

Studies in mice lacking the acetylcholine receptor *Chrna7* confirmed the effect of acetylcholine on haematopoiesis and indicated that it signals through stromal niche cells: wild-type bone marrow cells transplanted into irradiated *Chrna7*^{-/-} mice showed the similar increase in myelopoiesis to *Cd19*^{Cre}*Chat*^{fl/fl} mice, as did mice with a specific deletion of *Chrna7* in stromal bone marrow cells. Single-cell RNA sequencing of bone marrow cells identified nine cell types that express *Chrna7* in the bone marrow niche and localize close to acetylcholine-expressing B cells. *Cxcl12* was one bone marrow niche factor that was downregulated in *Chrna7*^{-/-} stromal cells in *Cd19*^{Cre}*Chat*^{fl/fl} mice, and blockade of CXCL12-induced signalling suggested a functional role for this factor in constraining leukocyte production. Gene expression analysis also suggested that in the absence of B cell-derived acetylcholine, bone marrow niche cells adopt a more inflammatory phenotype.

Finally, the authors examined the implications of acetylcholine-mediated regulation of haematopoiesis in

mouse models of cardiovascular disease. In an atherosclerosis model, *Cd19*^{Cre}*Chat*^{fl/fl} mice developed larger atherosclerotic plaques with a greater accumulation of myeloid cells than control mice. Similarly, following acute myocardial infarction (MI) induced by coronary ligation, *Cd19*^{Cre}*Chat*^{fl/fl} mice showed elevated myeloid cells in infarcted hearts and poorer survival than control mice. Moreover, wild-type mice treated with acetylcholine esterase inhibitor (raising acetylcholine levels) before induction of MI led to curtailed supply of inflammatory myeloid cells to the blood and infarcts, giving rise to less severe disease. Finally, the observation that acute MI occurring in patients taking donepezil was associated with a lower increase in blood leukocytes suggests that harnessing cholinergic signalling could be therapeutic opportunity for inflammatory cardiovascular disease.

Lucy Bird

ORIGINAL ARTICLE Schloss, M. J. et al. B lymphocyte-derived acetylcholine limits steady-state emergency hematopoiesis. *Nat. Immunol.* <https://doi.org/10.1038/s41590-022-01165-7> (2022)

T_H2 component seen in lean mice. T cells from lean mice showed 'early' T_H17 lineage-commitment (expressing *Rorc*, but not effector IL-17 cytokines) whereas T cell from obese mice showed 'late' T_H17 lineage-commitment (expressing *Rorc*, effector IL-17 cytokines and the IL-23 receptor). These changes made obese mice with AD resistant to anti-IL-4/anti-IL-13 therapy, which strongly protected lean mice from AD development. In fact, anti-IL-4/anti-IL-13 treatment actually worsened AD disease in obese mice.

The authors hypothesized that a transcription factor that protects the dominance of the T_H2 response may be downregulated during obesity and identified PPAR γ as a potential candidate. They found that expression of PPAR γ -regulated genes was decreased in T_H2 cells and naive-like T cells from obese mice. Notably, lean mice with a $CD4^+$ T cell-specific loss of *Pparg* developed normally but showed heightened disease in the AD models, characterized by an exaggerated T_H17 component. Therefore, the maintenance of T_H2 responses by PPAR γ seems to prevent the amplification of a more pathological

T_H17 -type inflammation. Finally, the authors treated obese mice with thiazolidinediones (TZDs, a class of PPAR γ agonists used as insulin-sensitizing agents to manage type 2 diabetes) to test if PPAR γ activation limits AD. Indeed, TZD-treated obese mice showed reduced AD severity, and this was associated with decreased T_H17 cells and increased PPAR γ activity in T cells. Of note, when the authors treated obese mice with a TZD regimen that was not in itself sufficient to reduce AD severity, they found that these animals regained responsiveness to anti-IL-4/anti-IL-13 therapy.

These findings suggest that obesity exacerbates atopic disease by exaggerating pathological T_H17 responses. Moreover, the data indicate that the metabolic status of an individual can alter the immune mechanisms underlying a particular disease and determine whether or not they respond to certain disease therapies.

