Glial cell development in the vertebrate central nervous system

Thesis by

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To my parents and Sally Suen

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ABSTRACT

Neurons and glial cells are the two most fundamental cell types of the vertebrate central nervous system (CNS). While neurons are directly responsible for information processing via their electrical activities, glial cells play essential supportive roles. For example, oligodendroglia insulates axons, microglia performs immune functions, and astroglia maintains homeostasis of the entire CNS. Malfunction of glial cells causes numerous debilitating diseases directly (such as glial tumors), or indirectly by disrupting the normal functions of neurons that they support (as in multiple sclerosis).

Despite their functional importance, relatively little is known about the development of vertebrate CNS glial cells. Focusing on the possibility that members of the basic helix-loop-helix (bHLH) transcription factors may play important roles in the development of vertebrate glial cells, similar to their functions in neurons, I searched for novel bHLH factors expressed in glial cells. A new family of bHLH factors was found and named *Olig*. Intriguingly, one member of this family, *Olig2*, is sequentially expressed first in motoneuron progenitors and later in the oligodendroglia. The sequence and expression pattern of *Olig2* is highly conserved among different vertebrate species including fish, birds and mammals.

To understand the role of *Olig2* in oligodendroglia development, I ectopically expressed *Olig2* singly or in combination with other factors in chick embryos. My result suggests that *Olig2* can promote oligodendrocyte formation in the absence of neurogenic bHLH factors, which are negative regulators of glial fate. Other groups of researchers reported that in the presence of neurogenic factors, *Olig2* promotes motoneuron development instead. *Olig2* gene is therefore sufficient to specify the fate of either a neuronal subtype or a glial subtype, together with neurogenic factors.

To further assess whether *Olig* genes are required for motoneuron and oligodendroglia development, I knocked out both *Olig2* and *Olig1* genes in mouse. In double null mutants, spinal motoneurons and oligodendroglia precursors from the entire CNS fail to develop, demonstrating that *Olig* genes are absolutely necessary for the

generation of these cell types. Unexpectedly, in the absence of both *Olig1* and *Olig2*, spinal motoneurons are transformed into V2 interneurons whereas oligodendroglial cells are respecified as astroglial cells. These results suggest that *Olig* genes are not involved in neuron-glia decision, but rather in specifying subtype identities of neuron and glia. Given that motoneurons and oligodendrocytes likely derive from common precursors, the expression of Olig may serve to couple the subtype identities of both neurons and glial cells sequentially generated from the same stem cells.

The series of studies on *Olig* genes contributed on two areas of neural development. First, they shed important light on the specification of oligodendrocyte and astrocyte, the two major glial types in the vertebrate CNS. Second, they revealed that cell fate determinations of neuron and glia are not two unrelated events as often believed, on the contrary, they are deeply intertwined.

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