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Does resource availability help determine the evolutionary route to multicellularity?

Olivier Hamant[1] | **Ramray Bhat**[2] | **Vidyanand Nanjundiah**[3] | **Stuart A. Newman**[4]

[1]Laboratoire Reproduction et Développement des Plantes, Univ Lyon, ENS de Lyon, UCB Lyon 1, CNRS, INRA, Lyon, France

[2]Department of Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore, India

[3]Centre for Human Genetics, BioTech Park, Bengaluru, India

[4]Department of Cell Biology and Anatomy, New York Medical College, Valhalla, New York

Correspondence
Olivier Hamant, Laboratoire Reproduction et Développement des Plantes, Univ Lyon, ENS de Lyon, UCB Lyon 1, CNRS, INRA, F-69342, Lyon, France.
Email: Olivier.hamant@ens-lyon.fr

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Abstract

Genetic heterogeneity and homogeneity are associated with distinct sets of adaptive advantages and bottlenecks, both in developmental biology and population genetics. Whereas populations of individuals are usually genetically heterogeneous, most multicellular metazoans are genetically homogeneous. Observing that resource scarcity fuels genetic heterogeneity in populations, we propose that monoclonal development is compatible with the resource-rich and stable internal environments that complex multicellular bodies offer. In turn, polyclonal development persists in tumors and in certain metazoans, both exhibiting a closer dependence on external resources. This eco-evo-devo approach also suggests that multicellularity may originally have emerged through polyclonal development in early metazoans, because of their reduced shielding from environmental fluctuations.

KEYWORDS

ecology, genetic heterogeneity, multicellularity

The aim of this article is to examine why certain kinds of multicellular organisms are genetically uniform clones while others are genetically heterogeneous polyclones. Multicellularity and sexual reproduction were major steps in the evolution of life. Among metazoans, multicellular development generally occurs in a clone of cells made up of the mitotic products of a fertilized egg. We call this mode of multicellularity "monoclonal." Consequently, intra-individual genetic differences (apart from those acquired by somatic mutation) are nonexistent or negligible. But because of sexual reproduction, there is a significant extent of interindividual genetic variation. There is another form of multicellular development, in which multicellularity follows from the aggregation of spatially segregated cells. It has been found in six of the seven supergroups of eukaryotes: examples are Dictyostelium and Copromyxa (supergroup Amoebozoa), Guttulinopsis (Rhizaria), Sorodiplophrys (Stramenopiles),

Sorogena and several ciliophora (Alveolata), Acrasidae (Acrasis, Excavata) and Capsaspora and Fonticula (Opisthokonta). We call this mode of multicellularity "polyclonal"; it is plausible that because of their mode of formation, multicellular organisms of this type can be genetic chimaeras with significant intra-individual genetic variation within the group (Sathe et al., 2010).

In contrast to the implications of Buss's theory of evolution and development through intra-individual selection (Buss, 1987; Radzvilavicius & Blackstone, 2018), multicellularity may be viewed as a facultative consequence of interactions between cells of the same or different genotypes, based largely on preadaptations (Nanjundiah, 2016): Multicellular development does not necessarily require monoclonality. Examples include, but are not limited to, polyclonal dictyostelids, polyembryonic insects, experimental intergeneric chimerism in fish and interspecific chimerism in mammals (Newman, 2014). Here we ask what the ecological determinants for the choice between these two modes of multicellularity may be.

