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Editorial: Emerging research organisms in regenerative biology

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Editorial on the Research Topic

Emerging research organisms in regenerative biology

To answer particular biological questions through mechanistic approaches, it seems sensible to adopt accessible and tractable organisms that simplify the experimental work. By electing a species as a model, the interest goes beyond the organism itself and the ultimate goal becomes a better understanding of a more general biological phenomenon. Then, around the chosen organism a scientific community takes shape, and the development of tools and resources comes along. Indeed, many of the established so-called “model organisms” are convenient for studying several aspects of biology but are not necessarily the best systems for others. In addition, when focusing on only one species, mainly if chosen for its lab amenability rather than for a specific trait, any evolutionary consideration should be taken with a grain of salt (Russell et al., 2017).

The field of regenerative biology seems to be a glaring example where the choice of one, or even a fistful of model organisms can limit or even mislead the comprehension of the whole phenomenon. For instance, the uneven distribution of regenerating capabilities across the whole metazoans seems to point toward multiple independent acquisitions, a scenario that is backed up by shreds of evidence against universal conserved cellular and molecular mechanisms behind regeneration (Carlson, 2007). At a finer phylogenetic resolution, the picture is even more complex. Variabilities in terms of regenerative capacity and regenerative mechanisms can be found at the taxonomic level of family, order, and even genus (Sinigaglia et al., 2022). Indeed, since Trembley's dissections of Hydra polyps, which helped to give birth to the field of regenerative biology, the descriptive and mechanistic study of animal regeneration has always been sourced from arrays of different organisms. Particularly T. H. Morgan, through his prominent work on regeneration, first advocated the importance of comparing the amplest diversity of organisms to recast the questions about regeneration and development in terms of experimentally testable hypotheses (Sinigaglia et al., 2022). Following Morgan's legacy, in the last decades, highly regenerating animal models such as a few species of flatworms, *Hydra*, zebrafish and axolotl, have significantly advanced the understanding of the cellular and molecular basis of their regeneration, highlighting both common and different mechanisms. Even more recently, thanks also to affordable sequencing techniques, cutting-edge imaging approaches, single-cell transcriptomics, and epigenetics, new research organisms for regenerative biology have emerged (Blanchoud and Gallio, 2022). Yet, some basic questions remain far from being answered. For instance, *how did regeneration evolve in metazoans, are there conserved cellular and molecular modules?* To better portray the complex evolutionary scenario that characterizes regeneration, it is fundamental to study as many possible organisms, and use their phylogenetic relationships as an interpretative fabric to formulate evolutionary hypotheses. When possible, multiple, closely related species should be compared as a strategy that can direct and facilitate the

search for potentially conserved modules (molecular and cellular toolkits) specific to each regenerative mode. In this issue, Chowdhury et al. compared the regeneration of two established model organisms from the same order of teleost fish but belonging to two different families: zebrafish (*Danio rerio*) and medaka (*Oryzias latipes*). The authors reviewed the different aspects of tissue regeneration and the established experimental tools in the two fish models, highlighting the importance of inter-species and inter-organ comparisons to reveal mechanistic insights for therapeutic strategies for human diseases. Shimizu and Kawasaki implemented such comparisons and used the same two Actinopterygii fishes to analyze the neural stem cell regenerative responses via activation of neural stem cells upon central nervous system injury. Their results revealed reduced neuronal differentiation and induction of pro-regenerative transcription factor expression in medaka when compared to zebrafish, uncovering significant differences in regenerative potential within these teleost species. Shifting to lungfishes, the sister group of tetrapods, Bothe et al. examined general morphological features of appendage regeneration. In their previous work, the same team observed that in salamanders, regeneration abnormalities are more frequently observed in limbs that were bitten in a natural habitat than in those amputated in a laboratory setting (Bothe et al., 2021), and in this issue, by examining regenerated fins resulting from natural bites, they reported also in lungfish various skeletal abnormalities similar to those observed in salamanders, further substantiating the hypothesis of a common origin of fin and limb regenerative abilities in Sarcopterygii. Another good example of the complex evolution of regenerative capabilities is the clade Tunicata, the sister group of vertebrates. This sub-phylum comprises species with limited regenerative capacities and species able to regenerate the entire body through different mechanisms. Their scattered distribution across the well-resolved tunicate phylogeny suggests many gains and losses of regenerative power (Alié et al., 2020). Ricci et al. described the first phases of whole-body regeneration in the tunicate species *Botryllus schlosseri* and pointed out potential differences in regenerative mechanisms with other species belonging to the same genus (Nourizadeh et al., 2021).

