Wake Forest®
School of Medicine

Antigen Presentation in Cancer

Opportunities for Improved Outcomes in Tumor Immunotherapy

Disclosures

- Nothing to disclose

Introduction

- Basics of tumor immunotherapy
- Key components of antigen presentation
  - Major histocompatibility complex
  - Antigen presentation cells
- Clinical trials efforts focused on APC in cancer

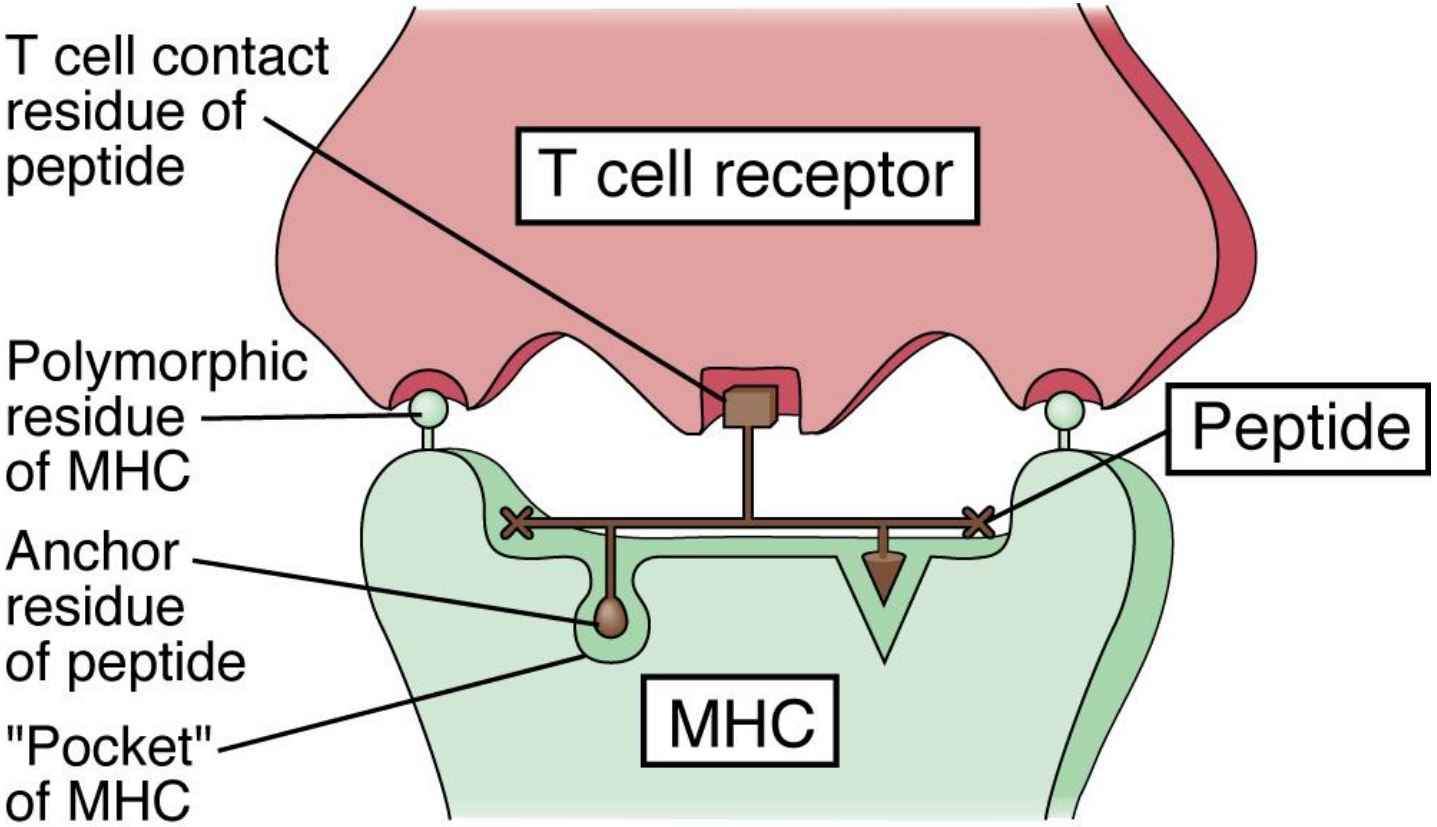
Basics of T-Cell Tumor Immunology

- Cytotoxic T cells
- Helper T cells
- Regulatory T cells
- T cell function requires cell:cell interaction

Key Components of Antigen Presentation

- Major Histocompatibility Complex
- Antigen Presentation Cells

T cell Recognition of Antigen



Abbas AK, Lichtman A, Pillai S. *Basic Immunology: Functions and Disorders of the Immune System.* Elsevier, 2014.

