STARS OF THE SHOW

The immune system plays a pivotal role in tumor formation, development, and metastasis. Cancer cells are inherently antigenic,[1] which normally allows immune cells to identify and eliminate them prior to tumor formation. Tumor formation occurs when cancer cells develop methods to evade or outpace immune-mediated killing. Understanding this relationship between immune and cancer cells is therefore integral to restoring immune system potency for cancer therapeutics.

T CELLS

The primary effectors of immune-mediated cell death, T cells exert their tumoricidal functions by recognizing antigens presented on tumor cells' surfaces.[2] Tumor cells evade T cells through nutrient deprivation,[3] promoting cell inactivation, and activating immunosuppression mechanisms.[4] Augmenting T cell activity to counteract these effects is a primary focal point of immuno-oncology research.

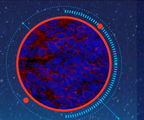
General T cell surface marker CD3 expression (orange) in FFPE human tonsil.

NATURAL KILLER (NK) CELLS

Mechanism:

- Effectively eliminates circulating cancer cells via cytotoxic mechanisms[11]
- Activity against solid tumors is dependent on extent of cytokine-mediated activation[11]

Markers:
CD95, CD117, CD62L, $CD56_{dim}$ or $CD56_{bright}$ 12



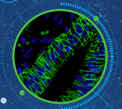
CD117 (red) in FFPE human small-cell lung carcinoma.

CYTOTOXIC T CELLS (CTLs)

Mechanism:

- Primed and activated through T cell receptor (TCR)-major histocompatibility complex (MHC)-antigen presentation
- Releases cytotoxins to kill cells expressing said antigen

Markers:
CD8, CD44, $CD62_L$ [4]



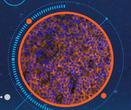
CD44 (green) in FFPE human colon carcinoma.

HELPER T CELLS (TH CELLS)

Mechanism:

- Regulates immune system function through cytokine secretion and activation of macrophages, B cells, and CTLs
- Vital for anti-tumor protection[5]

Markers: CD4; distinguished from T_{reg} cells (also CD4+) by secretion profile (T_{H1} cells secrete IFNγ, T_{H2} interleukins (ILs) 4, 13, and 5, and T_{H17} ILs 17 and 21)[6]



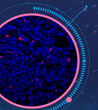
CD4 (orange) in FFPE human tonsil.

REGULATORY T CELLS (TREG CELLS)

Mechanism:

- Suppresses immune system activity to prevent deleterious inflammation and autoimmune disorders[7]
- Tumor cells promote T_{reg} recruitment, resulting in immunosuppression and evasion[8]

Markers:
FoxP3, CD25R



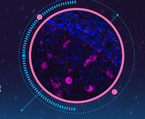
FoxP3 (magenta) in FFPE human tonsil.

DENDRITIC CELLS AND MACROPHAGES: ANTIGEN PRESENTING CELLS (APCs)

Mechanism:

- Dendritic cells (DCs) and macrophages are professional antigen-presenting cells (APCs) pivotal for activating T cells[13]
- Macrophages also kill cells via phagocytosis or cytotoxic mechanisms; phenotypes range from pro-inflammatory to anti-inflammatory/pro-repair[14]
- Cancer cell-secreted cytokines cause tumor-infiltrating DCs to switch to an immuno-suppressive phenotype, while tumor-associated macrophages (TAMs) present anti-inflammatory phenotypes, inhibit T cell activity, and promote angiogenesis, tumor growth, and metastasis[13,14]

DC Markers: CD1c, CD14, CD141 [15]
Macrophage Markers: CD14, CD11b, CD68, HLA-DR, CD163, CX3CR1 [16]



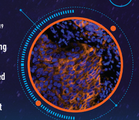
Macrophage-marker CD68 expression (magenta) in FFPE human tonsil.

IMMUNE CHECKPOINTS

Mechanism:

- Checkpoint proteins and the pathways they activate are critical for immune self-regulation[19]
- The ability to inhibit immune responses is key for limiting collateral damage and maintaining self-tolerance[19]
- Cancer cells have co-opted the activation of these pathways to deactivate immune-mediated tumoricidal mechanisms, thereby facilitating tumor immune evasion[19]
- Checkpoint inhibition – using exogenous agents to prevent cancer cell–mediated checkpoint pathway activation – is a popular anti-cancer therapeutic strategy undergoing intensive research[19]

Checkpoint Pathway Proteins: PD-1, PD-L1; CTLA-4, CD80/CD86 [19,20]



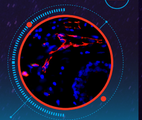
PD-L1 (orange) in FFPE human lung carcinoma.

ENDOTHELIAL CELLS

Mechanism:

- Regulates and promotes angiogenesis[23]
- Controls tumor cell intra/extravasation, metastasis, and immune cell infiltration[23]

Markers: CD31, von Willebrand Factor[24]



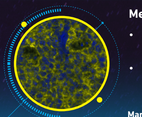
CD31 expression (red) in FFPE human breast carcinoma.

B CELLS

Mechanism:

- Produces antibodies that promote anti-tumor T cell, macrophage, and NK cell activity[9]
- Can encourage tumor development by producing growth factors and autoantibodies[9]

Markers:
CD19, CD20, CD21, CD40, CD80, CD86, & CD69[10]



CD20 (yellow) in FFPE human tonsil.

CANCER CELL MARKERS

Mechanism:

- Cancer stem cells are resistant to anti-tumor therapies and are capable of self-renewal, facilitating disease relapse and metastasis[17]
- Host mesenchymal stem cells can differentiate into immunosuppressive immune cells[18]

Markers: β-catenin, PCNA, Ki-67, cytokeratin

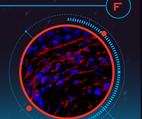
PCNA expression (magenta) in FFPE human head and neck squamous cell carcinoma.

FIBROBLASTS

Mechanism:

- Creates a favorable environment for tumor growth by secreting growth factors and extracellular matrix[21]
- Promotes angiogenesis as well as recruitment of vascular cells (e.g., endothelial cells and pericytes)[22]

Markers: α-smooth muscle actin, vimentin, desmin, platelet derived growth factor receptor[22]



Vimentin expression (red) in FFPE human breast carcinoma.

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