The Diverse Manifestations of Regeneration and Why We Need to Study Them

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The Diverse Manifestations of Regeneration and Why We Need to Study Them

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For hundreds of years, the question of why some organisms can regenerate missing body parts while others cannot has remained poorly understood. This has been due in great part to the inability to genetically, molecularly, and cellularly dissect this problem for most of the history of the field. It has only been in the past 20–30 years that important mechanistic advances have been made in methodologies that introduce loss and gain of gene function in animals that can regenerate. However, we still have a very incomplete understanding of how broadly regenerative abilities may be dispersed across species and whether or not such properties share a common evolutionary origin, which may have emerged independently or both. Understanding regeneration, therefore, will require rigorously practiced fundamental, curiosity-driven, discovery research. Expanding the number of research organisms used to study regeneration allows us to uncover aspects of this problem we may not yet know exist and simultaneously increases our chances of solving this long-standing problem of biology.

By focusing on a few and essentially randomly selected organisms, the life sciences have become a highly specialized endeavor promising mechanistic understanding to some of the most challenging questions in biomedical research today. And yet, after decades of research and mechanistic studies using a handful of organisms, we are still facing biological problems refusing to yield their secrets. Chiefly among these is the long-standing puzzle—dating back in the Western canon all the way to Aristotle—of the inability of some species to do what others so readily can: the regeneration of missing body parts after amputation.

As age progresses, the human body becomes more vulnerable to degenerative diseases, and its ability to recover from tissue injuries and organ damage are markedly diminished. Characterizing the underlying mechanisms critical for regeneration would be a significant advance to our understanding of biology and the practice of medicine. Compared to other species, many mammals, including humans, display highly specialized and specific modes of regeneration. For example, although humans cannot regenerate appendages such as limbs, we regenerate skin, blood, and liver (Carlson 2005; Michalopoulos 2007; Takeo et al. 2015). In contrast, other vertebrates such as fish and amphibians display much broader regenerative capacities. Studies on zebrafish and salamanders have significantly advanced the field of regeneration (Joven et al. 2019; Marques et al. 2019). These animals can regenerate their appendages, the lenses of their eyes, hearts, and even spine after amputation. Many years of phenomenological, pharmaco-

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logical, and transplantation studies in newts and salamanders laid down a foundation for understanding some of the fundamental principles underpinning regeneration (Carlson 2007). More recently, the adoption of zebrafish (*Danio rerio*) genetics and the introduction of genetic tools into the Mexican salamander (axolotl) have markedly increased our mechanistic understanding of vertebrate regeneration (Poss 2002; Whited et al. 2012; Jewhurst and McLaughlin 2016). Plants also show diverse forms of regeneration on loss or injury of body parts, similar to what is observed in animals. Consider, for example, apical meristem regeneration or the repair of damaged stem surfaces in plants to mammalian digit tip regeneration or skin regeneration (Ali et al. 2020; Storer and Miller 2020). As more cellular, molecular, and genetic data accumulate in many species defining events that favor regeneration, researchers have redoubled efforts not only to understand the fundamental principles underpinning regeneration but also to determine species-specific differences as a way to illuminate its convoluted evolution (Sánchez Alvarado 2012; Brockes 2015; Wang et al. 2020).

DIVERSITY OF REGENERATION RESPONSES

Modern biology frames regeneration as a natural process that is genetically codified and orchestrated by the functions of arrays of transcription factors, metabolites, signaling, and structural molecules. But regeneration remains a stunning, not fully understood biological choreography of maintenance and replenishment. Examples of regeneration abound that include animals as diverse as the tuatara (Alibardi and Meyer-Rochow 2019), crayfish (Cooper 1998), anoles (Hutchins et al. 2014), sharks (Fraser et al. 2020), cockroaches (Nakamura et al. 2008), and alligators (Xu et al. 2020) (see Tables 1 and 2). During regeneration, cells exhibit diverse rates of proliferation, growth, and turnover and follow a complex score dictated by the response of tissues to physiological and environmental demands. The many manifestations of regeneration described thus far in the literature can be categorized into three general classes: periodic, nonperiodic, and constrained.

Periodic Regeneration

Regeneration or replenishment of cells in tissues with constant turnover are examples of periodic regeneration. Exoskeletal shedding in crustaceans, skin shedding in snakes and other reptiles, the regeneration of antlers in deer, mammary gland reconstruction, and the replenishment of the endometrial lining after menstruation in mammals are all notable examples (Goss and Powel 1985; Li et al. 2014; Mykles 2015; Wang et al. 2019a; Fitzgerald et al. 2021). Periodic regeneration helps maintain optimal cell numbers in an organ by replacing dead cells and, in all cases studied thus far, appears to rely on resident populations of stem cells. For instance, antler regeneration in deer and other ungulates (Fig. 1) was believed to be a consequence of localized dedifferentiation of cells. However, grafting of antlerogenic periosteum (AP) tissue in young deer resulted in ectopic antler formation (Gao et al. 2010) and recent analyses have uncovered that the new cells being recruited to regenerate antlers originate from a specialized region of cranial bone known as the pedicle periosteum (PP), which in turn is produced by the progenitor cells of stem cells residing in the AP (Wang et al. 2019a). The capacity for self-renewal of this stem cell population must be extraordinary. The AP is estimated to provide nearly 3.3 million cells to each round of antler regeneration every year, or about 15 kg of tissue mass per year, and throughout the lifetime of the animal (Li et al. 2014; Wang et al. 2019a).

The mammalian endometrium provides an equally compelling example of periodic regeneration. The human endometrium undergoes approximately 450 monthly cycles of proliferation, differentiation, breakdown, and regeneration over a woman's reproductive lifetime (Short 1997). The lining of the human endometrium regenerates within 4–10 days during every menstrual cycle (Ferenczy 1976). Endometrial epithelial stem cells were first identified in hysterectomy tissue as clonogenic cells, comprising 0.22% of single-cell suspensions of $EpCAM^+$ epithelial cells (Chan et al. 2004; Schwab et al. 2005). Xenograft models have also documented the contribution of stem cells to endometrial

Table 1. Examples of vertebrates showing regeneration ability with several tissues listed

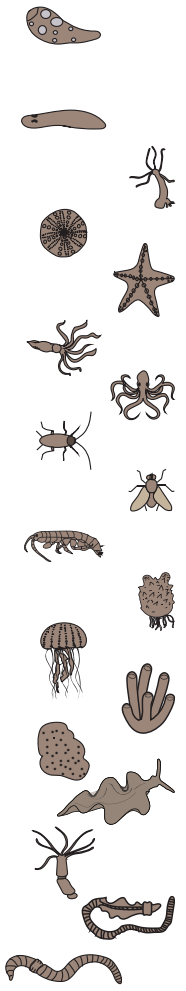
Organism	Regenerating tissue	
Skates	Cartilage	
Alligators	Tail, teeth	
Red deers	Antlers	
Axolotls	Tail, limbs, brain, retina, spinal cord, skin	
Sharks	Teeth	
Tuatara	Tail	
Spiny mouse	Skin	
Newts	Tail, limbs, brain, retina, spinal cord, skin, testis, lungs	
Xenopus	Tail, limbs	
Green anoles	Tail	
Zebrafish	Tail, fin, heart, spinal cord, skin, eye lens	
Mice	Liver, endometrium, digits	
Crayfish	Limbs	
Killifish	Tail, fin	
Fallow deer	Antlers	

regeneration (Masuda et al. 2007). Thus, as in the previous example, the maintenance and cyclical regeneration of this human tissue require the presence of stem cells.

