tissues, organisms, and even entire ecosystems. Despite the wide-reaching importance of polyploidy, communication across disciplinary boundaries to identify common themes at different scales has been almost nonexistent. However, a critical need remains to understand commonalities that derive from shared polyploid cellular processes across organismal diversity, levels of biological organization, and fields of inquiry – from biodiversity and biocomplexity to medicine and agriculture. Here, we review the current understanding of polyploidy at the organismal and suborganismal levels, identify shared research themes and elements, and propose new directions to integrate research on polyploidy toward confronting interdisciplinary grand challenges of the 21st century.

Highlights

Communication across disciplinary boundaries to identify common themes of polyploidy has been extremely limited.

Identifying commonalities that derive from shared polyploid cellular processes across disparate fields of inquiry holds promise to identify breakthroughs in numerous areas – from biodiversity and biocomplexity to medicine and agriculture.

We propose new directions to integrate research on polyploidy toward confronting interdisciplinary grand challenges of the 21st century.

Polyploidy: A Common Biological Phenomenon Lacking Cross-Disciplinary Study

Polyploidy [**whole-genome duplication (WGD)**; see Glossary], defined as having three or more sets of chromosomes, influences organisms in all clades of eukaryotic life and all levels of biological organization, from genes to cells to entire ecosystems (Figure 1). The intersection of these axes of biodiversity and biological scale offers new opportunity for insight and research innovation. Yet, polyploidy remains underexplored in many contexts, and its roles and impact in biological processes and across phylogeny are unclear. This lack of clarity derives, in part, from very limited communication across disciplinary boundaries to identify common themes at different scales. The genomics era has accelerated research on polyploidy and provided a shared platform for dialogue and potential interdisciplinary synergy. We argue that cross-disciplinary approaches are crucial to identifying common functions and regulation of polyploidy.

Polyploidy can arise at both the organismal and suborganismal levels. At the organismal level, **unreduced gametes** (e.g., diploid instead of haploid) formed during meiosis can fuse to generate whole-organism polyploidy. Organismal polyploidy is a major driver of biodiversity that extends across all life, from deep history to the recent past [1,2]. Most, if not all, extant species (including our own) carry a signature of at least one ancient WGD [2]. Within tissues, programmed or aberrant events also increase the ploidy of specific somatic cells and cell lineages, often playing an important role in tissue differentiation in animals and organ development in plants (Figure 1) [3,4]. New examples of polyploid tissues continue to emerge, such as in mammary tissue growth during mammalian lactation [5] or in repairing mammalian kidney and bladder tissue [6,7]. Events leading to suborganismal increases in ploidy include variant cell cycles such as **endoreplication** or cell–cell fusion and are reviewed elsewhere [8,9].

At both the whole-organism and suborganismal levels and across diverse areas of life, polyploidy increases cell size [4,10]. This essentially universal property of the polyploid cell results in a

