Preface. Mechanisms of Regeneration

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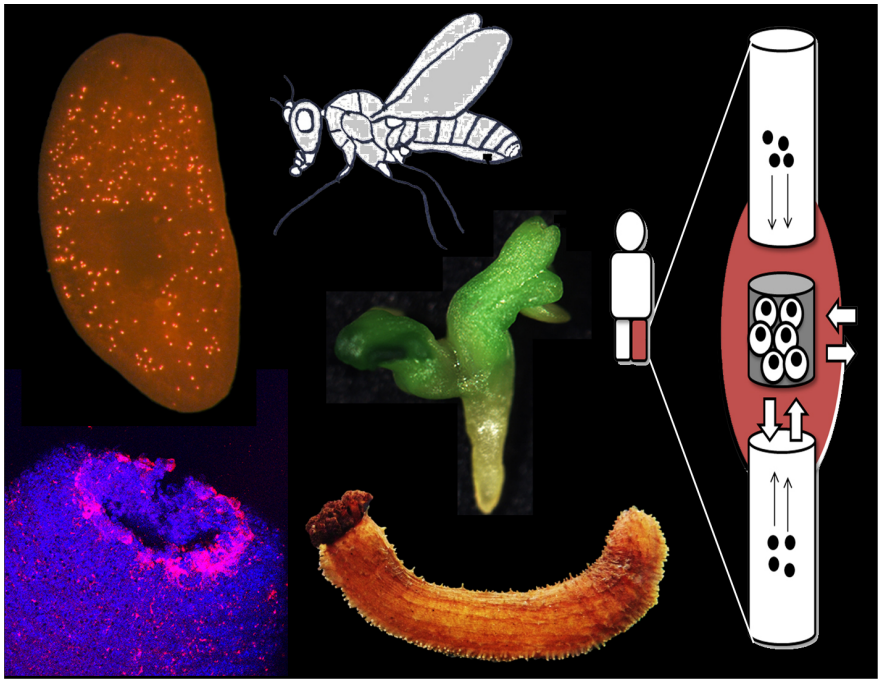
Current Topics in Developmental Biology, special issue dedicated to the **Mechanisms of Regeneration**



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PREFACE

The initial concept of this special issue was to invite a duo of experts for each chapter to discuss specific aspects of the mechanisms underlying regenerative processes. In some cases this invitation came at the right time and two colleagues mutually agreed to join their efforts and deliver their views on a particular topic, within this largely multidisciplinary field that regeneration covers. In other cases, this dialectic pairing could not materialize and close collaborators joined to help write some chapters. In all cases, however, I would like to express my gratitude to every contributor of this special issue. Indeed they all went far beyond their favorite model to discuss some of the most recent findings and strategies in their field, with a transversal view. As a result, this special issue offers both novel concepts and stimulating ideas on the various mechanisms at work during regeneration.

In Chapter 1, **Lin XU** and **Hai HUANG** (Shanghai, China) provide an overview of the genetic and epigenetic control of the different regenerative processes in plants, not only in *Arabidopsis thaliana* but also in rice and moss. With clear words and excellent illustrations the authors have made the three regenerative contexts where regeneration operates in plants, i.e. tissue repair, *de novo* organogenesis and somatic embryogenesis, accessible to any biologists. Each of these processes correspond to a cell fate transition, either from cells that retain partial pluripotency when the root tip repairs, or through the formation of an intermediate blastema-like structure named callus during *de novo* organogenesis, or through typical dedifferentiation of somatic cells during embryogenesis. Cell fate transition arises from a complex network of interactions involving chromatin, transcription factors and hormones. In the case of somatic embryogenesis, these processes start to be well known and show some similarity with the mechanisms involved in the dedifferentiation of induced Pluripotent Stem cells (iPS) from differentiated animal cells.

In Chapter 2, **Ying Hua SU** and **Xian Sheng ZHANG** (Shandong, China) continue along the same line, with a specific focus on how hormones that behave as morphogens in plants control *de novo* organogenesis and somatic embryogenesis in *Arabidopsi*s. The authors review recent advances on three important aspects, the biosynthetic regulation of hormonal functions, the crosstalk between the auxin and cytokinin hormone signaling pathways and the interactions between developmental and environmental cues. The authors of these two chapters leave us with a series of questions: What kinds of wound signals are released in the various contexts of plant regeneration? Which are the target genes of the plant hormones? How is the action of transcription and epigenetic factors coordinated? Which cells undergo callus initiation in natural conditions?

