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The journey of cells through regeneration

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The process of building an organ, appendage, or organism requires the precise coordination of cells in space and time. Regeneration of those same tissues adds an additional element of complexity, emerging from the chaos of disease or injury to build a mass of progenitors from mature tissue. Translating insights from natural examples of tissue regeneration into engineered regenerative therapies requires a deep understanding of the journey of a cell directly following injury to its contribution to functional, scaled replacement tissue. Here we step through the chronological phases of regeneration and highlight emerging work that brings us closer to elucidating the unique intrinsic and extrinsic properties of cells during epimorphic regeneration.

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Introduction

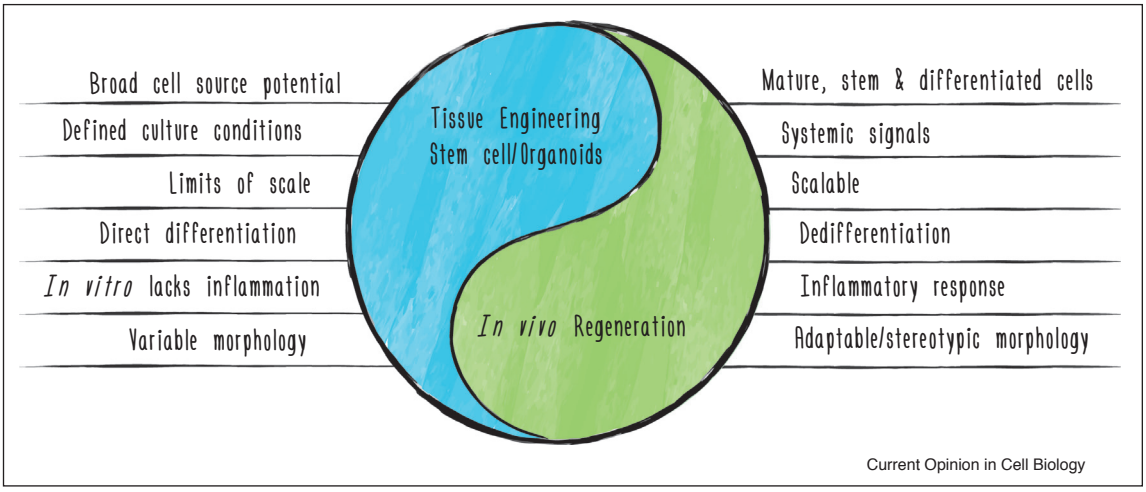
The ability to regenerate organs is an exceptional process in biology. Although the vast majority of animal species display narrowly-defined contexts of regeneration, a rare number of animals have bucked this trend and maintained the ability to reconstruct appendages, organs, and their entire body plan following resection. Understanding the molecular underpinnings of natural, epimorphic regeneration has clear implications to enhance regenerative therapies. Regenerative medicine functions as two complementary nodes: tissue engineering/stem & organoid biology and *in vivo* models of natural regeneration (Figure 1). Despite broad overlaps in approaches and techniques, each part has a unique perspective that skews toward particular scales of observation and starting points. For example, stem cell and organoid approaches often pursue a reductionist approach, taking advantage of pluripotent stem cells to reproduce broad developmental processes. In contrast, animal regeneration initiates from complex, mature tissue following an injury — a messy disruption of normal tissue architecture accompanied by an immune response. Are there opportunities to bridge insights from epimorphic regeneration in animal models to increase the efficacy of regenerative medicine? Although it is tempting to look for molecular 'silver bullets' that might have profound roles on the regenerative process, it is important to understand the sequential steps that cells, the basic building blocks and participants of organogenesis, must undergo to successfully reconstitute new tissues.

In this review we focus on new insights into the cell's experience of regeneration. We will specifically emphasize the temporal and spatial aspects that guide cells from the moment following an injury or resection, building to the completion of a perfectly scaled organ (Figure 2).

