Sox2 and its targets in Neural Stem Cells self-renewal and differentiation

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Abstract:

The transcription factor SOX2, expressed in Neural Stem Cells (NSCs), plays a major role in their self-maintenance and differentiation. SOX2 mutations in humans are associated with severe neurodevelopmental disorders, and conditional knockout murine models have revealed its role in various areas of the developing Central Nervous System. Regarding *in vitro* models, while wild-type NSCs can indefinitely grow as neurospheres and differentiate into both glial cells and neurons, Sox2-ablated NSCs self-renew just for few passages undergoing progressive exhaustion and differentiate almost exclusively towards glial lineages. However, the gene regulatory network downstream of Sox2 contributing to NSCs features is still not completely unravelled. Previous genomic studies, i.e. RNAseq performed on neurospheres, uncovered Sox2-regulated genes whose expression may be important for NSCs properties.

We then set out to test whether overexpressing Sox2, or its downstream targets identified by RNAseq, via lentiviral vectors could revert both the differentiation and the proliferation defects observed in Sox2-deleted NSCs; we focused on Socs3 and c-Fos, as these are the targets whose expression is mostly reduced in Sox2 absence according to our RNAseq data. First, we ensured that Sox2 overexpression could restore self-renewal and regular differentiation in $Sox2^{-/-}$ NSCs; both functions were recovered. Socs3 and c-Fos, individually re-introduced into Sox2-deleted NSC, rescue the proliferation defect; in differentiation culture conditions, the former inhibits glial differentiation, giving rise just to immature neurons, and the latter allows differentiation of neuronal and glial cells but generating at the same time also some mixed identity cells. Finally, to investigate the mutual relations between the aforesaid genes, we tested their expression levels in $Sox2^{-/-}$ neurospheres after transduction; we confirmed that Sox2 transduction enhances both c-Fos and Socs3 expression. Interestingly, c-Fos also turned out to be able to upregulate Socs3 expression, probably due to binding to its promoter; similarly, Socs3 promotes c-Fos expression back, though this might be an indirect effect. These transcription factors, therefore, represent a node in the genetic network regulating NSCs self-renewal.