Credit: Auscape/Getty

Ser381 phosphorylation. The graded phosphorylation status between the different variants consequently caused a graded reduction in A20 function and control of NF-κB (T108A/I207L > I325N > C243Y).

By introducing the human A20 mutations I207L and C243Y into C57BL/6 mice (which already have T108A) using CRISPR–Cas9 genome editing, the authors could study the physiological impact of the variants. Consistent with the biochemical data, the graded reduction in A20 phosphorylation led to correspondingly graded protective immunity to coxsackievirus. For example, mice with C243Y or I325N variants were fully protected from an otherwise lethal dose of the virus in wild-type mice, and T108A/I207L mice were partially protected. However, the opposite was found in a model of sepsis: mice homozygous for C243Y and I325N had higher mortality and IL-6 concentrations following injection with lipopolysaccharide than wild-type mice and T108A/I207L homozygous mice.

So, tuning A20, through variation in phosphorylation levels, to increase immunity is balanced by corresponding loss of bacterial tolerance. Specific alleles encoding A20 may have been crucial for genetic selection of indigenous populations in earlier environmental conditions.

Lucy Bird

ORIGINAL ARTICLE Zammit, N. W. et al. Denisovan, modern human and mouse *TNFAIP3* alleles tune A20 phosphorylation and immunity. *Nat. Immunol.* **20**, 1299–1310 (2019)

revealed differences in chromatin accessibility, particularly in regions enriched for binding motifs of certain transcription factors. In naive $CD8^+$ T cells from wild-type mice, these regions were enriched in binding motifs for the RUNX family of transcription factors, including RUNX3, which is known to be a positive regulator of epithelial T_{RM} cell differentiation. This implied that epigenetic changes driving epithelial T_{RM} cell differentiation occur before T cell activation.

In order to determine where this epigenetic preconditioning takes place, the authors analysed mice that lack lymph nodes and mice deficient in mDCs, a type of DC that, at steady state, migrates from peripheral tissues into draining lymph nodes but is absent from the spleen. In both cases, the preconditioning of naive $CD8^+$ T cells for epithelial T_{RM} cell fate was impaired. This was also the case in mice where DCs did not co-express MHC class I (MHC-I) molecules and αV integrin, leading to the conclusion that the preconditioning of naive $CD8^+$ T cells involves non-cognate, but MHC-I-dependent and αV integrin-dependent, physical interactions of the T cells with mDCs in lymph nodes, during which the naive T cells are presented with active TGFβ. This also exemplifies how a widely abundant cytokine can have very localized and specific functions.

In contrast to the general assumption that the naive T cell population is relatively uniform in its potential to differentiate into different effector and memory cell subsets, the study shows that naive $CD8^+$ T cells are preconditioned during steady state to efficiently form epidermal T_{RM} cells upon antigen encounter. The authors point out that this may have important implications for vaccine development, where optimized preconditioning might enhance vaccine-induced protection. Conversely, in conditions such as psoriasis where epithelial T_{RM} cells play a pathogenic role, one could envisage therapeutic approaches that interfere with preconditioning for T_{RM} cell fate.

Alexandra Flemming

ORIGINAL ARTICLE Mani, V. et al. Migratory DCs activate TGF-β to precondition naïve $CD8^+$ T cells for tissue-resident memory fate. *Science* **366**, eaav5728 (2019)

Journal Club

EFFECTS OF STROKE BEYOND THE BRAIN

In late 2000, after finishing my PhD and starting an overseas postdoctoral position, I was ready to move on from the topic of stroke. I was eagerly examining how immune cells in the liver are crucial for host antibacterial defence. However, I came across a paper that provided the first experimental proof of brain-mediated peripheral immune impairment in stroke, and I was back in the field of stroke once again.

Stroke-induced systemic immunosuppression and the subsequent development of infection were first described in the 1970s. These early observations challenged the accepted idea that fatal bacterial pneumonia following stroke arises simply due to aspiration secondary to dysphagia (difficulty swallowing). In 2003, Prass et al. provided a mechanistic basis for these observations and elegantly demonstrated that catecholamine-mediated lymphocyte dysfunction was the key factor in the impaired antibacterial immune response after stroke. Their study revealed that impaired natural killer cell and T cell function, particularly in their ability to produce IFNγ, is the crucial stroke-induced deficit in host antibacterial defence. Adoptive transfer of IFNγ-producing lymphocytes or early treatment with recombinant IFNγ was effective in halting bacteraemia and pneumonia after stroke, with both strategies clearly restoring immunity independent of aspiration.

> “the injured post-stroke brain transmits signals of immunosuppression via stress pathways”

It turns out that the injured post-stroke brain transmits signals of immunosuppression via stress pathways, namely the sympathetic arm of the autonomic nervous system. Inhibitors of the sympathetic adrenergic receptors efficiently limit lymphocyte dysfunction and bacterial infections after stroke. This discovery triggered subsequent efforts to reveal novel mechanisms and potentially harness neuroendocrine pathways to improve stroke outcomes. In addition, this study has broad implications in the field of immunology. Physiological systems have long been studied in isolation from each other. This study highlighted that immune cells are not only self-regulated but also function in close association with many other cell types, such as neurons, to maintain homeostasis and provide effective host responses to injury.

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ORIGINAL ARTICLE Prass, K. et al. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1–like immunostimulation. *J. Exp. Med.* **198**, 725–736 (2003)
RELATED ARTICLES Emsley, H. C. & Hopkins, S. J. Acute ischaemic stroke and infection: recent and emerging concepts. *Lancet Neurol.* **7**, 341–353 (2008) | Chamorro, Á. et al. The immunology of acute stroke. *Nat. Rev. Neurol.* **8**, 401–410 (2012)