Antigen presentation in Cancer

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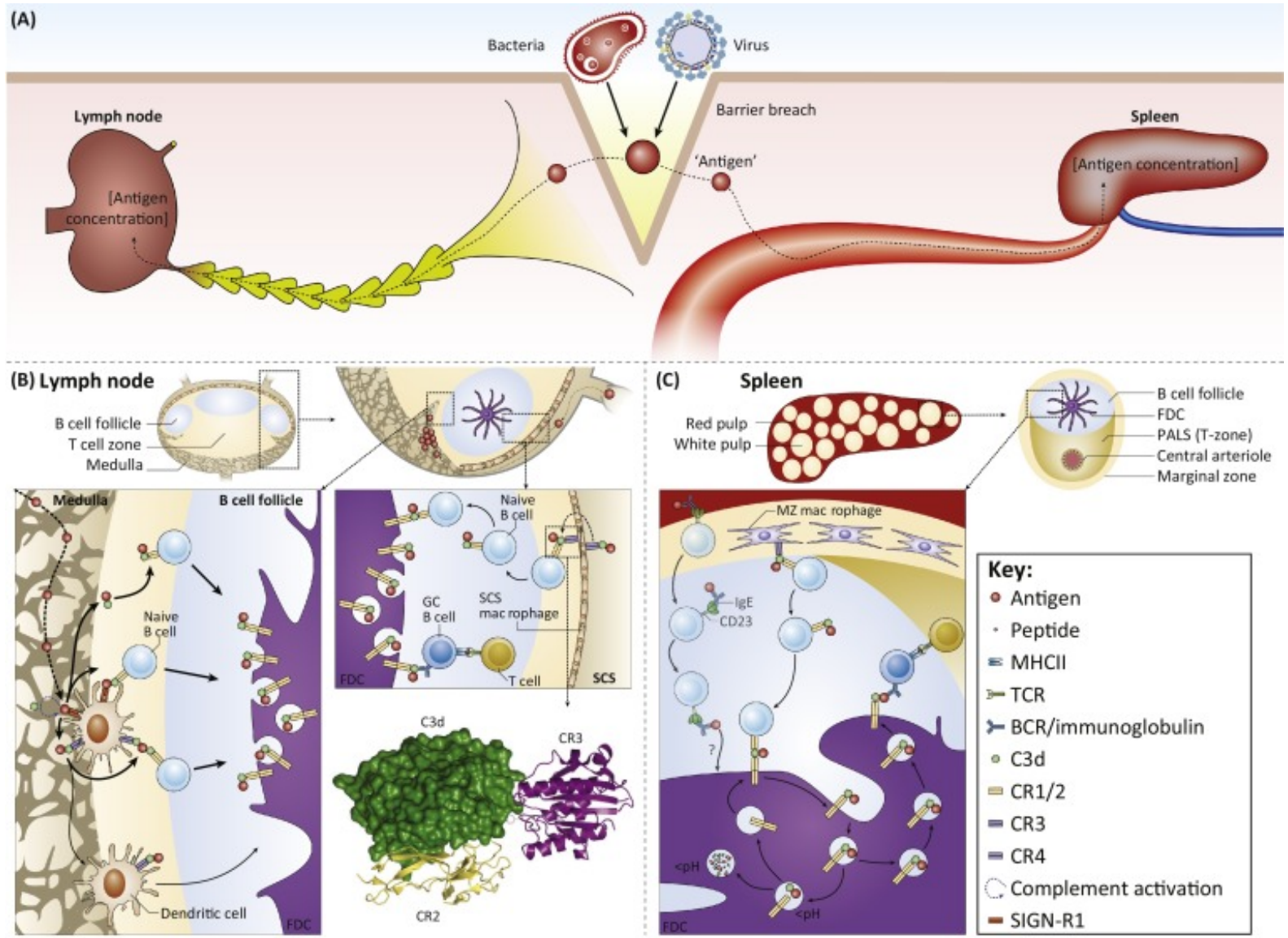
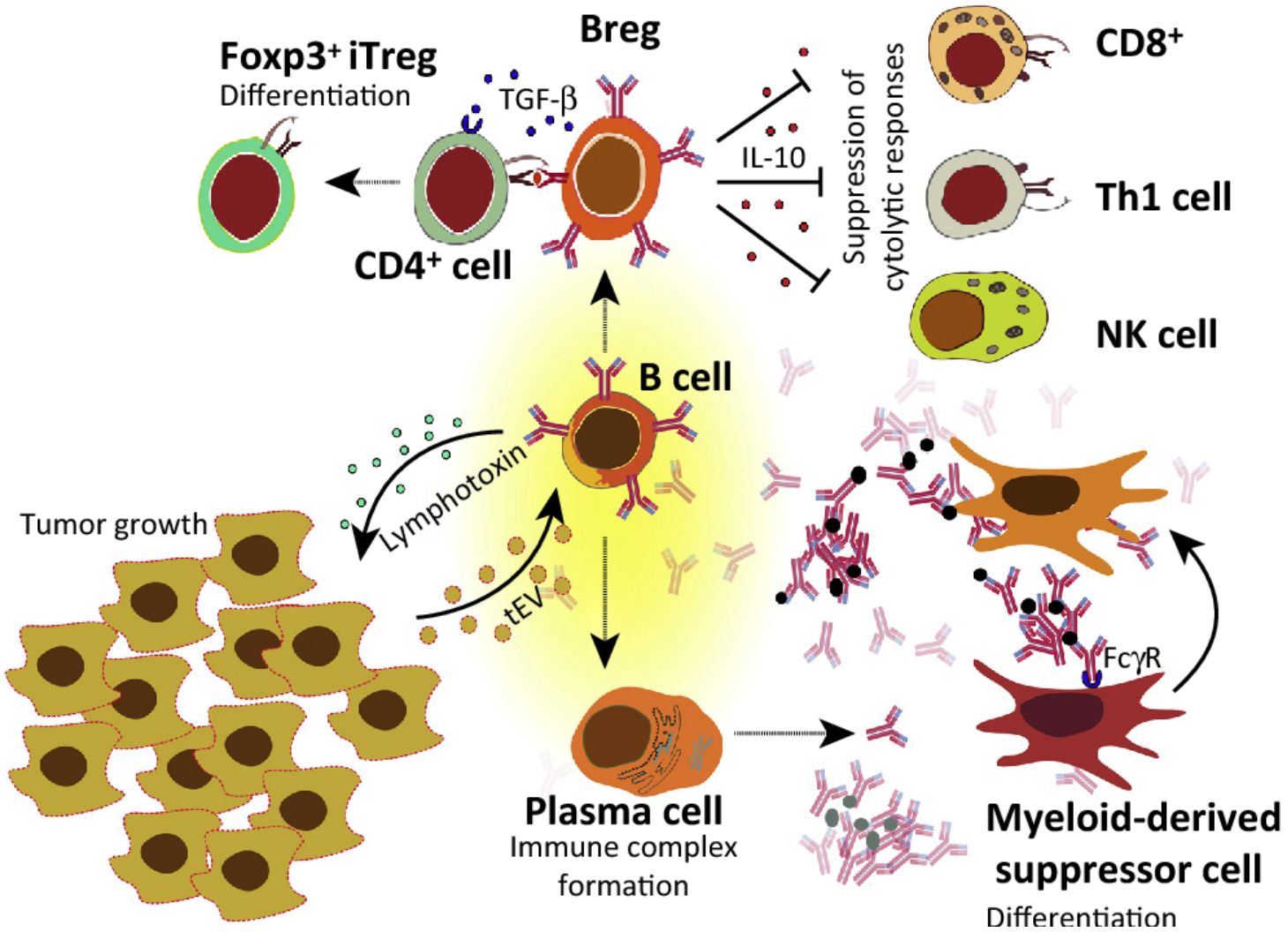
Antigen uptake and presentation to B cells in Lymph node versus Spleen

