MICROBIOTA

Antibodies and metabolites

Immunity https://doi.org/10.1016/j.immuni.2018.08.004 (2018)

Microbial metabolites such as short-chain fatty acids and aryl hydrocarbon receptor ligands shape host metabolism and immune functions. In *Immunity*, Macpherson and colleagues use stable isotope tracing of microbial and host metabolites to investigate the penetration of bacterial metabolites into host tissues, their transit through the host intestine, and the consequent immune and metabolic responses in the host. Transfer of labeled non-replicating *Escherichia coli* into fasting germ-free mice results in extensive penetration of a broad range of bacteria-derived molecules into most host tissues by 2 hours after transfer. The bacterial metabolites originate mostly from the small intestine, are cleared in the urine and have immunostimulatory effects. Mice lacking all antibody isotypes owing to deletion of the joining fragment in the immunoglobulin heavy chain have greater amounts of bacterial metabolites in some tissues than do wild-type mice, mostly as a result of the increased dwell time of the transferred bacteria in the small intestine, rather than loss of direct binding of antibodies to the bacterial metabolites. *IV*

https://doi.org/10.1038/s41590-018-0244-6

CANCER IMMUNOTHERAPY

Missile guidance for brain tumors

Nature https://doi.org/10.1038/s41586-018-0499-y (2018)

The blood–brain barrier (BBB) forms a formidable vascular hurdle. Tumor endothelium upregulates activated leukocyte cell adhesion molecule (ALCAM), which engages its counter-ligand CD6, expressed on activated T cells. However, tumor endothelium downregulates expression of the ICAM1 and VCAM1 adhesion molecules, thereby preventing sustained T cell adhesion and extravasation into brain tumors. In *Nature*, Samaha et al. engineer expression of synthetic CD6 molecules on cytolytic T cells to exploit the tumor-induced changes in brain endothelium to deliver tumor immunotherapies. Multimerization of the CD6 D3 exodomain, which recognizes ALCAM, increases the avidity of T cell binding to tumor endothelium but not to normal brain endothelium. Signaling via the CD6 endodomain elicits additional cytoskeletal changes in T cells to facilitate their extravasation into tumor tissue. Engineered T cells expressing tumor-specific chimeric antigen receptors (CAR T cells) and engineered CD6 molecules exhibit better control of glioblastoma than do control T cells in mouse models. These findings point to therapeutic strategies for attacking brain tumors. *LD*

https://doi.org/10.1038/s41590-018-0245-5

TUBERCULOSIS

CD153 combats Mtb infection

Nat. Microbiol. https://doi.org/10.1038/s41564-018-0231-6 (2018)

Millions of humans worldwide die of *Mycobacterium tuberculosis* (Mtb) infection each year. While CD4$^+$ T cells are essential for control of Mtb infection, correlates of protection remain ill-defined. In *Nature Microbiology*, Barber and colleagues identify CD153 expressed by CD4$^+$ T cells as being protective in Mtb infection. CD153, also known as 'CD30 ligand', is a member of the tumor-necrosis factor superfamily and is encoded by *TNFSF8*. CD4$^+$ T cells expressing CD153 increase in number in the lung tissues of infected mice. Mice lacking CD153 exhibit higher bacterial loads in infected lungs than do wild-type mice. While mice lacking the cytokine IFN-γ fail to contain Mtb infection, neither IFN-γ nor the transcription factor T-bet is required for CD153 expression. Importantly, CD153 expression in Mtb-specific CD4$^+$ T cells correlates with control of lung granulomas in rhesus macaques and latent infection in humans, as opposed to patients with active Mtb infection, in whom CD153 expression is lower. Thus, CD153 provides a correlate of protection against pulmonary Mtb. *LD*

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MULTIPLE SCLEROSIS

B–T in MS

Cell https://doi.org/10.1016/j.cell.2018.08.011 (2018)

T cells display spontaneous autoproliferation in multiple sclerosis (MS), but the mechanistic details underpinning this phenomenon are unclear. In *Cell*, Martin and colleagues observe that B cells from patients with MS that express the disease-susceptibility allele HLA-DR15 can drive the autoproliferation of T cells in an antigen-presentation-dependent manner. This autoproliferation of T cells is not observed in other organ-specific autoimmune diseases tested—neither Crohn's disease nor psoriasis. A peptide screen shows that the B cells of patients with MS present a brain-associated antigen, RASGRP2, to T cells and that this drives T cell activation and production of effector cytokines, especially IFN-γ. Analysis of the TCR repertoires of autoproliferating T cells shows that they are enriched in the brain lesions of patients with MS. These findings from human patients throw light on the mechanism of T cell autoproliferation and add further weight to the pathological role of B cells in MS. *ZF*

https://doi.org/10.1038/s41590-018-0248-2

CANCER IMMUNOLOGY

Targeting cancer by Siglecs

J. Clin. Invest. https://doi.org/10.1172/JCI120612 (2018)

Immune checkpoint inhibition has shown success in a subset of patients and for certain cancers; however, the majority of patients fail to respond, emphasizing the need to identify novel molecular targets. In the *Journal of Clinical Investigation*, Läubli and colleagues find that the immunoregulatory receptor Siglec-9 is expressed at very low levels on human peripheral blood T cells but is fairly consistently upregulated on T cells infiltrating certain types of tumors, such as non–small-cell lung carcinoma (NSCLC). Surprisingly, Siglec-9$^+$ tumor-infiltrating lymphocytes do not seem to be classically exhausted; however, tumors expressing sialoglycan ligands can inhibit T cell activation in a Siglec-9-dependent manner. A transgenic mouse tumor model shows that ligation of Siglec-9 on T cells impairs tumor control. Finally, when patients with NSCLC are stratified as Siglec-9^{hi} versus Siglec-9^{lo}, the Siglec-9^{lo} cohort shows better survival. Targeting Siglecs on T cells might therefore represent a promising avenue for improving cancer immunotherapies. *ZF*

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