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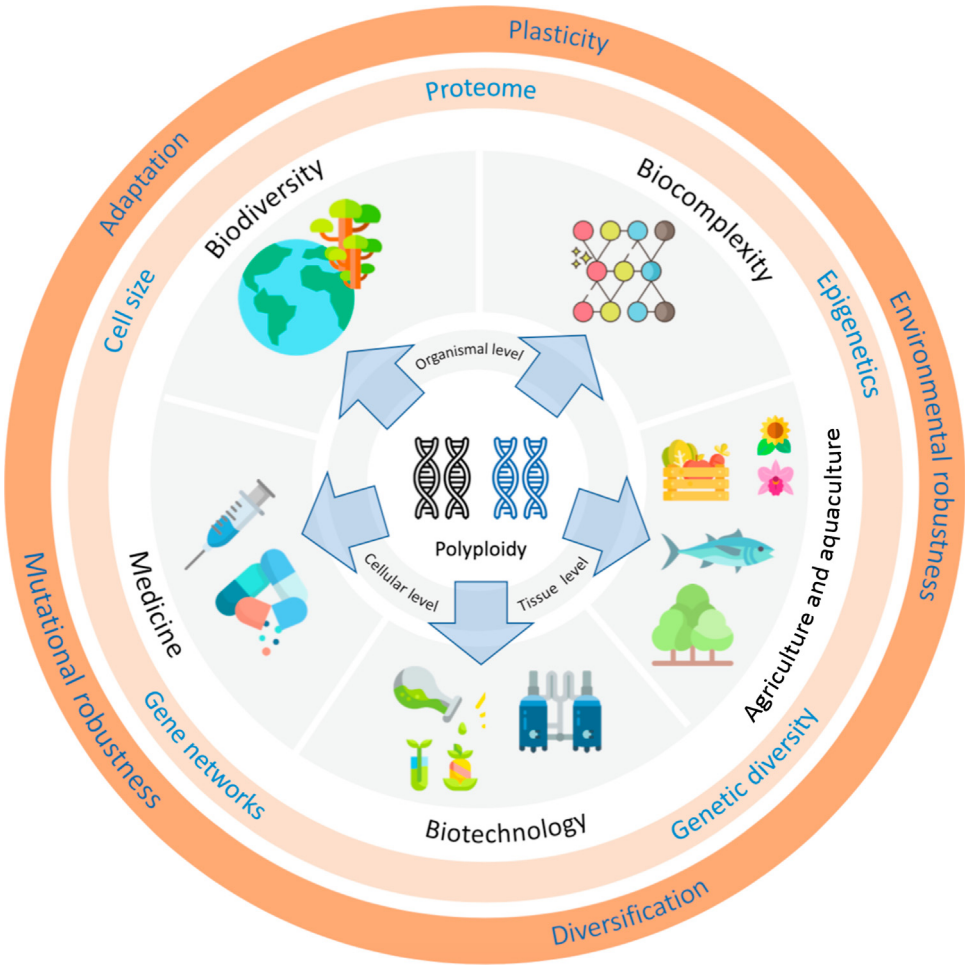

Figure 1. Central Role of Polyploidy [Whole-Genome Duplication (WGD)]. Polyploidy, explained in the center of the diagram, is a driving force in organismal evolution. Elucidating the consequences of WGD at multiple levels (cellular to organismal) is key to understanding global patterns of biodiversity and ecology in addition to cellular fates, physiology, and metabolism. The implications of polyploidy range from cells to ecosystems and from agriculture to medicine and more.

decreased cell surface/volume ratio. The full impact of these polyploidy-driven cell changes remains uncertain, but emerging data from across all life suggest profound shifts in numerous cellular processes following polyploidization. Moreover, as we highlight here, cellular and organismal polyploidy may be manifested as both an effect of environmental stress (i.e., increased rates of polyploidization) and an **adaptation** to it. This intimate relationship to stress makes the study of polyploidy increasingly important as cells, tissues, and whole organisms must respond to rapid changes in their biotic and abiotic environments.

Emerging Commonalities

Greater insight into the distinctive functions and regulation of polyploid cells and organisms can unravel strategies to fight some of the world's most pressing social crises. These efforts include sustaining biodiversity and ecosystem services, increasing and diversifying agricultural yield in rapidly changing environments, and advancing biotechnology and medical interventions. This is particularly true with respect to diseases such as cancer, where polyploidy is now appreciated

Glossary

Adaptation: genetic changes that lead to higher fitness (e.g., performance or population growth) in a certain environment; the result of natural selection.
Biotrophic: plant pathogens or mutualists that form long-term obligate feeding relationships with host cells (e.g., powdery mildew, mycorrhizae).
Diploidization: the generation of a diploid genome from a polyploid genome [68–72].
Ecoevolutionary dynamics: the result of reciprocal influences between ecological and evolutionary processes; that is, evolution and ecology occur on the same time scale such that evolution affects ecological interactions and vice versa.
Endoreplication: a general term for truncated cell cycles that duplicate the genome without completing cell division, leading to a polyploid cell.
Epigenetic remodeling: DNA sequence–independent alterations in chromatin, such as changes in the condensation state or of active/repressive histone chemical modifications, that lead to alterations in gene expression.
Epigenome: the chemical state of chromatin, such as histone chemical modifications, which can influence gene expression independently of DNA sequence.
Evolvability: the capacity of a population to evolve through natural selection, which depends on the amount of, and ability to generate, genetic diversity.
Genetic buffering: gene interactions whereby variation in one gene can be compensated for by variation in other genes, such as genes that function in the same biochemical process, leading to a stable phenotype.
Inbreeding depression: the reduction in fitness or a trait due to mating with close relatives (e.g., selfing) that results from expression of deleterious alleles or loss of heterozygosity.
Karyotypic: referring to the state and/or number of chromosomes in a given nucleus.
Neopolyploids: newly formed polyploids via synthetic manipulation or natural processes.
Unreduced gametes: gametes produced from an aberrant meiosis I, in which homolog disjunction fails and ploidy is not reduced.

