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# Triggering the regeneration and tissue repair programs

**Elly Tanaka[1] and Brigitte Galliot[2]**

In early October 2008, researchers from diverse backgrounds gathered at an EMBO conference entitled 'The Molecular and Cellular Basis of Regeneration and Tissue Repair' to discuss the basic biology of regeneration. Topics included cell plasticity in regenerative and developmental contexts, and the link between wound healing and regeneration. The meeting also highlighted the progress made in identifying the molecular networks that underlie regeneration in a variety of model systems.

## Introduction

'The Molecular and Cellular Basis of Regeneration and Tissue Repair', which took place in Palma de Mallorca (Spain) and which was co-organized by Enrique Amaya (University of Manchester, UK), Daniel Bachiller (CSIC, Mallorca, Spain), Andras Simon (Karolinska Institute, Stockholm, Sweden) and Panagiotis Tsonis (Center for Tissue Regeneration and Engineering, Dayton, OH, USA), was the fourth in a series of conferences on tissue repair and regeneration launched in 2002. One important aim of this conference was to interlink a mechanistic understanding of the wounding response with the generation of undifferentiated progenitors, collectively called the blastema, that undertake patterning, differentiation and morphogenesis to rebuild complex, multi-tissue structures. The cellular plasticity required for blastema formation in different vertebrate and invertebrate regeneration models was also a central theme of this meeting. An important advantage of this cross-species approach is that it reveals commonalities in the genetic circuitries underlying the regenerative response among species. In this review, we focus on questions emerging from the meeting that are particularly relevant to developmental biologists, such as the basis of cellular plasticity in developmental and adult contexts, and the contribution of stem cells to regenerative processes. Another important question pertained to whether regeneration responses and the genetic circuitry that they involve are conserved among vertebrate and invertebrate organisms.

## Wound healing and regeneration

The rapid re-epithelialization of a wound is a notable feature of regenerating systems. In newt and zebrafish appendages, as well as in hydra and planaria, a wound is closed within hours by the migration of a simple epithelium over the wound site, resulting in the 'scar-free' regeneration of underlying tissues. Genetic model systems for wound healing are hence extremely valuable for understanding initial regenerative events. Antonio Jacinto (University of Lisbon, Portugal) identified in a systematic genetic screen in *Drosophila* 31 mutants (out of 655) that exhibited retarded re-epithelialization. Among these 'wound-healing genes' were expected genes, such as *beta-heavy spectrin* (*karst*), a known cytoskeleton regulator, but also some that were unanticipated, such as *Polycomb* and *mitochondrial ribosomal protein S2*, the product of which might supply energy for wound closure. Michelle Juarez (McGinnis laboratory, University of California, San Diego, CA, USA) presented another *Drosophila* screen that uncovered six chromosomal regions affecting wound reporter-gene expression. One such region contains *reggie-1/flotillin*, a gene known to be involved in the regulation of epidermal wound-response genes.

By contrast, adult mammals heal wounds rather differently. The wound is filled with granulation tissue, the non-epithelial connective tissue that develops at the wound site, and is re-epithelialized more slowly than in regenerating tissues. Underlying fibroblasts often secrete an excess of poorly organized extracellular matrix, resulting in scarring. Therefore, the identification of factors that delay re-epithelialization and promote scar formation could have a major impact on promoting scar-free healing and even regeneration. An emerging issue in regeneration is the negative impact that immune cells might have on wound healing and regeneration. Paul Martin (University of Bristol, UK) has adopted a multi-pronged approach to study re-epithelialization by using flies, fish and mice (Fig. 1). In *Drosophila*, he showed that the stress-induced gene *Gadd45* is upregulated by the wound epithelium in an inflammation-dependent fashion (Stramer et al., 2008), as is the murine ortholog during wound healing in mice. He also showed that Polycomb-group genes are downregulated while their associated demethylases are upregulated, suggesting a mechanism for the 'unsilencing' of the wound transcriptome during skin repair. Finally, Martin described work showing that post-natal wound healing is improved in the *PU.1* (*Sfpi1*) knockout mouse, which lacks myeloid cells and in which the macrophage-secreted factor osteopontin (SPP1), which has a negative impact on scar-free healing, is downregulated (Mori et al., 2008). Other molecular factors that affect mammalian wound healing were also discussed. For example, Kimberly Mace (University of Manchester, UK) reported that the homeobox gene *HOXA3* might enhance regenerative angiogenesis and cutaneous wound repair in humans and mice by repressing pro-inflammatory pathways and myeloid differentiation within the wound environment, while activating pro-angiogenic pathways (Mace et al., 2005).

