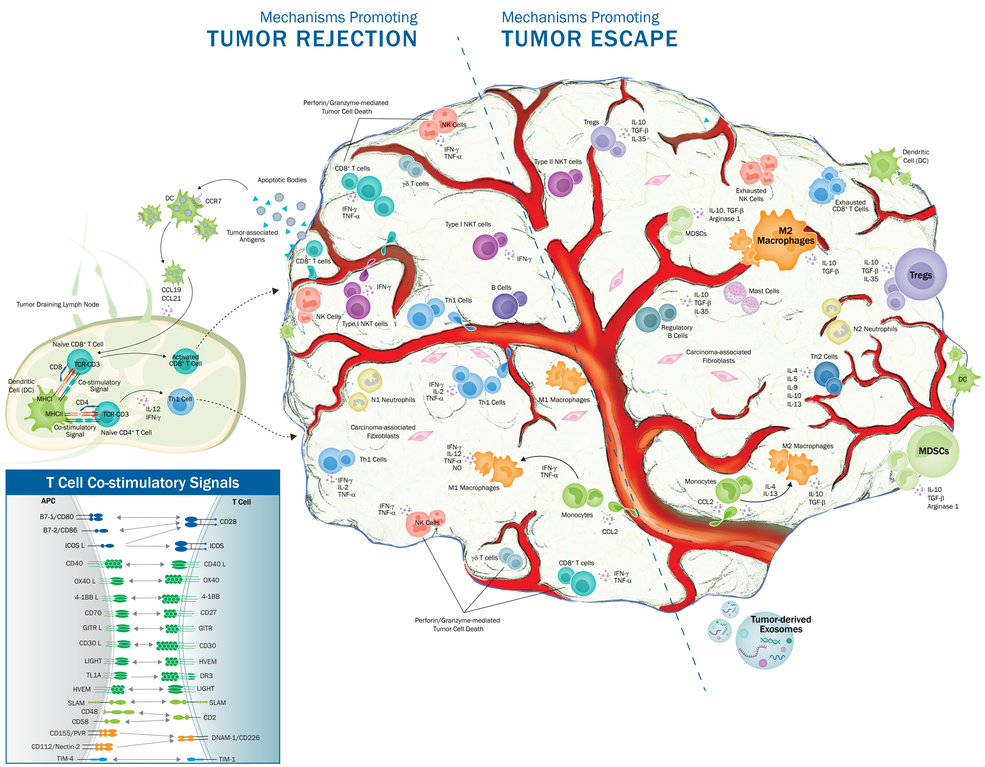
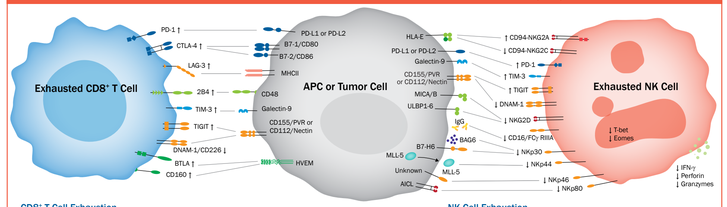
A Look Inside a Tumor: Mechanisms of Tumor Evasion and Immunosuppression in the Tumor Microenvironment



T Cell Co-stimulatory Signals

Characteristics of Exhausted CD8+ T Cells and Natural Killer (NK) Cells



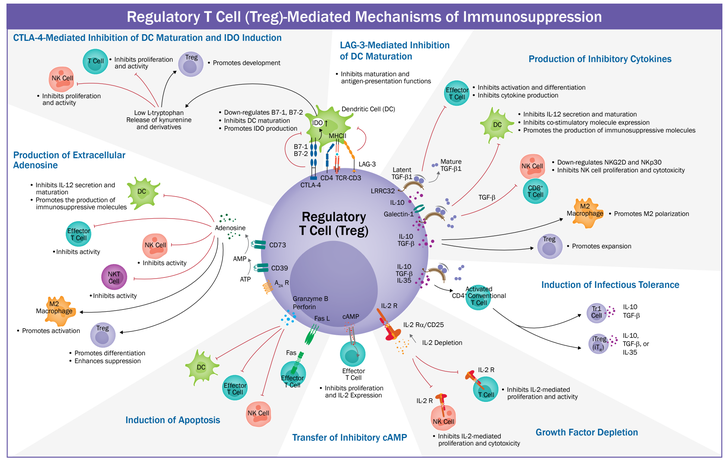
CD8+ T Cell Exhaustion

- Caused by persistent antigen exposure and chronic TCR signaling
- Associated with the elevated and sustained expression of multiple inhibitory receptors
- Reduced proliferative capacity and effector functions
- Alterations in gene expression and metabolism

