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MEETING REVIEW

# Regeneration, morphogenesis and self-organization

**Daniel Goldman***

## ABSTRACT

The RIKEN Center for Developmental Biology in Kobe, Japan, hosted a meeting entitled 'Regeneration of Organs: Programming and Self-Organization' in March, 2014. Scientists from across the globe met to discuss current research on regeneration, organ morphogenesis and self-organization – and the links between these fields. A diverse range of experimental models and organ systems was presented, and the speakers aptly illustrated the unique power of each. This Meeting Review describes the major advances reported and themes emerging from this exciting meeting.

**KEY WORDS: Regeneration, Reprogramming, Morphogenesis, Self-organization, Morphogens, Growth control**

## Introduction

Recent advances in regeneration research and cellular reprogramming made the 'Regeneration of Organs: Programming and Self-Organization' meeting a timely event that is sure to positively impact all those who attended. The meeting was organized by Kiokazu Agata (Kyoto University, Japan), Yoshihiro Morishita [RIKEN Center for Developmental Biology (CDB), Japan], Hitoshi Niwa (RIKEN CDB, Japan) and Elly Tanaka (Center for Regenerative Therapies Dresden, Germany). They brought together an eclectic mix of scientists whose research centered on the following themes: molecular mechanisms of regeneration; cell programming and reprogramming; determination of organ shape and size; and logistics of self-organization. The model systems used included plants, planaria, flies, fish, amphibians and mice (Fig. 1). Despite the apparently diverse topics of the meeting, there proved to be significant cross-fertilization of ideas across these fields and a number of common themes were apparent.

A major goal for those studying regeneration is to reveal mechanisms that may inform strategies for restoring function to damaged or diseased tissues in mammals. This requires the integration of a number of distinct processes; some that recapitulate development and others that are unique to the regenerative context, perhaps reflecting the more mature environment of the adult organism where regeneration is generally studied. Some of the key questions in the field were directly tackled at this meeting. For example, which cells contribute to regeneration: endogenous stem cells already present in the tissue and/or differentiated cells that dedifferentiate or are reprogrammed to new identities? How do regenerating systems balance cell proliferation with differentiation during regeneration and ensure tumors do not occur?

Regeneration often begins with the formation of a blastema, a mass of cells capable of regenerating tissues and organs. The mechanisms underlying blastema formation and by which signaling gradients and cellular identities emerge from a blastema remain poorly understood. Moreover, it seems certain that mechanical forces will influence cell behavior during regeneration – as they do during normal development, where (as discussed by several speakers) the impact of tissue strain and other forces have been better analyzed. Finally, the ability to generate organs in a dish from embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) provides new opportunities for restoring function to tissues damaged by injury or disease.

The meeting at the RIKEN CDB not only showcased the most recent findings in the fields of regeneration and self-organization, but also allowed for easy exchange of ideas in an informal setting during meeting breaks, poster sessions and meals. The recent blossoming of iPSC technology and demonstrations of self-organization emanating from Japanese laboratories made this venue ideal for the meeting, which proved a great success: I for one returned to my laboratory inspired to tackle new challenges.

## Molecular mechanisms of regeneration – cell programming and reprogramming

Among the most remarkable examples of regeneration is the ability of planarians to regenerate whole bodies from fragments. Interestingly, not all planarians exhibit the same regenerative potential: some, including the most common lab species, can regenerate heads from tail fragments, but others – such as *Phagocata kawakatsui* – cannot. Recent studies suggest β-catenin plays an important role in determining the planarian body plan (Reddien, 2011). Yoshihiko Umesono (University of Hyogo, Japan) described his lab's recent finding that extracellular-regulated kinase (ERK) signaling contributes to a planarian's anterior identity and that this signaling is inhibited by β-catenin (Umesono et al., 2013). He proposed that reduced ERK signaling resulting from excess β-catenin expression in *P. kawakatsui* explains the inability of this species to regenerate head tissue.

