TUMOR IMMUNOLOGY

β2-AR signaling in MDSCs

J. Clin. Invest. https://doi.org/10.1172/JCI129502 (2019).

Myeloid-derived suppressor cells (MDSCs) blunt effective immune responses against tumors and contribute to tumor progression. In the *Journal of Clinical Investigation*, Mohammadpour et al. report that β2-adrenergic receptor (β2-AR) signaling in MDSCs contributes to the immunosuppressive tumor environment. Chronic low-grade stress increased release of norepinephrine by sympathetic nerves, increasing MDSC accumulation within tumors. By contrast, β2-AR-deficient MDSCs were less suppressive in vitro and in vivo, as mice harboring β2-AR-deficient MDSCs exhibited better tumor control. β2-AR signaling in MDSCs activates the STAT3 transcription program and enhances expression of arginase-1, PD-L1 and prosurvival molecules, including Bcl-2. This β2-AR-dependent suppression program also appears to be conserved in human MDSCs, suggesting that targeting of this pathway could contribute to antitumor therapies. *LAD*

https://doi.org/10.1038/s41590-019-0574-z

IMMUNOLOGICAL MEMORY

Dirt and memory

eLife https://doi.org/10.7554/eLife.48901 (2019).

Immunological memory can develop even in the absence of overt infections; however, the nature and timing of signals that drive T cells to become either central memory (T_{CM}) or effector (T_{EM}) cells is unclear. Seddon and colleagues apply mathematical modeling based on quantitative comparisons of CD4+ T cells from conventionally housed mice (relatively 'dirty'), ventilated-cage-housed mice, and in some cases germ-free mice (the latter two being relatively free of environmental antigens), to investigate memory formation. Modeling suggests that memory cells develop serially from naive to T_{CM} to T_{EM} cells rather than naive cells directly to T_{EM} cells. The level of 'dirtiness' increases the size of the memory pool during an early-life expansion, but by adulthood the rates of memory cell formation and turnover are equivalent in the different groups and therefore largely controlled independently of the microbial environment. *ZF*

https://doi.org/10.1038/s41590-019-0575-y

NEUROIMFLAMMATION

Inflammasomes drive tau pathology

Nature **575**, 669–673 (2019)

Frontotemporal dementia (FTD) is characterized by the aggregation of hyperphosphorylated tau protein in neurofibrillary tangles, neuroinflammation and cognitive loss. In *Nature*, Heneka and colleagues show that activation of the NLRP3 inflammasome regulates the hyperphosphorylation and aggregation of tau. Cleaved caspase-1, ASC and mature interleukin (IL-1β) are increased in cortex samples from patients with FTD and from old (8–11 months) Tau22 mice, which express the tau mutations associated with FTD. Tau22 *Asc*$^{-/-}$ and Tau22 *Nlrp3*$^{-/-}$ mice have less cleaved caspase-1, mature IL-1β and aggregated tau; less PP2A, GSK-3β and CamKII, which regulate the phosphorylation of tau; more neuroprotective CD300lf and ARC; and less spatial memory loss than Tau22 mice. Tau monomers and oligomers increase secretion of IL-1β in microglia, and injection of brain homogenates from APP/PS1 mice, a model of Alzheimer's disease, induces the hyperphosphorylation of tau in Tau22 mice in a manner dependent on ASC and NLRP3. *IV*

https://doi.org/10.1038/s41590-019-0572-1

IMMUNE CHECKPOINT INHIBITION

Predictive biomarkers

Cell **179**, 1191–1206.e21 (2019)

Therapies that inhibit the immune checkpoint molecules PD-1 and CTLA-4 have demonstrated clinical success against 'hot', highly mutagenized tumors; however, triple-negative breast cancers (TNBC) have been less responsive. In *Cell*, Hollern et al. analyzed multiple mouse models of TNBC in response to combination anti-PD-1 plus anti-CTLA-4 therapy to identify predictive biomarkers in responsive tumors. They find that pretreatment covariant signatures indicative for follicular T helper (T_{FH}) cells and B cells correlate with reduced tumor burden and increased survival upon combination therapy with immune checkpoint inhibitors. Similar T_{FH}–B cell covariant signatures can be observed in human solid tumors. They show that clonally activated B cells within the tumor environment contribute as antigen-presenting cells and antibody-producing IgG+ cells. Depletion of either B cells, CD4+ T cells or the cytokine IL-21 diminishes the antitumor response to checkpoint blockade, demonstrating a role for B cells upon checkpoint blockade. *LAD*

https://doi.org/10.1038/s41590-019-0573-0

COMPARATIVE IMMUNOLOGY

Bizarre life, bizarre immunity

PLoS Biol. https://doi.org/10.1371/journal.pbio.3000528 (2019).

The naked mole rat (NM-R) is a eusocial, subterranean rodent species with a highly distinctive biology that includes extreme longevity and high resistance to age-related diseases and cancer. In *PLOS Biology*, Buffenstein and colleagues use single-cell RNA sequencing to characterize and compare the immune systems of NM-Rs and mice. In contrast to mice, which have a peripheral immune system numerically dominated by lymphocytes, NM-Rs instead have a myeloid-biased composition. More strikingly, NM-Rs apparently completely lack canonical NK cells and expression of molecules controlling NK cell functions. In particular, NM-Rs have a paucity of MHC class I molecules, with only 3 MHC I genes, as opposed to the 22 genes found in the mouse genome. This peculiar immune system might suggest that NM-Rs have undergone strong selection for antibacterial but not antiviral responses. *ZF*

https://doi.org/10.1038/s41590-019-0576-x

Laurie A. Dempsey, Zoltan Fehervari and Ioana Visan