Among the various mechanisms that fuel genetic diversification in populations, sexual reproduction is a key driver. The favored trait, in contrast to asexuality, is genetic diversity among the offspring of an individual, which translates to genetic diversity at the population level. Most metazoans reproduce sexually, which suggests that evolution has favoured interindividual genetic heterogeneity over clonal reproduction in populations. Yet, asexual reproduction dominates in some cases. For example, within several metazoan taxa, including sponges, acoelomorphs, annelid worms such as Pygospio, and Sabella, sea stars such as Stephanasterias, free-living flatworms, phytophagous insects, aquatic feeders, lizards, sharks, squamate reptiles, amphibians such as salamanders, the ability to multiply asexually as well, that is to switch between asexual and sexual reproductive modes, is retained (Bell, 1982; Hoshi, 2003; Scheu & Drossel, 2007). Most fungi and plants are also able to reproduce asexually and sexually, although the relation between reproduction modes and resource availability might be different in plants, as they are autotrophic. We thus observe two contrasting scale-dependent situations in metazoans (Figure 1). Genetic heterogeneity is exceptional in the multicellular development of individuals, but because of sexual reproduction, it is widespread in populations. Conversely, because of asexual reproduction during development, genetic homogeneity is common in individuals, but is exceptional in populations. Is there an explanation for this dichotomy?

The switch from asexual to sexual reproduction in populations often involves an environmental cue or stress (Hoshi, 2003). Such cues include resource availability. Typically, soil decomposers, which live in a rich environment, usually multiply asexually. More generally, asexual reproduction is positively correlated with resource abundance, while sexual reproduction is positively correlated with resource scarcity (Scheu & Drossel, 2007). A possible explanation for this behavior lies in the "tangled bank hypothesis": sexual reproduction shuffles alleles and exposes different gene combinations to selection (Bell, 1982). The resulting phenotypic diversity increases the probability that some offspring have an improved chance of survival and reproduction, especially in a challenging environment in which resources are scarce. The benefit of asexual reproduction when resources are abundant is evident: each offspring can reproduce by itself, and if the environmental conditions remain stable, these progenies are genetically well adapted to their habitat. Such a strategy is no longer effective when resources are scarce, because it leads to non-productive competition among offspring (Hardin, 1960). Scaling down and considering a population of cells, does resource scarcity favour genetic diversity via the polyclonal mode of multicellular development? Even though this appears a parsimonious hypothesis, a comprehensive analysis of polyclonal animals and their relation to resources would be required to fully address the question. The dictyostelids provide an interesting illustration.

These organisms have both a unicellular and, triggered by starvation, multicellular, phase in their life cycle. They can reproduce both asexually and sexually, and can exhibit polyclonal development following aggregation (Sathe et al., 2010). At the level of the multicellular unit, genetic heterogeneity can lead to phenotypic complementation (Bonner, 1967) or the means to survive in diverse environments when resources become scarce, or both. A similar logic underlies the argument that heterokaryosis in fungi is a substitute for sex (Haldane, 1955). In *Dictyostelium discoideum*, aggregation follows as a consequence of starvation, but that does not mean all cells aggregate. Some cells remain single and un-aggregated, plausibly because transiently nutrient-poor environments were such that waiting it out until food reappeared was a viable strategy as well (Dubravcic, van Baalen, & Nizak, 2014; Tarnita, Washburne, Martinez-Garcia, Sgro, & Levin, 2015). At the same time, aggregation is a necessary step for meiosis and sexual reproduction in the dictyostelids, consistent with the correlation between sexual reproduction and resource scarcity mentioned above.

Why do polyclonal multicellular organisms fare better in resource-poor environments than monoclonal multicellular organisms or unicellular organisms? The reasoning involves a combination of two factors: the strong likelihood that previously independently feeding (and

