



Editorial overview: Development and regeneration: Nervous system development and regeneration

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Current Opinion in Neurobiology 2014, 27:iv–vi

For a complete overview see the [Issue](#)

Available online 11th June 2014

<http://dx.doi.org/10.1016/j.conb.2014.05.007>

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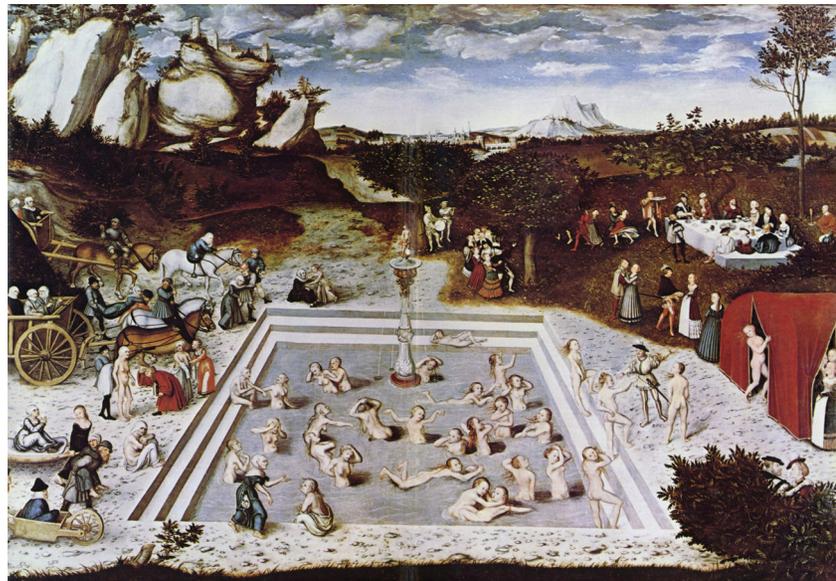
Frank Bradke is a senior group leader and full professor with the DZNE. His group studies the intracellular mechanisms underlying axon growth during both development and regeneration. Bradke and his colleagues have contributed to our understanding of how the cytoskeleton drives axon growth during neuronal polarization and how these mechanisms can be reactivated under pathological conditions, such as a spinal cord injury, to induce axon regeneration. His group has recently developed a whole tissue imaging approach, which allows imaging of the brain and spinal cord without prior histological sectioning.

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Oscar Marín is a group leader at the Instituto de Neurociencias in Alicante, Spain. He will become Director of the MRC Centre for Developmental Neurobiology at King's College London in July 2014. He is interested in understanding the mechanisms that control the development of the cerebral cortex, and how abnormal brain development leads to disease. The development of cortical interneurons is an important focus of his research.

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Lucas Cranach the Elder (1472–1553), The Fountain of Youth, 1546, Wikipedia.

The idea of rejuvenation has fascinated people throughout history. The famous painting of Lukas Cranach, which shows the imaginary fountain of youth, reflects the wishes and hopes of past and present societies only too well. Would it be possible to ‘rejuvenate’ processes in organisms to combat pathological conditions? This question has raised much attention over the recent years. For the nervous system, if and how pathological processes, including axon degeneration and cell death, could be counteracted by reactivating programs that drive neuronal development, is intensely discussed. In this issue, we have compiled a set of reviews that highlight neurodevelopmental mechanisms and discuss their potential to induce regeneration within the nervous system. Closely linked to this theme, the reviews also consider how aberrant developmental processes could lead to the pathological changes that result in neurological diseases. Rather than rejuvenating the system, these malfunctioning processes lead to decay. Together, these reviews give a current perspective on a range of neurodevelopmental processes, how these processes are affected in neural diseases and how these processes could be exploited toward regeneration.

The first part of the issue deals with the role of ligand receptor signaling in wiring the nervous system during development and how this signaling affects axon growth after a spinal cord injury. In a first group of reviews, the authors summarize recent findings on the signaling mechanisms that

