research highlights

VULNERABILITY TO HIV

HLA influence on HIV control

Science **359**, 86-90 (2018)

The expression of *HLA* alleles varies and can influence adaptive immune responses beyond the HLA peptide-presentation ability. In Science, Carrington and colleagues show that allelic variation that increases HLA-A expression results in an impaired ability to control infection with human immunodeficiency virus (HIV). Multi-study analyses of HIV-infected cohorts reveal a positive correlation between HLA-A expression and viral load and a reduced number of CD4+ T cells. HLA-A leader peptides are presented by HLA-E to form a ligand complex for the inhibitory receptor NKG2A expressed on natural killer cells. In vitro studies also show that impaired natural killer cell activity varies with the abundance of *HLA-A* expression, especially when combined with certain variants of HLA-B leader peptides. This suggests that blocking NKG2A-HLA-E interactions could be beneficial in combating HIV. LAD

https://doi.org/10.1038/s41590-018-0057-7

DANGER SIGNALS

Mitochondrial DNA webs

Proc. Natl. Acad. Sci. USA https://doi.org/10.1073/pnas.1711950115 (16 January 2018)

Mitochondrial DNA (mtDNA) released from myeloid cells acts as a damageassociated molecular pattern that drives inflammation. In the Proceedings of the National Academy of Sciences USA, Rosén and colleagues demonstrate that mtDNA can also be released by lymphocytes (T cells, B cells and natural killer cells) specifically in response to the oligonucleotide CpG-C but not in response to inflammatory cytokines or lipopolysaccharide. Released mtDNA forms characteristic 'webs' that are distinct from neutrophil extracellular traps in their function, structure and mode of release. The release of mtDNA does not require cell death, nor apparently do the mtDNA webs serve a bacteriostatic function, as they lack the antibacterial peptides present in neutrophil extracellular traps. Instead, mtDNA webs can elicit the production of type I interferons and might therefore be involved in certain ZFinflammatory diseases.

https://doi.org/10.1038/s41590-018-0058-6

NEURODEGENERATIVE DISEASE Inflammatory brain ripples

Nature **552**, 355-361 (2017)

Activation of innate immunity and the NLRP3 inflammasome has an important influence on the induction and progression of Alzheimer's disease (AD). In Nature, Heneka and colleagues show that ASC specks, a signature characteristic of activation of the NLRP3 inflammasome, are associated with both human AD and mouse AD. ASC specks bind to and aggregate amyloid-β in vitro and in vivo. Macrophages, such as microglia found in the brain, release ASC specks in response to exposure to amyloid-β. Collectively, these findings suggest that ASC specks are released from activated microglia that seed deposition of amyloid-β at distal sites throughout the brain. Targeting ASC specks with a specific antibody diminishes their ability to aggregate amyloid-β, a finding that might offers clues to novel therapies for AD. ZF

https://doi.org/10.1038/s41590-018-0059-5

CELLULAR ENERGETICS

B-1a cell metabolism

J. Exp. Med. https://doi.org/10.1084/ jem.20170771 (11 January 2018)

CD5+ B-1a cells function as a distinct subset of effector B cells. In The Journal of Experimental Medicine, Clarke et al. reveal that B-1a cells use a distinct metabolism that differs from that used by follicular B-2 cells. B-1a cells exhibit a higher rate of glycolysis, lipid uptake and fatty-acid synthesis than that of other B cell subsets and are more dependent on autophagy than are other B cell subsets. Notably, these cells are less flexible in their ability to alter their cellular metabolism, as inhibition of either glycolysis or autophagy induces the rapid death of B-1a cells. The latter scenario results in the hyperpolarization of mitochondria and probably increased oxidative stress within cells. Although this metabolism benefits rapid antibody production, it might explain why this B cell subset is restricted to lipid-rich niches. LAD

https://doi.org/10.1038/s41590-018-0060-z

CANCER IMMUNOLOGY

Tumor architecture

Immunity **48**. 107-119 (2018)

The presence of natural killer (NK) cells in tumors correlates with a better prognosis.

In Immunity, Glasner et al. show that secretion of interferon-γ (IFN-γ) by intratumoral NK cells after signaling via the NK cell receptor NKp46 (in humans) or Ncr1 (in mice) alters tumor architecture through induction of the extracellular matrix protein fibronectin1. Ncr1-deficient mice have less production of IFN-γ from intratumoral NK cells and worse tumor architecture and develop more metastases. Fibronectin1 is strongly induced in tumor cells by IFN-γ signaling, and its knockdown results in more-aggressive tumors. Treatment with recombinant IFN-y or overexpression of Ncr1 in NK cells results in fewer metastases. In humans, expression of NKp46, IFN-γ, the IFN-γ receptor and fibronectin1 correlates with improved IV

https://doi.org/10.1038/s41590-018-0061-y

Alu element risk

Cell https://doi.org/10.1016/j.cell.2017.12.016 (25 January 2018)

Gain-of-function mutations in the gene encoding the dsRNA sensor MDA5 result in enhanced basal signaling in the absence of viral infection. In Cell, Hur and colleagues show that constitutive activation of mutant MDA5 in Aicardi-Goutières syndrome results from loss of tolerance to cellular dsRNA formed by Alu elements. Both wild-type MDA5 and mutant MDA5 require dsRNAmediated bridging for activation. Alu is a 300-nucleotide interspersed element that constitutes 10% of the genome and can form Alu-Alu duplexes in an inverted-repeat configuration. Among endogenous dsRNAs, Alu-Alu hybrids formed by inverted-repeat Alu activate mutant MDA5, but not wild-type MDA5, probably because wild-type MDA5 is less tolerant of the structural irregularity of Alu-Alu hybrids and their posttranscriptional modification by adenosine deaminase. These observations indicate a delicate balance between recognition of self RNA and activation of innate immunity. IV

https://doi.org/10.1038/s41590-018-0062-x

Written by Laurie A. Dempsey, Ioana Visan and Zoltan Fehervari