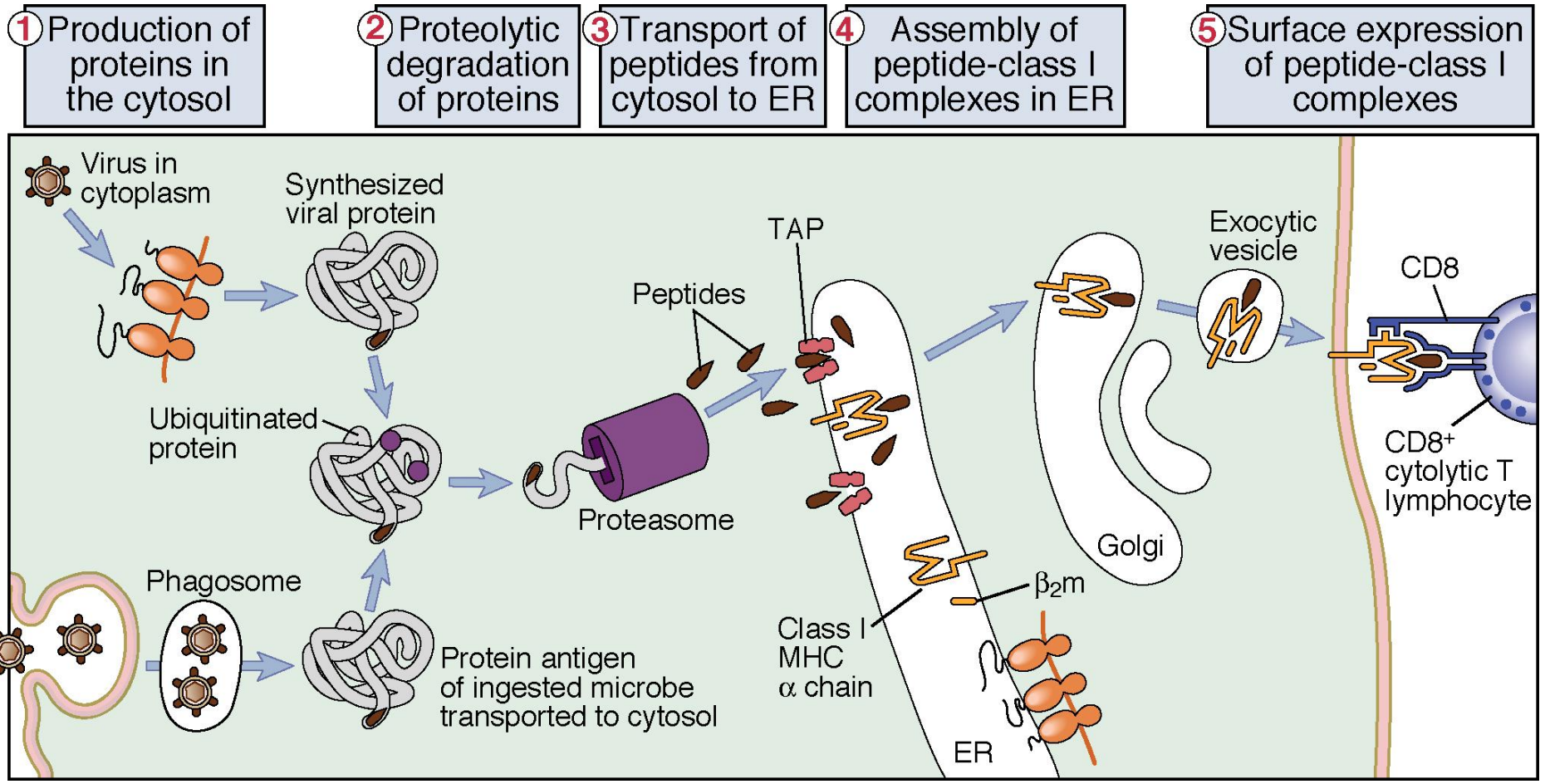
What is the MHC?