The potential role of chromatin modifications in tissue repair and during animal regeneration remains obscure. In Chapter 3, **Sofia ROBB** and **Alejandro SANCHEZ ALVARADO** (Kansas City, USA) discuss recent findings concerning the role of histone modifications in the planarian flatworm *Schmidtea mediterranea*, which can regenerate any missing part due to its abundant and dynamic population of adult stem cells (ASCs) refereed to as neoblasts. After an inventory of the histones and histone-modifiying enzymes present in *S. mediterranea*, the authors show that a number of these enzymes are distributed in a way reminiscent of either stem cells or nerve cells. Functional studies involving one such histone de-acetylase reveal that the regulation of the level of histone acetylation is essential to maintain the stem cell function of neoblasts, i.e. self-renewal and differentiation of cell progeny. Therefore, planarians may provide a promising model for deciphering the epigenetic mechanisms that either underly or accompany the regenerative potential in animals.

In Chapter 4, **Gongpin SUN** and **Ken IRVINE** (Piscataway, USA) discuss the control of growth, both at the initiation and the termination phases of regeneration. *Drosophila* offers a versatile model to address this central question in regeneration, as wound healing can be tested not only in the embryo in the absence of any regeneration, but also in the larvae either at the cuticle level or in the imaginal discs, where tissue ablation triggers regeneration. Finally, it can also be assessed in the adult cuticle or intestine, which display an efficient tissue repair response. In each of these biological contexts, like in mammals regenerating their liver, the JNK pathway plays a central role in the injury response triggering the activation of various downstream signaling pathways, which may vary between organs. Recent quantitative genetic analyses performed in *Drosophila* show that injured tissues are more sensitive to a decrease in key signaling components as JAK or Yki, when compared to developing tissues or organs. Consequently, if the

signaling pathways involved in the development and the regeneration of a given structure are the same, their interplay and their signaling strengths may importantly differ. This novel concept will surely generate further experiments in the future.

In Chapter 5, **Sophie VRIZ** (Paris, France), **Silke REITER** and **Brigitte GALLIOT** (Geneva, Switzerland) consider cell death as a possible motor for regeneration. After describing the various animal contexts where cell death positively influences regeneration, these authors discuss recent studies in *Drosophila*, zebrafish and *Hydra*, all pointing to the production of ROS upon injury and its potential to activate the cell death program through the JNK and/or MAPK pathways. Cell death, however, does not always occur at the time and in the area of injury and may also be observed in more distant tissues with some delay. An important issue is to understand the different roles of these dying cells. The signaling molecules released by apoptotic cells are diverse and can instruct survivor cells. Dying cells can also provide a strong "*sentiment de vide*" (feeling of emptiness) to the neighboring tissues, which can rapidly develop a compensatory response involving enigmatic signaling components. Injury-induced cell death might thus be quite versatile, activating and/or desactivating a variety of mechanisms to trigger a regenerative program.

In Chapter 6, **Won-Jae LEE** (Seoul, South Korea) and **Masayuki MIURA** (Tokyo, Japan) discuss the impact of Systemic Wound Response (SWR), a phenomenon they recently discovered whereby a local wound in the *Drosophila* adult skin (integument) can trigger long-distance responses. So far, these responses were identified in two distinct locations in the adult fly, in neuronal and intestinal cells by the Lee and Miura laboratories, respectively. Interestingly, both SWRs involve ROS signaling and are required for the survival of the adult animal. Consequently, we may no longer consider wound healing as a local process only, but also realize that injuries produce toxic systemic substances that engage reactions within the whole organism. What is the nature of these systemic factors? Which types of signaling do they elicit in each organ? Understanding how such toxic systemic factors circulating after a local damage affect the entire organism will help characterize the parameters that positively or negatively modulate the adult regenerative potential.

The evolution of regenerative processes is poorly understood. In Chapter 7, **Vladimir MASHANOV** and **José GARCÍA-ARRARÁS** (San Juan, Puerto Rico) provide a comparative analysis of intestine regeneration across eumetazoans. Indeed, while the gut is the target of repeated environmental stresses, it nevertheless maintains day after day its essential capacity to absorb nutrients. Adult mammals and *Drosophila* efficiently repair their intestine epithelium due to a large stock of active stem cells. In addition, progenitors and some differentiated cells can revert to a stem cell stage in mammals. While these organisms are capable of repairing their gut, they are unable to regenerate any portion of it. Why? The authors use the sea cucumber *Holothuria glaberrima,* which spontaneously regenerates its whole gut after evisceration, to address this question. *H. glaberrima* regenerates its gut by recruiting both resident enterocytes coming from the luminal epithelium left in the stumps, and external cells evaginating from the surrounding connective tissue thus providing new enterocytes after trans-differentiation. This dual contribution of resident and external cells is not restricted to echinoderms and is also observed in insects and vertebrates. Therefore, two distinct strategies, different from tissue self-renewal and each relying on differentiated and/or stem cells, likely emerged in the course of animal evolution. Future studies on the interactions between the gut epithelium and the connective tissue should help understand the underlying mechanisms. The may also contribute to the development of tissue bioengineering in humans.

