The mechanical control of nervous system development and regeneration

Kristian Franze

During development and pathological processes, cells in the central nervous system (CNS) are highly motile. Despite the fact that cell motion is driven by forces, our current understanding of the mechanical interactions between CNS cells and their environment is very limited. We here show how nanometer deformations of CNS tissue caused by piconewton forces exerted by cells contribute to regulating CNS development and pathologies. *In vitro*, growth and migration velocities, directionality, cellular forces as well as neuronal fasciculation and maturation all significantly depended on substrate stiffness. Moreover, when grown on substrates incorporating linear stiffness gradients, glial cells migrated towards stiffer, while axon bundles turned towards softer substrates. *In vivo* atomic force microscopy revealed stiffness gradients in developing brain tissue, which axons followed as well towards soft. Interfering with brain stiffness and mechanosensitive ion channels *in vivo* both led to similar aberrant neuronal growth patterns with reduced fasciculation and pathfinding errors. Importantly, CNS tissue stiffness significantly changed after traumatic injuries. Ultimately, mechanical signals not only directly impacted neuronal growth but also indirectly by regulating neuronal responses to chemical guidance cues, strongly suggesting that neuronal growth is not only controlled by chemical signals – as it is currently assumed – but also by the tissue's local physical properties.