NEUROIMMUNOLOGY

CD300f in depression

Proc. Natl Acad. Sci. USA **117**, 6651–6662 (2020).

A role for immunopathology or immune cell involvement has been suspected for human psychiatric diseases such as depression. In *The Proceedings of the National Academy of Sciences*, Lago et al. show that the immunoreceptor CD300f can modulate microglial metabolism and synaptic pruning activity associated with depressive behaviors. They first identify a protective allele of *CD300f* that curiously only affects women. Female but not male mice deficient for CD300f likewise show depression-like behaviors but do not develop classical neuroinflammation. CD300f is expressed by microglia and perivascular macrophages; however, while transcriptional profiles are similar between naive wild-type and *Cd300f*$^{-/-}$ microglial cells, the latter have increased expression of *Il6* and *Il1rn* and decreased expression of *Spp1*. Peripheral injury models induce profound metabolic differences in *Cd300f*$^{-/-}$ microglia as compared to wild-type cells, with reduced activation of glycolysis and oxidative phosphorylation pathways. In vitro assays show CD300f modulates neuronal synaptic strength. In vivo, hippocampal neurotransmission of noradrenaline was decreased, but synaptic serotonin and dopamine content remained unchanged. These findings show CD300f can influence the development of depressive behaviors, yet it remains unknown how sex influences CD300f activity. *LAD*

https://doi.org/10.1038/s41590-020-0682-9

IMMUNOSENESCENCE

Aged boost

Elife **9**, e52473

Germinal center (GC) formation, T follicular helper (T_{FH}) cells and vaccine responses all diminish with age. In *eLife*, Linterman and colleagues examine vaccine responses in elderly humans and mice to determine whether these impairments can be reversed. Following trivalent influenza vaccination, elderly (65–75 years old) volunteers showed significantly reduced frequencies of circulating T_{FH} cells as compared to their young (18–36 years old) counterparts. Aged mice (~2 years old) also showed greatly reduced numbers of T_{FH} cells and GCs and reduced antibody production as compared to young (~3 months old) mice following vaccination with nominal antigens. Conventional type 2 dendritic cells (cDC2s) are the main antigen presenting cells involved in driving T_{FH} cell differentiation, and they show reduced costimulatory molecules in aged mice; however, the defect is not cell intrinsic but rather a consequence of the aged microenviroment. In part, the impaired cDC2 function is caused by reduced type I interferon (IFN-I) production resulting from fewer plasmacytoid DCs — the key IFN-I-producing cell. Aged mice receiving the Toll-like receptor 7 (TLR7) agonist imiquimod topically at the vaccination site showed rescue of T_{FH} cell numbers; however, this did not require an intact IFN-I receptor to be present on DCs. These findings suggest that weakened vaccination responses in the elderly might be rescuable by TLR7 stimulation. *ZF*

https://doi.org/10.1038/s41590-020-0684-7

TUMOR IMMUNOLOGY

Regulatory DCs

Nature **580**, 257–262 (2020).

Antigen presentation by intratumoral conventional dendritic cells (cDCs) activates effector T cells to boost antitumor immunity upon checkpoint blockade therapy. Yet some tumors resist such therapy, despite the presence of cDCs, prompting the question of whether the tumor-resident cDCs are altered. In *Nature*, Maier et al. utilize single-cell RNA sequencing and CITE-seq (cellular indexing of transcriptomes and epitopes by sequencing) to identify a unique cDC subset, dubbed mregDCs, that express CD40, interleukin (IL)-12 and abundant major histocompatibility complex II (MHC-II) molecules, as well as immunoregulatory molecules that include PD-L1, CD274 and CD200. The mregDCs are distinct from previously described cDC1 and cDC2 subsets but appear to be derived from both subsets within the tumor environment. A similar mregDC subset is found in human lung tumors. Uptake of apoptotic cells within the tumor environment via recognition by the receptor tyrosine kinase molecule AXL induces mregDC formation, and these cells were more efficient at promoting Foxp3 expression in CD4$^+$ T cells during in vitro coculture. The AXL signaling pathway is also necessary for upregulation of PD-L1 expression; however, it is not needed for IL-12 expression in mregDCs. Rather, IL-12 expression by mregDCs is upregulated by interferon-γ but downregulated by IL-4, which is the predominant cytokine in resistant tumors. The authors show that combination therapy with PD-L1 blockade and anti-IL-4 enhances antitumor immunity in a mouse lung cancer model. These findings suggest that combination therapies that include anti-IL-4 might boost antitumor responses to PD-1 blockade. *LAD*

https://doi.org/10.1038/s41590-020-0683-8

CANCER IMMUNOLOGY

Complement swings the balance

Cell **180**, 1081–1097.e24 (2020)

It is increasingly appreciated that B cells have an important influence on the progression of cancer. In *Cell*, Su and colleagues characterize the role of B cells in both human patients and mouse models of breast cancer before and after neoadjuvant chemotherapy. Treatment results in tumor cell death and release of complement proteins, which in turn signal via complement receptor 2 (CR2) on B cells within the tumor microenvironment, leading to their expression of the T cell costimulatory molecule ICOSL. The frequency of ICOSL$^+$ B cells within the TME correlates with increased patient survival. Loss of ICOSL or CR2-mediated signaling on B cells impairs the antitumor response in mouse models of breast cancer. The complement-inhibiting molecule CD55 reduces the frequency of ICOSL$^+$ B cells and can swing the response in favor of the tumor. Modulating the strength of complement signaling might therefore be a useful immunotherapeutic approach for breast cancer. *ZF*

https://doi.org/10.1038/s41590-020-0685-6

Laurie A. Dempsey and Zoltan Fehervari