NK Cell Exhaustion

- Potentially caused by sustained proliferation, weakened signals from activating receptors, or immunosuppressive effects in the tumor microenvironment
- Associated with an up-regulation of NK cell inhibitory receptors and a down-regulation of NK cell activating receptors
- Reduced NK cell proliferation
- Impaired effector functions including cytokine production, degranulation, and cytotoxicity

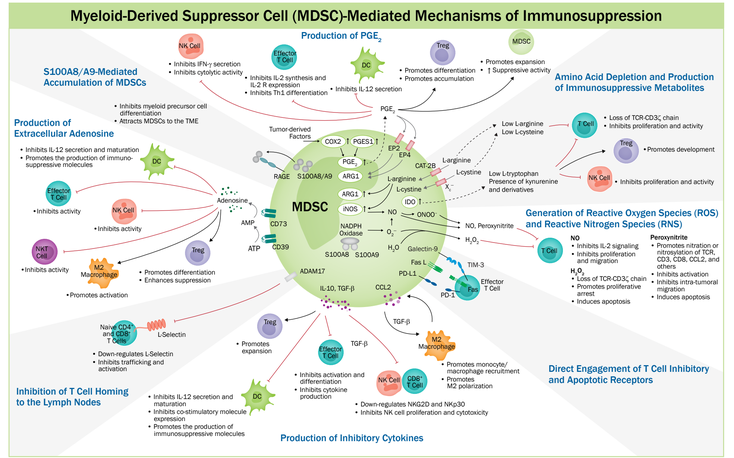
Regulatory T Cell (Treg)-Mediated Mechanisms of Immunosuppression



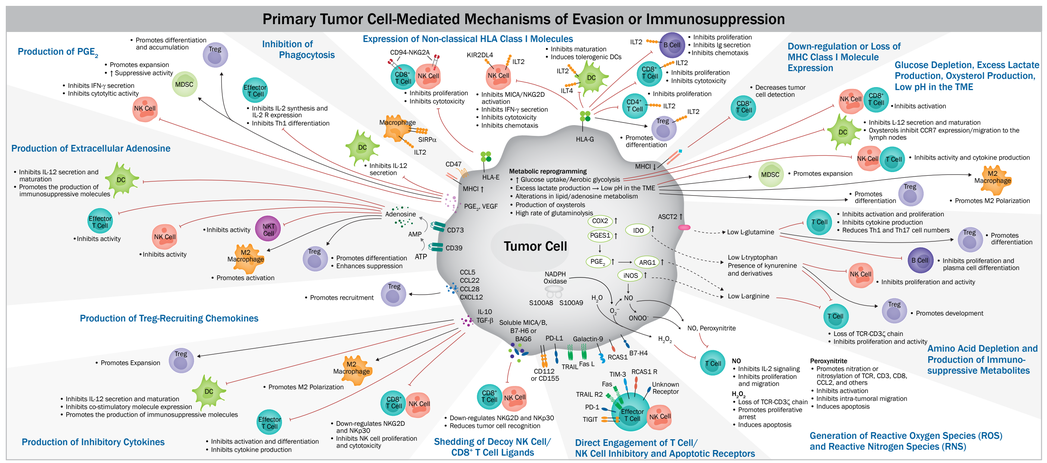
The Immune System Plays A Central Role in Regulating Tumor Rejection and Tumor Escape

