Previous studies showing that the commensal microbiota promotes norovirus infection can now be partly explained by the tuft cell tropism identified in this study. Antibiotic treatment, which prevents persistent infection with MNoV^{CR6}, decreased tuft cell-specific gene expression and the number of DCLK1^{+} cells in the colon. However, administration of IL-4 or IL-25 to antibiotic-treated mice rescued subsequent infection with MNoV^{CR6}, which shows that the effects of type 2 cytokines are dominant over the effects of the microbiome on tuft cells in promoting norovirus infection.

In conclusion, the authors suggest that tuft cells may be an immune-privileged site for enteric viruses that allows them to take advantage of type 2 immune responses, for example in response to intestinal helminths, to promote infection.

Kirsty Minton

ORIGINAL ARTICLE Wilen, C. B. et al. Tropism for tuft cells determines immune promotion of norovirus pathogenesis. *Science* **360**, 204–208 (2018)

eIF2α or block IκBζ and IL-6 induction in ATF3-deficient macrophages, despite inducing NRF2.

IκBζ is induced in epithelial cells by IL-17 and polymorphisms in *Nfkbiz* (which encodes IκBζ) are associated with psoriasis. Strikingly, the authors found that DI blocked IL-17-mediated induction of IκBζ and its target genes in keratinocytes. Furthermore, topical application of DI reduced skin inflammation in a mouse model of psoriasis.

These findings complement a recent study by Mills et al., which reported that itaconate drives anti-inflammatory responses through NRF2. Moreover, this study indicates that itaconate and its derivatives can inhibit inflammatory responses in cells other than macrophages and also act via ATF3 to block inflammation driven by the IL-17–IκBζ axis.

Yvonne Bordon

ORIGINAL ARTICLE Bambouskova, M. et al. Electrophilic properties of itaconate and derivates regulate the IκBζ–ATF3 inflammatory axis. *Nature* **556**, 501–504 (2018)
FURTHER READING Mills, E. L. et al. Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1. *Nature* **556**, 113–117 (2018)

INNATE IMMUNITY

The IFN road not taken

Credit: S. Bradbrook/Macmillan Publishers Limited

Mutations in the dNTPase SAMHD1 cause the interferonopathy Aicardi–Goutières syndrome (AGS) and have been linked to the development of certain cancers, but the underlying mechanisms have been unclear. Coquel et al. have found that SAMHD1 promotes the degradation of nascent DNA strands at stalled replications forks, thereby preventing the intracellular accumulation of single-stranded DNA (ssDNA) fragments that can induce the expression of pro-inflammatory type I interferons (IFNs).

SAMHD1 protects quiescent cells against viruses such as HIV, but its dNTPase activity is inhibited in cycling cells owing to phosphorylation by cyclin-dependent kinases (CDKs). As SAMHD1 has been shown to colocalize with DNA repair foci in cells exposed to genotoxic agents, the authors hypothesized that it might have a role in inhibiting ssDNA accumulation at stalled forks. They first showed that knockdown of *SAMHD1* expression in a cell line increased the presence of cytosolic ssDNA and induced mRNAs encoding IFNs and TNF. Moreover, ssDNA accumulation and inflammatory gene expression were increased when cells were treated with hydroxyurea, a genotoxic agent that causes replication fork stalling. The authors showed that the induction of IFN genes in the absence of SAMHD1 was driven by the cGAS–STING pathway and also depended on IRF3.

Subsequent studies showed that SAMHD1 colocalizes with replication forks in cells. Notably, SAMHD1-depleted cells grew more slowly than control cells and had a longer S phase owing to slower DNA synthesis. However, dNTP levels were not markedly altered in the absence of SAMHD1, suggesting that the roles of SAMHD1 in the S phase of the cell cycle extend beyond regulation of dNTP pools. To examine whether the phosphorylation of SAMHD1 by CDKs during the S and G2–M phases of the cell cycle affects DNA replication, the authors generated phosphomimetic (T592E) and non-phosphorylatable (T592A) SAMHD1 mutants. Complementing SAMHD1-depleted cells with T592E, but not with T592A, mutants rescued slowed replication forks, whereas both sets of cells had similar dNTP levels. Fork progression was also restored by a dNTPase-deficient SAMHD1 mutant. Therefore, phosphorylation of SAMHD1 by CDKs, but not the dNTPase activity of SAMHD1, seems to be necessary for fork progression.

Further detailed experiments showed that SAMHD1 promotes fork resection, a process involving the degradation of nascent DNA. The authors found that SAMHD1 activates the exonuclease activity of the double-strand break repair protein MRE11A, with SAMHD1 and MRE11A cooperating to activate the ATR–CHK1 checkpoint pathway and promote fork restart in cells exposed to genotoxic agents. Finally, the authors hypothesized that in the absence of SAMHD1, helicases and nucleases may promote the displacement of nascent DNA and the accumulation of ssDNA in the cytosol. In support of this, they found that an IFN response was not induced in SAMHD1-depleted cells lacking the ATP-dependent DNA helicase RECQ1.

In summary, SAMHD1 activates the ATR–CHK1 pathway at stalled DNA replication forks and prevents the release and accumulation of ssDNA molecules that can trigger pro-inflammatory responses via the cGAS-STING pathway. These findings provide important insight into why SAMHD1 mutations are linked to AGS and cancer development.

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ORIGINAL ARTICLE Coquel, F. et al. SAMHD1 acts at stalled replication forks to prevent interferon induction. *Nature* https://doi.org/10.1038/s41586-018-0050-1 (2018)

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