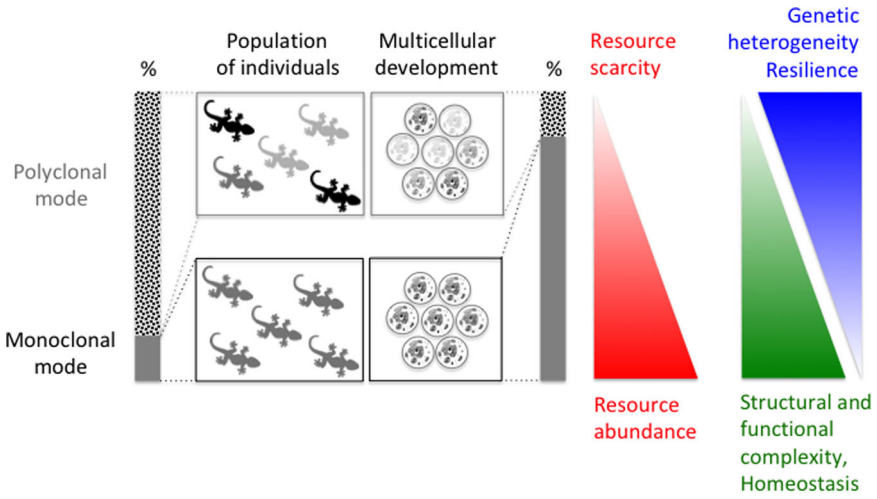

FIGURE 1 Genetic heterogeneity scales to resource availability in metazoans. The vertical bars mark the relative proportions of polyclonal versus monoclonal populations of individuals (left bar) or cells in multicellular organisms (right bar). Genetic homogeneity or heterogeneity in populations of individuals or cells is color-coded by different shades of grey. Resource availability is shown in red. Features of polyclonal versus monoclonal multicellular development are shown in blue and green respectively. In populations of individuals, genetic heterogeneity is prevalent and allows complementary use of scarce resources. In multicellular organisms, genetic homogeneity is prevalent and allows the evolution of complex structures and functions to ensure the homeostasis of the body environment, including the maintenance of abundant resources for cells in a feedback loop. Despite the associated differences in scales, population structures and modes of multicellularity seem to be determined at least in part by resource availability [Color figure can be viewed at wileyonlinelibrary.com]

therefore motile) cells that come together from different places are genetically nonuniform, along with a selective advantage for a facultative multicellular phase (Tarnita, Taubes, & Nowak, 2013).

Assuming that resource scarcity predisposes organisms toward the multicellular mode of development, why would clonal (i.e., monoclonal) development dominate in metazoans (Nanjundiah, Ruiz-Trillo, & Kirk, 2018), which themselves arose evolutionarily from unicellular progenitors? The answer may have to do with resource variation over different spatial scales. We suggest that most metazoans are "resource oases": from the viewpoint of a cell, the body can be compared to a resource-rich environment. Metazoans have indeed developed complex anatomies and behaviours to ensure better feeding and absorption, their body assimilates and concentrates nutrients (when compared to nutrient concentrations in the environment), and they also display multiple homeostatic mechanisms to ensure relatively stable microenvironments within their bodies. In such a resource-rich internal environment, the selection pressure for cells to explore novel niches, and hence to depart from clonal multicellularity would decrease dramatically. Conversely, organisms whose cells depend more on the external environment relative to internal bodily resources would benefit from phenotypic, and hence genetic variability, among the cells.

Complex organs involved in digestion, absorption and utilization of resources, and excretion of waste materials almost invariably consist of arrays of identically polar cells. Because such tissue architectures are largely incompatible with multiclonally aggregated collectives, we would expect to find polyclonal development only among organisms with either no, or very simple, organ systems, but which correspondingly have the latitude to disaggregate (dictyostelids), split in pieces (planarians) or fuse (ascidians). This appears to be borne out.

We thus propose that monoclonal and polyclonal multicellular developmental modes represent two distinct adaptive strategies. In the monoclonal case, body size, integrity, and tissue and organ specificity are strictly controlled. Resource homeostasis can be efficiently enforced, allowing for the benefits of clonal proliferation (robustness of shape and form between individuals and generations, organogenesis) but also carrying with it potential disadvantages (decreased evolvability, i.e., decreased ability to diversify interindividual phenotype/reduced exploration of phenotypic space). In the polyclonal case, body size and integrity are adaptable and also highly variable across individuals and generations. While this hinders the maintenance of a stable resource base (e.g. dictyostelids and planarians slowly reduce in size following starvation), it allows genetically heterogeneous populations of cells to exhibit division of physiological labor in the face of resource scarcity. Such trade-offs between modes of clonality are increasingly reported (e.g., Pineda-Krch & Lehtila, 2004).