Members of the transforming growth factor beta (TGFβ) family have an important impact on wound healing. By analysing activin-overexpressing mice, Sabine Werner (Swiss Federal Institute of Technology, Zürich, Switzerland) demonstrated that activin is promitogenic for keratinocytes, but also signals to underlying stromal cells to promote granulation tissue formation and scarring. In an interesting twist, she related how chronic wounding may be linked to tumorigenesis, as tumors use the host's wound-healing program for their growth and progression. Another TGFβ family member, TGFβ3, is the focus of Mark Ferguson's studies (University of Manchester, UK). He founded the company Renovo on the concept of using TFGβ3 as an anti-scarring agent. Ferguson presented results from human phase II clinical trials indicating that TFGβ3 can reduce scarring when administered around the time of wounding.

Whereas many of the mammalian studies presented at this meeting focused on ameliorating non-productive fibrosis, Cheng-Ming Chuong (University of Southern California, Los Angeles, CA,

[1]Center for Regenerative Therapies in Dresden (CRTD), D-01307 Dresden, Germany. [2]Department of Zoology and Animal Biology, University of Geneva, CH-1211 Geneva 4, Switzerland.

e-mails: tanaka@mpi-cbg.de; brigitte.galliot@unige.ch

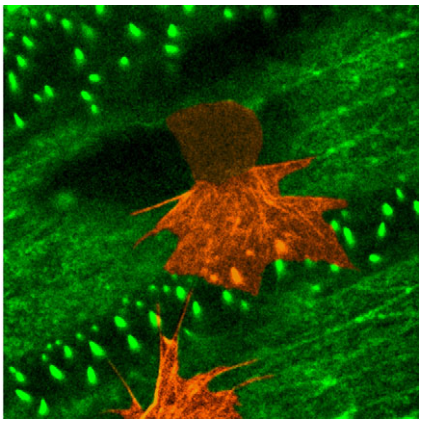

**Fig. 1. Hemocytes recruited to an epithelial wound in the epithelium of a *Drosophila* embryo.** Hemocytes are in red (false-colored), epithelium in green (GFP-moesin). Image courtesy of Brian Stramer and Paul Martin.

USA) described previous studies showing that when large wounds are not surgically treated, hair follicles reform at the wound center, indicating that in mammals, re-epithelialized sites can regenerate hair follicles in a Wnt-dependent manner (Ito et al., 2007). Chuong went on to describe his lab's studies of the bone morphogenetic proteins BMP2 and BMP4, the cyclic expression of which imposes a refractory phase on the mouse hair cell cycle. Strikingly, the dermally (and adipocytically) expressed BMPs coordinate interfollicular cycles of hair generation, resulting in waves of hair follicle activation across the skin (Plikus et al., 2008). This macro-environmental level of stem cell regulation might also exist in other organs.

## Cellular plasticity in different contexts

Whether and how mature cells already committed to a specific cell lineage can transdifferentiate or dedifferentiate to form other cell types is a key question in regeneration and stem cell research. The most prominent recent example of such plasticity is the forced induction of pluripotency in fibroblasts and other cells types by a limited set of transcription factors to create so-called induced pluripotent stem (iPS) cells. This field was represented at the meeting by Keisuke Okita (Yamanaka laboratory, Kyoto University, Japan) and by Todd Meyerrose (Jaenisch laboratory, Massachusetts Institute of Technology, Cambridge, MA, USA). Okita, who recently demonstrated that iPS cells can be induced by repeated transfection with plasmids (Okita et al., 2008), gave a clear historical account of how the iPS protocol arose. Meyerrose spoke about generating iPS cells from human B-cells. Whereas immature B-cells can be directly reprogrammed by the canonical pluripotency factors, mature B-cells must first be reverted by overexpressing the transcription factor CEBPα or by silencing the transcription factor PAX5, before reprogramming to the iPS state (Hanna et al., 2008). Perhaps because the audience was composed of scientists who had long thought about regenerating structures from somatic cells, these talks incited an interesting discussion on whether it was really necessary and wise to dedifferentiate cells to a pluripotent state in order to promote regenerative events, particularly in view of the tumorigenic potential of embryonic stem and iPS cells. Many delegates wondered whether it would be possible to locally stimulate somatic stem cells for regeneration.