Abnormal cells such as tumor cells are typically recognized and eliminated by the immune system. Immune cells such as natural killer (NK) cells, natural killer T (NKT) cells, and γδ T cells provide the first line of defense against tumor cells by exerting direct cytotoxic effects and secreting high levels of IFN-γ to promote tumor cell destruction. Under these conditions, macrophage polarization is skewed toward a tumoricidal M1 phenotype, which is associated with a high level of phagocytosis and secretion of pro-inflammatory cytokines that contribute to tumor cell elimination. Control of tumor cell growth is further achieved by activation of the adaptive immune response. Dendritic cells take up antigens from tumor cells and present these antigens in the presence of co-stimulatory signaling molecules and secreted cytokines to naïve CD8+ and CD4+ T cells to prime T cell activation. Like NK cells, activated CD8+ T cells have direct cytotoxic activity against tumor cells and both these cells and Th1 cells secrete high levels of IFN-γ to drive tumor rejection. Despite the activities of these cell types, some tumor cells can escape this process of elimination over time, leading to tumor growth. The tumor microenvironment (TME) plays a central role in this process. The TME consists of multiple different cell types including fibroblasts, endothelial cells, and infiltrating leukocytes, whose functions can be exploited or altered to create conditions that are favorable for tumor progression. Within this complex environment, tumor growth can be driven by many different factors including direct tumor cell-mediated mechanisms of immune cell evasion or immunosuppression, the development of CD8+ T cell or NK cell exhaustion, the recruitment and expansion of immunosuppressive immune cell types, the presence of high levels of immunosuppressive cytokines and other immunosuppressive factors that impair immune cell functions, and/or a shift in polarization toward a type II immune response. Type II polarization is associated with Th2-like cytokine secretion, M2 macrophage polarization, and the presence of type II NKT cells and N2 type neutrophils in the TME, which blocks the CD8+ T cell-/Th1-/M1 macrophage-/NKT type I-mediated anti-tumor immune response. The different sections of this poster show the characteristics of exhausted CD8+ T cells and NK cells and the key mechanisms by which tumor cells, tumor-derived exosomes (TEXs), regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated M2 macrophages (TAMs) mediate immunosuppression in the TME. Many of the molecules implicated in the immunosuppressive mechanisms detailed here are currently being investigated as targets for cancer immunotherapy.

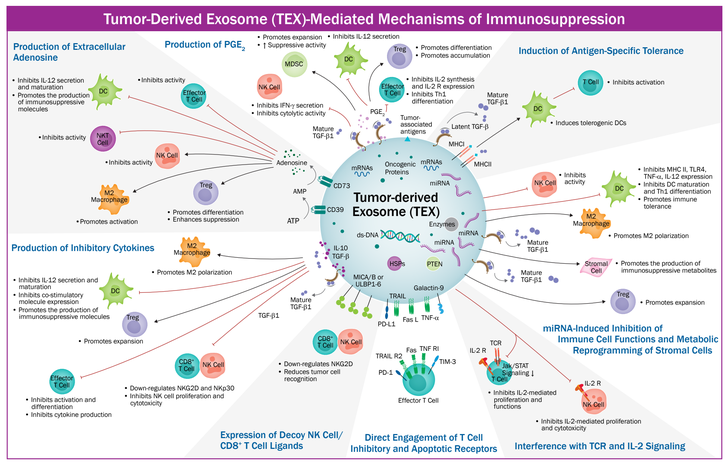
Myeloid-Derived Suppressor Cell (MDSC)-Mediated Mechanisms of Immunosuppression



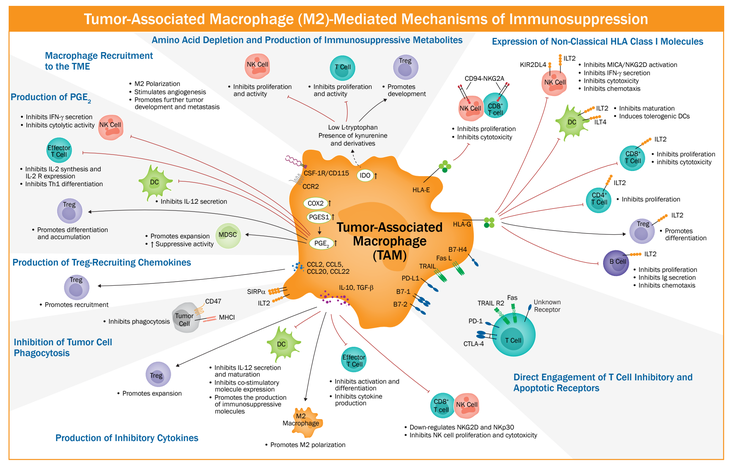
Primary Tumor Cell-Mediated Mechanisms of Evasion or Immunosuppression



