CDB SEMINAR

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Friday, July 28

16:00~17:00 C1F CDB Auditorium

Vertebrate limb patterning and innervation

Summary

We are studying how intercellular signaling influences early limb development. We have focused on the regulation of signaling centers that pattern the limb axes, and on how the limb mesenchyme influences motor axon projection decisions as the limb is innervated.

Early in limb development, signaling molecules must be expressed in precise spatial domains for normal patterning to occur. We have found that the bHLH transcription factors Twist1 and Hand2 interact antagonistically to regulate these signals and thus early limb patterning. Hand2 misexpression causes phenocopies of Twist1 loss of function phenotypes, and either can be suppressed by rebalancing Hand2 and Twist1 expression levels. We have also examined requirements for Twist1 using a murine Twist1 allelic series. As Twist1 activity is reduced, we find progressively more complex skeletal defects in the limb. The severity of these defects is sensitive to Hand2 dosage, underlining the importance of relative Twist1 and Hand2 levels. Molecular analyses show Twist1 has multiple targets that vary spatially, temporally and with levels of Twist1 activity. Integrating this information with the skeletal phenotypes is revealing unexpected ways in which Twist1 affects limb morphology through a network of downstream effectors.

Axons of motor neurons located in the lateral motor column (LMC) of the spinal cord assume specific trajectories as they innervate limb muscles. Lateral LMC axons project to dorsal limb mesenchyme, while medial LMC axons project ventrally. We are exploring how medial LMC axons choose trajectories to ventral limb mesenchyme. We analyzed the trajectories of LMC axons in a *Bmpr1a* mutant mouse in which ventral limb mesenchymal tissue is completely transformed to a dorsal identity. Our data indicate that in the absence of ventral limb mesenchyme, axons of medial LMC neurons innervate non-limb mesenchyme rather than enter inappropriate limb territory. We have also examined the molecular pathways that control the trajectory of medial LMC axons. Through a combination of gene expression analyses and gain and loss of function experiments, we have found that EphB signaling contributes to the selection of a ventral trajectory by axons of medial LMC neurons.

Our findings suggest that axons of LMC neurons exhibit a hierarchical preference for three lateral mesenchymal derivatives (flank, ventral limb, dorsal limb). This hierarchy differs for the axons of medial and lateral LMC neurons. Our findings also implicate EphB signaling as a regulator of medial LMC axonal trajectory choice, acting in a complementary manner to the EphA signaling system that guides lateral LMC axons into dorsal limb mesenchyme.

Host:

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