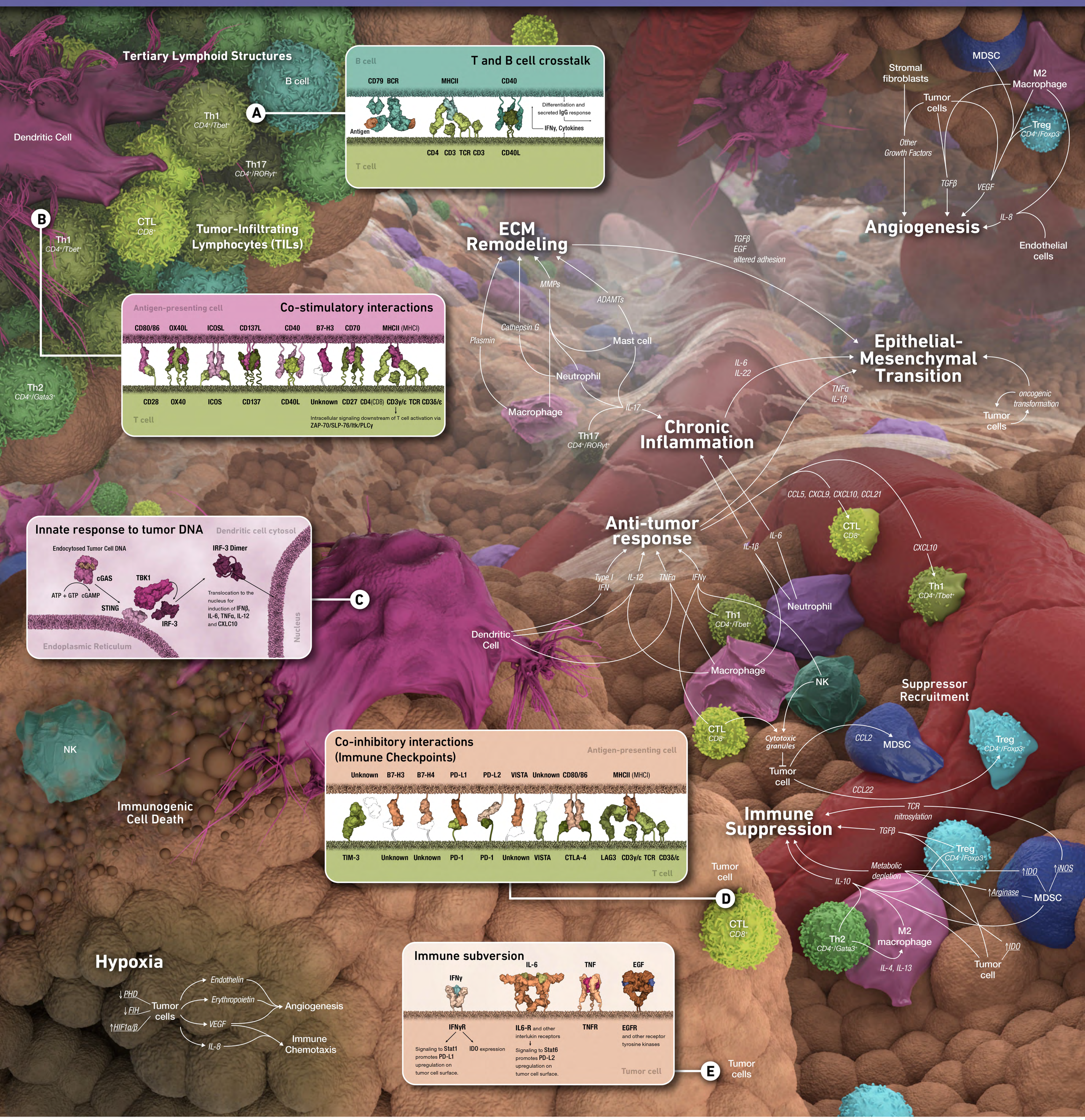
Tumor Immunology
examining the microenvironment

Tumor growth and propagation are fostered by a number of intertwined pathological phenomena: immune suppression (upregulation of immune checkpoints), chronic inflammation, hypoxia-induced angiogenesis, remodeling of the extracellular matrix (ECM), and epithelial-to-mesenchymal transition (EMT). These processes, and the cells (regulatory T cells (Treg), myeloid-derived suppressor cells (MDSC), and M2 macrophages) and secretory molecules that support them constitute the tumor microenvironment.