In sharp contrast to induced pluripotency, Elly Tanaka [Center for Regenerative Therapies (CRTD), Dresden, Germany] showed in studies employing transgenic axolotls that express green fluorescent protein that regenerating limb cells have limited potential. Her work showed that each tissue largely reforms itself, rather than contributing to many tissues, indicating that almost no transdifferentiation occurs during limb regeneration, with the exception of dermis differentiating into cartilage. Therefore, the regenerating limb blastema is a mixed group of tissue-restricted progenitor cells that derive from each limb tissue.

These findings notwithstanding, many other examples of cell transdifferentiation, and the molecular pathways underlying these events, were presented. One of the best-defined examples of transdifferentiation in vertebrates is the induction of lens from the dorsal iris pigmented epithelium (PE) in the newt eye, where dorsal but not ventral iris cells regenerate the lens after a lentectomy. Panagiotis Tsonis talked about the experimental induction of a lens from ventral iris. He discussed two possible mechanisms for how a ventral PE cell could become competent to transdifferentiate into a lens: first, microRNA (miRNA) regulation, and second, chromatin factor modifications, such as H3K27 trimethylation that might determine whether a PE cell is competent to undertake the transdifferentiation to lens or not. An interesting dimension of lens regeneration is its species specificity: the newt displays lens regeneration, whereas the axolotl, also a salamander, does not. Tsonis hypothesized that high H3K27 trimethylation levels throughout the axolotl iris might prevent regeneration.

Several talks focused on prompting cells to change their fate during embryogenesis using a limited number of intracellular or extracellular factors. For example, Enrique Amaya found that expressing *cebpa* (CEBPα) in *Xenopus* animal caps causes the formation of functional primitive myeloid cells that become migratory and efficiently home to embryonic wounds. Thus, *cebpa* alone can redirect pluripotent embryonic cells into functional primitive myeloid cells.

Katia Del-Rio Tsonis (Miami University, Oxford, OH, USA) spoke about transdifferentiation in the developing chicken eye, where the ciliary margin can be coaxed to form neural retina either by treatment with fibroblast growth factor (FGF) or by activation of either the sonic hedgehog (Shh) or the BMP pathway, both of which can in turn activate the FGF pathway (Haynes et al., 2007; Spence et al., 2007). David Tosh (University of Bath, UK) described how dexamethasone induces pancreatic cells to transdifferentiate into two hepatocyte populations, thus mimicking the normal hepatic cellular heterogeneity or zonation (Eberhard and Tosh, 2008). The transcription factor CEBPβ is required for this conversion.

The dissection of the molecular pathways that underlie transdifferentiation in a natural context is an important future goal. In this vein, Sophie Jarriault (Institute of Genetics and Molecular and Cellular Biology, Strasbourg, France) characterized a cell transdifferentiation event in *Caenorhabditis elegans* during which one of the six epithelial cells that form the rectum in young larvae changes to a neuronal fate in the absence of cell division (Jarriault et al., 2008). She described the isolation of mutants with defects at various stages of this process, which possibly reflect the role of different proteins or pathways in making this cell competent to transdifferentiate or in driving this process. It will certainly be interesting to learn the identity of these genes, and whether they have direct orthologs in other systems that display transdifferentiation.

Although some transdifferentiation events occur in the absence of cell proliferation, another important aspect of regeneration research is to understand how cells are induced to re-acquire proliferative

potential. In the newt, the ability of differentiated, syncytial myotubes to re-enter the cell cycle and to fragment into mononucleate cells in order to produce proliferative progenitors is well known. By studying newt myotubes in culture, Andras Simon showed that the activation of cell death pathways causes them to fragment into mononucleate cells. If these cells are kept alive, they continue to proliferate, providing the intriguing observation that activation of cell death pathways initiates the fragmentation aspect of dedifferentiation. It will be important to demonstrate that these proliferative cells are bona fide progenitors.