to be a major player in both promoting and suppressing tumor progression [11–15]. Yet, polyploidy research has long been compartmentalized, with investigators in evolution, ecology, genomics, agriculture, cancer, and other branches of biology having few, if any, interactions, despite often asking very similar questions about the drivers and consequences of polyploidy at cellular, tissue, organ, and organismal levels (Figure 1). WGD events likely result in a plethora of recurring downstream effects that are common across biological settings, including changes in gene expression and cell size, **epigenetic remodeling**, modifications to subcellular networks of gene interaction, and altered responses to environmental stress [4]. Thus, a WGD can alter the phenotype, not only at the level of the cell and cellular organization but also at the organismal level. Going forward, we argue that interdisciplinary collaboration aimed at identifying common themes of genome doubling/polyploidy will unify currently disparate fields, unearth novel insights, and generate paradigm shifts.

Whole-genome duplication (WGD): a general term for any process leading to a doubling of cellular or organismal DNA content.

Here, we present two major research themes that clearly illustrate common responses to polyploidy in plants and animals. These commonalities argue for increased interaction among scientists studying polyploidy at multiple organizational levels and across large phylogenetic distances.

Polyploidy as a Response to Acute Stress

At the organismal level, environmental stress (e.g., high or low temperature, water availability, or salinity) may induce meiotic events leading to unreduced gamete production [16–19] and organismal genome doubling, resulting immediately in a polyploid line. This stress-induced WGD plays a major role in agriculture and horticulture in generating new synthetic polyploids in a manner similar to the processes that lead to new polyploid species and ultimately polyploid lineages in nature.

Comparably, at the suborganismal level, tissue stresses such as acute wounding or viral infection can induce polyploidy at the cellular level [6,7,20–23], which can result in an increase in tissue mass via enlarged cells. This WGD response represents an alternative to generating new cells through cell division. In animals, several recent examples of WGD after injury have been described in vertebrate tissues such as the kidney, bladder, and epicardium as well as multiple insect tissues [20,24,25]. Such injury-triggered WGD may enable rapid tissue regrowth without compromising the integrity of a tissue barrier during cell division [26] or provide necessary mechanical force [27]. Similarly, in plants, endoreplication responses (cell cycle activation without mitosis) can be stimulated by both major pathogens of agricultural crops (e.g., powdery mildew, root knot nematodes [28]) and ancient mutualistic associations (e.g., mycorrhizal fungi and nitrogen-fixing rhizobia) in which most plants engage [29,30]. While endoreplication can arise via various shortcuts in the cell cycle, endoreplication in response to **biotrophic** interactions that involve penetration of the plant tissue results in upregulation of the same genes, suggesting that the effectors involved are generic reactions to cell stress [29]. Furthermore, recent work in root nodules that house nitrogen-fixing rhizobia demonstrated that changes in transcription are related to increasing ploidy and dynamic changes in the **epigenome** [31]. Interestingly, it has been proposed that cellular level plasticity for ploidy (endoreplication) may trade off with whole-organism ploidy [25,32], as both are different routes to mitigate stress.

In both organismal and tissue-level examples of environmental stress leading to WGD, molecular connections between stress-sensing and ploidy increases remain unknown. The above-mentioned examples suggest that a common response or set of responses linking stress to WGD may be awaiting discovery. For example, similar epigenetic processes could be involved in other endoreplication-mediated differentiation programs associated with injury and other stresses, a hypothesis that could be tested across human and plant systems, as it is now clear that WGD is a common response to tissue injury. The researcher investigating injury-induced

polyploidy in tissues such as the heart, where polyploidy has recently been shown to block therapeutic regeneration [33–36], has much in common with plant researchers similarly investigating stress-induced endopolyploidy in plant leaves or other tissues. Collaborative study in this area could potentially lead, for example, to new strategies to repair injured tissue in diverse organs and organisms or arrest growth of cancer cells with WGD.

