



Molecular mechanisms of dopaminergic pathway development

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The midbrain dopamine system is involved in the control of cognitive and motor behavior. Midbrain dopamine neurons (mDA) are grossly divided into two anatomically and functionally distinct subpopulations: substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) neurons. SNc neurons make precise connections with dorsal striatum (nigrostriatal projections), while VTA neurons target ventral striatum and cortex (mesocorticolimbic projections). Both pathways collectively run in the medial forebrain bundle (MFB) towards the forebrain. To distinguish between different subsets of dopaminergic projections *in vivo*, and to identify subset-specific developmental programs, we designed BAC transgenic mice called Pitx3-ITC mice. The subtractive genetic strategy we have developed relies on the expression of different fluorescent proteins in different subsets of mDA neurons in a single mouse. Pitx3-ITC mice display labeling of SNc neurons and selective visualization of nigrostriatal projections in the MFB and in striatum, from early embryonic development onwards. Combination of Pitx3-ITC mice with 3D-imaging of solvent cleared organs (3DISCO) technology and light sheet imaging allows for 3D analysis of neuronal migration and axonal/dendritic development of SNc neurons. Interestingly, Pitx3-ITC mice show that nigrostriatal axons are not dispersed throughout the MFB, but rather accumulate in the dorsal MFB. This pre-target sorting of nigrostriatal axons may be important for the correct innervation of the dorsal striatum. Further, Pitx3-ITC mice have begun to reveal the molecular mechanisms that are important for mDA neuron migration. In conclusion, the Pitx3-ITC genetic strategy offers the unique possibility of differentially labeling dopaminergic subsets and visualizing their projections, thereby comprising a unique tool for unveiling the molecular mechanisms underlying previously unexplored aspects of dopaminergic system development, such as the pre-target sorting of nigrostriatal axons in the MFB, and plasticity in health and disease.

Selected Publications

Brignani S, **Pasterkamp RJ** (2017) Neuronal subset-specific migration and axonal wiring mechanisms in the developing midbrain dopamine system. *Front Neuroanat* 11:55.

Kong Y, Janssen BJ, Malinauskas T, Vangoor VR, Coles CH, Kaufmann R, Ni T, Gilbert RJ, Padilla-Parra S, Jones EY, **Pasterkamp RJ** (2016). Structural Basis for Plexin Activation and Regulation. *Neuron* 91, 548-60.

Schmidt ER, Brignani S, Adolfs Y, Lemstra S, Demmers J, Vidaki M, Donahoo AL, Lilleväli K, Vasar E, Richards LJ, Karagogeos D, Kolk SM, **Pasterkamp RJ** (2014). Subdomain-mediated axon-axon signaling and chemoattraction cooperate to regulate afferent innervation of the lateral habenula. *Neuron* 83, 372-387.