Reprogramming metabolism to enhance T-cell immunotherapy

Both the local metabolic environment and intracellular metabolism are crucial aspects of T-cell development and function. Adoptive cell therapy (ACT) involves manipulating T cells, and then infusing them into patients; it is proving effective against many cancers but some solid tumors have an immunosuppressive metabolic microenvironment.

In their review article, Meghan Kates and Samuel D. Saibil begin by detailing the current model of metabolic programming and mitochondrial functions in effector T cells and memory T cells, and the consequences for T-cell functions. Next, the authors discuss how recent discoveries are challenging aspects of this paradigm, especially in effector T cell subsets. The authors then detail how a wide range of specific metabolic barriers in the tumor microenvironment (TME) can be circumvented by interventions that reprogram T-cell metabolism for ACT. Finally, they outline how CAR T-cell constructs can also be modified via e.g. co-stimulatory domains and cytokine signaling to alter T-cell metabolism and thus improve ACT options.

The crystal structure of ligand-free or antibody-bound CLEC12A

C-type lectin receptors (CLRs) can recognize, via their carbohydrate-recognition domain (CRD), a range of self-derived or pathogen-derived ligands to trigger activation or inhibition of immune responses. Human CLEC12A (hCLEC12A) is an inhibitory CLR especially important for myeloid cells whose ligands include monosodium urate (MSU) crystals and mycolic acid (MA) from mycobacterial cell walls; CLEC12A is also a potential diagnostic marker for leukemia. After crystallizing part of the hCLEC12A CRD, Mori et al. report on its atomic structure in detail, including a surface at the lateral face that is highly conserved among mammalian species. The antibody 50C1 is shown to recognize some residues only found on CLEC12A in humans. This antibody binds to the CRD of hCLEC12A and blocks its interaction with MA as well as MSU crystals, and the authors demonstrate that hCLEC12A recognizes these very different ligands via a similar interface (see figure). The authors discuss the potential diagnostic and therapeutic implications of their findings.
A novel approach to identify statin-mediated anti-cancer effects

Although various immunotherapy strategies are proving effective in many patients against many cancer types, there is still a demand for novel investigative methodologies to identify new approaches to complement existing therapies. Statins have a range of immunomodulatory effects, e.g. anti-inflammatory effects via the inhibition of HMG-CoA reductase (HMGCR) in the low-density lipoprotein cholesterol (LDL-C) pathway, and studies have suggested that statins can augment immunotherapy. In this article, Li and Wang use comprehensive drug-target Mendelian Randomization (MR) analysis to simulate the effects that inhibiting HMGCR variants (identified by genome-wide association studies) has on lipid metabolism (i.e. LDL-C levels) and that may enhance immunotherapy. They report that HMGCR inhibition causes pro-inflammatory and anti-tumor effects against diverse cancer types. These effects involve immune cell types, pro-inflammatory cytokines, immune checkpoint molecules, and immunotherapy-related gut microbiota. The authors discuss the implications of this approach to support the therapeutic targeting (e.g. by statins) of HMGCR or other aspects of lipid regulation, thus enhancing the efficacy of immunotherapy.

Inhibiting glycan-mediated lymphocyte homing ameliorates EAE

Experimental autoimmune encephalomyelitis (EAE) is a well-established model of multiple sclerosis (MS). Migration of activated lymphocytes into the central nervous system (CNS) is a crucial step in EAE. Lymphocyte L-selectin can bind high endothelial venule (HEV) 6-sulfo sialyl Lewis X (6-sulfo sLeX) glycans and thus home to peripheral lymph nodes (PLNs). Here, Liu et al., examine mice with double-knockout of GlcNAc6ST-1 and GlcNAc6ST-2 (DKO mice, which lack 6-sulfo sLeX glycans) and use their new anti-glycan monoclonal antibody (SF1), which blocks lymphocyte homing to PLNs. In DKO mice, a range of EAE symptoms are ameliorated and the numbers of effector/activated T cells in the draining LNs (dLNs) and the CNS are reduced. Intraperitoneal SF1 also ameliorates EAE symptoms and reduces antigen-specific T cells in dLNs and activated T cells in the CNS. RNA sequencing showed decreased expression of EAE-associated genes in dLN CD4+ T cells. Thus 6-sulfo sLeX is crucial for EAE pathogenesis and may be a therapeutic target in MS.
N-glycosylation of CD155 modifies NK cell activation

CD155 is an Ig-like receptor that can bind to DNAM-1, TIGIT, and CD96, and can activate or inhibit T cells and NK cells. CD155 is expressed on normal cells and on cancer cells, but high CD155 expression correlates with tumor progression. DNAM-1 and TIGIT are involved in responses to therapeutic antibodies such as anti-PD-1/PD-L1. In their Short Communication, Tahara et al. demonstrate that, although there are different glycosylation patterns in CD155 from various human tumor cells, residue 105 in the first Ig-like domain is N-glycosylated (N105). Importantly, the N105 glycosylation is essential for CD155 binding to DNAM-1 and TIGIT and is involved in signaling downstream from both molecules. DNAM-1 ligation increases NK cell activation, whereas TIGIT ligation decreases it; here, N105 glycosylation of CD155 is shown to contribute to both effects (although relatively less to TIGIT-mediated inhibition), affecting the overall outcome. The authors discuss how therapeutic anti-TIGIT antibodies (plus anti-PD-1/PD-L1) may be more effective against tumors expressing N105-glycosylated CD155.