
Credit: imageBROKER/Alamy

to a lesser degree, from endothelial cells. Given the low death rate of cardiomyocytes, the authors explored how cMacs obtain materials from these cells. They detected cardiomyocyte-derived subcellular particles (~3.5 μm in diameter and ~31 μm^3 in volume), which they named 'exophers', and showed that ~40% of these were in contact with or inside cMacs. Transmission electron microscopy revealed that extracellular exophers contain mitochondria and fragments of sarcomeres. Of note, exopher-like structures were also detected in human cardiac tissue.

Further experiments indicated that cardiomyocytes use autophagy in order to form exophers and that these structures preferentially transfer dysfunctional mitochondria to cMacs. The depletion of cMacs led to inflammasome activation in cardiac tissue, which inhibited autophagy and the release of exophers. By contrast, in the presence of cMacs, the induction of cardiac stress following β-adrenergic receptor stimulation or myocardial infarction was associated with increased exopher production. Depletion of cMacs led to more severe cardiac disease in both of these models. Finally, the authors showed that cardiac macrophages use the MER tyrosine kinase receptor (which recognizes 'eat me' signals on dying cells) to uptake exophers; heart tissue from *Mertk*$^{-/-}$ mice showed high extracellular accumulation of free mitochondria and inflammasome activation.

Thus, in addition to their well-described roles in clearing up dying cells, macrophages can also clean up after living cells in the heart.

Yvonne Bordon

ORIGINAL ARTICLE Nicolás-Ávila, J. A. et al. A network of macrophages supports mitochondrial homeostasis in the heart. *Cell* https://doi.org/10.1016/j.cell.2020.08.031 (2020)

specifically promoted the development of mucosal T helper 1 (T_H1) cells and $CD8^+$T-bet^+ T cells, but ICB therapy was required in addition to the bacterium to boost T cell effector function.

ICB therapy alters gut barrier integrity and therefore may allow translocation of bacteria or their products into the blood. In keeping with this hypothesis, serum from anti-CTLA4-treated *B. pseudolongum*-colonized mice, but not serum from anti-CTLA4-treated GF mice or mice colonized with control bacteria, was sufficient to reduce tumour growth and elicit strong antitumour immunity in GF mice.

Metabolomic analysis of the serum samples revealed an abundance of the metabolite inosine, and its degradation products, in *B. pseudolongum*-colonized mice compared with controls. Although previous studies have described an immunosuppressive role for inosine, Mager et al. show that inosine could enhance T_H1 cell activation in vitro. This effect depended on signalling through its receptor adenosine 2A receptor (A2AR). Indeed, the use of *Rag1*-deficient mice reconstituted with A2AR-deficient T cells showed that the ICB-enhancing activity of *B. pseudolongum* required T cell expression of A2AR. And studies involving in vivo depletion of conventional dendritic cells indicated a requirement for these cells (mediating antigen presentation, IL-12 production and T cell stimulation) in the response to ICB–bacteria co-therapy.

Importantly, oral or systemic administration of inosine led to reduced tumour size and increased antitumour immunity when given to tumour-bearing GF mice together with anti-CTLA4 and CpG as a costimulus. Inosine was effective even in mice with a diverse microbiota and in other tumour models.

These data suggest that this previously unknown immune-boosting metabolite may be useful for the development of microorganism-based adjuvant therapies.

Lucy Bird

ORIGINAL ARTICLE Mager, L. F. et al. Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. *Science* **369**, 1481–1489 (2020)

IN BRIEF

COVID-19

Convalescent plasma trial shows no benefit

Passive immunization with convalescent plasma (CP) is being evaluated as a treatment for COVID-19. A multicentre, open-label, randomized, controlled trial was conducted in India in which patients received either best standard of care (BSC) ($n = 229$) or BSC coupled with two 200 ml doses of CP ($n = 235$). Despite lower viral RNA measured in patients who received CP, there was no difference in 28-day mortality or progression to severe disease between treatment arms. Importantly, 83% of study participants showed detectable neutralizing antibodies (nAbs) at enrolment and nAb titres did not change after treatment. Although this trial failed to demonstrate therapeutic efficacy, future investigations using CP pre-screened for higher nAb titres or treating nAb-naive patients may be warranted.

ORIGINAL ARTICLE Agarwal, A. et al. Convalescent plasma in the management of moderate COVID-19 in India: an open-label parallel-arm phase II multicentre randomized controlled trial (PLACID Trial). Preprint at *medRxiv* https://doi.org/10.1101/2020.09.03.20187252 (2020)

COVID-19

Fatty monocytes in COVID-19

Dysfunctional myeloid cells in patients with severe COVID-19 are linked to emergency myelopoiesis, but the exact role of these cells in the disease remains unclear. In this preprint, the authors observed that monocytes from patients with COVID-19 accumulate lipid droplets (LDs). Ex vivo exposure of healthy donor-derived monocytes to SARS-CoV-2 resulted in LD accumulation and upregulation of lipid metabolism targets. Inhibition of LD biogenesis reduced production of pro-inflammatory cytokines, viral replication and death of infected monocytes. Interestingly, the authors also showed that SARS-CoV-2 proteins and double-stranded RNA localize near LDs in infected cells. These results suggest that lipid metabolic reprogramming benefits SARS-CoV-2 infection, and its targeting in myeloid cells may have therapeutic benefit in COVID-19.

ORIGINAL ARTICLE Dias, S. S. G. et al. Lipid droplets fuel SARS-CoV-2 replication and production of inflammatory mediators. Preprint at *bioRxiv* https://doi.org/10.1101/2020.08.22.262733 (2020)

COVID-19

SARS-CoV-2 antibody seroconversion in care home

In this preprint, Ladhani et al. analysed SARS-CoV-2 infection rate and seropositivity in residents and staff members from six care homes in London, UK. 40% of residents and 21% of staff had SARS-CoV-2 infection confirmed by RT-PCR at baseline. Five weeks later, 86% of the surviving residents and 73% of staff were tested for antibodies. Nearly all (97–100%) SARS-CoV-2 RT-PCR-positive individuals and the majority (66–85%) of SARS-CoV-2 RT-PCR-negative individuals seroconverted. Importantly, neutralizing antibodies were present in 89% of seropositive individuals, irrespective of gender, age, symptoms or PCR status. The finding that elderly residents can mount neutralizing antibody responses to levels similar to younger staff members offers hope for future vaccine efficacy in aged populations.

ORIGINAL ARTICLE Ladhani, S. N. et al. High prevalence of SARS-CoV-2 antibodies in care homes affected by COVID-19; a prospective cohort study in England. Preprint at *medRxiv* https://doi.org/10.1101/2020.08.10.20171413 (2020)

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