T cell clones proliferated in response to HCRT peptides presented by HLA-DRB1*15:01-expressing B cells.

Next, the authors compared the proliferative response of autoreactive T cell clones to HCRT and TRIB2 peptides versus soluble proteins, the latter of which require processing by antigen-presenting cells (APCs). Regardless of the type of APC, most of the T cell clones proliferated only in response to peptides, which suggests that the autoimmune process involves extracellular processing of self-antigens that bind to surface MHC class II molecules.

The results confirm the presence of memory T cells targeting self-antigens expressed by HCRT neurons in patients with narcolepsy. However, as none of these T cell clones proliferated in response to H1N1 influenza vaccine, the data do not support a model of molecular mimicry between neuronal and influenza virus antigens.

Kirsty Minton

ORIGINAL ARTICLE Latorre, D. et al. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. *Nature* https://doi.org/10.1038/s41586-018-0540-1 (2018)

in T_H2 cell-mediated immunity, chemotaxis, inflammation and signalling while inhibiting cytoskeleton remodelling and IgE-induced degranulation.

The relationship between IgD and IgE was further explored in a mouse model of lung inflammation, where IgD inhibited IgE-mediated basophil degranulation and thereby alleviated inflammation. In humans, a positive correlation between IgD levels and tolerance to bee venom and food allergens was observed. In vitro experiments with human basophils showed that IgD mitigates IgE-induced basophil and mast cell degranulation by inhibiting IgE-mediated cytoskeleton remodelling and degranulation.

The authors propose that strategies to boost the activity of IgD, such as galectin-9 administration, might serve to alleviate acute IgE-dependent allergic reactions to food antigens.

Alexandra Flemming

ORIGINAL ARTICLE Shan, M. et al. Secreted IgD amplifies humoral T helper 2 cell responses by binding basophils via galectin-9 and CD44. *Immunity* https://doi.org/10.1016/j.immuni.2018.08.013 (2018)

VACCINES

Statins as adjuvants

Statins are broadly known for their cholesterol-lowering effects. But a new study shows that their ability to inhibit protein prenylation through the mevalonate pathway enhances antigen presentation and adaptive immune responses. This suggests new applications for statins and other drugs that target the mevalonate pathway as vaccine adjuvants and in cancer immunotherapies.

Statins inhibit an early stage enzyme in the mevalonate pathway, effectively blocking the synthesis of cholesterol, squalene and geranylgeranyl diphosphate (GGPP) — the metabolite required for protein prenylation. To assess the effects of statins on immune responses, mice were immunized with ovalbumin (OVA) mixed with various statin drugs that varied according to their polarity. Lipophilic statins (such as simvastatin) triggered OVA-specific serum IgG titres that were 70 times higher than titres induced by OVA alone and 5 times higher than those induced by the positive control adjuvant alum. By contrast, polar statins did not increase antibody titres to levels higher than the alum control.

Indeed, compared with several other known adjuvants, simvastatin induced robust germinal centre formation and the highest antibody titres. Moreover, mice immunized with viral antigen plus simvastatin were completely protected against an otherwise lethal dose of influenza virus.

Next, the authors designed lipophilic bisphosphonates that inhibit enzymes further downstream in the mevalonate pathway. Inhibitors of GGPP synthesis, but not those blocking cholesterol and squalene synthesis, had strong adjuvant effects as well as prophylactic effects in the pathogenic influenza model. These effects could be abrogated if GGPP was co-administered to override inhibition of GGPP synthase. This suggests that inhibition of protein prenylation, and not cholesterol lowering, is the key mechanism by which statins and bisphosphonates alter immune function.

Unlike conventional adjuvants, inhibitors of the mevalonate pathway did not act as danger signals and directly induce innate immune responses. Instead, the authors observed a delay in endocytic processing in dendritic cells (DCs) treated with simvastatin. In addition, they observed increased antigen presentation by DCs to $CD4^+$ and $CD8^+$ T cells. They demonstrated that this was achieved by slowing down endosome maturation, which is expected to increase the availability of antigenic epitopes. Accordingly, the authors showed by three different methods that simvastatin-treated DCs had longer OVA

Credit: Zoonar GmbH/Alamy

retention and that this led to increased amounts of peptide–MHC complexes on the cell surface. Importantly, mice with DCs that lack GGPP synthase developed high IgG titres following OVA immunization and showed enhanced antigen presentation. Similarly, the addition of GGPP abolished the ability of simvastatin to slow endosomal trafficking in wild-type DCs and increase antigen presentation.

Protein prenylation is known to increase the affinity of proteins for membranes and thus to regulate proteins involved in endosomal trafficking, such as small GTPases. Using a library of small interfering RNAs, the authors found that knockdown of the small GTPase *Rab5* interrupted endosomal trafficking and increased antigen presentation in DCs. In addition, simvastatin altered the cellular distribution of RAB5, which suggests that simvastatin functions by inhibiting the synthesis of GGPP that is required for the prenylation of small GTPases.

To explore further its potential as an effective adjuvant, simvastatin was used in a therapeutic cancer vaccine. In the B16-OVA melanoma model, mice vaccinated with simvastatin–OVA showed markedly reduced tumour loads and extended lifespans. This therapeutic effect was found to depend on the presence of $CD4^+$ and $CD8^+$ T cells. Adoptive transfer of antigen-pulsed, simvastatin-treated DCs was also able to block the growth of pre-established tumours. Finally, combining simvastatin-mediated vaccination with checkpoint blockade dramatically increased survival rates in two mouse tumour models and protected mice from subsequent challenge with tumour cells, suggesting the induction of immune memory by the simvastatin-containing vaccine.

New adjuvant approaches are long overdue and this study identifies the mevalonate pathway as a new target for boosting immune responses.

Lucy Bird

ORIGINAL ARTICLE Xia, Y. et al. The mevalonate pathway is a druggable target for vaccine adjuvant discovery. *Cell* https://doi.org/10.1016/j.cell.2018.08.070 (2018)