Limb regeneration in amphibians is another remarkable example of regenerative capacity. This is strikingly demonstrated by the phenomenon of accessory limb formation (Endo et al., 2004). In this model, the anterior part of the limb's dermis is removed and replaced with a patch of dermis from the posterior limb. When this anterior/posterior discontinuity is combined with nerve deviation to the site of the graft, an accessory limb grows out from the wound site. Elly Tanaka reported on the role that Shh, Gli3, Hand2, gremlin and Fgf8 play in this process in axolotl. These studies revealed temporal and spatial constraints for these different signaling components and suggest that their interdependent expression patterns are important for mediating the effects of positional discontinuity on limb outgrowth. Although positional discontinuity is a necessary trigger for accessory limb outgrowth, it is not sufficient: nerve deviation is also required. Interestingly, skin wounding along with nerve deviation in the absence of positional discontinuity can induce blastema formation. Akira Satoh (Okayama University, Japan) described studies in axolotl investigating the identity of nerve-derived factors necessary for blastema formation and limb outgrowth (Makanae et al., 2013). Using deep sequencing of dorsal root ganglion neurons, his group identified several molecules that stimulate nerve-independent blastema and limb

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| Model system | | Regenerative capacity | Potential source |
|---|---|---|---|
| Plant |  | + + + + + + + | Stem cells; transdifferentiated, dedifferentiated and reprogrammed cells |
| Planarian |  | + + + + + + + | Stem cells (neoblasts) |
| Fly |  | + + + + | Stem cells; transdifferentiated, dedifferentiated and reprogrammed cells |
| Fish |  | + + + + + + | Stem cells; transdifferentiated, dedifferentiated and reprogrammed cells |
| Urodele |  | + + + + + | Stem cells; transdifferentiated, dedifferentiated and reprogrammed cells |
| Anuran |  | + + + + | Stem cells; transdifferentiated, dedifferentiated and reprogrammed cells |
| Mouse |  | + + | Stem cells; transdifferentiated, dedifferentiated and reprogrammed cells |

**Fig. 1. Regenerative capacity over the phyla.** Some of the systems used to study regeneration and discussed at the 'Regeneration of Organs: Programming and Self-Organization' meeting are listed on the left. Their relative regenerative capacity is indicated in the middle column and the potential sources of cells for organ repair are indicated in the right-hand column.

formation. Staying on the theme of limb regeneration, but moving away from the highly regenerative axolotl system, Shinichi Hayashi (Tohoku University, Japan) reported on limb regeneration in transgenic *Xenopus* tadpoles that conditionally express dominant-negative Yap – the transcriptional regulator downstream of the Hippo pathway (Hayashi et al., 2014). They found that Yap is expressed in the regenerating limb and that its inhibition perturbs expression of pattern formation genes and limb regeneration. These studies suggest a crucial role for Hippo signaling in limb regeneration. Towards identifying new strategies for stimulating limb regeneration in mammals, Alan Rodrigues (Harvard University, Cambridge, MA, USA) reported on his studies in which he is reprogramming fibroblasts to assume properties of limb progenitors. Together, the above studies not only inform us of mechanisms underlying limb development and regeneration, but may also suggest novel strategies for regrowing limbs in adult animals.

Koji Tamura (Tohoku University, Japan) described studies investigating wound healing in *Xenopus* where wounds heal without scarring (Kawasumi et al., 2013). In this system, a blastema-like structure forms that consists of proliferating cells expressing Prx1. Interestingly, wound healing in mammals does not result in Prx1 expression and this healing is accompanied by scarring. To better understand regenerative mechanisms in mammals, Ashley Seifert (University of Kentucky, Lexington, KY, USA) reported on a species of rodent (*Acomys*) that exhibits enhanced regenerative ability (Seifert et al., 2012) and generates a blastema-like structure in ear holes, including the formation of a wound epidermis and regenerative extracellular matrix. These rodents provide evidence that blastema formation may be possible in mammals and should prove a useful model for investigating the mechanisms underlying this process.

