VACCINES

Same but different

Vaccine https://doi.org/10.1016/j.vaccine.2019.11.060 (2019)

Since its first use in humans in 1921, the live attenuated tuberculosis vaccine bacille Calmette-Guérin (BCG) has been propagated under different conditions, which has led to the appearance of genetically distinct strains. In *Vaccine*, Levy and colleagues systematically compare five licensed BCG formulations to gain insights into the biological differences among these strains. The five formulations differ significantly in their in vitro viability, growth characteristics and RNA content when cultured under identical conditions. For example, BCG-India and BCG-Bulgaria show slower growth and are also more affected by changes in the culture media. BCG formulations also exhibit differences in their ability to stimulate immune responses, with BCG-India in particular being relatively poor at eliciting interferon-γ — a cytokine critical for effective antituberculosis responses. These findings highlight the need to consider BCG strain formulations in both clinical and laboratory contexts. *ZF*

https://doi.org/10.1038/s41590-020-0611-y

PERIPHERAL TOLERANCE

A new VISTA in tolerance

Science **367**, eaay0524 (2020)

VISTA is a negative regulatory molecule that, uniquely among checkpoint receptors, is expressed on naive T cells. In *Science*, Noelle and colleagues elaborate on the function of VISTA further and find that it has a cell-intrinsic role in maintaining naive T cell quiescence. VISTA's absence results in the acquisition of T cell activation and memory transcriptional and epigenetic signatures, appears to operate specifically in the periphery and does not obviously influence thymocyte development. VISTA ligation results in increased sensitivity to T cell receptor activation-induced cell death and thereby helps maintain peripheral tolerance. However, under inflammatory conditions (for example, in the presence of lipopolysaccharide) VISTA expression is lost, and T cells can undergo activation and clonal expansion. VISTA therefore seems to be a checkpoint inhibitory receptor that enforces the quiescence of naive T cells under steady-state conditions. *ZF*

https://doi.org/10.1038/s41590-020-0612-x

IMMUNOMETABOLISM

A killer diet

Nat. Metab. **2**, 110–125 (2020)

High-protein diets induce weight loss. In *Nature Metabolism*, Razani and colleagues show that hyperlipidemia-prone *Apo2*$^{-/-}$ mice on a high-protein Western diet (HPWD; 43% fat, 46% protein) develop more atherosclerosis, with more apoptosis and necrosis in the plaques, than mice on a 'standard' Western diet (42% fat, 15% protein), despite a reduction in whole-body fat. HPWD increases the amount of amino acids, especially leucine, in macrophages from the sclerotic aortas and increases the activation of the amino acid sensor mTORC1 in these cells. Macrophage-specific deletion of the mTORC1 component Raptor reduces atherosclerosis and plaque complexity in *Apo2*$^{-/-}$ mice on a HPWD. In cultured macrophages, leucine treatment decreases autophagy of mitochondria in a Raptor-dependent manner, while deletion of the autophagy regulator Atg5 abrogates the protective phenotype of Raptor deficiency in *Apo2*$^{-/-}$ mice on a HPWD. Thus, high levels of protein can worsen high-fat-diet-induced atherosclerosis, despite the weight loss benefits. *IV*

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IMMUNOMETABOLISM

Protective γδ T cells

Nat. Metab. **2**, 50–61 (2020)

A ketogenic diet (KD; 90% fat, <1% carbohydrate) induces the formation of ketone bodies and is linked to weight loss and reduced inflammation. In *Nature Metabolism*, Dixit and colleagues show that a 1-week-long KD (stKD) activates a subset of adipose-tissue-resident γδ T cells that support tissue repair and homeostasis, while a 2–3 months long KD (ltKD) depletes these cells and induces obesity and glucose intolerance. As indicated by single-cell and bulk RNA-seq in the epididymal fat, stKD increases a population of strictly tissue-resident γδ T cells; induces the expression of genes involved in fatty acid metabolism, mitochondrial oxidation, cell trafficking and adhesion; and reduces the expression of *Nlrp3* and *Il1b*. ltKD induces obesity, depletes the γδ T cells in adipose tissue and increases the expression of the proinflammatory genes *Tnf* and *Il1b*. ltKD in *Tcr*$^{-/-}$ mice, which lack γδ T cells, results in increased weight gain and metabolic alterations compared to those in wild-type mice, indicating these cells are protective. *IV*

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Laurie A. Dempsey, Zoltan Fehervari and Ioana Visan

ENTERIC IMMUNITY

Protection by neuronal IL-18

Cell **180**, 50–63 (2020)

The enteric nervous system forms an extensive network of intimate interactions with mucosal epithelial cells and tissue-resident immune cells. In *Cell*, Jarret et al. report that enteric neurons constitutively express interleukin (IL)-18 through a caspase-1-independent pathway. Importantly, neuronal IL-18 is non-redundant in providing protection against invasive Salmonella typhimurium (S.t.). Mice with a specific deletion of *Il18* in enteric neurons, generated using *Hand2* promoter-driven Cre recombinase, are more susceptible to S.t. infection, whereas specific loss of IL-18 in epithelial or hematopoietic cells is dispensable for S.t. control. Loss of neuronal IL-18 specifically affected goblet cell production of antimicrobial peptides in the colon and bacterial exclusion from the inner mucus layer; however, this effect is indirect, and it remains unclear which cells are the relevant IL-18R^{+} responding cells. Thus, neuronal IL-18 is essential for colonic barrier protection. *LAD*

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