Invertebrates also display periodic regeneration in the form of asexual reproduction. Animals like planaria, cnidarians, and *Botryllus* rely on periodic regeneration to perpetuate themselves. Planarians, for example, undergo fission, a process that leads animals to tear a posterior piece of their bodies (Arnold et al. 2019) that results in anterior and posterior fragments that proceed to restore the missing body parts and ultimately conclude in the generation of two individuals (Fig. 1). For example, cnidarians like hydra and *Nematostella* rely on buds that originate in their gastric regions to reproduce themselves. In hydra, the bud first manifests as a hemispherical outpouching that progressively elongates, becomes cylindrical, and develops tentacles. This outgrowth eventually pinches off to yield a new and independent organism (Holstein et al. 2003). And then there is the colonial ascidian *Botryllus schlosseri*, a close relative of vertebrates, which has the ability to replace every one of its individuals through a weekly budding cycle (Voskoboynik and Weissman 2015). Although stem cells are known to play a role in all of the above invertebrate examples of periodic regeneration, their respective regulation in fission and/or budding remains to be fully understood. Nevertheless, whether

Table 2. Examples of invertebrates showing regeneration ability with several tissues listed

Organism	Regenerating tissue
Protozoan	
Stentor	Whole cell
Invertebrates	
Planarians	Whole body
Hydra	Whole body
Sea urchins	External appendages
Sea star	Whole body
Squids	Limbs
Octopus	Limbs, nerve, part of eyes
Cockroaches	Limbs
Fruit flies	Wing disc
Parhyale	Limbs
Sea squirts	Whole body
Jellyfish	Nerve, internal organs
Sponges	Whole body
Trichoplax	Whole body
Sea slug	Posterior body
Nematostella	Whole body
Acorn worm	Whole body
Earthworm	Whole body



vertebrate or invertebrate, we refer to the type of tissue and or body regeneration that is manifested cyclically and irrespective of frequency as periodic regeneration.

Nonperiodic Regeneration

Regeneration triggered by physical injuries or stress are examples of nonperiodic regeneration. Even though planarians and hydra show periodic regeneration, adverse physical conditions such as amputation and physical injuries can activate a response in which the missing or damaged body parts can be regenerated or restored. Examples of nonperiodic regeneration are the whole-body regeneration displayed by single-cell organisms like Stentor, fragments from planarian, hydra, and ascidians on amputation and appendage regeneration in salamanders and fish (e.g., limbs and fins, respectively) (Morgan

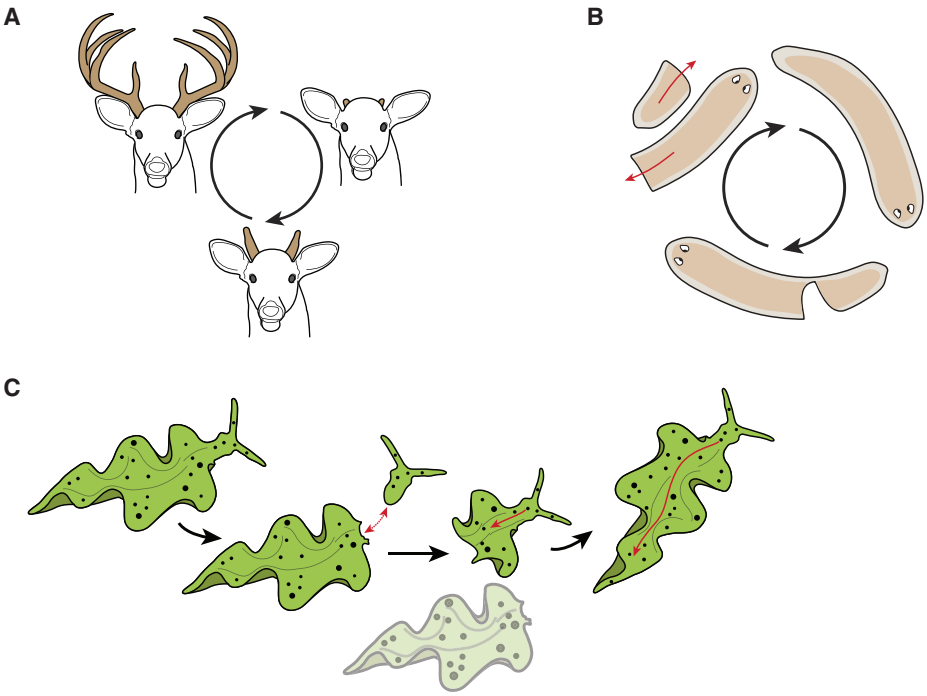


Figure 1. Different forms of regeneration. (*A*) Deer shed their antlers annually and have the ability to regenerate them. This process is mainly aided by pedicle periosteum, the antler stem cells. Deer antler regeneration is an example of periodic regeneration. (*B*) Another example of periodic regeneration is fissioning as exhibited by asexual planarians. Planarians adhere their posterior part to a rigid substrate and break its tail from the rest of the body. The fission fragments regenerate into two separate animals. (*C*) Nonperiodic regeneration is initiated by events that challenge the regeneration ability of the animals. Sea slugs have shown the ability to regenerate their entire posterior body after head amputation. The head grows back the amputated fragment within 20 days.

1901; Gierer 2012; Jeffery 2015; Pfefferli and Jaźwińska 2015; Tang and Marshall 2017; Reddien 2018).

