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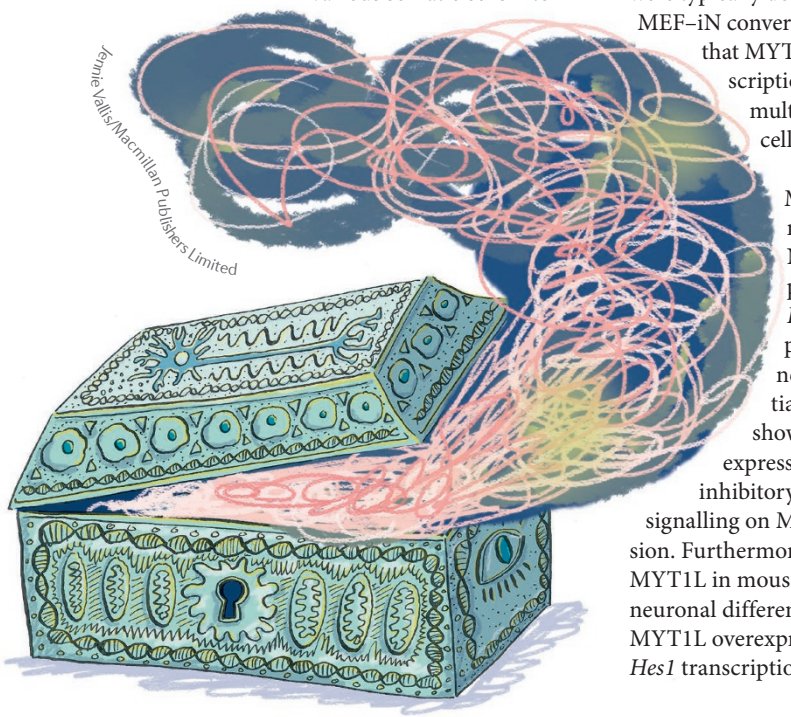
NEURAL DEVELOPMENT

Keeping a lid on alternative fates

> depletion of MYT1L in cultured adult hippocampal neurons resulted in a 'de-repression' of non-neuronal genes

Understanding the mechanisms by which somatic cells can be converted to a neuronal fate *in vitro* may provide insight into 'normal' neuronal development. Both processes require silencing of programmes that drive alternative cell fates, but how this is achieved is poorly understood. Mall *et al.* now show that the transcription factor MYT1L represses multiple somatic cell lineage programmes to establish and maintain neuronal identity.

MYT1L (together with the other 'BAM' transcription factors ASCL1 and BRN2) can convert various somatic cells into induced neuronal cells (iNs) *in vitro* and is expressed during neuronal development. Mall *et al.* combined chromatin immunoprecipitation with DNA and RNA sequencing to identify genetic targets of MYT1L and examine their expression in mouse embryonic fibroblasts (MEFs) undergoing BAM-mediated conversion to iNs. They found that MYT1L targets genes that encode negative regulators of neuronal cell fate and genes that drive the differentiation of several somatic cell types, including fibroblasts, myocytes, hepatocytes and keratinocytes. These targets were typically downregulated during MEF–iN conversion, demonstrating that MYT1L acts as a transcriptional repressor of multiple non-neuronal cell fates.



The targets of MYT1L included members of the Notch signalling pathway, such as *Hes1*, which encode proteins that inhibit neuronal differentiation. The authors showed that MYT1L expression overcame the inhibitory effects of Notch signalling on MEF–iN conversion. Furthermore, depletion of MYT1L in mouse embryos reduced neuronal differentiation, whereas MYT1L overexpression decreased *Hes1* transcription and increased neuronal differentiation in cultured neuronal stem cells. Thus, MYT1L is also involved in overcoming the effects of negative regulators of neuronal cell fate during 'normal' development.

MYT1L is expressed in neurons throughout life. The authors showed that depletion of MYT1L in cultured adult hippocampal neurons resulted in a 'de-repression' of non-neuronal genes and a corresponding loss of neuronal gene expression and some aspects of neuronal function, indicating that MYT1L continues to repress non-neuronal cell fate programmes in adult neurons.

This study demonstrates the importance of continuous active repression of non-neuronal cell fates in the induction and maintenance of neuronal identity and demonstrates an essential contribution of MYT1L to this process. By simultaneously repressing multiple (perhaps all) non-neuronal fates in neurons MYT1L thus acts in a manner that complements the actions of the lineage repressor REST, which blocks neuronal lineage programmes in non-neuronal cells.

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ORIGINAL ARTICLE Mall, M. *et al.* Myt1l safeguards neuronal identity by actively repressing many non-neuronal fates. *Nature* **544**, 245–249 (2017)
FURTHER READING Mertens, J. *et al.* Evaluating cell reprogramming, differentiation and conversion technologies in neuroscience. *Nat. Rev. Neurosci.* **17**, 424–437 (2016)