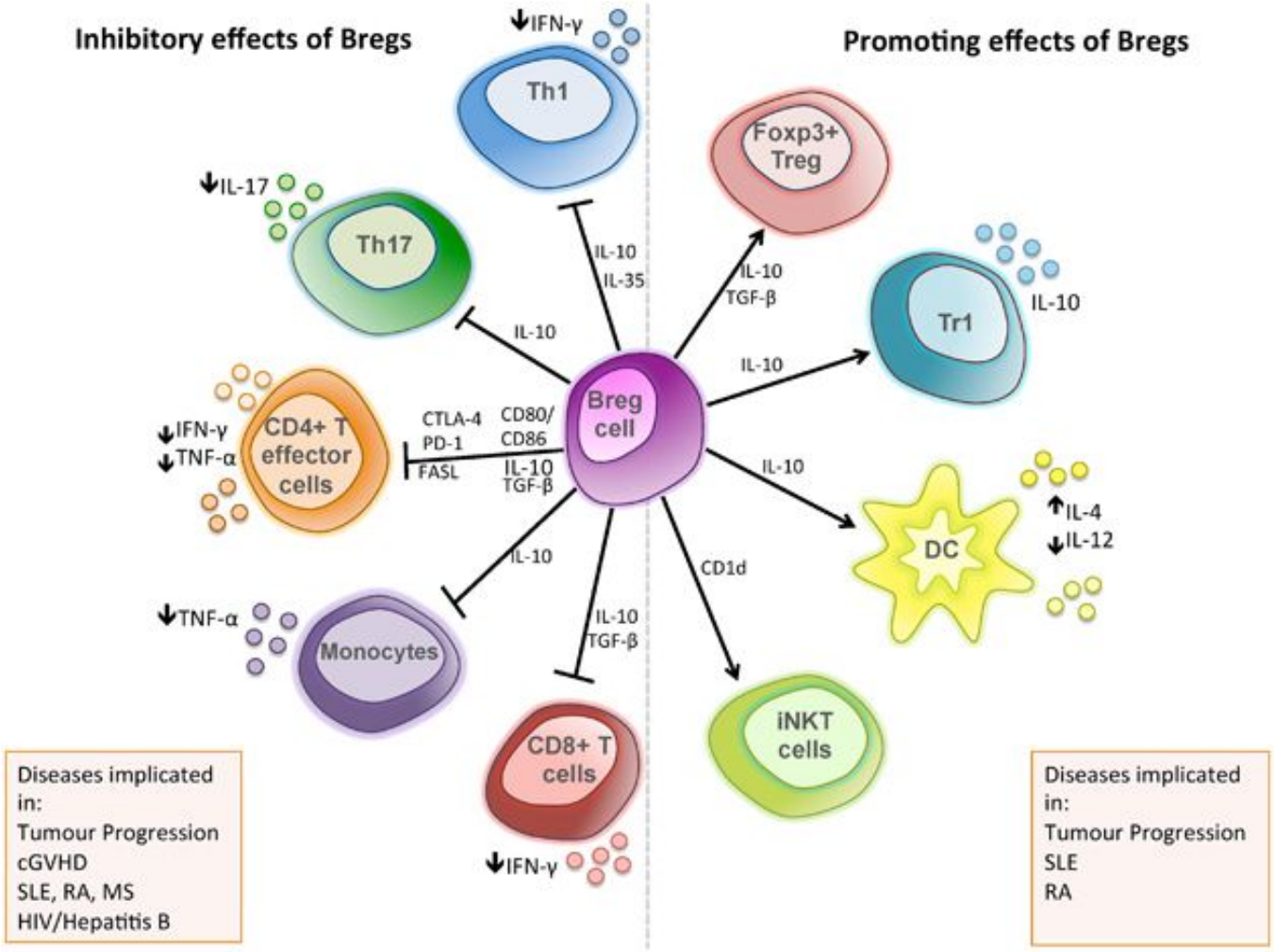


Trends in Immunology

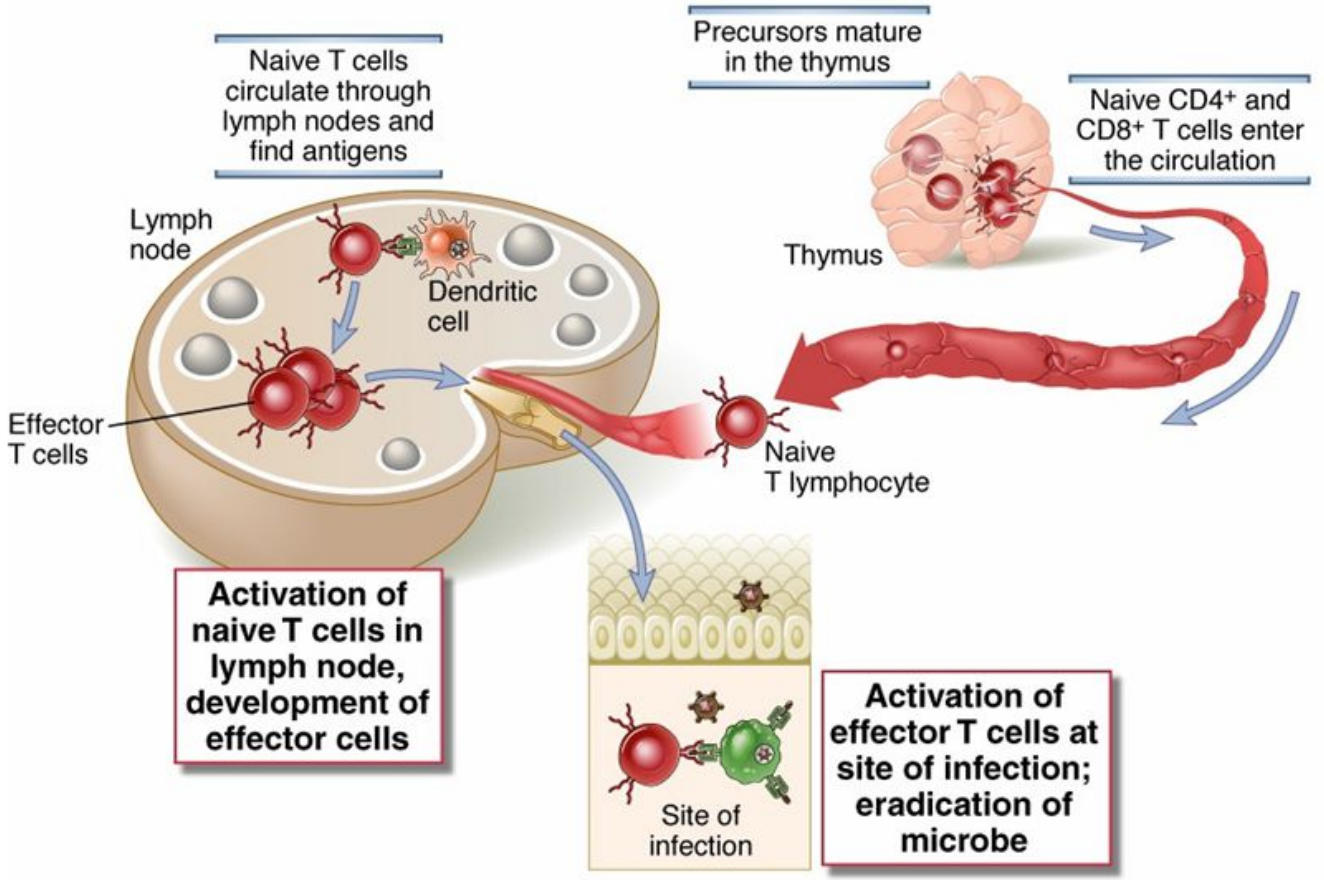
Immune regulation by B cells



Immune regulation by B cells: Bregs



T cell lifestyles and sites of Ag encounter



Abbas, Lichtman and Pillai. *Cellular and Molecular Immunology, 7th edition, 2011* © Elsevier