control the formation of the brain. Three of these reviews focus on the main families of classical axon guidance molecules, including Slit, ephrin and semaphorin signaling. [Blockus and Chédotal](#) discuss the many developmental processes that are controlled by Slit proteins through their Robo receptors, including neurogenesis, neuronal migration, axon guidance and dendritic outgrowth. They also emphasize the link between abnormal Robo signaling and important neurodevelopmental disorders, such as autism. [Klein and Kania](#) provide new vistas into another important family of guidance molecules, Eph tyrosine kinase transmembrane receptors and their ephrin ligands. These molecules, initially known for their role in guidance of developing axons, are now thought to mediate a wide range of events during brain development, from neuronal migration to synapse formation. Finally, [Koropouli and Kolodkin](#) focus their attention on the increasingly recognized role of Semaphorins in neural circuit development. In a separate article, [Garel and López-Bendito](#) take a complementary approach to review the main signaling events that participate in the development of the thalamocortical projection, one of the most important axonal tracts in the brain. The authors illustrate the difficulties posed by analysis of the concerted actions of multiple signaling pathways acting during the same developmental time window, and highlight the importance of identifying the functional consequences of these interactions. In a second set of reviews, the authors reveal how manipulation on the level of the cell surface ligands and receptors can lead to axon regeneration. The question of how axon guidance signals wires the brain during development and how the same signals prevent axons from regenerating after a spinal cord injury are explored by [Onishi et al.](#) for the wnt signaling pathway. In their review, [Schwab and Strittmatter](#) reveal how Nogo signaling, a major signaling cascade that prevents axons from regeneration after an injury in the central nervous system (CNS), also regulates experience-dependent neural plasticity and controls synapse formation as well as synaptic, dendritic and axonal anatomy. This review highlights an emerging role of growth inhibitory factors, namely, they also restrict growth and plasticity within the nervous system, which is important for a proper wiring. [Silver and Silver](#) highlight in their review how the chondroitin sulfate proteoglycans, another well-known class of molecules, which restrict axon growth during development and after a spinal cord injury, direct the migration of cancer cells. Hence, a theme emerges, whereby the same molecules can be used in very different contexts and diverse cell types to enable either attraction or repulsion. This part of the issue is concluded by a review from [Geoffroy and Zheng](#) who discuss myelin-associated inhibitors and their receptors in detail. The authors emphasize the different types of regenerative responses including sprouting and regeneration, which will help to better define and categorize axon regenerative processes in the future.

The second part of the issue focuses on cell-intrinsic signaling pathways. A large body of evidence suggests that these pathways control axon growth not only during development but that their manipulation can induce regeneration. [Mairet-Coello and Polleux](#) describe several molecular pathways that contribute to A β oligomer-induced synaptotoxicity and the potential contribution of these pathways to Alzheimer's disease. In particular, they review the involvement of 'stress-response' kinase pathways such as the CAMKK2-AMPK and the mTOR-JNK3 pathways, which have also been previously shown to mediate axon growth. [Navarro and Rico](#) review the pivotal role of the intracellular protein kinase Focal Adhesion Kinase (FAK) in the integration of multiple signaling pathways linked to the active remodeling of axons and dendrites. [Zhong and Zou](#) describe novel insights into BMP signaling, a well-known pathway for its role during neuronal development. They describe its effects, which ultimately lead to axon regeneration, down to the level of the cytoskeleton. [Eva and Fawcett](#) present the current finding of how integrin signaling mediates not only axon growth during neuronal development, but also how activation of integrin signaling can boost axon regeneration in the adult CNS. In this review, the authors highlight the importance of trafficking integrin signaling units to the axon. Novel insights into axon and dendritic trafficking are then presented in detail by [Maeder et al.](#), who discuss how cargo is sorted, delivered and kept at specific locations within the neuron. [Lu et al.](#) provide novel insights into signaling networks that control axon regeneration. They focus on the mTOR signaling pathway and several transcription factors, including STAT-3 and SOCS3. [Cho and Cavalli](#) present an exciting perspective of how epigenetic signaling accounts for the neuron intrinsic growth response focusing on histone modifications through HDAC signaling. While HDAC signaling is instrumental for neurogenesis during development, recent work reveals that HDAC signaling may facilitate a regenerative axon growth state. Finally, [Yoshimura and Rasband](#) focus on the role of the axon initial segment (AIS) in the generation of action potentials and in the maintenance of neuronal polarity. They describe how cytoskeletal proteins organize this important sub-cellular component and outline recent findings implicating the dysfunction of many AIS proteins in neurological disorders.

The third part of the issue highlights the power of systems other than mammalian models to decipher molecular regeneration and degeneration pathways. These organisms include *Caenorhabditis elegans*, *Drosophila* and zebrafish, all classical model systems to study neurodevelopmental questions. Here, [Hammarlund and Jin](#) present the current exciting efforts to identify regeneration causing genes in *C. elegans*. Their review highlights differences and similarities in the regeneration program in invertebrates in comparison to mammals. In fact,