Injury signals

Regardless of a regenerative outcome, the initial detection and response to any injury is to restore barrier function and clear away pathogens. The resulting immune response sets off a cascade of reactions that can profoundly influence subsequent steps toward regeneration or non-regenerative fibrosis. Emerging evidence suggests that the total immune repertoire is similar between regenerative and scarring outcomes. Instead, it is the unique spatial and temporal organization of cells and signals that plays a critical role in fostering a regenerative microenvironment. Transcription-independent molecules such as calcium [1] and reactive oxygen species (ROS) [2] act to recruit inflammatory cells as well as activate resident cells. In addition to mechanical stimulation by osmotic or necrotic cell swelling [3], damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) derived from dying cells and pathogens are an additional source of activation for macrophages and fibroblastic cells, two integral cell types that intimately communicate to drive the wound response (Figure 3). ROS production is a common attribute of both wound healing and regeneration, but in several regenerative contexts ROS production shows an increased intensity and duration that may be necessary for cell proliferation and axon regrowth [4,5,6••]. Once at the injury site, macrophages produce cytokines, ROS, and matrix metalloproteinases (MMPs) that help liberate participating cells and reactivate proliferation. Intriguingly, macrophages may play a broader role to regulate inflammatory cytokine release from non-immune tissues in

Figure 1

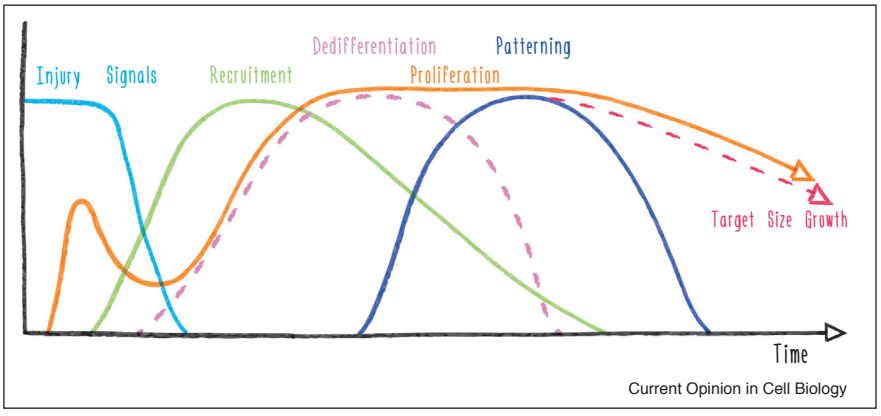


Complementary aspects of regenerative medicine. As two parts of regenerative medicine, tissue engineering, stem and organoid biology and natural examples of *in vivo* epimorphic regeneration. Each approach offers unique advantages that provide key insights into the process of regenerative organogenesis. What insights from animal regeneration can guide breakthroughs in engineered and stem-cell based therapies?

order to orchestrate the inflammatory response [7]. After the initial wound response, macrophages transition to a 'repair' state that is characterized by a change in their secretome and cellular behavior. During later stages of regeneration, this phenotypic switch from pro-inflammatory macrophages from the blastema [6••].

Despite recent efforts in comparative analysis of wound healing versus regenerative regrowth, the precise mechanisms that distinguish the two remain unknown [8–10]. Recent work comparing outcomes between regenerative and non-regenerative species has been fruitful in identifying specific steps that divert regeneration toward incomplete scar formation. In medaka, the delayed and weak recruitment of macrophages has cascading effects on the incomplete regeneration of the heart compared with zebrafish [11]. One additional possibility may be that tissue-specific cells or components possess regeneration-permissive signals such as 'missing part' or altered positional cues which are activated by 'generic' wound signals [12••].

Figure 2



Chronological progression of epimorphic regeneration. The distinct phases of regeneration represent a series of overlapping and inter-connected steps that take place following resection of an organ or appendage and persist to the proportionally scaled regenerated organ. Each phase represents a series of discrete signals that are spatially and temporally coordinated to achieve tissue regrowth. Certain phases such as dedifferentiation and final 'catch up' growth to reach the final tissue size remain poorly defined (dashed lines).