J. Vallis/NPG

CELL FATE

The patterns of fate

> The authors used an optogenetic gene expression to examine the effects of the oscillating and sustained transcription factor expression patterns

The mechanisms determining neural progenitor cell (NPC) fate choices remain incompletely understood. Now, Imayoshi *et al.* show that NPC differentiation is associated with the sustained, dominant expression of particular transcription factors, whereas the proliferation of NPCs is associated with oscillating patterns of expression of several factors.

Fate choices in NPCs involve various transcription factors: in mice, these include achaete-scute homologue 1 (ASCL1), HES1 and oligodendrocyte transcription factor 2 (OLIG2). The expression of ASCL1 can promote the differentiation of NPCs into neurons, whereas the expression of HES1 and OLIG2 can promote the formation of astrocytes and oligodendrocytes, respectively. However, these transcription factors may also have roles in NPC maintenance or proliferation, functions that seem to oppose their roles in fate determination.

To shed light on these apparent contradictions, the authors generated transgenic mice in which reporter expression was linked to ASCL1, HES1 or OLIG2 expression. In acutely dissociated NPCs and in NPCs maintained in culture, time-lapse imaging of reporter expression revealed that the expression levels of each of these transcription factors oscillated. The oscillation periods of ASCL1 and HES1 expression were similar (~175 min and ~150 min, respectively), but OLIG2 expression oscillated over a much longer period (~375 min). Moreover, there was an inverse correlation between ASCL1 and HES1 expression levels, whereas OLIG2 expression levels seemed to be independent of the expression levels of the other two factors.

The authors assessed whether the levels of the three transcription factors present in an NPC at any one time influenced its ability to differentiate. Among isolated NPCs cultured in differentiating medium, those transiently expressing high levels of ASCL1 but low levels of OLIG2 preferentially differentiated into neurons, those transiently expressing high levels of OLIG2 but low levels of ASCL1 preferentially differentiated into oligodendrocytes, and those transiently expressing low or high levels of HES1 preferentially differentiated into neurons and astrocytes, respectively. Thus, the expression pattern of these transcription factors in NPCs seemed to influence their ability to differentiate into particular cell types. However, these transient expression profiles were not required to determine cell fate because NPCs with other patterns of transcription factor expression were also found to differentiate into neurons, astrocytes or oligodendrocytes.

The authors examined whether transcription factor expression patterns change during cell fate choice. They found that in dissociated cultures of NPCs in which a parent cell gave rise to one neuron and one undifferentiated daughter cell ASCL1 expression rose and HES1 expression decreased in the parent NPC before cell division. In the daughter cell that differentiated into the neuron, ASCL1 continued to accumulate after cell division. Similar changes in the pattern of transcription factor expression could also be seen during astrocyte and oligodendrocyte differentiation, in which HES1 and OLIG2, respectively, became the dominant transcription factors that were expressed.

The authors used an optogenetic gene expression to examine the effects of the oscillating and sustained transcription factor expression patterns. They introduced an ASCL1-blue-light-inducible system into cultured *Ascl1*-null NPCs, which proliferate slowly and do not differentiate into neurons. Using this system, the authors created oscillating levels of ASCL1 in these cells, which had the effect of promoting NPC proliferation, although only if the oscillating period was ~3 hours. Moreover, light-induced sustained expression of ASCL1 increased neuronal differentiation.

Together, these data suggest that expression patterns, rather than simply the expression levels, of various transcription factors determine whether NPCs proliferate or differentiate.

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ORIGINAL RESEARCH PAPER Imayoshi, I. *et al.* Oscillatory control of factors determining multipotency and fate in mouse neural progenitors. *Science* http://dx.doi.org/10.1126/science.1242366 (2013)