Commentary

Stem Cell INVESTIGATION

Spotlight on the Schwann cells during the regeneration

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Despite the keen interest and decades-lasting efforts to puzzle out the enigma of regeneration capacity of diverse organisms, the desired key to the mammalian multi-tissue regeneration is still far from being discovered. It is obvious that with the increasing complexity of animal body plan and function, the ability to regenerate various tissues is being significantly reduced. While organisms such as cnidarians or flat-worms can regenerate significant parts of their bodies (1,2), the only multi-tissue regeneration known from mammals, specifically from mice and humans, is the re-growth of the lost digit tip (3). Interestingly, one of the common links found in the regenerative processes of diverse organisms turned out to be a nerve-dependence. For example, the nerve presence is essential in crustacean appendage regeneration as well as in a re-growth of amputated sea star limb (4). Vertebrate limb regeneration is no exception to this rule and, therefore, is also dependent on the presence of local innervations (5).

Since the initial discovery of the importance of the nerve presence for the regeneration, the Schwann cells got into the spotlight. Schwann cells, both myelinating and non-myelinating, were historically considered as a protective and trophic support for the nerves. However, many recent discoveries point out to their impressive phenotypical plasticity and a number of non-canonical functions these cells perform (6). Despite it is not absolutely clear yet whether the presence of Schwann cells is a key to regeneration of various tissues in all regenerating vertebrates, there is an increasing evidence that these nerve-associated cells are responsible for secreting factors strongly supporting the formation of regenerative blastema.

Developmentally, the Schwann cells originate from Schwann cell precursors (SCPs). SCP is a neural crest-derived unique cell type that possesses remarkable fate plasticity. It has been shown both *in vitro* and *in vivo* that SCPs can give rise, except of both myelinating and non-myelinating glia, to another cell types such as melanocytes, smooth muscle cells, neurons, mesenchymal cells and others (7-9). As the SCPs accompany nascent nerves to virtually every part of the developing body, they serve as an omnipotent embryonic source for both glial and non-glial cell types. Some degree of cell fate plasticity is maintained by adult Schwann cells and they are thus perceived as being oligopotent as well. This remarkable capacity of Schwann cells represents promising tool and research direction in regenerative medicine.

Recently, it has been shown that mouse digit tip can regenerate completely after the amputation (10). Moreover, this process is dependent on the innervations. In a more recent study by Johnston *et al.*, it has been shown that the re-growth of an amputated mouse distal digit tip is dependent on the presence of Schwann cells that produce special molecules boosting regeneration and improving morphogenesis (11). Authors performed series of elegant experiments to demonstrate that upon injury, Schwann cells detach from the terminal axons in the affected site, dedifferentiate, undergo multiple cell divisions and secrete factors that attract mesenchymal cells thus supporting the blastema formation. The ablation of Schwann cells from the future site of injury resulted in very limited and imperfect regeneration of the digit tip. This observation raised a question whether Schwann cells support the re-growth of the digit by having a paracrine function. Further investigation showed that during the process of blastema formation, two key ligands, ONCOSTATIN-M and PDGF-AA, are secreted by Schwann cells. Surprisingly,

these two molecules are completely sufficient to compensate the absence of Schwann cells and rescue the regenerative process when injected into an injured site.

A similar logic has been previously described for regenerating salamander limb: Schwann cells from the transected nerve secrete nAG ligand that stimulates blastemal formation through binding to PROD in other cells of the limb (12). Secretion of nAG leads to local dedifferentiation of mature cells types as a regeneration starting point.

It is not clear today, whether Schwann cells serve as a primary sensor cell type for tissue damage, or the signal about traumatic events is rather translated by other cell types/local molecular events. Also, our knowledge about phenotypic plasticity of Schwann cells suggests that they may enter a somewhat activated state potentially similar to what has been previously described as regenerative Bungner cell (13) or SCP. In any case, these issues deserve further in depth investigation.

Interestingly, despite particular differences in molecular messengers and receptors utilized to activate regeneration, the cellular logic of the process (also including nerve-dependence) in vertebrates seems to stay very conservative. The early predictions suggested that blastemal cells are multipotent and produce a wide range of derivatives not limited by fate restrictions. Could Schwann cells drive the surrounding tissues into a very early embryonic progenitor state? It turned out that in amphibians and mammals, the dedifferentiated cell lineages in blastema rather keep their major identity during regeneration, producing only a limited spectrum of mature cell types within their narrow competence range (14). This conservation between distant animal groups may suggest that basic cellular mechanisms of regeneration are more complex and ancient than we think, while the blastema-initiating molecular signals may vary between various groups of organisms.

It remains unclear what are the sequential steps of the regeneration process. Could the first signal come from the damaged skin or vasculature that would in turn attract the dedifferentiated Schwann cells into the forming blastema? The secretion of ONCOSTATIN-M and PDGF-AA by these regenerative Schwann cells might trigger activation of other cell types present in the injured site, possibly of mesenchymal cells. It has been shown that many more factors such as WNT5, FGFs (1, 5 and 9), SHH, DHH and others strongly influence the successful digit tip regeneration (15,16). Since the administration of ONCOSTATIN-M and PDGF-AA itself provides a sufficient starter for the regeneration of amputated digit tip without forming any molecule gradient that would be expected from natural *in vivo* situation, we can assume the Schwann cells play a role of a response mediator in this process. Of highest interest is to find out what is the main difference between the digit tip and other parts of mammalian body that cannot be easily regenerated. As suggested by other authors, the presence of a specific tissue, in this case the nail bed and the mesenchyme expressing Msx1 (10) can be one of the missing links to the mammalian tissue regeneration.

The study by Johnston *et al.* most definitely accelerated our search for the Holy Grail of human regeneration given high degree of genetic and molecular similarity between mice and humans. Also, in terms of regenerative potential and limitations, we are very much similar to mice. For example, humans also possess a capacity to fully regenerate the lost digit tip. However, unlike in mice, this capacity is strictly limited to a very young age (17). Still, it gives us a hope that the system of ligands activating and boosting regeneration might be the same. Further investigation and clinical trials of ONCOSTATIN-M and PDGF-AA-based therapies should bring us closer to a new age of regenerative medicine.

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Footnote

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