Adaptation via Ploidy-Induced Genomic Change

Genome doubling in both whole organisms and individual cells ultimately results in numerous downstream effects, regardless of the context. First, the increased copies of each chromosome greatly enhance genetic diversity. This diversity can then seed additional modifications to gene expression, epigenetics, gene networks, the proteome, cell size, and altered responses to stress. This overall increased genetic diversity/versatility in the new polyploid cell line or organism represents the fuel that, once filtered by selection, ultimately leads to adaptation. Stress may not only induce polyploidy; substantial data reveal that WGD also provides an adaptive advantage to both cells and organisms, particularly under unstable, stressful environments. As one example, polyploidy promotes increased salinity tolerance in both animals [37] and plants [38–40]. In the sweet potato, polyploids better maintain K^+/Na^+ homeostasis under saline conditions than diploids, begging the question whether a similar mechanism may operate more broadly.

At the organismal level, in a stable environment, gradual processes can successfully explain many aspects of evolution. However, despite the buffering imposed by duplicate gene copies and the consequent delay in fixation of beneficial and deleterious alleles, the dynamic nature of polyploid genomes may drive organismal change. This increased **evolvability** provides a mechanism of rapid adaptation to a quickly changing environment, whether it be in response to local/regional stresses on populations or the massive environmental changes that accompanied meteor impact at the Cretaceous–Paleogene boundary [41]. Moreover, polyploids may be better able to respond rapidly to projected rapid climate change scenarios in the remainder of this century.

At the cellular level, the adaptability of polyploid cell lines has numerous implications. The adaptive advantage of polyploidy may have deleterious consequences when genome doubling occurs in tissues that are normally diploid. In many cancers, the occurrence of polyploidy is now appreciated to significantly shape the evolution and prognosis of tumors [11–13], perhaps by increasing rates of **genomic instability** [4,42,43] and therefore cancer-driving mutations or drug resistance [4,12,44]. In support of this idea, polyploidy was recently found not only to be present in roughly one-third of solid tumors [11,12] but also to be even more prevalent (>50%) in advanced metastatic disease [45].

Likewise, increases in ploidy (followed by mis-segregation of chromosomes) in *Candida albicans*, a prevalent human pathogenic fungus, occur in response to the antifungal drug fluconazole (FLC) [46], creating FLC-resistant aneuploid progeny. By contrast to the oft-described negative attributes of aneuploidy [47,48], many FLC-resistant aneuploids that were derived from WGD show little fitness cost. Aneuploidy may also provide occasional opportunities for adaptation to stress and cancer [49,50]. Experimental evolution systems can offer additional insight into mechanisms. In yeast (single cells), for example, polyploid cells adapt faster than haploids or diploids, especially in stressful environments, as a result of more frequent beneficial mutations and stronger fitness effects [51]. In plants, researchers are just beginning to understand how polyploidy in some tissues leads to increased adaptation and evolutionary and agronomic success; for example, polyploid cells are important in the development of structures such as trichomes, fruits, and root nodules [3,52].

While the above discussion centers on polyploidy fueling increased adaptability, the converse can also occur. The duplicated gene copies in a polyploid cell or organism can minimize deleterious

phenotypic variation, because the additional genomic copies provide a buffer against the impact of deleterious mutations [53,54]. In a newly formed polyploid organism, this buffering can be advantageous, but negative mutations may accumulate over time, eventually reaching a high frequency that could be disadvantageous for a population [55,56]. However, these copies are rarely exposed because of duplicate gene copies, leading to reduced **inbreeding depression** in most polyploids [56–59]. At the suborganismal level, a recent example of **genetic buffering** by polyploidy is the demonstration that polyploidy prevents tumor growth that is driven by homozygous recessive tumor suppressor mutations [60]. Overall, the above examples highlight similarities in the adaptive responses conferred by polyploidy from plant genomes to tumors and show that commonalities are beginning to be revealed across systems, emphasizing the need for much more coordinated, cross-disciplinary research.