Tumor-Derived Exosome (TEX)-Mediated Mechanisms of Immunosuppression

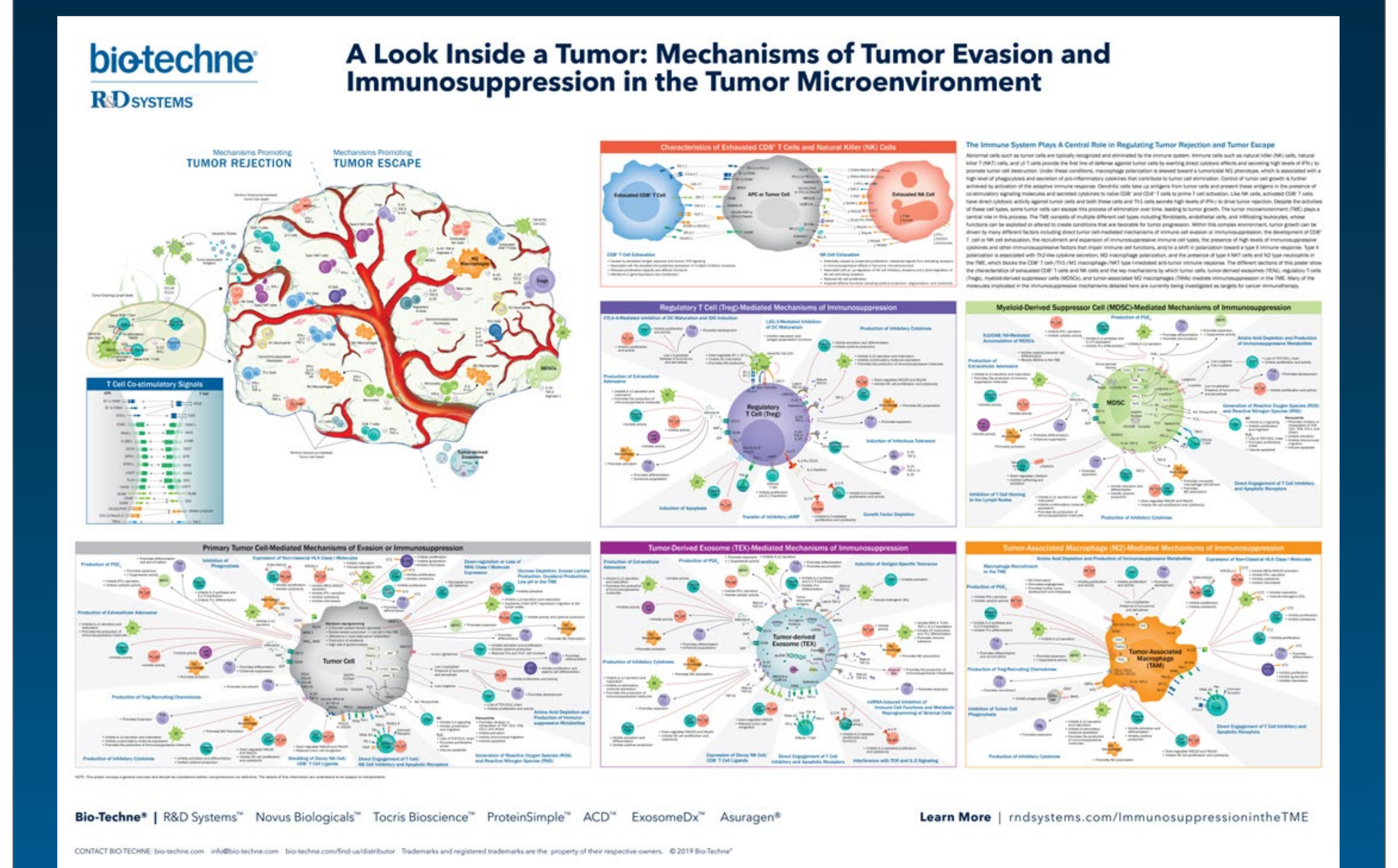


Tumor-Associated Macrophage (M2)-Mediated Mechanisms of Immunosuppression



NOTE: This poster conveys a general overview and should be considered neither comprehensive nor definitive. The details of this information are understood to be subject to interpretation.

WALL POSTER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TUMOR ESCAPE
Tumor Cell
Tumor-derived Exosome (TEX)
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