Yvonne Bordon

ORIGINAL ARTICLE Bapat, S. P. et al. Obesity alters pathology and treatment response in inflammatory disease. *Nature* <https://doi.org/10.1038/s41586-022-04536-0> (2022)

IN BRIEF

COVID-19

Are variant-specific vaccines warranted?

The efficacy of current COVID-19 vaccines wanes over time, and viral variants, particularly Omicron, have lost many of the binding sites for neutralizing antibodies — leading to large numbers of breakthrough infections in vaccinated individuals. Vaccine boosters can restore protection (at least for a few months), and variant-specific boosters are currently being trialled. In a mouse model of COVID-19, Ying et al. demonstrate that boosting with an Omicron-specific version of mRNA-1273, as compared to the 'original' mRNA-1273, leads to enhanced protection against Omicron. However, full vaccination with the Omicron-adapted vaccine provided poor cross-protection against the ancestral virus. Meanwhile, Gagne et al. compared mRNA-1273 and Omicron-matched booster shots in macaques that had been vaccinated with mRNA-1273 months earlier. Following challenge with Omicron, both boosters induced 70–80% cross-protective B cells and provided complete protection in the lungs as well as comparable, limited protection in the upper airways. Given the uncertainty around potential new variants, broad protection may be preferable to variant-specific protection.

ORIGINAL ARTICLES Gagne, M. et al. mRNA-1273 or mRNA-Omicron boost in vaccinated macaques elicits similar B cell expansion, neutralizing antibodies and protection against Omicron. *Cell* <https://doi.org/10.1016/j.cell.2022.03.038> (2022) | Ying, B. et al. Boosting with variant-matched or historical mRNA vaccines protects against Omicron infection in mice. *Cell* <https://doi.org/10.1016/j.cell.2022.03.037> (2022)

COVID-19

New tool to investigate spike-specific CD4⁺ T cells

Both $CD8^+$ and $CD4^+$ T cells against the SARS-CoV-2 spike protein have been associated with reduced severity of COVID-19, indicating a role for T cells in limiting viral pathogenesis. In addition, spike-specific $CD4^+$ T follicular helper (T_{FH}) cells support B cell maturation and neutralizing antibody production. Using a novel peptide–MHC tetramer to track human spike-specific $CD4^+$ T cells, Wragg et al. now demonstrate that SARS-CoV-2 infection or vaccination induces robust CXCR5⁺ T memory and circulating T_{FH} cell responses, which are efficiently recalled upon antigen re-exposure and may contribute to long-term protection against SARS-CoV-2.

ORIGINAL ARTICLE Wragg, K. M. et al. Establishment and recall of SARS-CoV-2 spike epitope-specific $CD4^+$ T cell memory. *Nat. Immunol.* <https://doi.org/10.1038/s41590-022-01175-5> (2022)

COVID-19

Do individuals who have recovered from COVID-19 still benefit from being vaccinated?

To address this question, Cerqueira-Silva et al. analysed the national disease surveillance and vaccination databases from Brazil to estimate the effectiveness of CoronaVac, ChAdOx1 nCoV-19, BNT162b2 and Ad26.COV2.S in individuals with previous SARS-CoV-2 infection. All four vaccines conferred a high degree of protection against second symptomatic infections (ranging from 39.4% (CoronaVac) to 64.8% (BNT162b2)) and death (>80% for all two-dose vaccines) in previously infected individuals. Another study by Nordström et al. of Swedish nationwide registers also found that 'hybrid immunity' (from both infection and vaccination) provided additional protection compared to virus-induced immunity alone.

ORIGINAL ARTICLE Cerqueira-Silva, T. et al. Effectiveness of CoronaVac, ChAdOx1 nCoV-19, BNT162b2, and Ad26.COV2.S among individuals with previous SARS-CoV-2 infection in Brazil: a test-negative, case-control study. *Lancet Infect. Dis.* [https://doi.org/10.1016/S1473-3099\(22\)00140-2](https://doi.org/10.1016/S1473-3099(22)00140-2) (2022) | Nordström, P. et al. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden. *Lancet Infect. Dis.* [https://doi.org/10.1016/S1473-3099\(22\)00140-2](https://doi.org/10.1016/S1473-3099(22)00140-2) (2022)