The born identity: molecular mechanisms of dopaminergic subset specification

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In Parkinson's Disease (PD), mesodiencephalic (mdDA) neurons of the Substantia Nigra (SN) specifically degenerate, whereas Ventral Tegmental Area (VTA) neurons are relatively unaffected. Differential molecular programming of developing mdDA neurons along the rostral/caudal axis may underlie this specific vulnerability. We used a combination of molecular, pharmacological and developmental techniques to elucidate the molecular mechanisms of dopaminergic subset specification. We demonstrated critical, but subset specific roles of the transcription factors En1 and Pitx3 and the signaling molecules Retinoic Acid and Dlk1 during mdDA development. We performed genome-wide expression profiling of FACS-purified rostral versus caudal mdDA neurons, and demonstrated how, on a genome-wide scale: 1) the molecular signature of the SN and VTA originates from differential developmental programming along the rostral/caudal axis, a relation that is conserved in human, 2) rostral (SN) and caudal (VTA) neurons already differ in their functional genome during mdDA development 3) transcription factor regulation relates to developmental position, 4) expression of rostral enriched genes is mostly decreased in the SN of PD patients. Also, we used comparative expression profiling to compare inducible pluripotent stem cell (iPSC-)derived mdDA neurons with their in vivo counterpart, and demonstrated critical differences at the genetic and epigenetic level. The data from this thesis impact the many fields that profit from detailed *a priori* knowledge of subset-specific molecular coding of mdDA neurons and its relationship with PD pathogenesis, ranging from clinical genetics to cell replacement paradigms.