Aging processes are an important factor that down-regulates the strength of regeneration in mammals. In Chapter 8, **Konstantinos SOUSOUNIS, Joelle BADDOUR and Panagiotis TSONIS** (Dayton, USA) synthesize the results of studies assessing the impact of aging in five distinct types of adult mammalian stem cells (endothelial, hematopoietic, skeletal muscle, neural, mesenchymal). They also discuss the age-dependent changes of the regenerative potential of those organs capable of regeneration or repair, such as the lungs, the skeletal muscle, the liver, the nervous system or the cochlear hair cell. They conclude that both the self-renewal of stem cells and regeneration are dramatically altered upon aging in mammals. This negative impact of aging factors may be better understood in the future, either through parabiosis approaches, or by looking at non-mammalian model displaying less sensitivity to aging. For example, newts keep regenerating their lens with a similar efficiency over decades and hence comparative studies between aging and 'non-aging' organisms may help elucidate which are the factors negatively impacting tissue repair and regeneration in the aged organisms.

In Chapter 9, **Mamta RAI, Upendra Nongthomba (**Bangalore, India) and **Miranda GROUNDS** (Perth, Australia) compare the factors that regulate the maintenance, degeneration and regeneration of skeletal muscles, focusing on limb muscles in mice and indirect flight muscles in *Drosophila*. Mice make use of ASCs, the quiescent satellite cells, to regenerate their muscles after injury, but probably do not use them to maintain the muscle function in case of moderate usage. Similarly, the maintenance of muscular function in *Drosophila* does not rely on myogenesis, since adult muscles lack ASCs. In fact, mice and *Drosophila* skeletal muscles share numerous characteristics including the genetic networks used for their development, a similar cellular organization and the metabolic pathways necessary to maintain their activity. Both species exhibit neuromuscular diseases and sarcopenia, the age-dependent loss of muscles. As a consequence, flies may offer an amenable model to investigate the respective contributions of intracellular oxidative stress, mitochondrial defects, accumulation of protein aggregates and the modifications of the extra-cellular matrix on these processes. Flies can be trained to exercise and, beside local benefits, this muscular training provides a systemic positive effect.

In Chapter 10, **Osvaldo CHARA, Elly TANAKA** and **Lutz BRUSCH** (Dresden, Germany) look at regeneration from a different prospective, reviewing existing mathematical models and identifying a series of parameters to progress from injury signaling to tissue restoration. To model the initiation phase of regeneration, they integrate various models applied to four distinct cellular events; cell proliferation, cell differentiation, apoptosis and cell migration. Regarding the patterning phase of regeneration, the authors take us through a journey from the Source-Sink model to different versions of the reaction-diffusion model. They also consider cell-based models that better integrate cellular properties such as cell polarity, cell shape and cell mechanics. Finally they propose a multicultural model to terminate the regenerative response, which integrates the feedback of mechanical forces, a regulation of growth based on reaction-diffusion as well as some slope sensor of concentration gradient. The authors raise a series of open problems, since current models do not fully address the complexity of adult regeneration. Compared to developing organisms, regenerating tissues or organs are much larger and quite heterogenous in terms of cell types, a feature, which will have to be integrated in future models.

Finally, in Chapter 11, **Beatrice TONNARELLI, Matteo CENTOLA, Andrea BARBERO, Rolf ZELLER** and **Ian MARTIN** (Basel, Switzerland) show how engineers and developmental biologists can elaborate strategies to implement developmental mechanisms into artificial materials, which will instruct tissues or organs to regenerate in adult bodies. By taking regeneration of long bones as model, they go through three levels of complexity using first progenitor cells cultured in bioreactos to produce bone tissue through membranal ossification. This rather simple form of ossification, however, does not recapitulate the genuine endochondral mode of long bone formation. Therefore, in a second step, they implement endochondral ossification by applying to endogenous skeletal progenitors the signaling involved in the development and growth of long bones, using morphogenetic gradients. The third step requires to adapt this engineered development to the adult parameters, i.e. the environmental cues, the aging of progenitors, the innate and adaptative immune responses involved in tissue repair etc. Ultimately, the authors plan to re-engineer a developmental process able to adapt to adult specificities. We are still far from this but the proposed strategy, integrating developmental, biotechnological and biophysical informations, definitely opens the way to restaure stable functional structures, non-invasive and prone to adapt to their new environment.

These complex engineering approaches are admittedly far from clinical applications. They nevertheless represent an ambitious and necessary task for the years to come. Their future successes may significantly improve the lives of people affected by pathologies destroying their tissues or organs. This includes disabled children recovering after major diseases or traumatisms occuring during their infancy, adult fighting chronic diseases or aging people. However, significant breakthrough in this field will likely result from integrative strategies involving a deep knowledge of the basic cellular, developmental and regenerative mechanisms. These essential steps will require the combine used of multiple competences as well as diverse mammalian and non-mammalian animal models. We hope this special issue illustrates the importance of these various approaches and will raise some more interest for this fascinating field of research.