TWO-FACED MACROPHAGES

Tumors use chemokine signals to draw monocytes and tissue-resident macrophages into the tumor microenvironment, where the cells become tumor-associated macrophages (TAMs). Once believed to be wholly supportive of cancerous growth, these cells also play important roles in protecting against disease.

MENACING MACROPHAGES: THE M2 PHENOTYPE

TAMs can take on a variety of roles to support cancer cell survival and dissemination. Originating either from monocytes that come from bone marrow, or tissue-resident macrophages that arise during embryonic development, they can repress antitumor immunity by secreting cytokines such as IL-10, which blocks dendritic cell activation, and TGF-β, which blunts T-cell responses. A specific subset of TAMs that produce a protein called Tie2 can also stimulate angiogenesis through secretion of vascular endothelial growth factor (VEGF) and other molecules. At the same time, Tie2+ macrophages come together with cancer cells and blood vessel endothelial cells to form complexes, called tumor microenvironments of metastasis (TMEMs), that create openings in blood vessels. Macrophages at distant sites then help cancer cells exit blood vessels and seed new tumors.

TUMOR-KILLING TAMS: THE M1 PHENOTYPE

TAMs have the potential to aid antitumor immune responses by presenting cancer cell antigens to T cells and producing cytokines that activate dendritic cells and T cells. Macrophages are also experts at phagocytosing and degrading foreign cells, including cancer cells.

- Drugs that inhibit the protein Tie2 limit the ability of TAMs to stimulate angiogenesis and assist in cancer cell metastasis.
- Some compounds can keep macrophages out of tumors in the first place by blocking chemotactic signals such as CCL2 and CSF-1, which tumors emit to attract macrophages and monocytes.
- Stimulation with cytokines or immune agonists can reprogram TAMs and coax them toward the proinflammatory, phagocytosing M1 phenotype. Lately, epigenome-altering drugs have also been used to skew TAM phenotypes toward M1.
- Antibodies and peptides that block the cancer cell “don’t eat me” signal CD47 give TAMs free reign to phagocytose cancer cells. Blocking the inhibitory protein PD-1 on TAMs also increases the cells’ phagocytic activity.