A key attribute of nonperiodic appendage regeneration in vertebrates is the formation of a regeneration blastema, a specialized structure composed of an overlying epithelial layer and underlying mesenchyme (Sánchez Alvarado 2000). For instance, on fin amputation, the epidermis and the connective tissue around the injury site become disorganized, which triggers a local remodeling of the resident fibroblasts and mesenchymal cells to reorganize and form a blastema. The blastema, in turn, undergoes a process of differentiation that eventually results in the formation of the lost fin ~20–30 days after the initial amputation (Pfefferli and Jaźwińska 2015; Wang et al. 2020). As seen in vertebrates, blastemas are also observed in invertebrate nonperiodic regeneration. Planaria and the hemichordate *Ptychodera flava* form the specialized structures after amputation. In both cases, a wound epidermis forms, followed by the accumulation beneath the epithelium of mesenchyme-derived cells (Gurley and Sánchez Alvarado 2008; Luttrell et al. 2016). Yet, not all nonperiodic regeneration occurs by first forming a blastema. In vertebrates, heart, liver, brain, and lens regeneration do not develop canonical blastemas (Eguchi et al. 2011). And whole-body regeneration in hydra also proceeds in the absence of this specialized structure.

Irrespective of whether or not a blastema forms after amputation, most of the above examples of regeneration involve the participation of either stem or progenitor cells. For instance, both hydra and planarians are aided by specialized stem cell populations that meticulously car-

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ry out their whole-body regeneration (Sánchez Alvarado and Kang 2005; Reddy et al. 2019). In hydra, three major cell lineages with varying rates of self-renewal activity (ectodermal, ectodermal, and interstitial cells) are responsible for regeneration in this organism (Govindasamy et al. 2014; Siebert et al. 2019; Vogg et al. 2019). And in planarians, adult stem cells known as neoblasts maintain the high regenerative ability of these animals (Zeng et al. 2018). In the case of vertebrates, particularly in animals in which organs like the brain and liver can regenerate, adult stem or progenitor cells in the vicinity of these wounded organs play a vital role in their repair. For example, in zebrafish ablation of dopaminergic *tyrosine hydroxylase* 2 (*th2*) neurons in the hypothalamus prevents fish from swimming. The proliferation of a progenitor population in the hypothalamus not only restores the cells but also the swimming behavior of the injured fish (McPherson et al, 2016).

Yet, exceptions exist in which stem and/or progenitor cells are not invoked to regenerate missing body parts but rather through dedifferentiation, a process by which cells within injured tissue lose the expression of critical genes necessary for the function of that particular cell type. This functional reduction is thought to reprogram the cells, facilitating proliferation or differentiation to other cell types (transdifferentiation) in support of tissue regeneration. Newt lens, tail, and limb have been shown to undergo dedifferentiation during regeneration (Eguchi et al. 1974; Lo et al. 1993; Echeverri 2002). Another fascinating animal exhibiting nonperiodic regeneration is the sea slugs. They have shown exceptional posterior regeneration on head amputation (Mitoh and Yusa 2021). In sum, nonperiodic regeneration is often triggered by injury or amputation, includes blastemal- and nonblastemal-based regeneration, and the deployment of stem cells or the activation of either dedifferentiation of preexisting cells to restore missing body parts.

Restricted Regeneration

Regeneration can also be restricted to defined periods of development or specific life cycle stages. Restricted regeneration has been observed in mammals, where cardiac regeneration does not occur in adults but can be efficiently sustained in neonates following apical resection and myocardial infarction up to 2 days after birth (Porrello et al. 2011; Wang et al. 2019b). Integration of gene expression profiles with histone marks associated with active or repressed chromatin uncovered differences between the transcriptional programs underlying neonatal heart regeneration and the heart's response to injury and inability to regenerate later in life. Among these differences were a unique immune response and the retention of embryonic cardiogenic programs during neonatal heart regeneration (Wang et al. 2019b).

Amphibians are also known for displaying restricted regeneration (Fig. 2). For instance, and unlike newts and salamanders, the tails of *Xenopus* tadpoles can only regenerate at defined stages of larval development (Godwin and Rosenthal 2014; Amaya 2016) and display a regeneration incompetent or refractory period between stages 45 and 47 (Beck et al. 2003). This is in marked contrast to the regenerative capacities of other amphibians like newts and axolotls, even though the *Xenopus* tadpole tail is composed of similarly discrete cell types that form spinal cord, notochord, dorsal aorta, and skeletal muscle cells. However, the behavior of *Xenopus* tadpole cells in response to amputation is conspicuously different from what is observed in newts and axolotls (Gargioli and Slack 2004; Mochii et al. 2007). Ependymal cells, for example, which are required for the regeneration of the spinal cord, differ in their gene expression profiles between *Xenopus* and salamanders (Chernoff et al. 2018). Hence, the study of such clearly defined developmental restrictions to regenerative abilities in animals may help shed some light on understanding what may or may not make a tissue or animal competent to launch a regenerative response after injury.

REGENERATION IN PLANTS: A FACET OF THE SAME OR AN ALTOGETHER DIFFERENT PROCESS?

Plants also display remarkable powers of regeneration (Fig. 3; Birnbaum and Sánchez Alvarado 2008). Compared to animals, regeneration appears to be both broadly and evenly distributed