Despite the suppressive microenvironment of the tumor, immune infiltrates in the form of tumor infiltrating lymphocytes (TILs) and tertiary lymphoid structures have been associated with a positive clinical outcome. In these settings the primary immune protagonists that mediate an adaptive anti-tumor response are the CD8⁺ cytotoxic T lymphocytes (CTLs). Humanized neutralizing antibodies targeting the immune checkpoint receptors on TILs, otherwise known as checkpoint inhibitors, have proven tremendously successful in provoking a meaningful therapeutic response.



Insets A-E

A T and B cell crosstalk

The B cell receptor (BCR) in complex with CD79 mediates antigen recognition, which is followed by the presentation of processed antigenic peptides to CD4⁺ T cells in the context of MHC Class II. The engagement of CD40 with its ligand on T cells provides a co-stimulatory signal resulting in full-fledged activation of resting B cells. This together with a host of cytokines released by T cells triggers the proliferation and differentiation of B cells into antibody producing effector cells.

B Co-stimulatory interactions

T cell activation requires two independent signals: 1) ligation of the T cell receptor (TCR) with cognate antigen on the surface of antigen presenting cells such as dendritic cells (DCs); 2) co-stimulation mediated by CD28 on T cells and CD80 (B7-1) and CD86 (B7-2) on DCs. Ancillary interactions involving OX40, ICOS, CD137, and others further contribute to the strength of this co-stimulation. T cell activation initiates a series of signaling events involving recruitment and activation of intracellular protein kinases including ZAP-70 and Itk that mediate the phosphorylation of the adaptor protein SLP-76 and the enzyme PLCγ, respectively.

C Innate response to tumor DNA

Tumor-derived cytosolic DNA is recognized as a danger signal triggering a signaling cascade, which prompts cyclic GMP-AMP synthase (cGAS) mediated synthesis of 2'3'-cGAMP, a high affinity ligand for stimulator of interferon genes (STING). Binding of cGAMP to STING results in a TBK-1 and IRF-3-dependent interferon (IFN) response. This ultimately leads to the production of Type I IFN by dendritic cells, thus rendering them proficient to present tumor antigens and prime CD8⁺ cytotoxic T cells.

D Co-inhibitory interactions (Immune Checkpoints)

The B7 protein family includes the following immune checkpoints: CD80 (B7-1), CD86 (B7-2), PD-L1 (B7-H1), PD-L2 (B7-DC), B7-H3, B7-H4, and others. These proteins impose inhibitory signaling circuits that negatively regulate T cell function post T cell receptor activation. Tumor cells often evade immune detection by co-opting such inhibitory signaling axes, normally in place to curb excessive and detrimental immune cell expansion. This manifests as the upregulated expression of immune checkpoint ligands PD-L1, PD-L2, VISTA and others, on the surface of the tumor and its surrounding tissues. The binding of these ligands to corresponding receptors on T cells acutely attenuates the T cell response.

E Immune subversion

Overexpression of PD-L1 on tumor cells is mediated via a number of intracellular signaling pathways such as IFNγR signaling to Stat1, as well as oncogenic signaling through several receptor tyrosine kinases (EGFR and others) to activate the MAPK, Akt, and Stat3 pathways. PD-L2, on the other hand, shows increased expression in response to Th2 cytokines (e.g. IL-6), IFNγ and Toll-like receptor ligands and is primarily regulated by the Stat6 and NFκB signaling pathways.

IFNγR engagement can additionally prompt upregulation of idoleamine 2,3-dioxygenase (IDO), a cytosolic enzyme that can induce metabolic depletion of tryptophan (an essential amino acid), thus disabling T cell function.

Note: the globular structural representations for the depicted receptor-ligand complexes are derived from the Protein Data Bank. In some cases the structures correspond to the homologs of the featured proteins.

The rich scientific content presented in this poster was curated by our scientists at Cell Signaling Technology. The poster also features many of the targets recognized by the rigorously validated rabbit monoclonal antibodies that make up CST's comprehensive tumor immunology portfolio.

For more information please visit: **www.cellsignal.com/tumor-microenvironment.**

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