Integrating Disciplines to Identify Common Rules to Polyploidy

Greater integration of research on WGD promises to identify further commonalities across biological scales and phylogenetic distances while also clarifying which responses might be unique to a specific organ, biological process, or species. Such interdisciplinary collaborations could potentially reveal underlying 'rules' to polyploidy that cut across organisms and disciplines (from agriculture to medicine). We suggest that knowing such 'rules' can help address a host of outstanding 'moon shot' questions that are important in diverse WGD settings (see Outstanding Questions).

We are also reminded that 'nothing in biology makes sense except in the light of evolution' [61]. With this in mind, replaying the 'genome duplication' tape of life with populations of fast-growing cells or organisms should offer novel insights regarding when and how WGD confers a selective advantage. This can be done through 'evolve and resequence' experiments, where genomes of natural and/or artificial polyploid cells or organisms, including experimental tumor models, are (re)sequenced after many generations of selection [62,63]. This approach could provide clues, for example, to how WGD facilitates adaptations to different environmental or stressful conditions. Similarly, mathematical modeling can reveal possible effects of WGD from an evolutionary dynamics perspective in ecological, developmental, and disease settings. Applications of such an approach are broad. Such forward-time simulations that can accommodate **ecoevolutionary dynamics** of mixed-ploidy populations could, for example, inform us on the fate of polyploid plants during increasing frequency/severity of drought or of a fungal parasite following exposure to an antifungal agent in a human host environment [46]. Importantly, mathematical modeling suggests that tumors derived from WGD may optimally converge on a narrow **karyotypic** range [13], supporting the validity and importance to human health of such evolutionary/modeling approaches in this field.

Concluding Remarks and Future Perspectives

That many normal and malignant cells, tissues, and even entire organisms often possess, or at some time in their evolutionary history have possessed, multiple copies of their genome, has intrigued scientists across disciplines for over 100 years. However, research on polyploidy has long been siloed; medical, agricultural, and evolutionary biologists who study genome doubling have much in common but currently have only limited contact. We argue that an integrative approach is now needed to fully understand the many facets and intricacies of 'life with multiple genomes.' We propose that joint research ventures across diverse disciplines will promote a better understanding of polyploidy at both the cellular and organismal levels. Undoubtedly, research that seeks commonalities will have important downstream benefits to our own species through novel discoveries spanning medicine, agriculture, and evolution/ecology. Polyploidy's link to biological novelty and innovation [64] and the success of polyploid cells within organisms, of polyploid organisms in nature, and of polyploid lines in plant domestication and synthetic

Outstanding Questions

How does the increased complexity of duplicated gene regulatory networks affect polyploid cells (both normal and diseased), tissues, and organisms?

What advantageous gene expression networks may explain the emergence of polyploidy in specific plant and animal tissues following acute stress?

What are the signature characteristics of polyploid cancer cells that can be exploited for preventive and therapeutic purposes?

Why is the polyploid state in ecological niches or tumors often transient, leading to the process of '**diploidization**' – the return of at least part of a polyploid genome to a diploid state?

evolution experiments [51] suggest that polyploidy is an untapped resource for advances in many fields (Figure 1). Knowledge gained from natural polyploid cells and organisms, coupled with the potential of synthesizing **neopolyploids**, may lead to new technologies to solve pressing global problems. We anticipate, for example, that it may soon be possible to edit genes in polyploids [65,66] or engineer synthetic polyploid cells or organisms with novel functions, including mitigation of greenhouse gases or plastics pollution or organ repair.

We thus propose that researchers engage in a broad interdisciplinary grand challenge, 'polyploidy 2030,' within the next decade. This effort would involve researchers studying polyploidy in the entire tree of life and in diverse areas, including evolutionary biology, ecology, agriculture, and medicine, working collectively to provide a meaningful synthesis of the role of polyploidy in biological systems and subsystems. Polyploidy 2030 should address major questions of central importance to human health and well-being. Additional funding will be needed to accomplish these goals. For example, polyploidy is more common in human tumors than some of the most well-studied mutations in oncogenes, such as the Ras gene family [11,67], yet funding for polyploidy lags well behind funding for such important cancer mutations. Central questions to be answered include, but are not limited to, the role of genome doubling in generating biodiversity, in addition to improvements in agriculture and medicine.