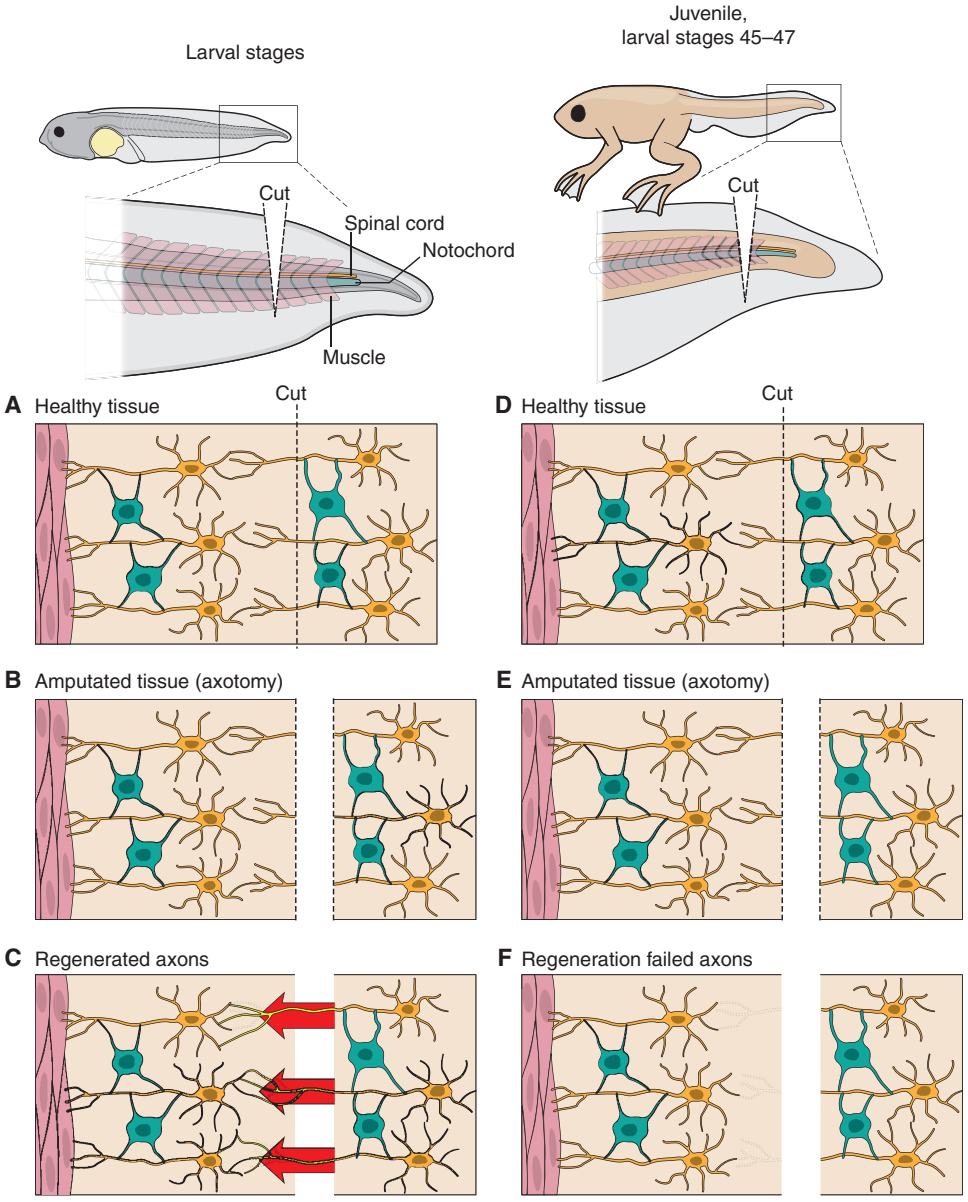

Figure 2. Restricted regeneration. Few known animals showcase regenerative ability only during a specific period of their life cycle. *Xenopus* exhibits regeneration ability throughout their larval stage except for a period between stages 45 and 47. The illustration depicts the regenerative capacity of *Xenopus* larvae after axotomy. (*A–C*) *Xenopus* larvae are subjected to axotomy, and the animals can regain their lost neurons within 21 days of amputation. (*D–F*) These larvae have a refractory period between stages 45 and 47, during which they cannot exhibit regeneration. Axotomy performed in these animals failed to regenerate new neurons. Yellow cells, axons; green cells, glial cells.

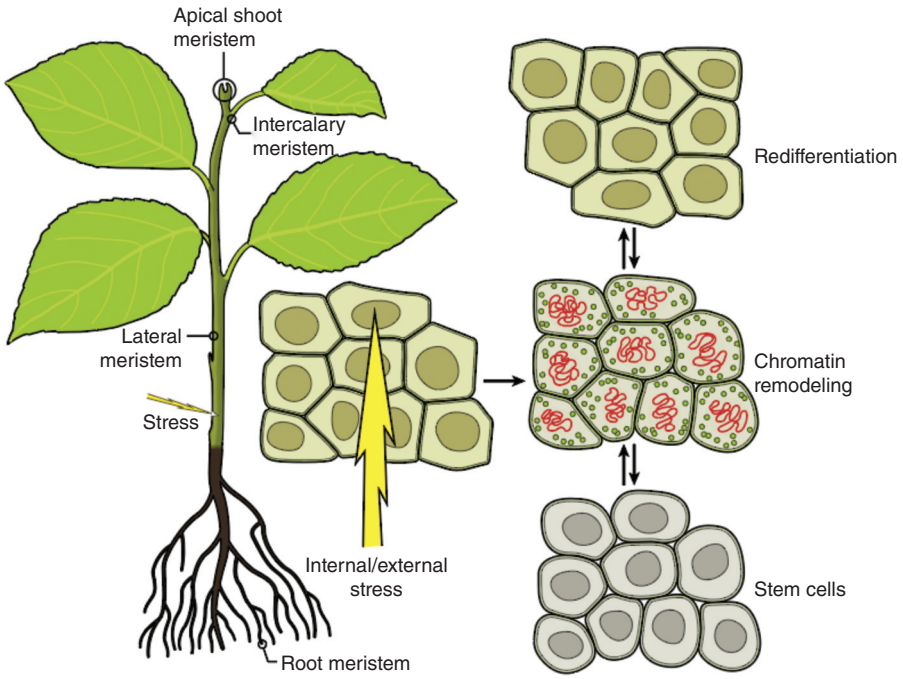

Figure 3. Plant regeneration. Plants rejuvenate themselves throughout their lifecycle. The plant stem cell population is mainly camped at the growing tips, such as shoots, roots, cambium, etc. These growing tips have a specialized tissue known as meristem, which houses all the stem cells. Meristem is mainly made up of stem cells, which have shown the potential to differentiate any cell type in plants. Plants also exhibit a notable ability to reprogram somatic cells into stem cell–like cells when subjected to stress.

across the plant kingdom. Plants display both periodic and nonperiodic regeneration. The seasonal shedding and regeneration of leaves in deciduous tree species and the regeneration of whole plants from small collections of cells are, respectively, examples of these two general modes of regeneration. Plants harbor specialized tissue known as meristems, which are made up of undifferentiated cells capable of undergoing cell division and further differentiation (Su et al. 2011). Meristems are responsible for the periodic regeneration of leaves. Leaf formation is initiated by the recruitment of a cohort of cells flanking shoot apical meristems, and its organogenesis depends on the functions of distinct meristems established and spatiotemporally differentiated after the initiation of leaf primordia (Ichihashi and Tsukaya 2015). The jaw-dropping diversity and natural variation of leaf morphology seen in plants is a consequence of how genes and their networks modulate leaf meristems.

Meristems paved the way to the discovery of a type of nonperiodic regeneration in plants known as somatic embryogenesis (Guan et al. 2016; Méndez-Hernández et al. 2019). Somatic embryogenesis is an artificial process in which a plant or embryo is derived from a single somatic cell. The process involves culturing cells in the presence of plant growth factors/hormones such as auxin and cytokinins (Schaller et al. 2015) to trigger their proliferation to yield embryogenic cultures, which can then be matured into plants or plant organs (Zimmerman 1993; Hazubska-Przybył et al. 2020). Another type of nonperiodic regeneration that can be elicited in plants is de novo organogenesis, which can result in the regeneration of an entire plant—including meristems—from a very tiny piece (Pulianmackal et al. 2014; Ikeuchi et al. 2016). Such high potential regenerative ability is what has allowed humans to clonally propagate plants via cutting and grafting.