The talk by Marco Crescenzi (Italian National Institute of Health, Rome, Italy) on mammalian myotube cell cycle re-entry provided an interesting contrast to Simon's results. Crescenzi's lab has shown recently that the derepression of cell cycle inhibitors can prompt cultured murine myotubes to re-enter the cell cycle (Pajalunga et al., 2007). However, this reactivation is partial, as these fibers do not generate proliferative cells. The resulting mitotic cells also show an abnormal morphology, and, unlike in the newt myotubes, their DNA replicates incompletely and is damaged. These two talks highlight major differences between cultured newt and mouse myotubes in their competence to proceed through S phase once they have re-entered the cell cycle.

## Stem cells and regeneration

Christine Mummery (Leiden University, Leiden, The Netherlands) discussed how human embryonic stem cells (hESCs) are fulfilling some, but not all, of their promise for stem cell-based therapies. hESCs can be efficiently induced to form cardiomyocytes (hESC-CMs), facilitating the dissection of the gene activation events that underpin this process, which, in turn, could lead to the identification of new candidate genes for congenital heart defects (Passier and Mummery, 2005). However, the transplantation of such hESC-CMs into infarcted rodent hearts has yielded disappointing functional improvements (van Laake et al., 2007; van Laake et al., 2008).

Adult stem cells are viewed as a valuable 'natural' source of progenitors to regenerate injured tissues, but one central issue is the characterization of adult stem cell niches. Michael Brand (CRTD, Dresden, Germany) showed that the zebrafish brain offers a suitable model for comparing juvenile and adult neuronal stem cell niches, with neuronal progenitor proliferation identified in 16 distinct zones in adults (Grandel et al., 2006). In the cerebellum, where the adult niche is a continuation of the fetal niche, FGF signaling is required for niche maintenance and also for the proliferation of progenitors (Kaslin et al., 2008). Along the same lines, Wieland Huttner [Max-Planck-Institute (MPI) Dresden, Germany] showed that in mammals, the zinc-finger transcription factor insulinoma-associated 1 (INSM1) promotes the formation of basal progenitors that undergo neurogenic divisions (Farkas et al., 2008). In rodents, basal progenitors generally divide only once, generating two neurons. By contrast, in primates, a subpopulation of neurogenic basal progenitors with epithelial-like characteristics accumulates (Fish et al., 2008). Whether these cells could be used to repair adult brains remains to be shown.

Nestor Oviedo (Levin lab, Forsyth-Harvard Medical School, Boston, MA, USA) described an essential role for the PTEN/TOR signaling pathway in maintaining stem cells in planaria. Downregulation of PTEN by RNA interference (RNAi) resulted in massive overgrowth due to neoblast overproliferation, the disorganization of differentiated tissues and the loss of basal membrane integrity, events similar to those of mammalian metastasis (Oviedo et al., 2008). These data point to the evolutionary conservation of the signaling pathways that regulate stem cells in bilaterians. Finally, in an amazing and unusual observation for scientists more familiar with vertebrate model systems, Phil Newmark (HHMI/University of Illinois at Urbana-Champaign, IL, USA) described how adult planaria regenerate germ cells from somatic tissues that contain neoblasts by activating *Nanos* (Wang et al., 2007). Based on this work, a differential expression screen has been performed through which hundreds of genes downregulated after germ cell loss have been identified.

## The regeneration-specific genetic circuitry

An important question when comparing wound healing with the regeneration of various bodily structures is whether common signaling pathways are implemented in these situations. Are different cells programmed to respond differently to common signals, or are unique signals present in regenerating structures? Although there is still much to be learnt about this, information on the signaling pathways that are employed during regeneration is beginning to accumulate, and arguments on both sides were presented at this meeting.

In contrast to mammals, but as in zebrafish, adult newts repair their hearts without fibrosis or scarring (Laube et al., 2006). Through a combination of approaches, the laboratory of Thomas Braun (MPI Bad Nauheim, Germany) has identified an essential role for the MAPK/ERK pathway in this regenerative process. Such integrated approaches should soon reveal the specific signals that trigger the regenerative response in injured vertebrate hearts.