Sharing of data, knowledge, and expertise across disciplines should catalyze new research into the roles, rules, and diverse impacts of polyploidy. Such cooperation can lead to breakthroughs in the major interdisciplinary grand challenges of the century, such as maintaining human health, food security, and ecosystem services in the face of rapid population growth and environmental change.

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References

1. Soltis, D.E. *et al.* (2009) Polyploidy and angiosperm diversification. *Am. J. Bot.* 96, 336–348
2. Van De Peer, Y. *et al.* (2017) The evolutionary significance of polyploidy. *Nat. Rev. Genet.* 18, 411–424
3. Orr-Weaver, T.L. (2015) When bigger is better: the role of polyploidy in organogenesis. *Trends Genet.* 31, 307–315
4. Schoenfelder, K.P. and Fox, D.T. (2015) The expanding implications of polyploidy. *J. Cell Biol.* 209, 485–491
5. Rios, A.C. *et al.* (2016) Essential role for a novel population of binucleated mammary epithelial cells in lactation. *Nat. Commun.* 7, 11400
6. Wang, J. *et al.* (2018) Polyploid superficial cells that maintain the urothelial barrier are produced via incomplete cytokinesis and endoreplication. *Cell Rep.* 25, 464–477 e4
7. Lazzeri, E. *et al.* (2018) Endocycle-related tubular cell hypertrophy and progenitor proliferation recover renal function after acute kidney injury. *Nat. Commun.* 9, 1344
8. Edgar, B.A. *et al.* (2014) Endocycles: a recurrent evolutionary innovation for post-mitotic cell growth. *Nat. Rev. Mol. Cell Biol.* 15, 197–210
9. Aguilar, P.S. *et al.* (2013) Genetic basis of cell-cell fusion mechanisms. *Trends Genet.* 29, 427–437
10. Marshall, W.F. *et al.* (2012) What determines cell size? *BMC Biol.* 10, 101
11. Zack, T.I. *et al.* (2013) Pan-cancer patterns of somatic copy number alteration. *Nat. Genet.* 45, 1134–1140
12. Bielski, C.M. *et al.* (2018) Genome doubling shapes the evolution and prognosis of advanced cancers. *Nat. Genet.* 50, 1189–1195
13. Laughney, A.M. *et al.* (2015) Dynamics of tumor heterogeneity derived from clonal karyotypic evolution. *Cell Rep.* 12, 809–820
14. Lin, Y.H. *et al.* (2020) Mice with increased numbers of polyploid hepatocytes maintain regenerative capacity but develop fewer hepatocellular carcinomas following chronic liver injury. *Gastroenterology* 158, 1698–1712.e14
15. Wilkinson, P.D. *et al.* (2019) The polyploid state restricts hepatocyte proliferation and liver regeneration in mice. *Hepatology* 69, 1242–1258
16. Ramsey, J. and Schemske, D.W. (1998) Pathways, mechanisms, and rates of polyploid formation in flowering plants. *Annu. Rev. Ecol. Syst.* 29, 467–501
17. Mason, A.S. *et al.* (2011) Production of viable male unreduced gametes in *Brassica* interspecific hybrids is genotype specific and stimulated by cold temperatures. *BMC Plant Biol.* 11, 103
18. Pécrix, Y. *et al.* (2011) Polyploidization mechanisms: temperature environment can induce diploid gamete formation in Rosa sp. *J. Exp. Bot.* 62, 3587–3597
19. de Storme, N. *et al.* (2012) Production of diploid male gametes in *Arabidopsis* by cold-induced destabilization of postmeiotic radial microtubule arrays. *Plant Physiol.* 160, 1808–1826
20. Losick, V.P. *et al.* (2013) Polyploidization and cell fusion contribute to wound healing in the adult Drosophila epithelium. *Curr. Biol.* 23, 2224–2232

