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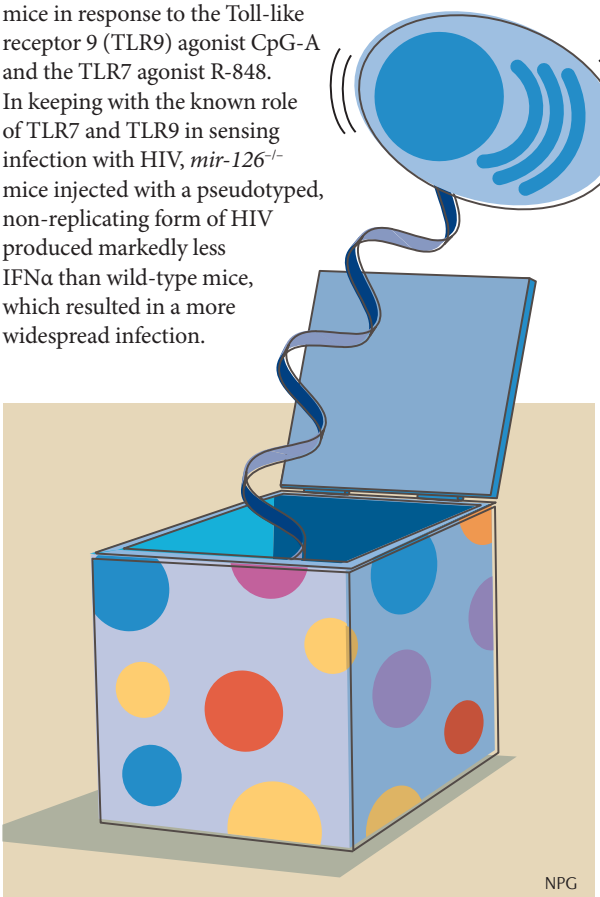
INNATE IMMUNITY

A surprise regulator of plasmacytoid DCs

The unexpected discovery of a role for the microRNA miR-126 in controlling the innate immune response to viral nucleic acids has led to evidence that the vascular endothelial growth factor receptor 2 (VEGFR2) pathway — well known for its endothelial cell function in mediating angiogenesis — also regulates the survival and function of plasmacytoid dendritic cells (pDCs).

mir-126$^{-/-}$ mice produced less interferon-α (IFNα) than wild-type mice in response to the Toll-like receptor 9 (TLR9) agonist CpG-A and the TLR7 agonist R-848. In keeping with the known role of TLR7 and TLR9 in sensing infection with HIV, *mir-126*$^{-/-}$ mice injected with a pseudotyped, non-replicating form of HIV produced markedly less IFNα than wild-type mice, which resulted in a more widespread infection.

> “miR-126 regulates pDC number through effects on survival”



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So miR-126 is required for a normal innate immune response to viral nucleic acids, but previous studies have reported that expression of this microRNA is specific to endothelial cells, which do not express TLR7 or TLR9. Surprisingly, this study showed that miR-126 is also expressed highly by human and mouse pDCs; miR-126 was one of the most abundant microRNAs in mouse splenic pDCs, making up 5% of the total microRNA pool. As pDCs are major producers of IFNα in response to viral infection, and the impaired response of *mir-126*$^{-/-}$ mice to pseudotyped HIV could be rescued by the transfer of wild-type pDCs, the authors investigated the effect of miR-126 on pDC development and function.

The frequency and absolute number of pDCs was 50% lower in *mir-126*$^{-/-}$ mice than in control mice. Both *ex vivo* and during *in vitro* differentiation there was no difference between wild-type and *mir-126*$^{-/-}$ pDCs in terms of proliferation, but the apoptosis of *mir-126*$^{-/-}$ pDCs was significantly increased. The results indicate that miR-126 regulates pDC number through effects on survival. Further experiments showed that miR-126 is also required for normal pDC function; the few pDCs that develop in *mir-126*$^{-/-}$ mice had decreased activation, migration and IFNα production in response to CpG-A compared with wild-type pDCs.

Transcriptional profiling of *mir-126*$^{-/-}$ mice showed altered expression of 253 genes, most of which were known receptors, signalling intermediates or transcription factors of innate response pathways. Unexpectedly, the expression of *Kdr*, which encodes VEGFR2, was downregulated in *mir-126*$^{-/-}$ pDCs. VEGFR2 expression was detected on tissue pDCs from wild-type mice and humans but was decreased on *mir-126*$^{-/-}$ pDCs. In keeping with the pro-survival role of VEGFR2 signalling in endothelial cells, mice with a DC-specific deletion of *Kdr* had 40% fewer splenic pDCs. Furthermore, inhibition of the pro-survival mammalian target of rapamycin (mTOR) pathway downregulated VEGFR2 expression by pDCs, which supports a role for miR-126-mediated positive regulation of VEGFR2 expression — possibly through mTOR — in pDC survival. Using *in silico* analysis and a luciferase reporter assay, the authors identified tuberous sclerosis 1 (*Tsc1*) as a direct target of miR-126; *Tsc1* is expressed by pDCs and encodes a negative regulator of mTOR. *mir-126*$^{-/-}$ pDCs had higher levels of TSC1 than wild-type pDCs.

In summary, the results suggest an unanticipated role for miR-126 in pDCs in repressing TSC1 expression; this leads to increased mTOR activity, which increases pDC survival, in part through increased VEGFR2 expression. The authors also showed that VEGFR2 expression is required for the normal function of pDCs in terms of IFNα production. Drugs targeting VEGFR2 might, therefore, have so far unexplored effects on innate immunity.

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