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Comparative analysis of oligodendrocyte and Schwann cell plasticity after lesion

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The peripheral nervous system (PNS) is able to regenerate after a lesion, whereas the regeneration of the central nervous system (CNS) is mostly inefficient. The efficiency of PNS regeneration is mainly due to the remarkable plasticity of Schwann cells (SCs), the myelinating glia of the PNS. In contrast, oligodendrocytes (OLs), the myelinating glia of the CNS, do not have these abilities. Understanding mechanisms involved in SC plasticity could help enhance OL plasticity and potentially CNS regeneration.

In a first part of my PhD, I developed *in vitro* lesion models of neurons/SCs and neurons/OLs myelinating co-cultures in a microfluidic device, and I showed that these models recapitulate all regeneration steps of the PNS, and CNS regeneration failure. Interestingly, RNA sequencing analyses of myelinating glia at 1 day post axonal lesion compared to no lesion revealed novel gene regulations and major differences between SC and OL transcriptional programs after lesion.

In addition, I showed that Schwann cells disintegrate distal cut axons after lesion to allow their timely clearing. This mechanism is induced by distal cut axons, which signal to Schwann cells through PlGF mediating the activation of VEGFR1 in Schwann cells. In turn, VEGFR1 activates Pak1, leading to the formation of constricting actin spheres, which fragmentate distal cut axons. Interestingly, oligodendrocytes can acquire a similar behavior as Schwann cells by enforced expression of VEGFR1. These results thus identify controllable molecular cues of a neuron/glia crosstalk essential for timely clearing of damaged axons.

In another part of my PhD, I found *in vivo* that major regulators of SC plasticity are oppositely regulated in OLs after lesion. Indeed, cJun and Oct6 are downregulated and Sox10 is upregulated in OLs after a spinal cord lesion. Interestingly, overexpression of the stemness factor Sox2 induces the upregulation of cJun, as well as the downregulation of Sox10, suggesting a potential strategy to modulate mature OL plasticity. Moreover, I found that the chromatin remodeling enzyme HDAC2 is highly expressed in OLs and maintains a high level of Sox10 in OLs, either in unlesioned or lesioned spinal cords. This work provides new potential strategies to enhance the plasticity of mature OLs after lesion and therefore CNS regeneration.

Jury:
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