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Errors of Geometry: regeneration in a broader perspective

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> "If you want to build a ship, don't herd people together to collect wood, and don't assign them tasks and work, but teach them to long for the endless immensity of the sea." - Antoine de Saint-Exupery, "Wisdom of the Sands"

This is the second of our 2-issue set focused on the biology and applications of regeneration. The fundamental problem of regenerative medicine boils down to understanding and learning to modulate the conserved higher-order mechanisms controlling 3-dimensional shape of biological growth. Although regeneration does not always recapitulate embryonic mechanisms, the information for rebuilding the needed structures are clearly present in organisms that achieved the initial morphogenesis as embryos. It may be possible to re-activate these programs in adults; this effort will surely be facilitated by advances in understanding of morphostasis, the mechanisms that maintain shape against environmental demands and cellular senescence, or go awry in cancer. Thus, a major direction of this field must involve a more fundamental understanding of morphogenetic controls that underlie the development-regeneration-cancer triad [1]. The reviews in this issue demonstrate the powerful model systems and regulatory pathways that offer significant opportunity for identifying high-level morphogenetic control points and developing biomedical applications that integrate highly specific and powerful signals with the patient's own morphogenetic program. Here, I outline a few key questions centering around the right theoretical formalism for understanding biological control of pattern and the wider implications of linkage between development, regeneration, and cancer.

Micromanagement vs. top-down control of endogenous mechanisms: what is the right strategy for understanding and controlling regeneration?

Regeneration of entire organs can be seen as an extension of mechanisms that continuously maintain an organism's shape against cellular turnover and repair minor damage during simple wound healing. However, damage on different size scales (whole appendage amputation, tissue puncture, or individual cell senescence) may involve radically different mechanisms for sensing and repair. Understanding the initiation and guidance of different types of repair presents important challenges and opportunities for the field and its application towards biomedicine [2]. This requires molecular elucidation of how the 3-dimensional pattern of structures is encoded in living systems and recalled during the regeneration process. Work in several model systems (e.g., planaria) strikingly illustrates that the correct pattern, on multiple

scales, is a type of attractor towards which the system strives despite perturbations that differ in numerous mechanistic details.

A key question when thinking about how to translate reductive molecular pathway information into biomedical interventions concerns the topology of control networks [3]: what is the correct level of organization for functional interventions? Tissue engineers seek to directly micromanage the production of specific cell types and structures [Levenberg, Kaplan, and Vunjak-Novakovic chapters]. In contrast, work in highly-regenerative model systems strongly suggests the existence of master-level control points, which when activated by simple stimuli, result in the induction of complex downstream cascades that rebuild complex structures. Examples include the *Xenopus* tail and the flatworm head, both induced in regeneration blastemas by simple physiological signals that bear very little intrinsic information [Tamura, Kierdorf, Oviedo, and Levin chapters]. An interplay of approaches at both levels of organization – artificial creation of tissues/organs *in vitro*, and molecular activation of endogenous repair mechanisms, are being used to address the full range of opportunities in biomedical regeneration.

Regeneration: a unique problem or one facet of a fundamental common thread?

One framework for understanding the processes of regeneration is by analysis and modeling of the morphogenetic fields [4] that impact cells and cell groups (where a morphogenetic field is the spatio-temporal integration of all of the non-cell-autonomous signals that impinge upon and determine cell behaviors). This set of cues consists of both local and long-range field-like signal distributions mediated by planar cell polarity systems [5], bioelectric gradients [6], and perhaps others physical modalities [7,8].

This perspective views cancer, regeneration, and embryonic development as three faces of a single phenomenon organizing low-level cell and tissue behaviors into higher-order structures. Cancer can be seen as an error of geometry, in as much as tumor cells grow, migrate, and function without regard for the orderly structure within which they occur [9–11], and alter their physiological functions towards “selfish” processes and away from normal altruistic roles [12]. The suggestion that regeneration, neoplasm, and embryogenesis may be best understood from a field approach to morphogenesis is controversial. However, the classical idea that cancer results from a failure of cells to attend to the morphogenetic field has been strengthened by recent data showing that regulation of stem and somatic cell behavior in both cancer and normal tissue is directed by some of the same signaling factors and bioelectrical properties [13–15]. Moreover, it is now clear that neoplastic transformation can result from the failure to receive global patterning signals driving both regeneration and development including: planar polarity [5,16], gap junctional communication [17], innervation [18–20], and bioelectrical fields [21, 22].

Large-scale morphogenetic control

Teratomas display differentiation of numerous cell types but an absence of orderly organization of the whole. A similarly striking uncoupling of lower-level histogenesis from large-scale pattern formation occurs when long-range bioelectrical signals are disrupted during embryogenesis [23]. The *Disorganization* mouse mutant is likely to be an important entry-point into understanding this phenomenon; while not yet molecularly characterized, its phenotype reveals a remarkable confusion of the large-scale bodyplan of the mouse despite normal organ development [24–26].

Crucially, induction of large-scale morphogenetic remodeling can re-exert control, resulting in coherent patterning. Teratoma cells become normal mice when implanted into embryos [27], and induction of limb regeneration is known to tame neoplasm when amputation occurs through the tumor [28–34]. In the future, it is imperative for regenerative biology to deepen its links to cancer research. Importantly, a number of the model systems discussed in this issue could be ideal contexts in which to explore the profound cancer-regeneration connection, including the relationship between tumor susceptibility and regenerative potential among species and tissues. It has been suggested that a “tumor is a wound that does not heal” [35]; progress in the induction of regenerative and wound-healing response may have profound implications for the biomedicine of cancer [Zhao and Emming chapters].

The suggestion that a fundamental, field-based description of morphogenesis is the best way to address regeneration is a minority view. Certainly near-term applications exist for direct bioengineering solutions to specific types of injury and induction of distinct cellular responses by transcription factors and soluble molecules. At the same time, developmental biology is actively seeking a systems-level understanding of large-scale regeneration. Highly-regenerative model species clearly illustrate that endogenous mechanisms of the host can rapidly rebuild organs and appendages that are too complex for us to assemble directly. Activating programs containing multiple, well-integrated lower level processes could coax the body to re-create its target morphology, providing a broadly-relevant strategy. These complementary approaches are beautifully contrasted by Antoine de Saint-Exupery in his statement, albeit made in another context. The development of biotechnology to assist the organism in its homeostatic longing for the complete, correct morphology on multiple scales is an incredibly exciting project with likely transformative effects on many aspects of biomedicine.

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