- MHC molecules are the peptide display molecules of the immune system
- Any T cell can recognize an antigen on an APC only if that antigen is displayed by MHC molecules

What is the MHC?

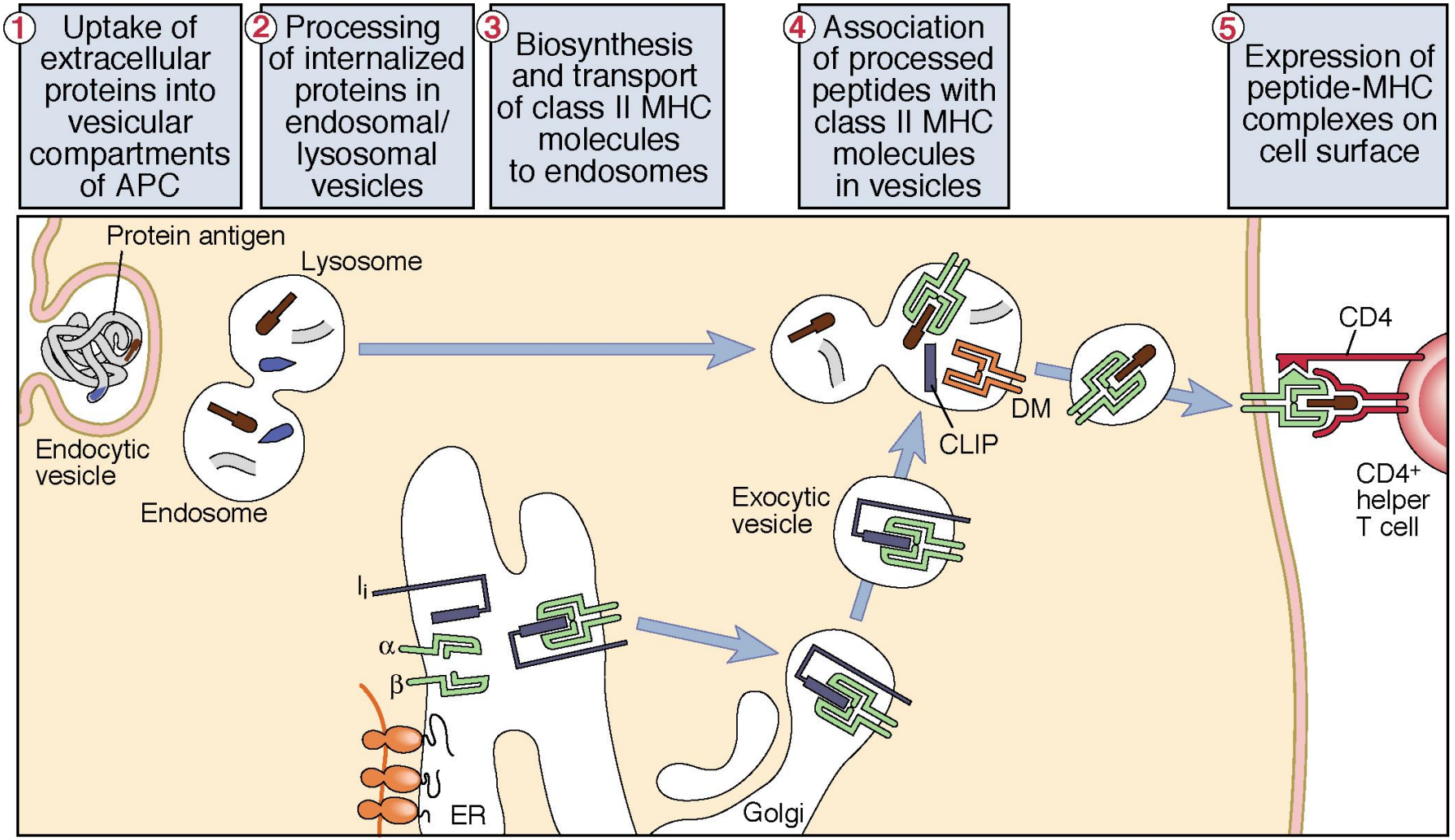
- A genetic locus discovered on the basis of transplantation (major histocompatibility complex)
- Different alleles of MHC molecules bind and display distinct but overlapping sets of peptides
- MHC molecules determine how antigens in different cellular compartments are recognized by different classes of T cells (CD4+ and CD8+)

