Tumor Associated Macrophages as a Novel Target for Cancer Therapy

Tumor Associated Macrophage

Tumor mass
Tumor apoptosis

Cancer development is strongly influenced by the immune system. Both innate and adaptive immunity contribute to immune surveillance, allowing the host to recognize and eliminate nascent tumors. The complex interactions that facilitate effective immune-mediated destruction of malignant cells have been described as the cancer-immunity cycle. Each step of the cancer-immunity cycle requires the coordination of numerous factors that are both stimulatory and inhibitory in nature. A T cell response is initiated when tumor antigens are captured, processed, and presented to T cells on MHC I and II molecules. Dendritic cells (DCs) play a critical role in the activation of the adaptive immune system. Activated DCs travel to tumor-draining lymph nodes where they prime naïve T cells to become effector T cells capable of killing cancer cells. Activated effector T cells migrate to the tumor and infiltrate the tumor bed, where they kill cancer cells and trigger additional antigen release that can induce subsequent rounds of anticancer immunity. 

**The Immune System Can Detect and Destroy Cancer Cells**

- **STEP 1**: Tumor antigens are taken up by dendritic cells.
- **STEP 2**: Dendritic cell
- **STEP 3**: Priming of T cells
- **STEP 4**: Co-stimulatory molecules influence the T cell response
- **STEP 5**: Infiltration of T cells into tumors
- **STEP 6**: Tumor cell
- **STEP 7**: Tumor apoptosis
The interaction between various cells in the tumor microenvironment promotes tumor growth and progression. Crosstalk between parenchymal and stromal cells representative of cancer cells, cancer stem cells, endothelial cells, immune inflammatory cells, pericytes, cancer-associated fibroblasts, stem cells and progenitor cells of the tumor stroma promotes tumor growth and progression. Cancer cells themselves act to evade immune cell attack by interfering with multiple components of the immune system and suppressing cytolytic T cells. Furthermore, recruitment of immunosuppressive T regulatory cells into the tumor can also contribute to the breakdown of an effective antitumor immune response.

While the immune system utilizes several mechanisms to mount an immune response, several processes can diminish the effectiveness of the host immune response. For example, poor detection of tumor antigens or misidentification of tumor antigens as self, can limit the effectiveness of antigen presentation, provoking an inhibitory T regulatory response rather than an effector T cell reaction. To further decrease the effectiveness of an immune response, T cells may fail to properly localize to the tumor microenvironment or they may not effectively infiltrate the microenvironment, thereby diminishing T cell access to cancer cell targets. Locally, factors produced in the tumor microenvironment may also abrogate the anti-tumor activities of effector T cells that do gain access. Cancer cells may secrete immunosuppressive factors that inhibit cytotoxic T cells, and/or recruit immunosuppressive inflammatory cells that include macrophages, mast cells, and neutrophils.
Tumor-associated macrophages (TAMs) have been shown to play an important role in tumor progression by promoting tumor invasion, migration and angiogenesis. Direct contact between cancer cells and TAMs can facilitate tumor metastasis, wherein pre-metastatic tumor cells direct TAM recruitment through the secretion of numerous chemokines or cytokines. TAMs express a variety of mediators that promote an immunosuppressive microenvironment that abrogates an effective host anti-tumor immune response. Local expression of potent immunosuppressive factors, including interleukin-10 and TGF-ß, directly inhibits the anti-tumor activities of effector T cells and suppresses the capacity for effective tumor-associated antigen presentation. Within the tumor microenvironment, the production of immunostimulatory molecules such as IL-12 is suppressed by TAMs, impeding the proliferation and cytotoxic actions of T cells and NK cells. Furthermore, TAMs express inhibitory ligands for receptors on T cells, including the programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4). When activated immune effector cells bind these ligands to TAMs, immune cell receptor signaling is disrupted and T cell cytotoxic activity is inhibited, further promoting an immunosuppressive environment. TAMs also produce an array of molecules that encourage recruitment of, and enhance the survival of regulatory T cells, diminishing effective host immune anti-tumor activity. Within the tumor microenvironment, the production of immunostimulatory molecules such as IL-12 is suppressed by TAMs, impeding the proliferation and cytotoxic actions of T cells and NK cells. Furthermore, TAMs express inhibitory ligands for receptors on T cells, including the programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4). When activated immune effector cells bind these ligands to TAMs, immune cell receptor signaling is disrupted and T cell cytotoxic activity is inhibited, further promoting an immunosuppressive environment. TAMs also produce an array of molecules that encourage recruitment of, and enhance the survival of regulatory T cells, diminishing effective host immune anti-tumor activity. Together with other stromal components including cancer-associated fibroblasts and endothelial cells, TAMs prevent recruitment and infiltration of cytotoxic T cells into the tumor. TAMs promote angiogenesis, especially in hypoxic areas within the tumor microenvironment, by secreting factors including IL-8, TNF-ß, thymidine phosphorylase, and vascular endothelial growth factor (VEGF). Importantly, CSF1 stimulates VEGF production by TAMs, promoting angiogenesis. TAMs promote angiogenesis, especially in hypoxic areas within the tumor microenvironment, by secreting factors including IL-8, TNF-ß, thymidine phosphorylase, and vascular endothelial growth factor (VEGF). Importantly, CSF1 stimulates VEGF production by TAMs, promoting angiogenesis.
The CSF1R-signaling pathway is responsible for the recruitment of circulating monocytes to tumors, as well as their development into macrophages and their subsequent differentiation. Within the microenvironment, growth factors, cytokines and chemokines are believed to reprogram TAMs towards specific phenotypic and functional roles, whether tumorigenic or tumoristatic. In return, tumorigenic TAMs further support tumor development using a variety of mechanisms including creation of an immunosuppressive milieu, production of mitogenic factors, as well as promoting angiogenesis, and degrading the tumor extracellular matrix thereby aiding invasion and metastasis.
Therapeutic strategies aimed at inhibiting the CSF1R-CSF1 axis may result in diminished TAMs infiltration in tumors and may decrease the tumor-supporting actions of TAMs. Agents currently under investigation include monoclonal antibodies, antisense oligonucleotides, peptides, and kinase inhibitors. Studies specific to inhibition of CSF1R-CSF1 signaling demonstrated a marked diminution in the number of TAMs within 24–96 hours of exposure. Interruption the CSF1R-CSF1 pathway thus may support the immune response to cancer from targeting PD1, PD-L1, or CTLA-4.
Although cytotoxic T cells play a central role in the anti-tumor effects of the immune system, tumors themselves promote development of microenvironments that actively impede the host immune response. TAMs are a phenotypically diverse group of cells that populate the tumor microenvironment and can inhibit anti-tumor immune responses and promote tumor growth. The CSF1R signaling pathway drives recruitment of TAMs to the tumor microenvironment and promotes the differentiation of these cells toward a pro-tumorigenic phenotype. As such, targeting the CSF1R-CSF1 axis may result in diminished TAM infiltration into tumors and may allow for enhanced host anti-tumor immune responses. Interfering with CSF1R may represent a promising strategy to abrogate the tumor-supporting activities of TAMs.

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References