The challenge for T lymphocytes

- Very few lymphocytes in the body are specific for any one microbe (or antigen)
  - Specificity and diversity of antigen receptors: the immune system recognizes and distinguishes between 10^6-10^9 antigens
  - The body contains ~10^{12} lymphocytes;
  - Therefore, few lymphocytes (~1,000) can recognize any one antigen
  - They need to find that antigen (within the 3 weeks of their lifespan)

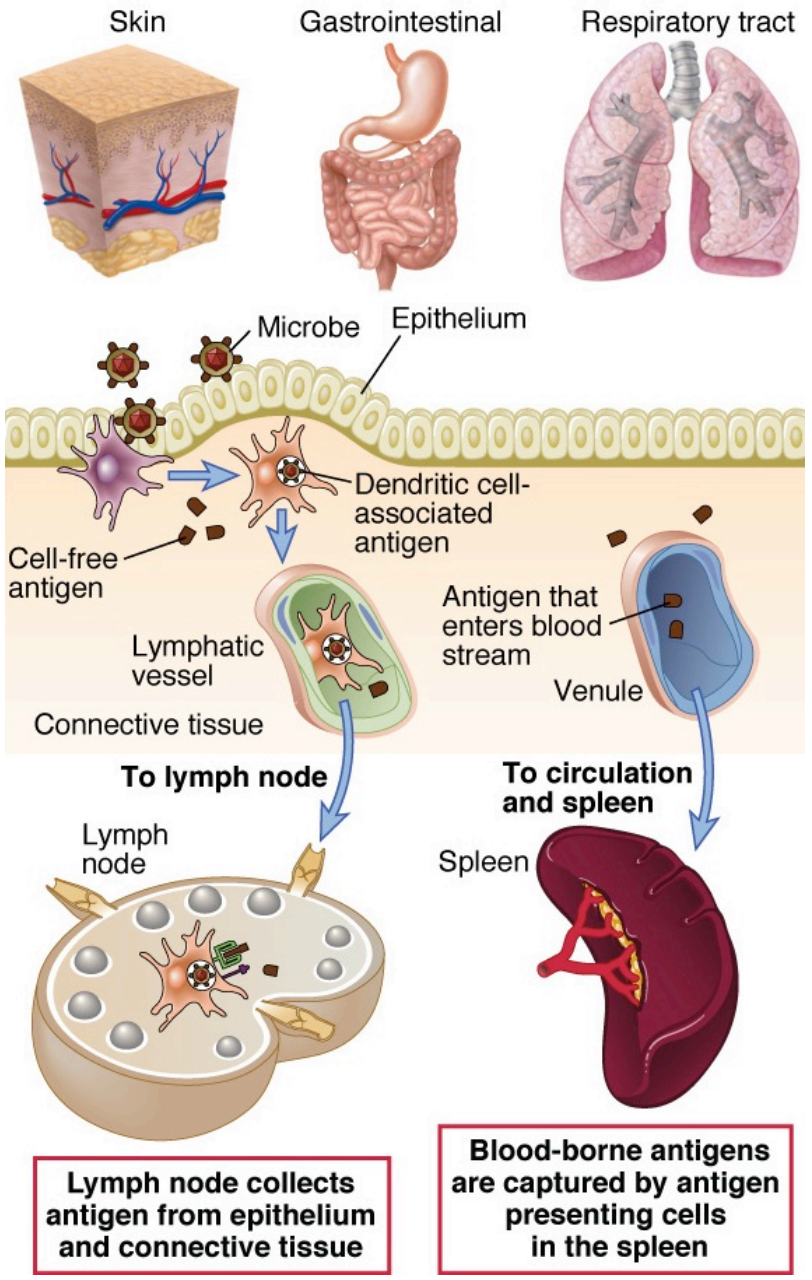
The answer: Dendritic Cell APCs

Antigen capture

Sites of antigen entry

Sites of
initial antigen capture

Sites of antigen
collection and capture



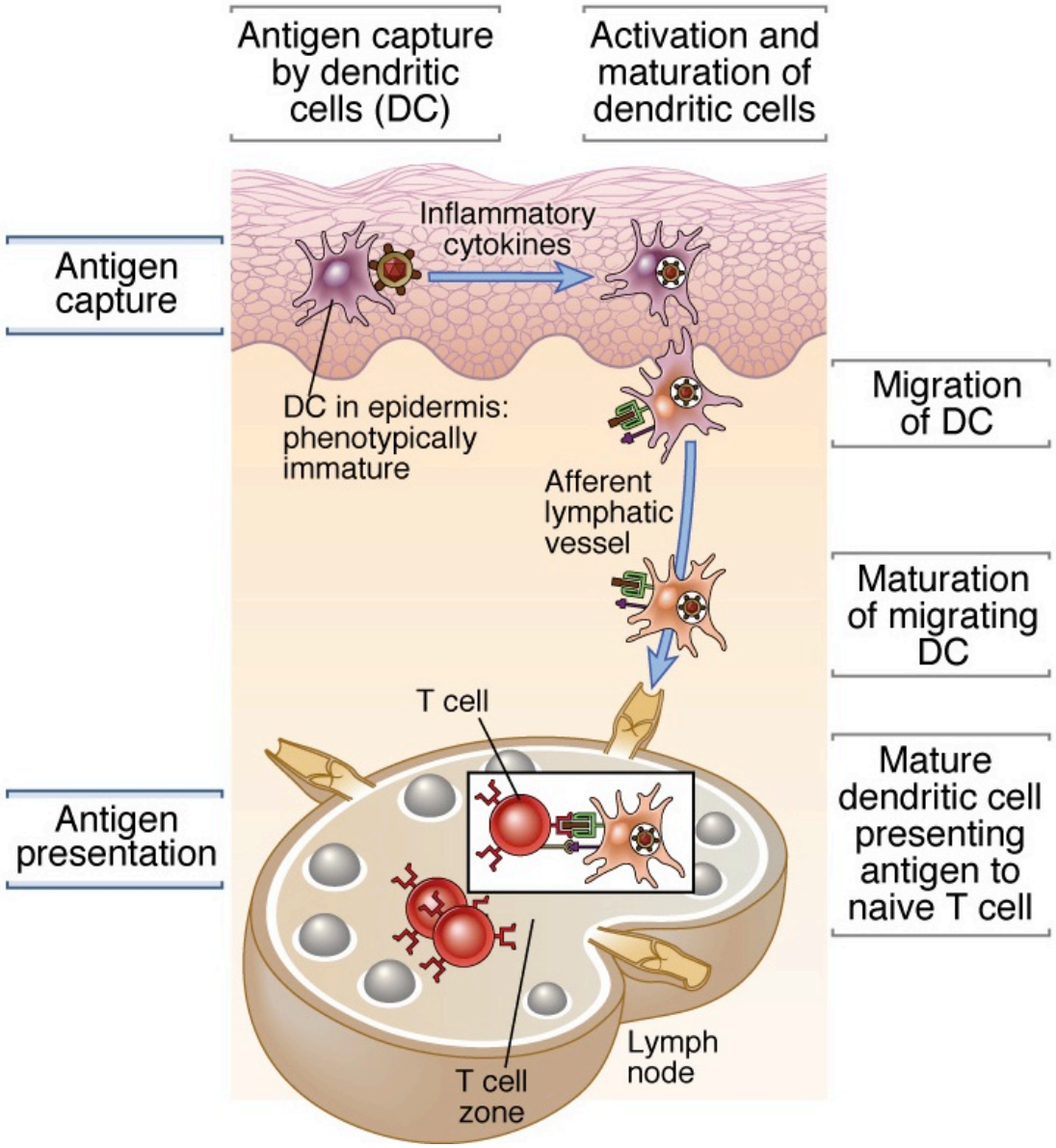
Functions of APCs

- Capture antigens and take them to the “correct” anatomic site
  - Antigens are concentrated in peripheral lymphoid organs, through which naïve lymphocytes circulate
- Display antigens in a form that can be recognized by specific lymphocytes
  - For T cells: MHC-associated peptides (cytosolic peptides to class I, vesicular peptides to class II)
  - For B cells: native antigens
- Provide “second signals” for T cell activation

Why are dendritic cells the most efficient APCs for initiating immune responses?

- Location: at sites of microbe entry (epithelia), tissues
- Receptors for capturing and reacting to microbes: Toll-like receptors, mannose receptors, others
- Migration to T cell zones of lymphoid organs
  - Role of CCR7
  - Co-localize with naïve T cells
- Maturation during migration: Conversion from cells for antigen capture into cells for antigen presentation and T cell activation
- Practical application: dendritic cell-based vaccines for cancer immunotherapy