*Xenopus* tadpoles, which can regenerate several bodily structures, including tail, limb buds and lens, until metamorphosis, offer a genetically tractable larval model of regeneration (Slack et al., 2008). Juan Larrain (Catholic University of Chile, Santiago, Chile) reported that induction of hyaluronic acid synthesis is required during the early stages of tail regeneration and appears to be upstream of Wnt pathway activation. According to Jonathan Slack (University of Minnesota, Minneapolis, MN, USA), the activation of several signaling pathways follows an almost completely linear hierarchy, with BMP being upstream of Wnt, which in turn is upstream of FGF (Lin and Slack, 2008). Interestingly, these three pathways, which are likely to control progenitor cell proliferation but not the initiation of the regeneration program, also appear to be crucial for the regenerative process in the *Xenopus* limb bud and the zebrafish caudal fin. Using a comparative microarray analysis of regenerating versus BMP-deficient non-regenerating hindlimb buds in *Xenopus*, Caroline Beck (University of Otago, Dunedin, New Zealand) has identified new targets for regenerative research. As well as embryonic genes, such as the BMP inhibitor *Gremlin*, many genes involved in the stress response, such as *Hsp60*, are upregulated in regenerating limbs (Pearl et al., 2008). These stress-activated pathways are candidates for the factors that enable the reactivation of developmental pathways after amputation.

In the regenerating zebrafish fin, the epidermis plays an essential role in blastema formation and growth. Ken Poss (Duke University Medical Center, Durham, NC, USA) interrogated the complexity of these interactions by characterizing the cross-talk between the FGF, Shh and Wnt signaling pathways in different regions of the basal epidermal cell layer with respect to the regeneration blastema. He described opposing roles of FGFs on blastema proliferation at distinct levels of the epidermis: at distal positions, FGFs have a negative effect through the activation of the blastema-repressive Wnt5b, but at more-proximal positions they have a positive effect through the activation of Shh and Wnt/Lef1. The maintenance of this epidermal code during the regenerative process, Poss proposed, is essential for its success. Christopher Antos (CRTD, Dresden,

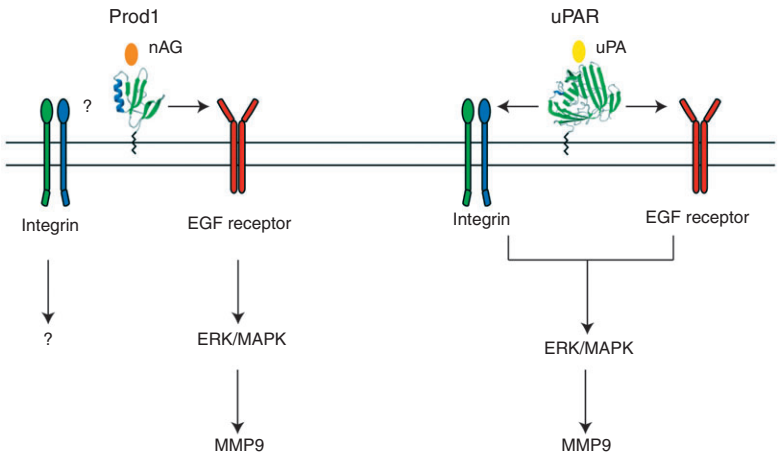


**Fig. 2. Parallels between the signaling pathways of Prod1 and the urokinase plasminogen activator receptor.** Prod1 is a salamander three-finger protein with a GPI anchor and a secreted protein ligand, nAG. The mammalian urokinase plasminogen activator receptor (PLAUR; uPAR) is also GPI-linked and has 3 three-finger domains. Both proteins can activate the MAP kinase pathway (ERK/MAPK) by interacting with the EGF receptor, and can activate transcription of the matrix metalloprotease MMP9, which is an early player in limb regeneration. Putative interactions are indicated by question marks. Image courtesy of Jeremy Brockes.

