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NEURAL REPAIR

Tagging mRNA drives regeneration

The regeneration of peripheral axons after injury involves a gene transcription programme that is driven by genetic and epigenetic mechanisms. A new study by Ming and colleagues highlights the role of an additional regulatory mechanism — mRNA methylation — in peripheral axon regeneration in mice.

Methylation of adenosine bases at the nitrogen-6 position generates N6-methyladenosine (m^6A), an abundant, dynamic and reversible mRNA modification (or 'tag'). m^6A modifications have been linked to regulation of neuronal development and function; however, their influence in the adult nervous system remains unknown. Here, the authors observed an increase in m^6A levels in peripheral sensory neurons in the adult dorsal root ganglia (DRG) after a sciatic nerve lesion (SNL), suggesting a role for this modification in the regenerative process.

Transcriptome-wide m^6A profiling revealed that injury-induced m^6A tagging was observed in transcripts that included those encoded by many regeneration-associated genes that are upregulated during regeneration and those encoding components of the protein translation machinery.

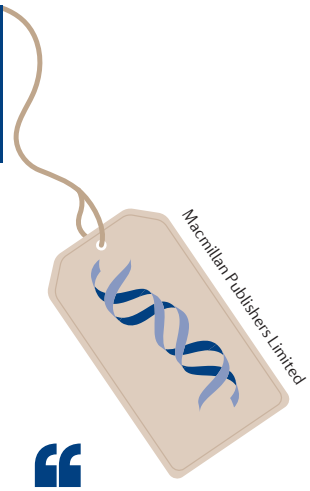
m^6A modifications could function to alter the stability, processing or translation of the tagged mRNAs. In this study, the authors' findings suggested that m^6A tagging can influence global protein translation in DRG neurons in response to injury. Indeed, the authors showed that mice in which *Mettl14* (encoding a component of the enzymatic complex responsible for m^6A tagging) was conditionally deleted in postmitotic neurons, and mice lacking *Ythdf1* (encoding an m^6A 'reader' protein that is thought to mediate some of the effects of m^6A on protein translation) exhibited a clear reduction in SNL-induced protein synthesis in the DRG.

Next, the authors assessed the contribution of the dynamic changes in m^6A to axon regeneration. Deletion of *Mettl14* in DRG neurons *in vivo* reduced the extension of regenerating axons, the re-innervation of the epidermis and the recovery of heat-induced paw withdrawal latency after SNL, compared with control animals. The absence of *Ythdf1* likewise reduced axon regeneration. Although CNS regeneration is limited, mice lacking *Pten* exhibit enhanced regeneration of adult retinal ganglion cell (RGC) axons; however, when short hairpin RNA was used to knock down *Mettl14* in RGCs *in vivo*, their regeneration after an optic nerve crush injury was reduced, confirming that m^6A tagging is also required for effective CNS regeneration.

These findings widen our understanding of the complex transcriptional, epigenetic and epitranscriptomic mechanisms that regulate axonal regeneration and the contributions of mRNA methylation to adult nervous system function.

Katherine Whalley

ORIGINAL ARTICLE Weng, Y-L. *et al.* Epitranscriptomic m^6A regulation of axon regeneration in the adult mammalian nervous system. *Neuron* **97**, 313–325. (2018)



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