21. Tamori, Y. and Deng, W.M. (2013) Tissue repair through cell competition and compensatory cellular hypertrophy in postmitotic epithelia. *Dev. Cell* 28, 350–363
22. Payne, E.H. *et al.* (2018) Polyploidy and mitotic cell death are two distinct HIV-1 Vpr-driven outcomes in renal tubule epithelial cells. *J. Virol.* 92, e01718-17
23. Li, T.N. *et al.* (2018) Intrahepatic hepatitis B virus large surface antigen induces hepatocyte hyperploidy via failure of cytokinesis. *J. Pathol.* 245, 502–513
24. Lazzeri, E. *et al.* (2019) Surviving acute organ failure: cell polyploidization and progenitor proliferation. *Trends Mol. Med.* 25, 366–381
25. Neiman, M. *et al.* (2017) Endopolyploidy as a potential driver of animal ecology and evolution. *Biol. Rev.* 92, 234–247
26. Cohen, E. *et al.* (2018) Fizzy-Related dictates a cell cycle switch during organ repair and tissue growth responses in the Drosophila hindgut. *eLife* 7, e38327
27. Cao, J. *et al.* (2017) Tension creates an endoreplication wavefront that leads regeneration of epicardial tissue. *Dev. Cell* 42, 600–615 e4
28. Paige, K.N. (2018) Overcompensation, environmental stress, and the role of endoreduplication. *Am. J. Bot.* 105, 1105–1108
29. Smant, G. *et al.* (2018) Parallel adaptations and common host cell responses enabling feeding of obligate and facultative plant parasitic nematodes. *Plant J.* 93, 686–702
30. Forrester, N.J. *et al.* (2020) Polyploid plants obtain greater fitness benefits from a nutrient acquisition mutualism. *New Phytol.* https://doi.org/10.1111/nph.16574
31. Nagymihály, M. *et al.* (2017) Ploidy-dependent changes in the epigenome of symbiotic cells correlate with specific patterns of gene expression. *Proc. Natl. Acad. Sci. U. S. A.* 114, 4543–4548
32. Pacey, E.K. *et al.* (2020) The influence of experimentally induced polyploidy on the relationships between endopolyploidy and plant function in *Arabidopsis thaliana*. *Ecol. Evol.* 10, 198–216
33. Han, L. *et al.* (2020) Lamin B2 levels regulate polyploidization of cardiomyocyte nuclei and myocardial regeneration. *Dev. Cell* 53, 42–59.e11
34. González-Rosa, J.M. *et al.* (2018) Myocardial polyploidization creates a barrier to heart regeneration in zebrafish. *Dev. Cell* 44, 433–446 e7
35. Gan, P. *et al.* (2020) Cardiomyocyte polyploidy and implications for heart regeneration. *Annu. Rev. Physiol.* 82, 45–61
36. Patterson, M. *et al.* (2017) Frequency of mononuclear diploid cardiomyocytes underlies natural variation in heart regeneration. *Nat. Genet.* 49, 1346–1353
37. Schoenfelder, K.P. *et al.* (2014) Indispensable pre-mitotic endocycles promote aneuploidy in the Drosophila rectum. *Development* 141, 3551–3560
38. Liu, Y. *et al.* (2019) Root-zone-specific sensitivity of K^+- and Ca^{2+}-permeable channels to H_2O_2 determines ion homeostasis in salinized diploid and hexaploid Ipomoea trifida. *J. Exp. Bot.* 70, 1389–1405
39. Chao, D.-Y. *et al.* (2013) Polyploids exhibit higher potassium uptake and salinity tolerance in *Arabidopsis*. *Science* 341, 658–659
40. Ruiz, M. *et al.* (2016) Tetraploidy enhances the ability to exclude chloride from leaves in carrizo citrange seedlings. *J. Plant Physiol.* 205, 1–10
41. Fawcett, J.A. *et al.* (2009) Plants with double genomes might have had a better chance to survive the Cretaceous-Tertiary extinction event. *Proc. Natl. Acad. Sci. U. S. A.* 106, 5737–5742
42. Storchova, Z. (2014) Ploidy changes and genome stability in yeast. *Yeast* 31, 421–430
43. Chen, J. *et al.* (2018) Polyploid giant cancer cells (PGCCs): the evil roots of cancer. Curr. *Cancer Drug Targets* 19, 360–367