Class I MHC Processing of Protein Antigens



Abbas AK, Lichtman A, Pillai S. *Basic Immunology: Functions and Disorders of the Immune System.* Elsevier, 2014.

Class II MHC Processing of Protein Antigens



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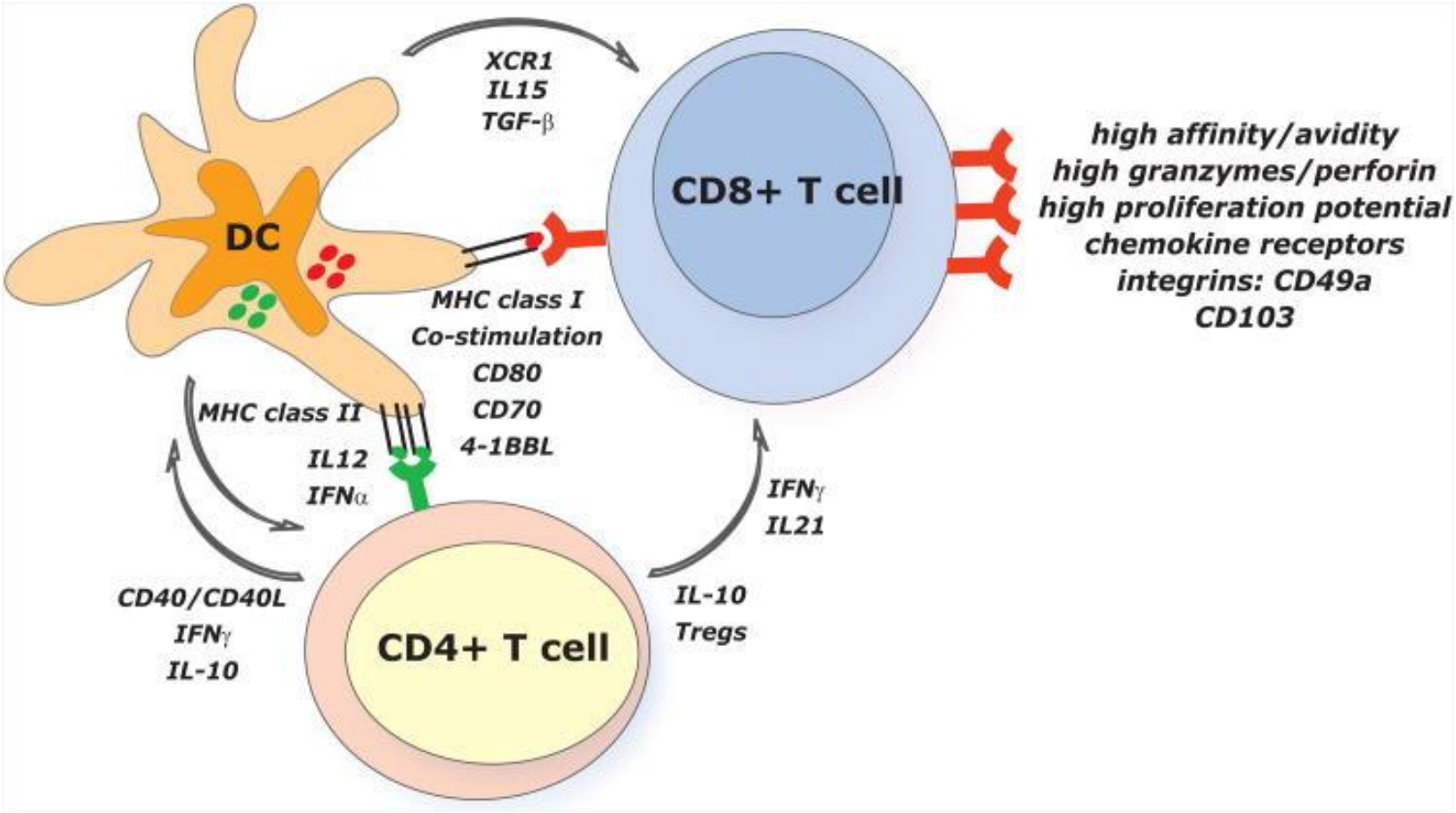
Antigen Presentation Cells

