IMMUNOMETABOLISM

Tolerance factor

Cell https://doi.org/10.1016/j.cell.2019.07.033 (2019)

GDF15, a member of the TGF-β family of cytokines, signals through its receptor GFRAL, expressed on neurons in the brain stem, to mediate appetite-suppressive effects. In *Cell*, Medzhitov and colleagues show that GDF15 coordinates tolerance to inflammatory damage through the regulation of triglyceride metabolism. GDF15 is upregulated in the serum of patients with sepsis and in the myeloid and non-hematopoietic cells of mice challenged with lipopolysaccharide or the synthetic RNA duplex poly(I:C). During bacterial or viral infection, neutralization of GDF15 increases mortality and cardiac and renal injury, with no effect on the amount of pro-inflammatory cytokines or the pathogen burden. GDF15 blockade reduces the production of triglyceride species in the liver in a manner dependent on β-adrenergic signaling. Administration of triglycerides rescues GDF15-neutralized mice from the mortality and cardiac damage, while subcutaneous administration of GDF15 improves survival in sterile and infectious models of sepsis. *IV*

https://doi.org/10.1038/s41590-019-0506-y

INNATE IMMUNITY

Nuclear viral sensors

Science **365**, eaav0758 (2019)

Recognition of DNA viruses within the nucleus triggers the production of type I interferon. In *Science*, Wang et al. report that the host ribonucleoprotein hnRNPA2B1 serves as a nuclear sensor of viral DNA. Nuclear hnRNPA2B1 dimerizes after recognition of viral DNA, which promotes demethylation of hnRNPA2B1 by the arginine demethylase JMJD6 and translocation of hnRNPA2B1 to the cytosol; there, it associates with the adaptor STING and the kinases Src and TBK1 to activate the transcription factor IRF3, which ensures expression of type I interferon. Additionally, hnRNPA2B1 enhances anti-viral innate immunity by promoting N6-methyladenosine modification of mRNAs encoding STING, cGAS and IFI16 to enhance their export from the nucleus and translation and thus boosts the abundance of these cytosolic anti-viral sensors at later time points after the recognition of DNA viruses. Thus, the recognition of viral DNA by nuclear hnRNPA2B1 coordinates the cellular anti-viral immune responses. *LAD*

https://doi.org/10.1038/s41590-019-0507-x

IMMUNOMETABOLISM

Modulation by hypusination

Cell Metab. **30**, 352–363 (2019)

It is becoming increasing clear that cellular metabolism via glycolysis and oxidative phosphorylation greatly affects the functionality of activated immune cells. In *Cell Metabolism*, Puleston et al. show that hypusination, a polyamine-dependent post-translational modification, of the translation factor eIF5A boosts mitochondrial respiration by enhancing the translation of mitochondrial enzymes that catalyze multiple steps of the tricarboxylic acid cycle. Inhibition of the hypusine–eIF5A axis diminishes oxidative phosphorylation and the abundance of metabolites of the tricarboxylic acid cycle. In contrast, glycolytic enzymes are not as sensitive to hypusination of eIF5A. Hypusination of eIF5A is upregulated in macrophages stimulated with the cytokine IL-4 but not in those stimulated with the cytokine IFN-γ. In vivo modulation of eIF5A hypusination reduces macrophage-dependent control of the parasite *Heligmosomoides polygyrus* but does not alter responses to the injection of lipopolysaccharide, which shows that this modification influences macrophage function. *LAD*

https://doi.org/10.1038/s41590-019-0508-9

MECHANOIMMUNOLOGY

Brief forces measure up

Proc. Natl Acad. Sci. https://doi.org/10.1073/pnas.1904034116 (2019)

Forces transmitted via interactions between the T cell antigen receptor (TCR) and its peptide–major histocompatibility complex ligand are generally weak and fleeting, which makes study of these interactions challenging. In the *Proceedings of the National Academy of Sciences*, Salaita and colleagues use a fluorescent DNA hairpin probe coupled to TCR ligands (antibody to the TCR invariant chain CD3ε or peptide–major histocompatibility complex) that unfolds when force over a definable threshold is applied. Normally the hairpin refolds rapidly, but this modified probe can be selectively and reversibly 'locked' open, which allows measurement of the highly transient forces generated by TCR–ligand interactions. Force maps show that cognate peptides generate a characteristic ring structure, whereas altered peptide ligands or interactions between the inhibitory receptor PD-1 and its ligand PD-L1 are highly disorganized. This modified DNA-probe approach for measuring transient forces may be widely applicable across immunological systems. *ZF*

https://doi.org/10.1038/s41590-019-0509-8

REGENERATIVE MEDICINE

Not so silent

Nat. Biotech. https://doi.org/10.1038/s41587-019-0227-7 (2019)

Full realization of the therapeutic promise of induced pluripotent stem cells (iPSCs) will require that they be immunologically tolerated by the recipient; however, even autologous iPSCs can sometimes elicit an immune response. In *Nature Biotechnology*, Schrepfer and colleagues assess the mutation rates of mitochondrial DNA (mtDNA) in both mouse cells and human cells undergoing reprogramming to iPSCs. mtDNA is known to have less-reliable repair mechanisms, and indeed the investigators observe that the number of non-synonymous mutations in the mtDNA of iPSCs directly related to the number of in vitro passages. These mtDNA mutations can generate neoantigens able to stimulate immune responses and immunological rejection. These findings reveal a mechanism that underpins the loss of autologous iPSC immunological silence and suggest that screening of mtDNA may be important. *ZF*

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