the DLK-1 kinase was identified as a central player in the axon regenerative response of *C. elegans*, which triggered much research in the mammalian system. It will be fascinating to see how this field further develops, and the review helps to follow these exciting developments. [Becker and Becker](#) discuss the current understanding of axon regeneration in zebrafish. This invertebrate model shows neither an inhibitory scar that prevents axons from regenerating nor is the zebrafish myelin inhibitory for regenerating axons. Moreover, some zebrafish neurons, such as Mautner cells, have a low regenerative capacity, which make this system attractive to study the neuron-intrinsic regenerative programs in genetic screens. [Chang](#) and colleagues draw intriguing parallels between the mechanisms that control the development of the peripheral nervous system in *Drosophila* and the pathogenesis of multiple human neurodegenerative disorders. [Soldano and Hassan](#) describe the power of *Drosophila* genetics to understand the role of Amyloid Precursor Proteins (APPs) in normal development. They propose that APP plays a fundamental role in sustaining the robustness of brain wiring, a function that may contribute to explain their role in the pathogenesis of Alzheimer's disease (AD). [Yu and Schuldiner](#) review recent insights into more general mechanisms controlling axon and dendrite pruning in *Drosophila*. The authors use mushroom body and dendritic arborization neurons as model systems to compare pruning mechanisms in axons and dendrites. This part is rounded up by a review from [Freeman](#) that discusses the signaling mechanisms underlying Wallerian degeneration exploiting different organisms. In this review, the power of the different organisms to elucidate the signaling pathways is highlighted.

In the fourth part, we have compiled a set of reviews that deal with cell populations and their differentiation during development and under pathological conditions. Two reviews focus on novel strategies to reshape neurons and circuits. [Anderson and Vanderhaeghen](#) describe the use of embryonic and induced pluripotent stem cells (PSC) to generate specific populations of neurons from the cerebral cortex. [Arlotta and Berninger](#) focus on new strategies to achieve direct lineage reprogramming of cells *in vivo*, challenging the very fundamental notion of brain immutability. They also describe how these approaches have the potential to be used for the regeneration of specific brain circuits. [Boije et al.](#) present a model of how recent findings showing a stochastic contribution to the cell proliferation and fate choice of retinal progenitor cells fits into the progress of their temporal competence. Their review may help to solve potential conflicts regarding the multipotency of retinal progenitor cells. [Funahashi et al.](#) discuss how neurons polarize in a complex environment. They emphasize in their review that some neurons have their polarity inherited from their precursors, whereas other types of neuron, including neurons derived from the neocortex, establish their

polarity at later stages. [Borrell and Götz](#) also look at cortical progenitors, but from a different angle. They describe recent findings identifying novel classes of cortical progenitor cells and their role in gyrification, a complex process with important evolutionary implications. [Sloan and Barres](#) present novel insights into astrocyte development and how dysfunction of these processes contributes to neurodevelopmental disorders. Also here, the differentiation program of neural stem cells separates cell fates temporally, that is, first showing a neurogenic and later a gliogenic prevalence. The review highlights the identified signaling factors regulating gliogenesis and discusses their contributions to scarring after a spinal cord injury. [Ueno and Yamashita](#) take a fresh look at a distinct population of non-neuronal brain cells, microglia, and their role in modulating multiple processes during development, from neurogenesis to synaptogenesis. This review also highlights the idea that disruption of microglia function can lead to CNS disorders. The review of [Lu et al.](#) highlights recent progress in exploiting the differentiation of neural stem cells to enable axon growth and re-wiring of the injured spinal cord. The progress in this area has been substantial, and it appears that the formation of appropriate synapses by regenerating axons will be a topic for the years to come. In fact, the issue is rounded up by two reviews on our new insights into how synapses are formed and maintained. [Schreiner](#) and colleagues review the function of polymorphic receptors, such as DSCAM1 and Neurexins, in neuronal self-avoidance and synaptic connectivity. They compare the function of these receptors across different species and discuss how their function may have evolved over time. Finally, [Andreae and Burrone](#) summarize recent findings on the role of neuronal activity in the formation of synapses. One of their main conclusions is that the influence of activity in synapse development and plasticity varies enormously depending on the circuits involved, even at the level of individual synapses, which poses a great challenge for future studies.

In summary, the compiled reviews give a fresh perspective on a longstanding question in neuroscience, how can pathological processes be counteracted to ensure the maintenance of proper wiring and processing of information? There is no single answer to this question, but here, the authors argue that part of the answer is found in mechanisms that drive neuronal development. Thus, rejuvenating the system through activating mechanisms that drive neuronal development may help us to combat the devastating effects of neurological diseases. Clearly, the fountain of Youth will remain a fantasy. Nevertheless, the elucidation of regenerative mechanisms that may help to soften the outcome of diseases affecting the nervous system is now in sight.

Acknowledgement

We thank Dr. Charlotte Coles for thoroughly reading and commenting the Editorial.