- APCs include
  - Dendritic Cells
  - B cells
  - Macrophages

- Conversion of native antigen into peptides capable of binding to MHC molecules and then presented to immune effector cells

Dendritic Cell Priming

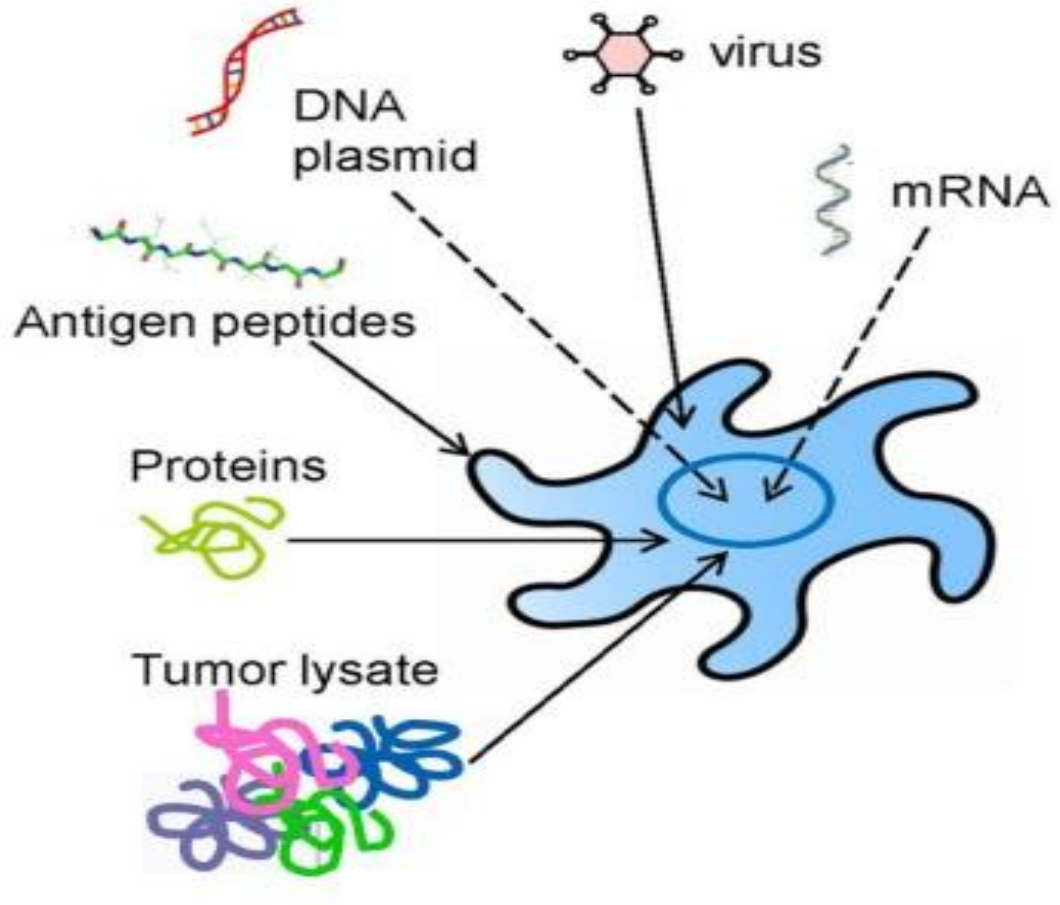


Palucka K, Banchereau J. Dendritic-cell-based therapeutic cancer vaccines. Immunity. 2013 Jul 25;39(1):38-48.