We then turned to healing a broken heart, which does not readily occur in mammals. This is partly due to the loss of proliferative potential in maturing cardiac myocytes and it is thought that reawakening their proliferative capacity may provide a means for heart repair. With this goal in mind, Takashi Takeuchi (Tottori University, Japan) described studies on G1- and M-phase inhibitory systems that maintain cardiomyocyte cell cycle exit in mammals, as well as his group's efforts to establish a newt molecular genetic system to examine how these regulators change in newt cardiomyocytes during heart regeneration. Ryo Nakamura (University of Tokyo, Japan) discussed her work examining epigenetic changes in relation to the age-dependent decline in mammalian cardiac repair. She found that age-related changes in a component of the SWI/SNF chromatin remodeling complex correlates with reduced cardiomyocyte proliferation and heart regeneration. Importantly, gain-of-function studies suggested this factor improves the regenerative response of cardiomyocytes. Ken Poss (Duke University, Durham, NC, USA) described new studies investigating epicardial regeneration in zebrafish heart. He reported that epicardial cells are crucial for heart regeneration and that injury to the heart stimulates a global epicardial regenerative response. Remarkably, his lab discovered that signaling from the cardiac outflow tract plays a key role in modulating epicardial regeneration. These studies suggest that unsuspected communication between these adjacent tissues may be crucial during heart regeneration.

Continuing the muscle theme, but with a focus on skeletal muscle, Andras Simon (Karolinska Institute, Solna, Sweden) reported on new data connecting the cell death pathway with myonuclear dedifferentiation during newt limb regeneration. Work from his lab revealed that transient activation of the apoptotic pathway may be needed for myofiber fragmentation, whereas sustained activation of caspases may contribute to myonuclear dedifferentiation and proliferation.

Reflecting the wide range of regenerative systems under active investigation and presented at this meeting, Feng Chen (Stanford

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University, CA, USA) described recent studies on how *Drosophila* replace trachea during metamorphosis using a fibroblast growth factor signal emitted by decaying tracheal branches that attract and guide progenitors from their niche (Chen and Krasnow, 2014). Finally, Dan Goldman (University of Michigan, Ann Arbor, USA) reported on new work from his lab identifying injury-induced growth factors and cytokines that stimulate Müller glia to produce multipotent progenitors for retinal repair in zebrafish. These factors exhibit extensive crosstalk and are derived from injury-responsive Müller glia, suggesting Müller glia contribute to their own reprogramming.

## Pattern formation, and determination of organ shape and size

Understanding how signaling gradients emerge from an amorphous mass of cells and how they scale are major questions in regenerative biology – as they are for developmental biologists. Hans Meinhardt (Max Planck Institute, Tübingen, Germany) reported that reactions based on local self-enhancement and long-range inhibition have strong self-regulatory properties, and help both to generate organizers and to contribute to their regeneration during axis formation. However, such reactions have the inherent tendency to generate supernumerary organizers during growth, which could lead to malformations such as axis duplication. Using modeling approaches, he presented evidence that, dictated by their different sizes, *Hydra* and *Planaria* have found different mechanisms to suppress unwanted organizers, yet retain the ability to generate new organizers in case regeneration is required.

Naama Barkai (Weizmann Institute, Rehovot, Israel) described her ideas about scaling morphogen gradients based on an expansion-repression model where an expander expands the morphogen gradient, but is itself repressed by morphogen signaling. Examples included scaling of Dpp signaling in the growing *Drosophila* imaginal wing disc (Ben-Zvi et al., 2011) and of the Bmp signaling gradient that controls dorsal-ventral patterning in the *Xenopus* embryo (Ben-Zvi et al., 2008). Barkai suggested that scaling of the Bmp morphogen gradient with animal size is controlled by the expression of Admp, which has properties of an expander. Also looking at the scaling of dorsal-ventral patterning in *Xenopus*, Tatsuo Shibata (RIKEN CDB, Kobe, Japan) described recently published studies suggesting the Chordin proteinase inhibitor Sizzled may be the major determinant of scaling in this system (Inomata et al., 2013). Shibata presented a mathematical model based on protein interactions, diffusion, degradation and bone morphogenetic protein (BMP)-regulated production that recapitulated the gradients of these molecules observed in the embryo. The mathematical analysis indicated that the embryo size-dependent accumulation of Sizzled regulates the range of Chordin activity by protein stabilization, which generates a BMP signaling gradient proportional to the embryo size.

