Cytokines in Cancer Pathogenesis and Cancer Therapy

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Preface

- The mixture of cytokines in tumor microenvironment for cancer pathogenesis
  - Infection inhibit tumor
  - Inflammation cytokines → development
  - Immunity & progression

- Cancer cells host-derived cytokines growth↑, apoptosis↓ invasion & metastasis

- Cytokine-tumor-cell interactions → cancer immunotherapy
Tumor arise and progress around much healthy, non-transformed cells.

Stromal cells at tumor formation:
- early ➔ regulate cancer cell growth and differentiation
- late ➔ modulate cancer cell invasion and metastasis

Maintain enough blood supply:
- commandeer existed or stimulate new vessels
Immunology and tumor

- Immune cells, prominent component of host response to cancer in some cases
- Dense intratumoral lymphocyte infiltration in early stage neoplasms ➔ reduced frequency of metastasis and improved pt. Survival e.g. melanoma (first), colorectal cancer, renal cell carcinoma, epithelial ovarian ca. ➔ some host response attenuate disease progression
Immunology and tumor

- Diverse forms of chronic inflammation ➔ malignant transformation ↑
- Unresolved host immune reactivity can promote tumor development
- In disseminated disease of cancer: no immune cell infiltration ➔ tumor undetected by the immune system
Immunology and tumor

- Cytokines produced in tumor micro-environment influence mould the host immunologic reaction
- Cytokines regulate growth, differentiation and activation of immune cells
- Cell alternate to cancer provoke changes in local cytokine expression ➔ stimulate immune reaction ➔ additional cytokine released act as autocrine and paracrine
Cytokines and tumor development

- Cytokine function during tumor development and development are complicated ➔ pleiotrophy and redundancy of cytokine action
- Loss- and gain-of function experiments yield the complex association
- Cytokine: role of tumor formation cytokine balance for cancer therapy
Immune recognition of tumors

- Innate and adaptive immune response
- Innate response:
  - soluble factors \(\rightarrow\) complement proteins
  - cellular effectors \(\rightarrow\) granulocytes, mast cells, macrophages, dendritic cells (DCs), natural killer (NK) cell
- First line of defense against infection via pattern recognition receptors and other cell surface molecule
Immune recognition of tumors

- Adaptive immune response, mediated by antibodies and CD4, CD8, is slower to develop.
- Antigen presented by major histocompatibility complex (MHC) molecules rearranged immunoglobulins or T-cell receptors specific for it.
- NK T cells and γδ T cells function at the intersection of innate and adaptive immunity.
Innate Immunity

- Use pattern-recognition receptors and other cell-surface molecule to detect tumor cells
- Cancer cells express families of stress-related genes, such as MICA & MICB ligands for NKG2D receptors expressed by NK cells, other cytotoxic lymphocytes and phagocytes
- NK cells monitor loss of MHC class I at tumor cells via killer-cell immunoglobulin receptors (KIRs)
Innate Immunity

- DCs use CD36 and the $\alpha_v\beta_5$ integrin to phagocytose apoptotic tumor cells.
- Heat-shock proteins released from necrotic tumor cells with tumor-derived peptides are taken up by DCs and macrophage through scavenger receptor or CD91.
Adaptive Immunity

- Indirect pathway -- termed cross priming -- to achieve initial recognition of cancers
- Tumor cells lack the expression of important co-stimulatory molecules, such as B7.
- However, DCs phagocytosed tumor-cell debris for MHC presentation ➔ upregulation of co-stimulatory molecules (B7-1, B7-2) ➔ migrate to lymph node ➔ ⊕ tumor-specific lymphocyte
Adaptive Immunity

- MHC-restricted tumor peptides → presentation to CD4 and CD8 T cells
  
  # Endogenous antigens → MHC class I → CD 8
  Exogenous antigens → MHC class II → CD 4

- DCs secrete IL-12 and IL-18 to promote T\textsubscript{H} 1 CD4 T-cell response and cytotoxic CD8 T-cells

- Activated CD4 T cells and NKT cells express CD 40 ligand → further stimulate DCs maturation, CD4 & DCs → B cell → antibodies
Tumor and Immunity

- Host response includes innate and adaptive immune response
- Clinically evident cancers → tumor cells escape immune recognition and elimination
- The mechanisms for this immunity failure → inefficient cross-priming, maintain immune tolerance to host self-antigens, tumor-derived immunosuppressive factors, and tumor genomic instability