Immunologic Challenges in Dendritic Cell Vaccines in Advanced Tumors

- Advanced tumors have immuno-inhibitory functions
  - Infiltrating T-regs
  - Myeliod Derived Suppressor Cells
  - Immature Macrophages
  - Inhibitory Cytokines
- Decreased MHC Class I expression
- Down regulation of antigen process machinery
- Heterogeneous antigen expression in metastatic tumors

Variation in Early Clinical Trials

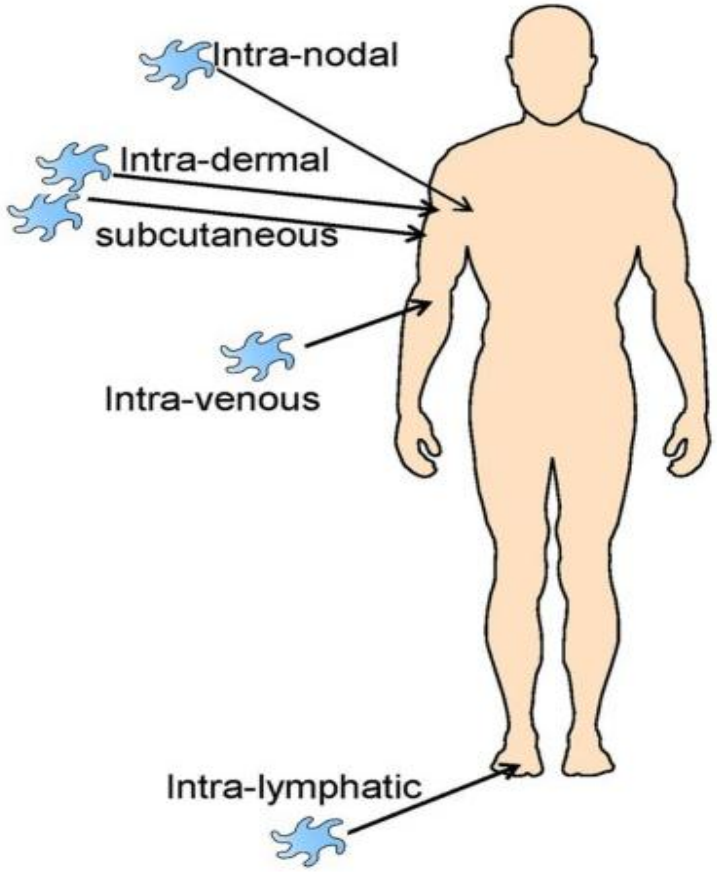


Butterfield LH. Dendritic cells in cancer immunotherapy clinical trials: are we making progress? Frontiers in Immunology. 2013 Dec 13;4:454.

Cell Culture and Maturation

- Immature DCs obtained after 5-7 days of culture in GM-CSF and IL-4
- Immature DCs are potentially tolerogenic
- Current efforts focused on cocktails that are geared toward mature DCs including TLR and Type I agents including interferon