Indeed, despite the variety of mechanisms that, in different species, characterize the development of a particular regenerating unit, some similarities and conserved molecular pathways have been found also across relatively distant animals. One fairly conserved process that precedes injury-induced regeneration is wound healing (Fumagalli et al., 2018). Adamska et al. showed via comparative transcriptomics that conserved wound healing-related molecular players, such as FGF and Wnt signaling pathways, are expressed during the initial wound closure of injured colonies of *Acropora millepora* (phylum: Cnidaria Class: Anthozoa). The *Acropora*'s ability to quickly regenerate upon mechanical and chemical damage is probably one of the strategies that made scleractinian corals as widespread and successful as niche-constructing organisms in coral reef ecosystems. Yet, such hypotheses are difficult to be tested and lead to another general and so far unanswered issue in regenerative biology, which is *why some species can regenerate while others cannot*. The question is tightly related to the single or multiple origins of regenerative capacities but it carries a more adaptationist flavor. The advantages of regenerating one part of the body, or the whole organism, may seem pretty evident. Yet, the real challenge is to explore what are the consequences of regeneration

on the survival and/or reproductive fitness of individuals of a particular species. In other words, to test the adaptive role of regeneration, or the loss of it. In this issue, Elchaninov et al. reviewed different hypotheses that try to explain different trends in the evolution of regenerative capacity, putting the emphasis on the cost and benefits that regeneration has for the individual and notably for the species. While studying empirically the adaptive value of regeneration is not an easy task, it most likely requires an understanding of the ecological context in which the given species is in and how the species responds to it. Klein et al. analyzed the effect of common pollutants on the development and regeneration of the Anthozoa *Nematostella vectensis*, showing either inhibition or failure in the tentacle regeneration as well as observing a shifting in the microbiota composition. The observations on microbiota compositions and its role in different aspects of animal development and homeostasis have been a topic of particular interest in the last decades. Díaz-Díaz et al. summarized the recent studies on the relationship between microbiota and the regenerative processes of their hosts, focusing mainly on the potential influence on Echinoderm's regenerative capacity, but also reviewing possible roles of microorganisms during wound healing and regeneration in other models.

Besides the evolutionary and adaptation-driven questions, which demand the study and comparison of many species, there are also other compelling questions in regenerative biology where the use of one model *per se* can help to point out general aspects of regeneration in metazoans. For instance, *to what extent embryogenesis, asexual reproduction, cancer, and regeneration can be seen as different angles of the same phenomenon?* In other words, are the mechanisms of regeneration shared with, or co-opted from, other developmental phenomena? To explore these questions, different levels of comparisons can be done within one single species. For instance, mechanistic connections between uncontrolled cancerous growth, highly regulated embryonic development, and epimorphic regeneration have been theorized since the beginning of the last century by Waddington. More recent literature endorsed Waddington's theory and highlighted striking similarities between wound healing, regenerative phenomena and the progression of some tumors (Flier et al., 2010; Leigh et al., 2018). In this issue, Demirci et al. use the canonical model organism zebrafish to explore molecular mechanisms shared between early stages of brain regeneration, where cell proliferation activity spikes, and two brain cancers. By comparing transcriptomic profiles the authors highlighted early convergence and later divergence in the two phenomena, providing a trampoline dataset to further mechanistic studies and the development of target therapies for vertebrate brain cancers (Demirci et al.).

In conclusion, this issue brings together original findings and reviews on very different aspects of regeneration, and that cover both established and less-established research organisms. The articles above-mentioned underscore the importance of broadening the scope beyond the study of the molecular and cellular processes of regeneration in a single species and also demonstrate the importance of studying imperfect, limited regeneration or even the absence of regenerative abilities in light of phylogenetic and ecological contexts. The current availability of thousands of animal genomes and the techniques allowing molecular studies at the single-cell level should only prompt the proliferation of comparative studies. The inclusion of understudied novel species in the roll of regeneration model

systems becomes a condition *sine qua non* to understanding the many mechanisms behind regeneration and their evolution.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships

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