CELL DEATH

Shifting pathways

Cell https://doi.org/10.1016/j.cell.2022.06.038 (30 July 2020)

Mutations in the gene encoding the GTPase LRRK2 are associated with human diseases. In *Cell*, Weindel et al. show that the disease-associated gain-of-function allele *Lrrk2*^{G2019S} enhances inflammasome-triggered necroptotic cell death through a process that is dependent on mitochondrial reactive oxygen species (mtROS) and is driven by N-GSDMD-mediated pore formation in the mitochondrial membrane. Mouse embryonic fibroblasts expressing *Lrrk2*^{G2019S} have greater mitochondrial fragmentation and depolarization than that of wild-type cells, whereas inflammasome activation in *Lrrk2*^{G2019S} bone marrow–derived macrophages (BMDMs) triggers more release of mtROS than that in wild-type BMDMs, which in turn drives the increased association of N-GSDMD with the mitochondria and necroptosis mediated by the kinase RIPK3. Inflammasome activation in *Lrrk2*^{G2019S} BMDMs does not lead to release of the pro-inflammatory cytokine IL-1β. Thus, excess mtROS shifts cells away from pyroptosis and release of IL-1β and toward activation of RIPK3 and necroptotic cell death. *IV*

https://doi.org/10.1038/s41590-022-01303-1

BROADLY NEUTRALIZING ANTIBODIES

Isotype matters

Sci. Transl. Med. **14**, eabn9662 (27 July 2022)

Elicitation of broadly neutralizing antibodies (bnAbs) is a key goal for human immunodeficiency virus (HIV) vaccine strategies, yet most vaccines induce responses that involve multiple immunoglobulin G (IgG) isotypes. In *Science Translational Medicine*, Brady et al. systematically investigate the effectiveness of human isotypes IgG1–IgG4 against HIV infection. The authors utilize two different humanized mouse NOD–SCID–γc (huNSG) models that express adeno-associated virus vector transgenes encoding distinct IgG isotypes that carry identical the bnAb VRC07 V(D)J variable regions. Although in vitro antigen recognition is similar, IgG1 and IgG3 bnAbs are superior in eliciting antibody-mediated cellular cytotoxicity and antibody-mediated cellular phagocytosis of target cells expressing HIV envelope protein, whereas IgG2 bnAbs are not protective. Notably, even low titers of VRC07–IgG1 protect huNSG mice against repeated vaginal HIV challenge; VRC07–IgG3 is less protective. These findings suggest vaccines that can specifically trigger IgG1 bnAbs may provide substantial protection against HIV infection. *LAD*

https://doi.org/10.1038/s41590-022-01304-0

INFLAMMASOMES

Leaky mitochondria

Immunity https://doi.org/10.1016/j.immuni.2022.06.007 (7 July 2022)

Mitochondrial stress can drive the release of oxidized mitochondrial DNA (mtDNA), which can both induce cGAS–STING-mediated interferon signaling and also bind and activate the Nlrp3 inflammasome. Research by Xian et al. now published in *Immunity* further links these two pathways and shows how release of oxidized mtDNA is regulated. Nlrp3 activators (such as alum) stimulate rapid mitochondrial calcium influx, which leads to uncoupling of the electron-transport chain, the generation of reactive oxygen species, and the opening of mitochondrial channels; this enables oxidized mtDNA fragments to pass into the cytoplasm, where they can be detected by cGAS–STING or activate Nlrp3. The authors also show that the generation of oxidized mtDNA fragments, which is blocked by the DNA glycosylase OGG1, depends on cleavage of oxidized genomic mtDNA by the endonuclease FEN1, inhibitors of which limit mtDNA release and alum-induced peritonitis in mice, potentially circumventing a feed-forward activation process. *NB*

https://doi.org/10.1038/s41590-022-01305-z

TUMOR IMMUNOLOGY

γδ T cells in tumorigenesis

Science https://doi.org/10.1126/science.abj8695 (14 July 2022)

γδ T cells in the intestinal epithelium have been linked to colorectal cancer (CRC). In *Science*, Reis et al find that γδ T cell subsets can either promote or prevent CRC and that this is linked to usage of the T cell antigen receptor (TCR) γ-chain variable region (V_γ). In human CRC samples and mouse CRC models, tumor-infiltrating γδ T cell subsets produce the cytokine IL-17 and express V_γ4 or V_γ6. In non-tumor tissue, γδ T cell subsets produce the cytokine IFNγ and express V_γ7 or V_γ1. When IL-17-producing γδ T cell subsets are restricted, there is less tumor growth and, conversely, when IFNγ-producing γδ T cell subsets are restricted, there is more tumor growth. Therefore, there are differences between pro- and anti-tumorigenic γδ T cell subsets in their TCR usage. *SH*

https://doi.org/10.1038/s41590-022-01307-x

COVID-19

Ketogenesis and COVID-19

Nature https://doi.org/10.1038/s41586-022-05128-8 (28 July 2022)

In response to acute infection, there is a metabolic switch toward ketogenesis and the production of ketone bodies, including β-hydroxybutyrate (BHB). In *Nature*, Karagiannis et al. show that impaired ketogenesis is linked to T cell dysfunction in severe COVID-19. Patients infected with influenza virus have more serum BHB than that of healthy people, but patients infected with SARS-CoV-2 do not. When CD4$^+$ T cells are cultured with BHB, interferon-γ (IFNγ) production is increased and BHB acts as an alternative carbon source to fuel oxidative phosphorylation. Supplementing mice with BHB increases the number of IFNγ$^+$ CD4$^+$ T cells, which reprograms CD4$^+$ T cells toward oxidative phosphorylation and diminishes their glycolytic capacity. When mice infected with SARS-CoV-2 are given BHB, there is increased IFNγ production, viral clearance and survival. Thus, impaired ketogenesis may have a role in severe COVID-19. *SH*

https://doi.org/10.1038/s41590-022-01306-y

Nick Bernard, Laurie A. Dempsey, Stephanie Houston and Ioana Visan