Capture and presentation of antigens by dendritic cells

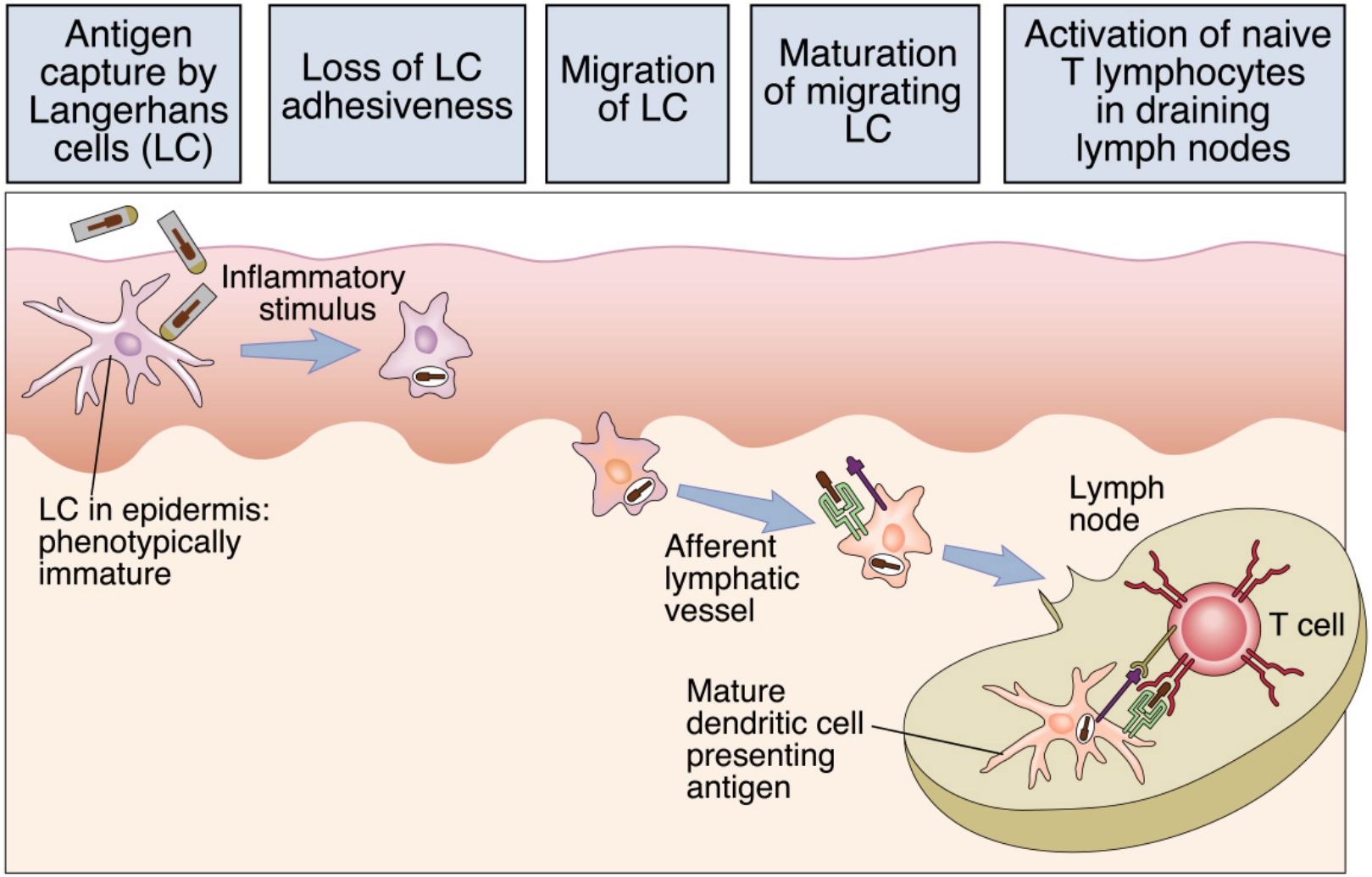


Sites of microbe entry: skin, GI tract, airways (organs with continuous epithelia, populated with dendritic cells). Less often -- colonized tissues, blood

Sites of lymphocyte activation: peripheral lymphoid organs (lymph nodes, spleen), mucosal and cutaneous lymphoid tissues)

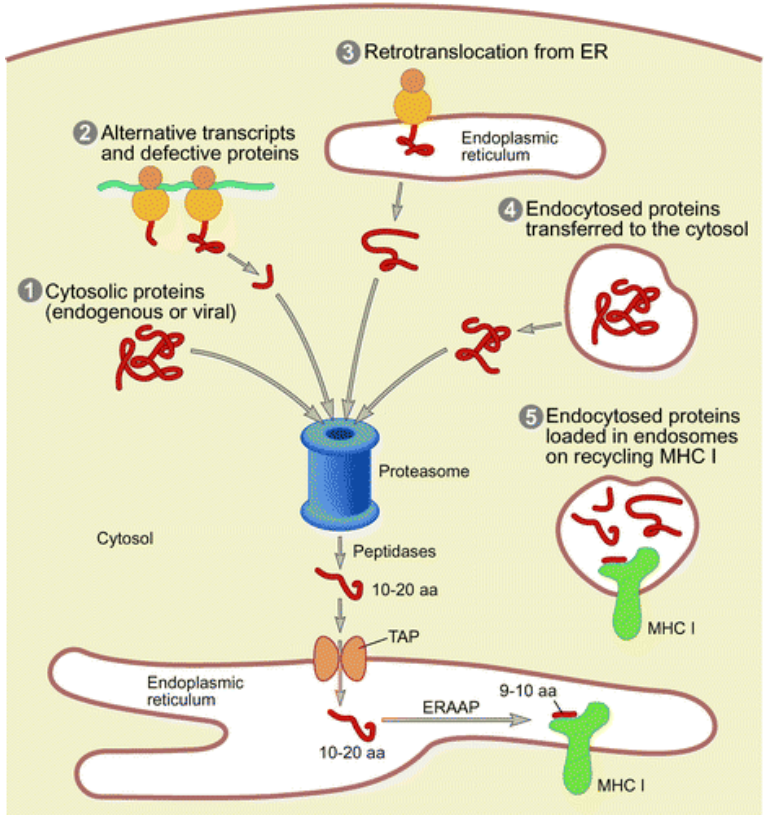
Antigens and naïve T cells come together in lymphoid organs