Delivery Variation in Early Clinical Trials

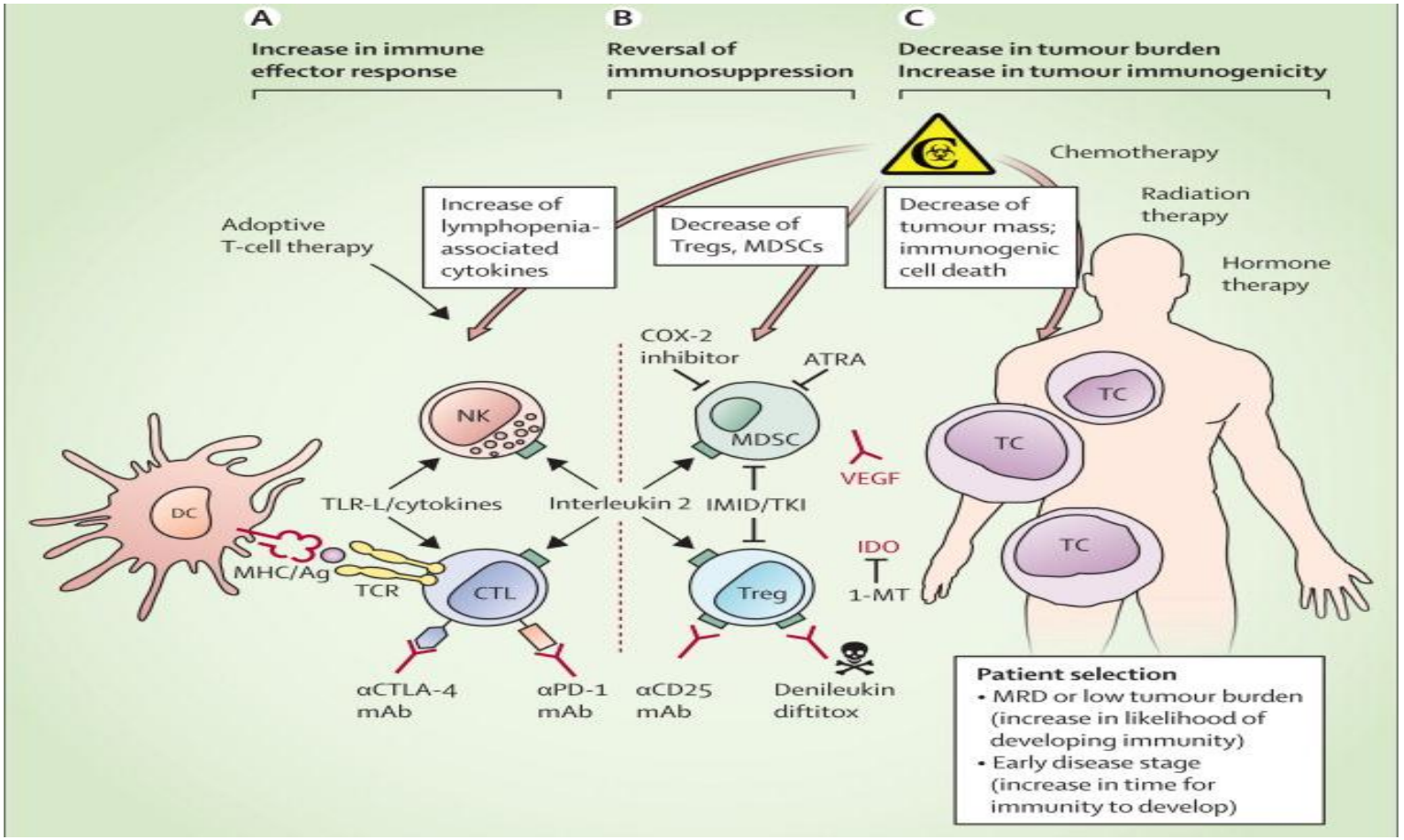


Butterfield LH. Dendritic cells in cancer immunotherapy clinical trials: are we making progress? Frontiers in Immunology. 2013 Dec 13;4:454.

Ongoing Clinical Trials with Dendritic Cells

Disease	DC Product	Control	Trial Number
Melanoma	Autologous DC mixed with irradiated autologous tumor cells	Autologous PBMCs in GM-CSF	NCT01875653
Prostate	Autologous APCs loaded with PAP/GM-CSF	Autologous APC	NCT00005947 NCT00065442 NCT00779402 NCT01133704
Brain	Autologous DCs pulsed with autologous tumor lysate	Autologous PBMCs	NCT00045968
Renal	Autologous DCs electroporated with autologous tumor mRNA and CD40L mRNA in combination with sunitinib	Sunitinib	NCT01582672

Future of the Field



Anguille S, Smits EL, Lion E, van Tendeloo VF, Berneman ZN. Clinical use of dendritic cells for cancer therapy. Lancet Oncology. 2014 Jun;15(7):e257-67.

Conclusions

- Antigen presentation is an essential part of tumor immunotherapy
- Defects in the MHC component can result in tolerance
- Dendritic cells are the most important cell in TAA presentation
- Clinical trials with dendritic cell-based vaccines are on-going