Regeneration, like development, involves morphogenetic processes that shape tissues and organs. Insights from developmental studies are revealing the crucial importance of mechanical considerations during tissue formation/deformation. Although this has been little studied during regeneration, a better understanding of tissue mechanics during organ growth is likely to reveal novel principles underlying the regenerative process. A theme emerging from this field is that cell division, shape and tension are key interrelated factors in tissue morphogenesis. Modeling tissue deformations allows one to hone in on crucial parameters of this process. Taiji Adachi (Kyoto University, Japan) presented his work on modeling and simulation of morphogenetic processes such as eye cup formation. He described a mathematical model, the reversible networks reconnection model, that better simulates large tissue deformations and expansions, and also takes into account cell division and growth (Okuda et al., 2013). Yanlan Mao (University College London, UK) described elegant studies combining biology and modeling to investigate mechanisms of tissue morphogenesis during *Drosophila* wing disc development (Mao et al., 2013). She reported on how orientated cell division is controlled by tissue tension anisotropy that affects cell shape. Furthermore, she showed how modeling the *in vivo* spatial and temporal proliferation rates *in silico* can predict cell shape changes and growth patterns, and how this modeling can inform one of mechanisms underlying tissue growth. Richard Adams (University of Cambridge, UK) presented beautiful time lapse images of zebrafish neural tube closure and forebrain development. The optical clarity of zebrafish embryos makes them an excellent organism for imaging. Adams' laboratory has developed automated cell tracking tools to quantify cell shape changes and movements that underlie neurulation and its defects. Tsuyoshi Hirashima (Kyoto University, Japan) discussed computational and biological studies of mouse epididymal tube formation. Combining computational models and immunofluorescence labeling, Hirashima found that folding of the tube is driven by its interaction with external structures that cause resistance and a non-uniform gradient of cell proliferation along the tube. These kinds of studies may help define the mechanics that drive tissue deformations and organ formation in self-organizing systems.

The molecular genetic tools that can be applied to *Drosophila* make it an ideal system for teasing out mechanisms underlying organ growth, regeneration and morphogenesis. Ken Irvine (Rutgers University, Howard Hughes Medical Institute, Piscataway, NJ, USA) described elegant work that connects cell signaling and cell tension with organ growth. Previous studies have suggested Jnk signaling is crucial for tissue repair and regulates cell proliferation via activation of the Hippo signaling pathway (Sun and Irvine, 2011). Using a combination of genetic and biochemical approaches, the Irvine lab has now found that these two signaling pathways are linked by Ajuba family proteins (Sun and Irvine, 2013). Irvine also presented recent data suggesting cytoskeletal tension regulates organ growth. The idea is that as cells become compressed with tissue growth, the ensuing cytoskeletal tension results in signals that restrict further growth. Remarkably, the Ajuba proteins also play a role here, linking the mechanotransducer α-catenin with Yorkie signaling and the Hippo pathway. Pierre Leopold (Institute de Biologie Valrose, Nice, France) reported on a screen for regulators of neoplastic growth in *Drosophila* that identified Grindelwald (Grnd), a transmembrane receptor for the *Drosophila* tumor necrosis factor ligand Eiger. Interestingly, Grnd mediates the pro-apoptotic functions of Eiger and couples Crumbs induced loss of cell polarity with Jnk activation and neoplastic growth. Gines Morata (Universidad Autonoma De Madrid, Spain) reported on studies that use the *Drosophila* wing disc as a model to investigate cell reprogramming during regenerative growth. Morata found that following damage to anterior or dorsal compartments of the wing disc, positional boundaries break down and cells responsible for tissue regeneration infiltrate the damaged area and reprogram to take on the identity of neighboring cells. Importantly, these changes in cell identity are associated with Jnk pathway activation and relaxation of epigenetic controls (Herrera and Morata, 2014).

