The Roles of Tumor-derived Exosomes in Immuno-Oncology

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Therapeutic Strategies to Defeat Cancer

- Surgery
- Radiation therapy
- Chemotherapy
- Hormone therapy
- Immunotherapy
Tumor escape from immune surveillance

- Avoidance of recognition by the host immune cells
- Apoptosis of immune cells
- Exploitation of immune checkpoints
- Myeloid derived suppressor cells (MDSCs)
- Expansion of regulatory T cells
- M2 macrophages expansion
- Release of immune suppressive mediators
Exosomes

✓ Constitutively released by cells at different levels

physiological functions:
- Immune function
- Heart and brain function
- Stem cell function
- Pregnancy

pathological functions:
- Alzheimer’s disease
- Heart failure
- Liver disease
- Cancer
Exosomes in Cancer Biology

✓ Cancer Exosomes Promote

- Tumor growth
- Tumor proliferation
- Angiogenesis
- Organotrophic metastasis
- Drug resistance
- Immune-escape
Secretion of exosomes by tumor cells
Secretion of exosomes by tumor cells
Exosomes interfere with anti-tumor immunity

Exosomal HLA-G, MICA/B, PD-L1, TGF-B, CD73, Fas-L

- Directly by inhibiting the function of effector cells:
  - NK cells
  - TCD8+
  - TCD4+

- Indirectly by:
  - Induction of MDSCs
  - Inhibiting the function of antigen presenting cells (APCs)
The roles of tumor-derived exosomes in altered differentiation, maturation and function of dendritic cells

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Abstract
Tumor-derived exosomes (TDEs) have been shown to impede anti-tumor immune responses via their immunosuppressive cargo. Since dendritic cells (DCs) are the key mediators of priming and maintenance of T cell-mediated responses; thus it is logical that the exosomes released by tumor cells can exert a dominant influence on DCs biology. This paper intends to provide a mechanistic insight into the TDEs-mediated DCs abnormalities in the tumor context. More importantly, we discuss extensively how tumor exosomes induce subversion of DCs differentiation, maturation and function in separate sections. We also briefly describe the importance of TDEs at therapeutic level to help guide future treatment options, in particular DC-based vaccination strategy, and review advances in the design and discovery of exosome inhibitors. Understanding the exosomal content and the pathways by which TDEs are responsible for immune evasion may help to revise treatment rationales and devise novel therapeutic approaches to overcome the hurdles in cancer treatment.

Keywords: Exosome, Tumor, Dendritic cell, Immunity
The effects of tumor exosomes on DCs Differentiation

- TDEs containing:
  - COX (1,2), PGE2, TGFβ, IL6, HSP70, HSP72, Glycolytic enzyme
  - HLA-G

- Effect:
  - MDSCs↑
  - Differentiation↓
The effects of tumor exosomes on DCs Maturation
The effects of tumor exosomes on DCs Function
Small Particles; Large Effects
Exosomal tumor-associated antigens (TAAs) are involved in resistance to immunotherapies.
Exosomal TAAs interfere with immunotherapies

- Exosomal HER2 counters Trastuzumab-based therapy
- Higher exosomal PD-L1 is associated with poor anti-PD-1 response
- Circulating exosomes as **liquid biopsy** for cancer:
  - Diagnosis
  - MRD detection
  - Prognosis
  - Therapy selection
  - Therapy monitoring
Future Directions:
Exosome inhibition as adjunctive therapy

- Chemotherapy
- Immunotherapy (mAbs, TDEs-loaded DCs, NK-92 cells, etc.)
- Inhibition or Removal of TDEs
- Primary or Advanced Tumor
- Tumor-derived exosomes
THANK YOU!