

## NEUROIMMUNOLOGY

## Uncovering new roles for microRNAs and TLRs

Previous studies have shown that Toll-like receptors (TLRs) on neurons and glia can cause CNS damage through mechanisms that are not pathogen-induced, but the identity of these alternative triggers remained elusive. Lehnardt and colleagues now show that the microRNA (miRNA) let-7 can act as a potent activator of TLR7 signalling in neurons and that

this activation can induce neurodegeneration, thus also revealing a new role of miRNAs beyond their function as regulators of gene expression.

let-7 is one of the most abundant miRNAs expressed in the human brain, and its sequence contains a core GU-rich motif that is also present in the single-stranded RNA40, which is a known ligand for TLR7. Thus, the authors hypothesized that let-7 can activate this receptor.

Preliminary experiments in microglia and macrophages indicated that synthetic let-7 can directly activate TLR7. Furthermore, exposure of extracellular let-7 to purified cortical and hippocampal neurons induced dose-dependent and time-dependent cell death. let-7, however, did not induce cell death in cortical neurons derived from *Tlr7<sup>-/-</sup>* mice. Interestingly, exposure of extracellular let-7 to co-cultures of neurons and microglia or neurons and astrocytes did not enhance neuronal cell death, which indicates that

non-neuronal cells are not necessary for let-7-induced neuronal cell death.

The authors subsequently showed that the addition of culture supernatants from apoptotic or necrotic neurons (in which high levels of let-7 were detected) to fresh primary neurons induced injury and loss, an effect that could be abrogated by pretreatment of neurons with a let-7 inhibitor. These *in vitro* results were recapitulated *in vivo*, as intrathecal injection of let-7 into mice induced time-dependent axonal injury and neuronal (both cortical and striatal) loss, and these effects were blocked by pretreatment with a let-7 inhibitor.

Together, these data uncover a new role of miRNAs as endogenous activators of TLRs in microglia and neurons, and also imply that TLRs function as death receptors in neurons under pathological conditions.

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**ORIGINAL RESEARCH PAPER** Lehmann, S. M. *et al.* An unconventional role for miRNA: let-7 activates Toll-like receptor 7 and causes neurodegeneration. *Nature Neurosci.* **15**, 827–835 (2012)



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