Germany) presented the zebrafish as a model for identifying novel regeneration factors. He and his colleagues have identified the intracellular protein simplet as being upregulated during zebrafish fin regeneration. The perturbation of this gene reduces cell proliferation and dysregulates the spatial expression domain of Shh, a morphogen important for regeneration. Future findings might come from other zebrafish mutants that fail to properly regenerate their fins. Using a miRNA array screen to look for regulators of regeneration, Karen Echeverri (CRTD, Dresden, Germany) identified *miR-196* as a key regulator of axolotl tail regeneration that restricts the dorsal expression domain of the transcription factor Pax7 within the regenerating spinal cord.

Sumihare Noji (University of Tokushima, Japan) showed that leg regeneration in the nymphal cricket provides a model system in which developmental and regenerative programs can be easily compared (Nakamura et al., 2008a). The epithelial growth factor (EGF) pathway is influential in patterning the distally regenerated structures of the cricket limbs. Moreover, as observed during development, it appears to act downstream of the canonical Wnt pathway, suggesting that EGF plays a similar function during regeneration and development in insects (Nakamura et al., 2008b). Emili Salo (University of Barcelona, Spain) highlighted the central role of both BMP and Wnt signaling in the morphogenesis of regenerating planaria. Inactivation of the BMP pathway results in the disruption of the dorsal-ventral axis, giving rise to double-ventral planaria (Molina et al., 2007), whereas inactivation of the Wnt pathway disrupts the anterior-posterior axis, generating the amazing phenotype of a regenerated head where a tail should be (Iglesias et al., 2008). These studies emphasize the important role of morphogen-controlled axial information in the regeneration process.

The dependence of blastema cell proliferation on innervation is a key feature of many regenerating systems. Jeremy Brockes (University College London, UK) showed in the newt that the newly identified nAG/Prod1 signaling pathway is a key mediator of nerve-dependent blastema growth that appears to operate, in part, through EGF-receptor dependent activation of the MAPK pathway, leading to matrix metalloproteinase MMP9 upregulation (Kumar et al., 2007). This pathway is similar to that activated by the mammalian urokinase plasminogen activator receptor (PLAUR) (Fig. 2), although phylogenetic evidence indicates that Prod1 might be a salamander-specific member of the three-finger protein family. This suggests that the evolution of new gene family members might underlie some aspects of an animal's regenerative ability – a hypothesis that merits further, thorough testing.

Interesting insights into the cell biology that initiates regeneration signaling were presented by Gines Morata (Molecular Biology Center, Madrid, Spain) working on *Drosophila*, and Brigitte Galliot (University of Geneva, Switzerland) working on hydra. They reported that following injury, dying cells release Wnt and, in *Drosophila*, the BMP signaling molecule Decapentaplegic (DPP), to surrounding cells, which respond by proliferating. In both model systems, MAPK pathway activation is involved in the initiation of the process (Perez-Garijo et al., 2004; Kaloulis et al., 2004). In *Drosophila*, JNK pathway activation can induce the release of DPP and the Wnt ligand Wingless even in the absence of apoptosis, proving that a non-canonical JNK pathway is triggered. In hydra, this amputation response is specifically seen in the cut end that will form the head. Astonishingly, the ectopic induction of cell death in the side of a hydra that should regenerate a foot causes a head to regenerate instead.

## Conclusions

The immediate activation of the MAPK pathway after injury and/or the early activation of the Wnt pathway to support blastema formation and growth appear to be a recurrent feature of the regenerative programs of zebrafish, the chick embryo, axolotl, *Xenopus* tadpoles, planarians, *Drosophila*, cricket larvae and head-regenerating hydra. Whether these processes reflect shared features of homologous regenerative programs remains to be demonstrated. In addition, a common pattern for the cellular composition of the blastema remains to be established: in *Xenopus* and now axolotl, the blastema is clearly heterogeneous and composed of distinct subpopulations of progenitors, whereas in newt and zebrafish, its composition remains unclear.

A key proposition to emerge at this conference is the likelihood that essential regulators of the regeneration puzzle, such as signaling pathways, chromatin modifiers and miRNAs, are likely to be conserved among eumetazoans. Some pieces of this puzzle are likely to have traversed evolution together, although with variations that remain largely unknown. It is also possible that other pathways, such as the nAG/Prod1 pathway, might have been recruited in a few animal groups to perform specific regenerative tasks as positional information (Brockes and Kumar, 2008). Future research should shed further light on how the puzzle fits together, and how missing pieces can be replaced.

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