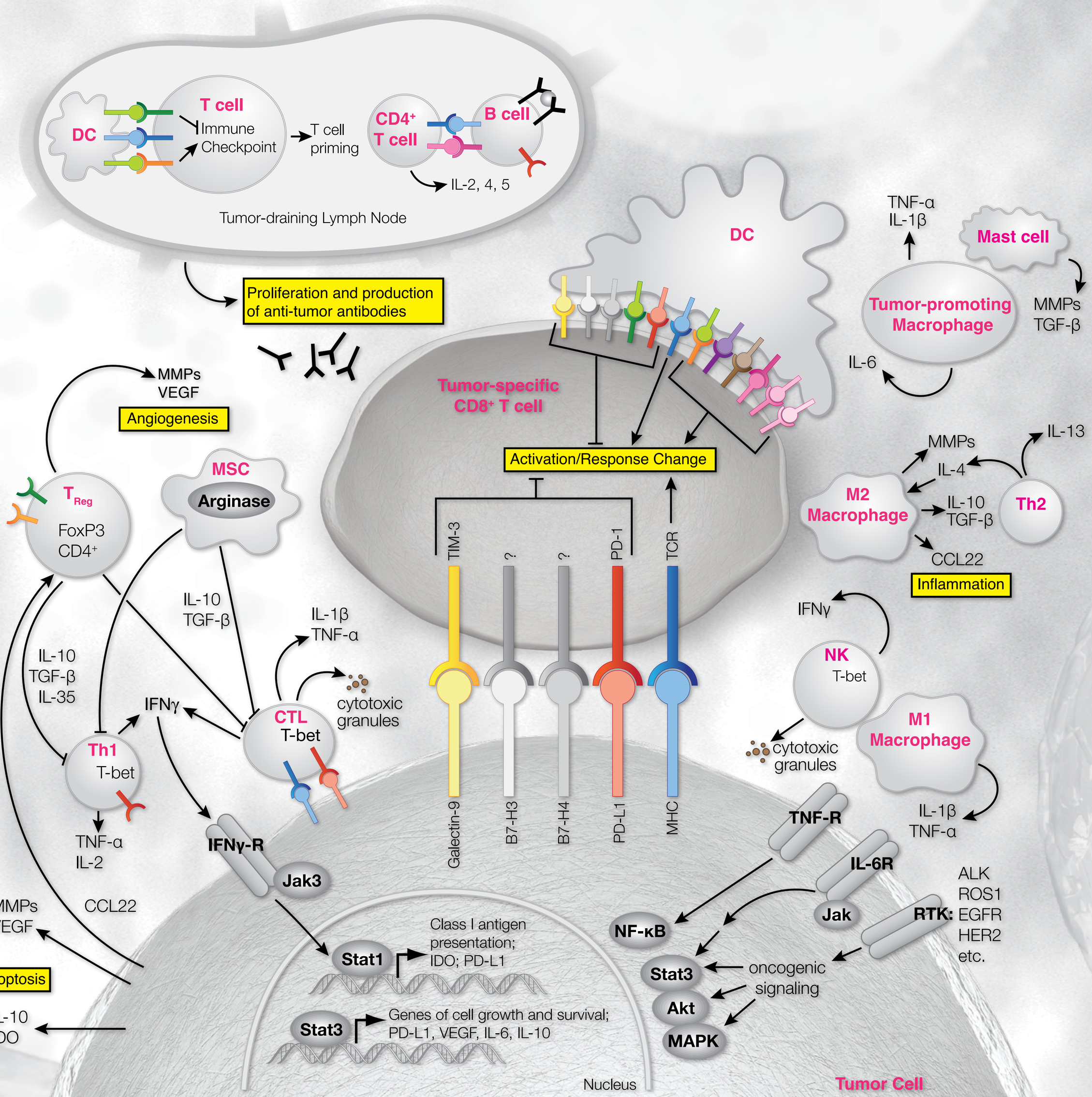
Tumor Immunology



Pathway Diagram Key

Tentative Stimulatory Modification | Direct Stimulatory Modification | Direct Inhibitory Modification

TIM-3 | B7-H3 | CTLA-4 | PD-1 | TCR | ICOS | OX40 | CD40 | CD27 | CD137 | CD28

Galectin-9 | B7-H4 | CD80, 86 | PD-L1 | MHC | ICOSL | OX40L | CD40L | CD70 | CD137L | ?

Tumor cells employ multiple defense strategies to evade detection by the immune system. One common strategy, upregulation of immune checkpoint proteins and ligands, takes advantage of a natural immune mechanism for self-tolerance and prevention of collateral tissue damage (1,2). Immune checkpoint proteins, such as PD-1, CTLA-4, and many others, are located on T cells and engage with their corresponding ligand on tumor cells or dendritic cells, sending inhibitory signals that repress T cell activation or response (1,2). One of the first discovered checkpoint proteins, CTLA-4, plays a role at the stage of T cell priming by binding to the CD28 ligands CD80 or CD86 to prevent co-stimulatory signals necessary for T cell activation (1). In contrast, the PD-1/PD-L1 checkpoint acts later in the process, inhibiting anti-tumor immune responses by effector T cells such as $CD4^+$ T helper 1 (Th1) cells and $CD8^+$ cytotoxic T lymphocytes (CTLs), leading to decreases in IFNγ production and cytolytic activity (1). Upregulation of PD-L1 expression on the tumor cell surface is mediated by IFNγR signaling to Stat1, as well as oncogenic signaling through several receptor tyrosine kinases (EGFR, ALK, ROS, HER2, and others) to activate the MAPK, Akt, and Stat3 pathways (1–3).

Cells in the tumor microenvironment can also influence tumor progression. $FoxP3^+/CD4^+$ T regulatory cells (T_{Regs}) and myeloid-derived suppressor cells (MSCs) secrete immunosuppressive cytokines IL-10 and TGF-β to inhibit the activity of Th1 cells and CTLs (1,2,4). Natural killer (NK) cells release cytotoxic granules against the tumor cell and secrete IFNγ, which stimulates surrounding pro-inflammatory M1 macrophages (5). Pro-tumorigenic M2 macrophages suppress anti-tumor immune responses via production of IL-10 and TGF-β and promote metastasis through release of MMPs (4,6). MMPs and TGF-β are also released by surrounding mast cells (7).

Select Reviews:

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