The evolutionary scenario we have presented does not preclude mixed monoclonal/polyclonal modes of

development and repair in established species. There is evidence, for example, that what have been assumed to be clonal organisms can in fact be chimeras. The first documented human chimera, Mrs. McK, was identified in 1953 thanks to a test that revealed the presence of two different DNA sets in her blood (Martin, 2007). This condition can arise by aggregation of monochorionic twins in utero and is likely to be under-reported. As noted above, development of the metazoan body plan is tolerant to experimental chimerism across species (Fehilly, Willadsen, & Tucker, 1984) and even genera (Hong et al., 2012). It remains to be seen what degree of polyclonality exists in naturally occurring metazoans. One recently explored case involves planaria, which despite developing via the monoclonal mode following sexual reproduction, also reproduce asexually. The totipotent stem cells in adult animals undergo somatic mutation, establishing stably polyclonal propagative forms (Fields & Levin, 2018). Knowing how prevalent chimeric animals are, or the relative proportions of different genetic identities within an individual, will help further evaluate the relation between the modes of multicellularity and resource scarcity and test its wider applications.

Significantly, the relation between polyclonality and resource scarcity has gained recent prominence in the context of cancer progression. Data from single-cell deep sequencing reveal aggressive tumors as cellular populations in which genomic instability, chromosomal aberrations, and gene mutations result in multiple coexistent heterogeneous phenotypes. As a result, neoplastic populations are subject to both selection pressure as well as neutral evolution (Bhat & Pally, 2017; McGranahan & Swanton, 2017; Nik-Zainal, 2014). Such coexistence of multiple clones (divergent lineages within growing cancers) is increasingly evident in situations in which cancer cells migrate and metastasize, i.e. exist transiently in spatiotemporally fluctuating environments that can compromise survival as a result of heightened immune surveillance and poorer ability to utilize nutrients (Ishiguro et al., 2017; Sodek, Ringuette, & Brown, 2009; Xu et al., 2014). Polyclonal seeds of metastasis have been observed in a wide range of cancers including, but not limited to, in mouse models of breast, pancreas, prostate and small cell carcinoma, and in human patients with metastatic cancers of prostate and ovary. The concurrence of clonal heterogeneity and a temporary quiescence in cell division (also known as dormancy) results in the emergence of organization, stem cell-like behavior, resistance to chemotherapy and a heightened propensity for metastasis (Ip et al., 2016). Upon colonization in a solid tissue environment where they have access to degradable extracellular matrix (Gouirand & Vasseur, 2018) and to enhanced vascular nutrition through neoangiogenesis, cancer cells often revert to being mono- or oligoclonal rather than retaining the complete gamut of diverse phenotypes associated with dissemination. There is experimental evidence for this behavior in ovarian cancer and fibrosarcoma (McPherson et al., 2016; Yamamoto et al., 2003).

We suggest that the correlation between multicellularity modes and resource availability can provide insights into the origin of metazoan multicellularity. While the polyclonal mode is often thought to derive from the monoclonal mode, the former may well be more primitive and precede the latter. In particular, the analysis of development through the lens of "dynamical patterning modules" explains the diversification of body plans without requiring a single-cell "egg" stage (also called the "unicellular bottleneck"; Newman, 2011, 2014). Within the framework of the relation between the mode of achieving multicellularity and resource scarcity, and because early metazoans likely were small and weakly buffered from environmental vagaries, the generalized relation to resource scarcity would also support a primitive origin of polyclonal, over monoclonal, multicellularity in this clade (Nanjundiah et al., 2018).

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

O. H. drafted the initial version of the manuscript, and all authors contributed to the final version and revision of the article.

ORCID

Olivier Hamant http://orcid.org/0000-0001-6906-6620
Ramray Bhat http://orcid.org/0000-0001-6113-4043
Stuart A. Newman http://orcid.org/0000-0002-3569-6429

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