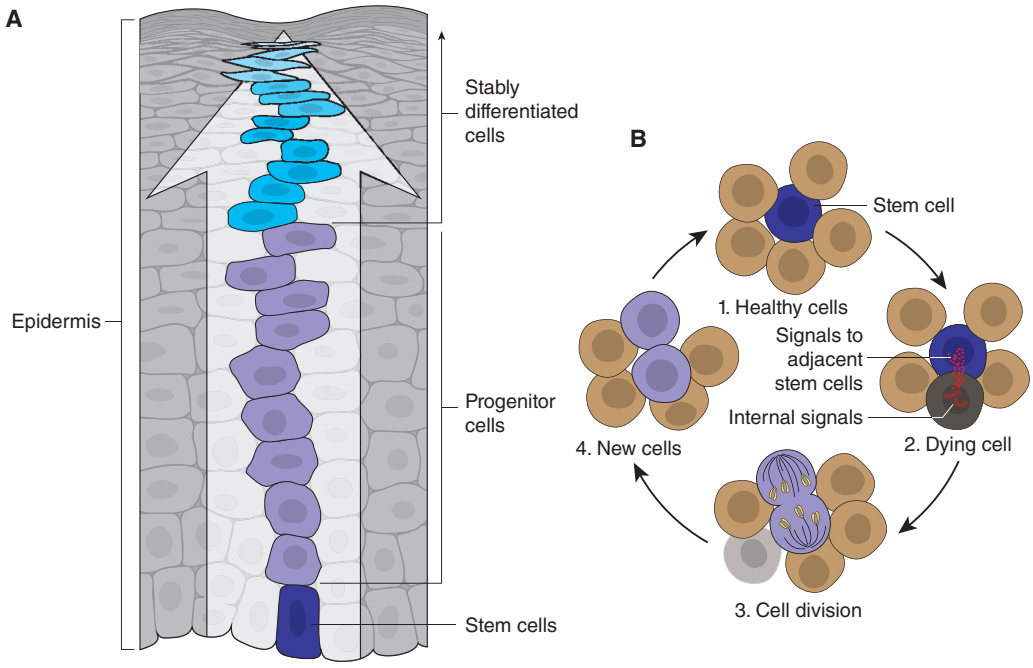

Figure 4. Cellular and molecular signaling leading to regeneration. (*A*) Skin protects the organism from various abiotic stress factors such as ultraviolet rays (UVs), pathogens, climatic changes, etc. They form a protective layer for the organism; hence their renewal is of utmost importance. The illustration depicts the transition of a stem cell located in the basal epidermis to a stably differentiated cell while passing through different epidermis layers. These epithelial stem cells keep replacing injured/dead skin cells aiding the re-epithelialization process. (*B*) A stem cell niche always provides a microenvironment for stem cells to proliferate, differentiate, or maintain their stemness. They also hold strict control over the number of stem cells present. Apoptotic signals from a dying stem cell trigger the neighboring stem cells to divide and fill in the void created by the dying cells.

Given the remarkable technological advances to measure both genetic and epigenetic changes at great levels of granularity and in thousands of cells simultaneously, we expect that vigorous comparisons between plants and animals will provide critical insights that may significantly help unlock the potential of organisms to repair themselves.

DIVERSITY OF CELLULAR RESPONSES TO REGENERATION ACROSS RESEARCH ORGANISMS

Just as diverse modes of regeneration exist across the plant and animal kingdoms, so are the variety of cellular responses that underpin them (Fig. 4). Periodic, nonperiodic, and restricted regeneration involve the replacement of injured cells with healthy ones (Tanaka and Reddien 2011). How such replacement occurs may involve the production of new cells from dividing stem and/or progenitor cells, dedifferentiation from other cell types, or via transdifferentiation of existing somatic cells (Jopling et al. 2011). In addition to these, cell migration can also aid in wound healing and tissue regeneration (Palmberg 1986). Below are but a few notable examples of the cellular strategies known to be deployed during regeneration.

Mammals

Many of the cellular behaviors invoked by regeneration are readily manifested in epidermal and epithelial tissues. Organs that are regularly interacting with the outside world such as the skin, intestine, and lungs, possess dynamic cellular composition. In all cases, participation of

stem and progenitor cells, de- or transdifferentiation, and cell migration have been shown to play roles in periodic and nonperiodic regeneration. In vertebrates, the multilayered skin is considered one of the most complex organs that can regenerate. However, periodic and nonperiodic skin regeneration varies from species to species (Blanpain and Fuchs 2009; Chang et al. 2009). The mammalian skin, for example, primarily possesses two kinds of stem cells responsible for maintaining skin integrity: epidermal and melanocyte stem cells (Blanpain and Fuchs 2006). Epidermal stem cells populate the skin's basal layer and divide asymmetrically, giving rise to stem cells and multipotent transit-amplifying cells that further divide and differentiate to form keratinocytes (Koster 2009). On the other hand, melanocytes reside in the basal region of hair follicles, where they remain primarily quiescent. Wounding triggers the migration of melanocyte stem cells from their resting place to basal epidermal regions, where they differentiate into epidermal melanocytes (Botchkareva et al. 2003; Cichorek et al. 2013). Although wounding of the skin in the house mouse (*Mus musculus*) and humans results in scars, nonperiodic, injury-induced regeneration in rodents like *Acomys* sp. is mostly devoid of scarring, suggesting that even between mammalian species there are likely to exist marked differences in how stem cells are regulated to effect regenerative capacities (Seifert et al. 2012; Denis et al. 2013; Richardson et al. 2013).

The maintenance and restoration of epithelia in vertebrate intestine and lungs share with skin the presence of specialized stem cells. In the mammalian intestine, a dedicated, active stem cell population exists for the periodic regeneration of the gut epithelium (Kim et al. 2017), whereas a quiescent or reserve stem cell population is deployed when the active intestinal stem cell population is perturbed or reduced in numbers (Bankaitis et al. 2018). Lineage tracing studies have shown that both cell populations can self-renew and differentiate into other cell types present in the intestine (Barker and Clevers 2010; Buczacki et al. 2013; Yan et al. 2017; Santos et al. 2018). Lung epithelial cells also undergo physiological turnover and, when injured, can be regenerated. The epithelial cells of the alveolar sacs consist of "alveolar type 1 cells" (AT1) and "alveolar type 2 cells" (AT2) (Gonzalez and Dobbs 2013; Schilders et al. 2016). Damage to the AT1 lineage cells activates rapid proliferation in the AT2 cell population, which later transdifferentiates into AT1 cells, hence repairing the damaged tissue lineage (Olajuyin et al. 2019). And in extreme cases where both AT1 and AT2 cell populations are equally affected, a stem cell/progenitor cell population known as the alveolar epithelial progenitors (AEPs) is recruited to aid in the repair process. These cells maintain a constant number during developmental alveologenesis, are widely distributed in the lung airways and are also a part of the AT2 cell lineage (Zacharias et al. 2018).

