

Module 4 Assignment

585.751 Immunoengineering

1. Briefly describe (1-2 sentences) the following suppressive cell types of the TME and how they modulate the immune response to cancer. (40 points)

- a. MDSCs (10 points)

Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells which, under certain conditions, may differentiate into neutrophils, eosinophils, basophils, macrophages, or dendritic cells (DCs). MDSCs could not only limit immune response by inducing Treg, inhibiting T-cells, modulating macrophages or DCs but also directly stimulate tumor growth by facilitating angiogenesis and metastasis.

- b. Tregs (10 points)

Natural Treg can develop in the thymus or be generated by CD4+ Fox3 T cells.

In cancer, CD4 regulatory T-cells, are immunosuppressive. Tumor cells recruit and stimulate them to suppress the immune system, and Tregs induce immune tolerance to cancer antigens. Additionally, they secrete immunosuppressive cytokines, such as TGF-beta and IL-10, which further stimulate Tregs and impair the effects of CD8, CD4 helper cells, and NK cells. Tregs have a high affinity receptor for IL-2, which competes with CD8 T cells for IL-2 binding, impairing the activation of cytotoxic T-cells.

- c. M2 macrophages. Additionally, how are M2 macrophages different from M1 macrophages? (20 points)

Macrophages activated with TNF-alpha have an anti-tumor activity and have the M1 phenotype. These M1 macrophages are involved in cytotoxicity. M2 phenotype is associated with tumor promotion and can be induced by IL-4, IL-10 or IL-13. In addition, M2 macrophages contribute to tumor progression by facilitating angiogenesis, extracellular matrix remodeling, and suppress inflammation.

2. Describe (in a few sentences each) two ways in which cancer can evade the immune system. (40 points)

- **Low immunogenicity:** tumors downregulate peptides-MHC expressions, this downregulation limits the ability of T cells to recognize and bind to tumor antigens. Tumors may also downregulate co-stimulatory molecules, such as CD80 and CD86, which decrease the levels of T cell activation, further dampening the immune response against the tumor.
- **Tumor-induce immune suppression:** tumors secrete immunosuppressive factors such as TGF-beta, IL-10 which inhibit immune stimulatory cytotoxic T cells (CD8+ T cells) or helper T cells (CD4+ T cells) and, induce immunosuppressive regulatory T cells (Tregs), which further suppress immune responses by inhibiting effector T cells and promoting tolerance to tumor antigens.



3. Identify a tumor-associated antigen either described in lecture or from your own research. Describe what class of tumor antigen it is (i.e. oncoviral, overexpression, germ cell, differentiation, mutations, or abnormal posttranslational/posttranscriptional modification), how it arises, and what cancer(s) express it. (20 points)

In the normal glandular epithelial cell, MUC1 proteins are typically found on the apical surface bordering the lumen of the glandular structure. In most adenocarcinomas (e.g., breast or pancreas cancers), MUC1 can undergo post-translational alterations, including changes in glycosylation patterns. In adenocarcinomas, such as breast cancer, MUC1 is found in an underglycosylated form and is often upregulated. This alteration can affect the structure and function of MUC1, such as increasing cell adhesion to extracellular matrix, contributing to cancer progression and metastasis. Adenocarcinomas often exhibit a loss of cell distribution resulting in the disruption of the demarcation between the apical and basolateral epithelial surfaces of the epithelial cells, leading to disorganized growth pattern. In addition, it has been reported that patients with adenocarcinomas shed large amount of mucin protein into the circulation making it a disease status biomarker; elevated serum MUC1 levels may indicate aggressive tumor phenotype, increase metastatic risks or resistance to therapy [1], [2].

[1] R. Singh and D. Bandyopadhyay, "MUC1: A target molecule for cancer therapy," *Cancer Biol. Ther.*, vol. 6, no. 4, pp. 481–486, 2007, doi: 10.4161/cbt.6.4.4201

[2] J. Taylor-Papadimitriou, J. Burchell, D. W. Miles, and M. Dalziel, "MUC1 and cancer," *Biochim. Biophys. Acta (BBA) - Mol. Basis Dis.*, vol. 1455, no. 2–3, pp. 301–313, 1999, doi: 10.1016/s0925-4439(99)00055-1