44. Coward, J. and Harding, A. (2014) Size does matter: why polyploid tumor cells are critical drug targets in the war on cancer. *Front. Oncol.* 4, 123
45. Priestley, P. *et al.* (2019) Pan-cancer whole-genome analyses of metastatic solid tumours. *Nature* 575, 210–216
46. Harrison, B.D. *et al.* (2014) A tetraploid intermediate precedes aneuploid formation in yeasts exposed to fluconazole. *PLoS Biol.* 12, e1001815
47. Torres, E.M. *et al.* (2007) Effects of aneuploidy on cellular physiology and cell division in haploid yeast. *Science* 317, 916–924
48. Sheltzer, J.M. *et al.* (2011) Aneuploidy drives genomic instability in yeast. *Science* 333, 1026–1030
49. Zhu, J. *et al.* (2018) Cellular stress associated with aneuploidy. *Dev. Cell* 44, 420–431
50. Sheltzer, J.M. and Amon, A. (2011) The aneuploidy paradox: costs and benefits of an incorrect karyotype. *Trends Genet.* 27, 446–453
51. Selmecki, A.M. *et al.* (2015) Polyploidy can drive rapid adaptation in yeast. *Nature* 519, 349–352
52. Barow, M. and Meister, A. (2003) Endopolyploidy in seed plants is differently correlated to systematics, organ, life strategy and genome size. *Plant Cell Environ.* 26, 571–584
53. Stebbins, G.L., ed (1972) *Chromosomal Evolution in Higher Plants*, Arnold
54. Ohno, S., ed (1970) *Evolution by Gene Duplication*, Springer
55. Otto, S.P. and Whitton, J. (2000) Polyploid incidence and evolution. *Annu. Rev. Genet.* 34, 401–437
56. Otto, S.P. (2007) The evolutionary consequences of polyploidy. *Cell* 131, 452–462
57. Charlesworth, D. and Charlesworth, B. (1987) Inbreeding depression and its evolutionary consequences. *Annu. Rev. Ecol. Syst.* 18, 237–268
58. Hedrick, P.W. (1987) Genetic load and the mating system in homosporous ferns. *Evolution* 41, 1282–1289
59. Soltis, P.S. and Soltis, D.E. (2000) The role of genetic and genomic attributes in the success of polyploids. *Proc. Natl. Acad. Sci. U. S. A.* 97, 7051–7057
60. Zhang, S. *et al.* (2018) The polyploid state plays a tumor-suppressive role in the liver. *Dev. Cell* 44, 447–459 e5
61. Dobzhansky, T. (1964) Biology, molecular and organismic. *Am. Zool.* 4, 443–452
62. Yao, Y. *et al.* (2019) Using digital organisms to study the evolutionary consequences of whole genome duplication and polyploidy. *PLoS One* 14, e0220257
63. Burny, C. *et al.* (2020) Secondary evolve and resequencing: an experimental confirmation of putative selection targets without phenotyping. *Genome Biol. Evol.* 12, 151–159
64. Albertin, W. and Marullo, P. (2000) Polyploidy in fungi: evolution after whole-genome duplication. *Proc. R. Soc. B Biol. Sci.* 279, 2497–2509
65. Shan, S. *et al.* (2018) Application of CRISPR/Cas9 to Tragopogon (Asteraceae), an evolutionary model for the study of polyploidy. *Mol. Ecol. Resour.* 18, 1427–1443
66. Shan, S. *et al.* (2020) Considerations in adapting CRISPR/Cas9 in nongenetic model plant systems. *Appl. Plant Sci.* 8, e11314
67. Hobbs, G.A. *et al.* (2016) RAS isoforms and mutations in cancer at a glance. *J. Cell Sci.* 129, 1287–1292
68. Wolfe, K.H. (2001) Yesterday's polyploids and the mystery of diploidization. *Nat. Rev. Genet.* 2, 333–341
69. Wendel, J.F. (2015) The wondrous cycles of polyploidy in plants. *Am. J. Bot.* 102, 1753–1756
70. Soltis, D.E. *et al.* (2016) Polyploidy: pitfalls and paths to a paradigm. *Am. J. Bot.* 103, 1146–1166
71. Robertson, F.M. *et al.* (2017) Lineage-specific rediploidization is a mechanism to explain time-lags between genome duplication and evolutionary diversification. *Genome Biol.* 18, 111
72. Duncan, A.W. *et al.* (2010) The ploidy conveyor of mature hepatocytes as a source of genetic variation. *Nature* 467, 707–710