Other Vertebrates

Whereas most mammals are unable to grow back their skeletal frames, amphibians and cartilaginous fishes can. On appendage amputation, the somatic cells of urodele amphibians like newts and salamanders undergo reprogramming, followed by proliferation and eventual differentiation of the resulting progenitor cells into the lost tissues of the limb, including skeletal structures. For many years, it was noted that the blastema was composed of a homogenous population of dedifferentiated cells. Recent single-cell RNA sequencing (scRNA-seq) and lineage tracing studies suggest that dedifferentiated blastema cells do not abandon their original cell lineage (Tanaka 2003; Tamura et al. 2010; Tanaka et al. 2016; Zielins et al. 2016). In other words, during limb regeneration, new muscle cells are made from preexisting postmitotic, multinucleated muscle fiber cells, which form mononucleate progenitor cells that undergo mitosis to become a part of the blastema. Like connective and bone tissues, other cell types also undergo a similar process (Tanaka et al. 2016).

Cartilaginous fishes like skates use cartilage to build their skeletons, which provides their body structure and facilitates movement. In general, most animals lose their ability to rejuvenate their cartilages on aging (Decker 2017),

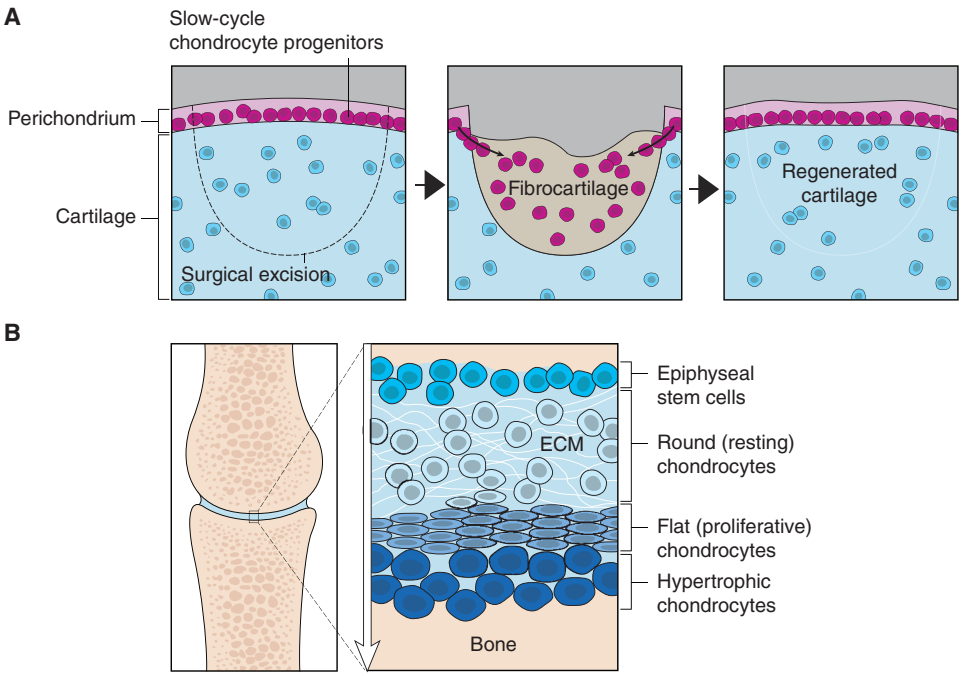

Figure 5. Cartilage regeneration in vertebrates. Cartilage regeneration is shown by various model organisms differently. (*A*) Recent study of skate cartilage regeneration sheds more light on the perichondrial progenitor population that assists in the process. A small portion of the cartilage was surgically removed to study the regeneration process. By 2 months, the wounds were filled in by fibrous connective tissue, and during the following months these tissues started to slowly differentiate into cartilage-like tissue. They were able to complete regeneration by the end of 12 months postsurgery. (*B*) Mammalians show a different approach to replenish their cartilage. The growth plate in mammalians is composed of a specialized stem cell known as epiphyseal stem cell. In the postnatal developmental phase, they undergo a series of differentiation processes to maintain the chondrocyte population, which supports the bones' smooth mechanical function and growth. These stem cells pass through three different cell stages to reach their destination: round (resting) chondrocytes, flat (proliferative) chondrocytes, and hypertrophic chondrocytes. The hypertrophic chondrocytes either undergo apoptosis or dedifferentiate into osteoblasts. (ECM) Extracellular matrix.

but skates retain a lifelong potency to replenish cartilage cells (Marconi et al. 2020). Tissue turnover in cartilage is undertaken by constant cellular arrangement and increases in chondrocyte cell populations. A recent study on skate cartilage regeneration showed the presence of slow cycling chondrocyte progenitor cells residing in the inner perichondrium (Fig. 5). Surgical studies also revealed the order of cell proliferation and differentiation during cartilage regeneration. On injury/amputation, the first response is to fill in the wounded site using fibrous connective tissue consisting of progenitor cells, which eventually differentiate into cartilage. These findings uncovered a correlation between the persistence of cartilage progenitor cells and chondrogenesis and their ability to replenish/repair injured cartilage. Recent studies on growth plate cell renewal in mice have shown the existence of epiphyseal stem cells (skeletal stem cells) that replenish the chondrocyte cell population and aids in bone repair and elongation (Chagin and Newton 2020). Such findings suggest that the cellular strategy used by skates to regenerate skeletal structures may be conserved in mammals.

Amphibians also display other equally remarkable cellular strategies to restore missing

body parts. During lens regeneration in the urodele amphibians, the ventral pigment epithelial cells residing in the dorsal iris lose their pigmentation and change shape (Suetsugu-Maki et al. 2012). The respecification of these cells is followed by the transformation of once epithelial cells into a lens vesicle and subsequently into a mature lens. This cellular mechanism is known as transdifferentiation, a process where a somatic cell from a specific lineage transforms into a mature somatic cell type of another lineage (Jopling et al. 2011).

