**Studies of Cell Fate Specification and Reprogramming in the Nervous System**

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**Abstract**

In the nervous system, cellular diversity is generated through progenitor cells that contain varying levels of potential for differentiating into mature neural cell types. The degree of cell fate potential is dictated through a combination of cell-intrinsic gene regulatory programs and cell-extrinsic signaling factors in the niche. Once a cell is differentiated, it must also maintain this mature state to enable tissue function. A mechanistic understanding of cell fate specification and maintenance is important for regenerative medicine efforts to replace lost or damaged cells in the nervous system and to diseases that may arise due to an improper maintenance of cell identity. In this thesis, I use two different model systems to explore these features of developmental neurobiology: the cell fate specification of photoreceptors in the mammalian retina and direct reprogramming of neurons from cells in the skin. In the retina, progenitor cells can be multipotential or more restricted in the types of cells they can differentiate into. I questioned to what extent factors in the progenitor niche restrict retinal progenitors to differentiate into photoreceptors. These experiments show, for the first time, that unique combinations of retina niche factors cause individual retinal progenitors to adopt a photoreceptor-restricted fate. Taurine and retinoic acid exposure creates clones composed of only rod photoreceptors and COCO exposure creates clones of only cone photoreceptors. Furthermore, retinal progenitors maintain competence for this photoreceptor restriction throughout every embryonic developmental stage. I also identify a novel retinal transcription factor, *Sox15*, that acts downstream of COCO to facilitate cone-restricted differentiation. Functional studies suggest that *Sox15* works to promote cone differentiation through inhibiting differentiation towards rod photoreceptors. Direct reprogramming involves conversion of one fully differentiated cell type into another through manipulation of transcriptional programs. This contests traditional developmental models where cell fate restriction is a unidirectional process. I use the example of directly reprogramming fibroblasts from the skin into neurons to challenge the extent to which mature cells can destabilize and alter their identity. My experiments reveal that a previously unrecognized neural crest progenitor cell in the skin is the primary source of neurons in this model. This calls into question the original interpretation that a cell from a different embryonic germ layer is switching its identity to a neuron without passing through a developmentally immature state. Neural crest progenitors from the skin are developmentally derived from the brain and have an intrinsic bias to differentiate into neurons. Therefore, this is directed differentiation of an immature precursor cell, suggesting that the barriers a fully differentiated cell must overcome to reprogram are greater than previously anticipated.