Returning to mice and mechanisms underlying the shaping of organs during development, Manuel Serrano (Spanish National Cancer Research Center, Madrid, Spain) discussed his lab's work indicating that cell senescence contributes to tissue development and organ morphogenesis (Munoz-Espin et al., 2013).

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## Reprogramming and self-organization

The generation of tissues from an undifferentiated cell mass is a remarkable process that suggests a certain degree of self-organization. In plants, a mass of cultured callus cells can give rise to new, well-organized, plant tissue. Kaoru Sugimoto (California Institute of Technology, Pasadena, USA) described studies suggesting plants harbor endogenous stem cells that may be derived from pericycle cells that surround the plant vasculature. Sugimoto reported that the callus is derived from these pre-existing stem cells rather than from a dedifferentiation process (Sugimoto et al., 2011). Thus, like animals, plants may use adult stem cells residing in vascular niches for regenerative purposes.

The ability to generate organs from primordial cells has potential for treating disease, replacing damaged tissue parts, drug screening and disease modeling along with informing us of developmental processes. Takashi Tsuji (RIKEN CDB, Kobe, Japan) described his approach for bioengineering organs for transplantation and organ replacement in mice (Hirayama et al., 2013; Ogawa et al., 2013). A key to the success of this is the use of a 3D culture system where epithelial-mesenchymal interactions are reconstructed at high cell density with cell compartmentalization in a collagen drop. Once the organ germ develops they are transplanted into their native compartment for further maturation *in vivo*. Using this strategy, his lab has successfully bioengineered teeth, salivary gland, lachrymal gland and hair follicles. With the arrival of iPSC technology, it will be interesting to see whether these cells can be used for generating the organ germs needed for transplantation into humans. Karl Koehler (Indiana University, Bloomington, USA) presented recent success in using ESCs to generate inner ear organoids in 3D culture (Koehler et al., 2013). The organoids appeared to mature normally with structural and functional characteristics of sensory epithelia of the inner ear. Remarkably, otic neurogenesis was also observed and hair cells were innervated and responsive to mechanical stimulation. Atsuhiro Taguchi (Kumamoto University, Japan) described his work on generating kidney structures from ESCs (Taguchi et al., 2014). The team used development to inform them of cues that would drive pluripotent stem cells to form metanephric mesenchyme that forms most kidney structures. Importantly this approach revealed the developmental origin of the metanephric mesenchyme. Manuel Serrano described recently published work on *in vivo* reprogramming with pluripotency factors in mice (Abad et al., 2013). His studies suggest that *in vivo* reprogramming is possible in mammals and that under the right conditions one might be able to activate a regenerative program for tissue repair.

Many of these talks beautifully illustrated the ability of cells to self-organize into complex structures and Yoshiki Sasai's (RIKEN CDB, Kobe, Japan) presentation on the generation of retina and cerebral cortex-like structures from ESCs emphasized this point (Eiraku and Sasai, 2012). The recapitulation of tissue folding, cell layering and cell polarization in a dish demonstrates that intrinsic mechanisms drive these events. Although we know very little about how these patterns are generated, it seems likely that the formation of gradients, local differences in cell proliferation and cell forces along with the changing mechanical strains will play important roles.

## Concluding remarks

The field of regeneration research is vast when considering the model systems studied, the structures that are repaired and the mechanisms underlying this repair. By bringing together a diverse group of scientists with a common interest in regeneration and organ growth, this meeting pushed its participants to think in new ways about their research and this can only have a positive impact on the field. Although the event highlighted our successes in understanding the processes underlying organ growth and regeneration, it also revealed how far we still need to go before these findings can be applied in the clinic. Nonetheless, the progress demonstrated by researchers at this meeting suggests that this is an achievable goal.

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The author declares no competing financial interest.

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