Another cellular strategy recently uncovered in amphibians during the restricted regeneration of *Xenopus* tadpole tails is the use of a novel cell type referred to as regeneration-organizing cell (ROC) (Aztekin et al. 2019). ROCs are localized in the epidermis of healthy *Xenopus* larval tail; on injury or amputation, they migrate to the wound site and form a significant component of the wound epidermis. Depletion of ROC populations by genetic or chemical methods can perturb regeneration potential in *Xenopus* larvae. Grafting of ROCs to ROC-depleted regions of a host embryo was able to induce ectopic tail/ fin-like structures, indicating that ROCs carry instructive signals that cause growth in developmental and regenerating *Xenopus* tails.

Invertebrates

The extraordinary ability of many invertebrates to regenerate appendages (Das and Durica 2013; Joven et al. 2019) and complete organisms from small body fragments has been and continues to be an active area of research. To date, the study of regenerative capacity in animals such as planarians, hydra, and colonial ascidians, for example, has largely focused on signaling mechanisms near the injured tissue required for stem cell proliferation and differentiation following injury (Sánchez Alvarado 2007; Gurley and Sánchez Alvarado 2008; Handberg-Thorsager et al. 2008; Bergmann and Steller 2010; Sato et al. 2011; Beumer and Clevers 2016). For instance, the stem cells of planarians, known as neoblasts, have been under intense scrutiny. Neoblasts are small, mostly oval cells with a high nuclear cytoplasm ratio, numerous and broadly distributed in the animals except for the area in front of the photoreceptors and the pharynx (Newmark and Sánchez Alvarado 2000). The ability of neoblasts to migrate, repopulate, and differentiate into an entire range of cell types/organs upon injury make these cells a unique and experimentally accessible adult pluripotent stem cell (Aboobaker 2011; Baguñà 2012; Guedelhoefer and Sánchez Alvarado 2012). The relative abundance of neoblasts underscores their complex transcriptional heterogeneity, which has recently been revealed by scRNA-seq and single-cell transplantation studies (Zeng et al. 2018; Raz et al. 2021).

Although much knowledge has been accrued on the role of stem cells (including neoblasts) in regeneration, little is known about how differentiated cells may contribute to whole-body regeneration and the role that these cells may play in regulating stem cells and their immediate progeny. A recent, comprehensive single-cell reconstruction of whole-body regeneration has revealed the cellular dynamics of successful and unsuccessful regeneration across an entire animal for the first time (Benham-Pyle et al. 2021). This approach determined cellular states dependent on stem cell proliferation and identified genes enriched in amputation-induced states required for tissue regeneration and remodeling of preexisting tissues.

Notably, amputation-specific cell states were identified in derivatives of all three planarian germ layers. In all cases, amputation-specific cell states arose in the absence of cell divisions, amounted to less than 1% of captured cells, and were only a subset of cells within their respective tissues. These results indicate that regenerative capacity may depend on the ability of an organism to produce rare, transient, and functionally distinct cell states within a subset of differentiated tissues after injury. Such states have been termed transient regeneration-activating cell states (TRACS). Altogether, the data support a model in which regenerative capacity may be linked to transcriptional plasticity in differentiated cells distributed across multiple tissue lineages. If generally applicable, reactivation or transient restoration of regeneration-activating

cell states could unleash regenerative capacity in systems in which such abilities are presently limited (Benham-Pyle et al. 2021).

Plants

The past two decades have yielded an unprecedented understanding of the cellular mechanism activated during plant regeneration (Ikeuchi et al. 2016). Stem cells in plants play an essential role during postembryonic development. Plants maintain and regulate their stem cells in meristems. These specialized structures are distributed at distinct locations in mature plants such as the apical shoot, root, cambium, and phellogen (Morus et al. 2014). Unlike animal cells, plant cells cannot migrate, and because plants do not have resident stem cells in every part of the plant anatomy that could be exposed to damage, plants possess the ability to reprogram most somatic cells into stem cell-like cells by switching cell fates via redifferentiation. As in animals, extrinsic and intrinsic signals mediate these reprogramming processes, forcing them to exit their differentiated state to transform and acquire new ones. Studies on the effect of stressors on plant regeneration, such as temperature, salinity, osmotic changes, and droughts, have provided intriguing details on the reprogramming abilities of plant somatic cells (Florentin et al. 2013). Somatic plant cells undergoing stress readily recondense their chromatin in ways that are indistinguishable from those seen in adult stem cells. This response forces cells to reenter the cell cycle and is followed by a defined transcriptional output that allows cells to differentiate into multiple cell types (Grafi et al. 2011). Given the fundamental conservation of chromatin components between plants and animals, plants' mechanisms to reprogram their differentiated somatic cells may also be shared with organisms populating the animal kingdom, including humans.

In sum, a great diversity of complex cellular strategies exists in multicellular organisms involving both undifferentiated and differentiated cells to effect regeneration. Some are highlighted here, yet it is more than likely that many others remain undiscovered and that revealing them will be greatly facilitated by interrogating the many plant and animal species that presently remain understudied and thus greatly underappreciated.

IS REGENERATION DIVERSITY UNDERSCORED BY SHARED MOLECULAR MECHANISMS?

The list of organisms known to regenerate, and the number and variety of species currently being subjected to genetic, cellular, and molecular interrogation continue to grow. The molecular dissection of periodic, nonperiodic, and restricted regeneration has followed the general guiding principle of determining what role known effectors of embryonic development may play during regeneration. For instance, multiple signaling molecules are now known to regulate whole-body regeneration in planarians (Gurley et al. 2008; Forsthoefel and Newmark 2009; Reddien 2018), and similar molecular mechanisms are conserved in other species. Secreted molecules like wingless (wnt), bone morphogenetic proteins (BMPs), and fibroblast growth factors (FGFs) play critical roles in orchestrating tissue homeostasis and regeneration across species (De Robertis 2010; Bastakoty and Young 2016; Brandão et al. 2019; Houschyar et al. 2019). FGFs are also known to work synergistically with other signaling molecules such as Sonic hedgehog (Shh), vascular endothelial growth factor (VEGF), and BMPs (Nacu et al. 2016; Rodrigues et al. 2017; Turwankar and Ghaskadbi 2019; Vieira et al. 2019). The apparent ubiquity of FGF signaling has received particularly close attention. FGFs have now been shown to play roles in limb, tail, fin, lens, liver, digit regeneration, and skin, intestinal, and lung repair (Mullen et al. 1996; Makanae et al. 2014; Maddaluno et al. 2017). Additionally, FGFs play central roles in the regeneration of cerebellar structures in zebrafish embryos (Koster and Fraser 2006) and in facilitating the regeneration of injured spinal cords in zebrafish (Goldshmit et al. 2012).

Peptides and small molecules have also been implicated in regenerative processes. Head regeneration in hydra is supported by a group of peptides known as head activator peptides. These peptides activate/modulate the CREB nu-

clear transcription factor activity, resulting in the regeneration process's activation (Galliot et al. 1995; Kaloulis et al. 2004). Additionally, activation of mitogenic activity in somatic tissues has been shown for the neuropeptides substance P and neurokinin A. These peptides modulate planarian whole-body regeneration (Baguñà et al. 1989; Collins et al. 2010), and neurokinin A has also been shown to stimulate limb regeneration in newts (Smith et al. 1995; Choi et al. 2017; Sinigaglia and Averof 2019). The list of neuropeptides involved in regeneration continues to grow. In planarians, neuropeptide F and Y families stimulate stem cell proliferation and central nervous system (CNS) regeneration (Collins et al. 2010). Neuropeptides also participate in the modulation of the germ cell niche in planarians and *Drosophila*.

Roles in regeneration for small molecules like retinoic acid (RA) and steroidal hormones have also been reported. Reporter-mediated studies have shown the expression of RA receptors during nerve damage to promote repair (van Neerven and Mey 2007; Puttagunta and Di Giovanni 2011), implicating RA in the regeneration of damaged axons. Hormones such as ecdysteroids in arthropods have been shown to play essential roles in limb regeneration. Fiddler crabs exhibit controlled circulation of ecdysteroids during different limb regeneration stages (Hopkins 2001). If higher doses of this steroid are provided, limb regeneration in these organisms is impeded. Also, RNAi experiments on ecdysteroid receptors showed reduced cell proliferation during regeneration, resulting in blastemas with stunted growth (Das and Durica 2013; Sagi et al. 2013). In mammals, organs undergoing periodic regeneration, such as the mammary glands, are regulated by hormones. Estrogen, progesterone, prolactin, oxytocin, etc., play a role in converting nonmammary cells to mammary epithelial cells (Boulanger et al. 2015). In cooperation with gonadotrophin-releasing hormones from the hypothalamus and follicle-stimulating hormone from the pituitary gland, these hormones stimulate the mammary gland morphogenesis during the pre- and progestation period (Brisken and O'Malley 2010).

More recently, roles in regeneration for the broadly evolutionarily conserved small RNA molecules known as microRNAs (miRNAs) have been reported. miRNAs are small 20–24-nt-long, single-stranded RNAs, which posttranscriptionally regulate the translation of mRNAs to finely balance cellular and molecular responses (O'Brien et al. 2018). Presently, miRNAs have been implicated in recovering injuries of multiple tissues such as the spinal cord, liver, heart, and muscle (Nakasa et al. 2010; John et al. 2014; Zhu et al. 2016; Almurshidi et al. 2019). miRNAs are known to regulate a broad gamut of activities from cell proliferation to lineage-specific differentiation (Lee et al. 2016; Shim and Nam 2016). For example, in the mammalian liver, regeneration of this organ after injury revealed a role for miRNAs during the dedifferentiation of hepatocyte cells (Lauschke et al. 2016). Functional knockdown studies of the identified miRNAs led to metabolic and tumorigenic defects (Hsu and Ghoshal 2013). miRNAs also play a role in planaria regeneration in which it has been shown by RNAi knockdown studies that miR-124 plays an important role in head regeneration and neural wiring (Sasidharan et al. 2017).

In summary, organisms from multiple phyla and covering large tracts of evolutionary distance appear to rely on a set of conserved genes and molecules to execute regeneration. This is quite puzzling, as such profound conservation of components is present in both regenerating and nonregenerating organisms. Therefore, much remains to be understood. First, do we have a complete parts list for regeneration, or are there other processes that are not readily manifested in the species studied thus far that remain to be identified? Importantly, how do the parts we have identified thus far are put together in response to injury such that regeneration can occur?

ARE THERE FIRST REGULATORY PRINCIPLES UNDERPINNING REGENERATION?

How cells respond and adapt to environmental changes depends on a complex integration of

inputs and outputs of differing durations, intensities, and frequencies. Such responses include the activation of gene expression, which allows organisms to produce the necessary molecular agents (proteins, RNAs, metabolites) to execute the function. A vital component of this complex machinery is the interaction between transcription factors and *cis*-regulatory DNA elements, which in the case of regeneration, are required to initiate the repair and restoration of damaged cells, tissues and organs. Stretches of DNA known as enhancers and dispersed in the genomes of organisms are among these *cis*-regulatory DNA elements. Enhancers are essential in mobilizing gene expression spatiotemporally during development and in response to changes that perturb organismal homeostasis. The presence and activation of enhancers have been implicated not only in organogenesis but also in regeneration. Enhancers that were first identified as responsible for driving the formation of limbs in embryos (Lettice et al. 2002; Rodriguez and Kang 2020) were later shown to be involved in limb regeneration (Suzuki et al. 2018). Similar activities have also been shown for epicardial enhancers that are active during heart development and injury response in mice (Huang et al. 2012).

Changes in *cis*-regulatory elements are a significant source of morphological diversity, and recent evidence indicates that injury-responsive enhancer elements may control injury-dependent gene expression. However, ablations of these previously characterized elements from zebrafish (*D. rerio*) and *Drosophila* have shown that they are generally dispensable for regeneration (Kang et al. 2016; Harris et al. 2020; Thompson et al. 2020). Therefore, whether conserved regeneration-responsive and/or injury responsive elements exist in vertebrate genomes, and how they may have evolved are both matters that remain to be satisfactorily resolved. Using a comparative approach, recent work has identified a cohort of regeneration-responsive enhancers (RREs) in both zebrafish and the African turquoise killifish *Nothobranchius furzeri*. Deletion of a killifish RRE significantly perturbed caudal fin regeneration and abrogated cardiac regeneration altogether. The existence of RREs allows the postulation of a model for the loss of regenerative capacities during evolution. In this model, the ancestral function of RREs was to activate a regenerative program in response to both injury and regeneration without distinction. Through the course of evolution and speciation, regeneration and injury responses became dissociated from each other in some but not all enhancers. In some species, regeneration competent animals maintain the ancestral enhancer activities to activate both injury and regeneration responses. In contrast, in regeneration incompetent animals, repurposing of ancestral enhancers may have led to the retention of injury response activities but to the loss of the regeneration response.

CONCLUSIONS

The study of new species and the mechanistic dissection of their respective biological properties is indispensable to our understanding of regeneration (Tables 1 and 2). This will require rigorously practiced, fundamental, curiosity-driven discovery research. By expanding the number of research organisms and studying their biology, our chances of solving the long-standing problem that is regeneration is dramatically improved.

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