Antigen capture, migration, and maturation of dendritic cells

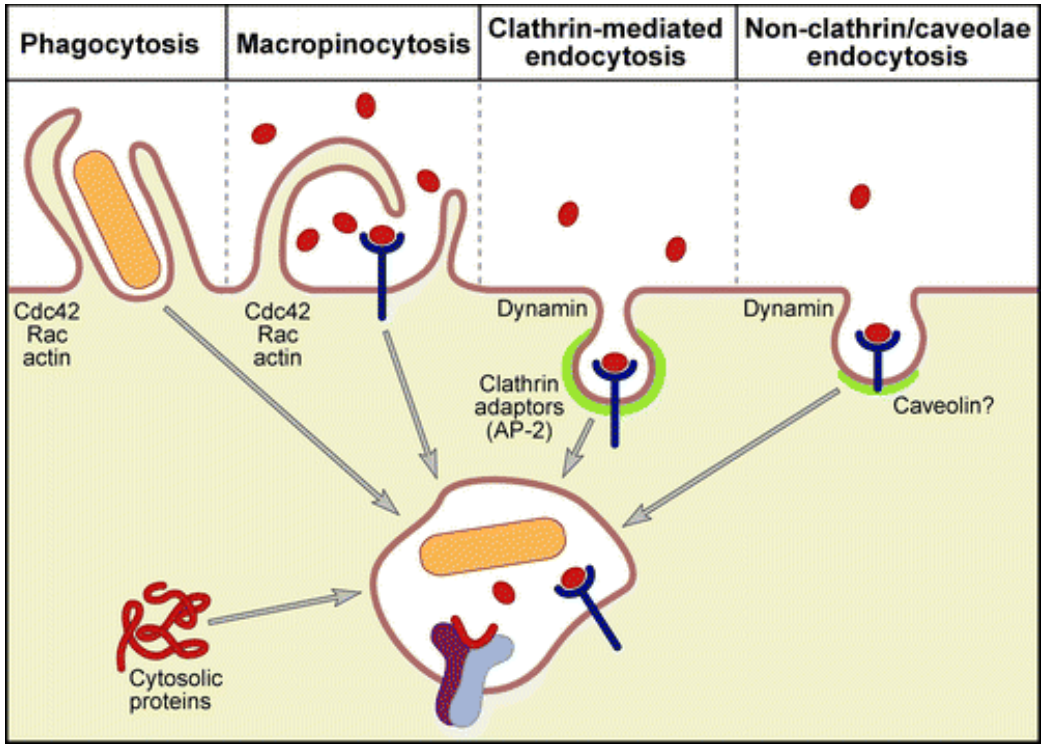


From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 5-

Sources of antigen for MHC I presentation:



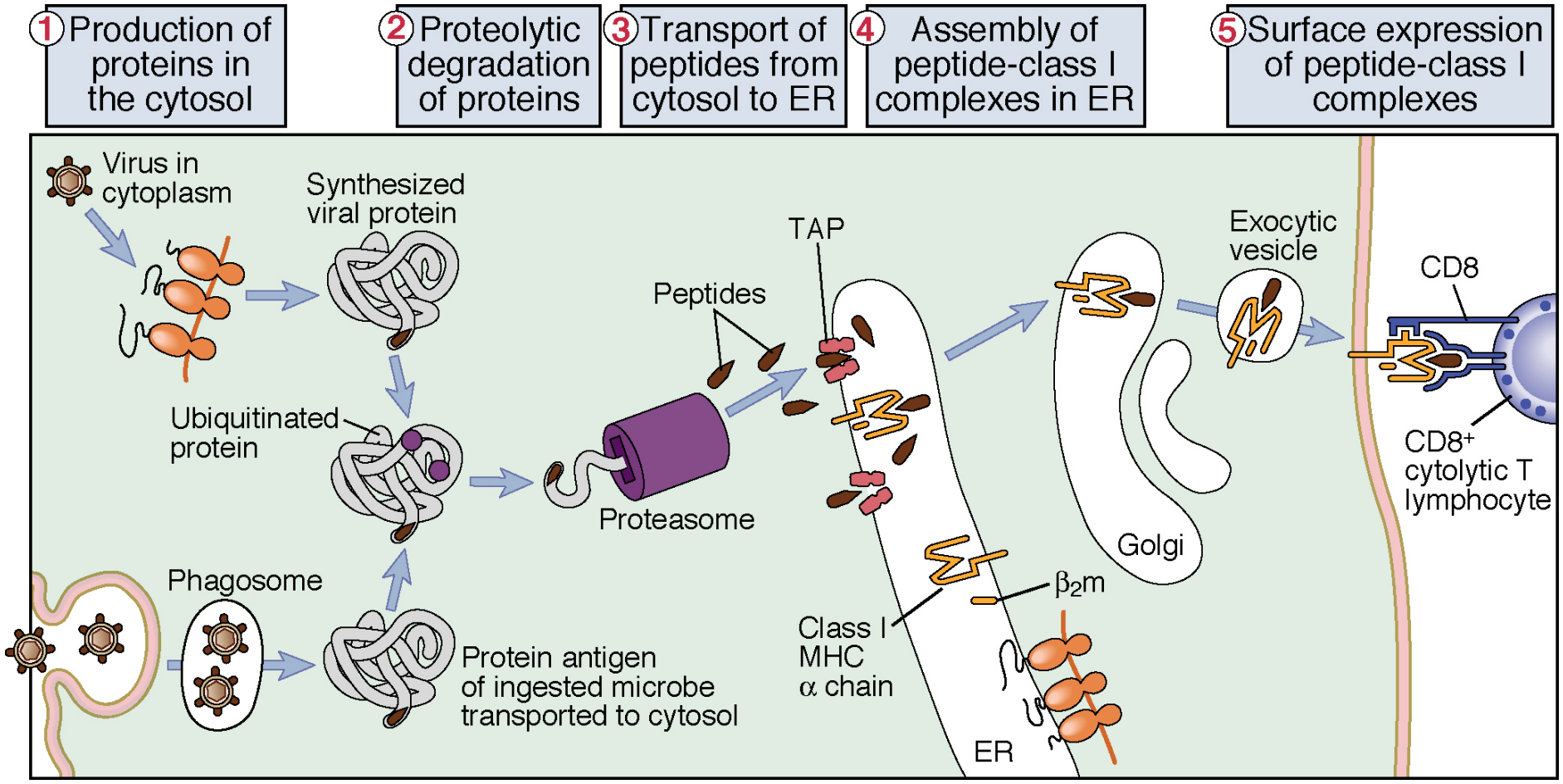
Sources of antigen for MHC II presentation:



Q: If this is true, how is are $CD8^+$ T cell responses to cancer generated?

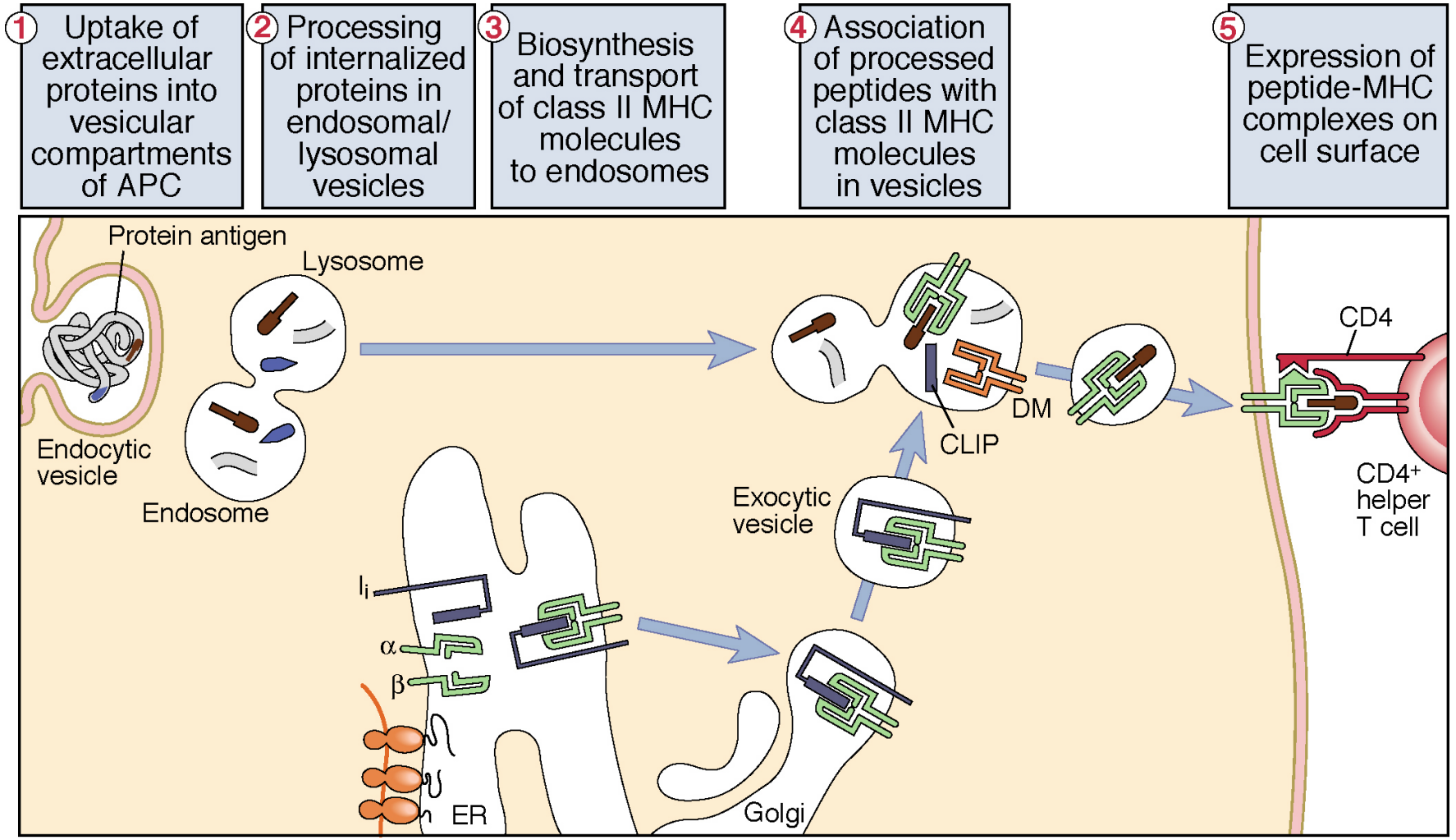
Trombetta and Mellman, Annual Reviews of Immunology, 23:975, 2005

The class I MHC pathway of processing of endogenous cytosolic protein antigens



Cytoplasmic peptides are transported into the ER where class I MHC molecules are available to bind them

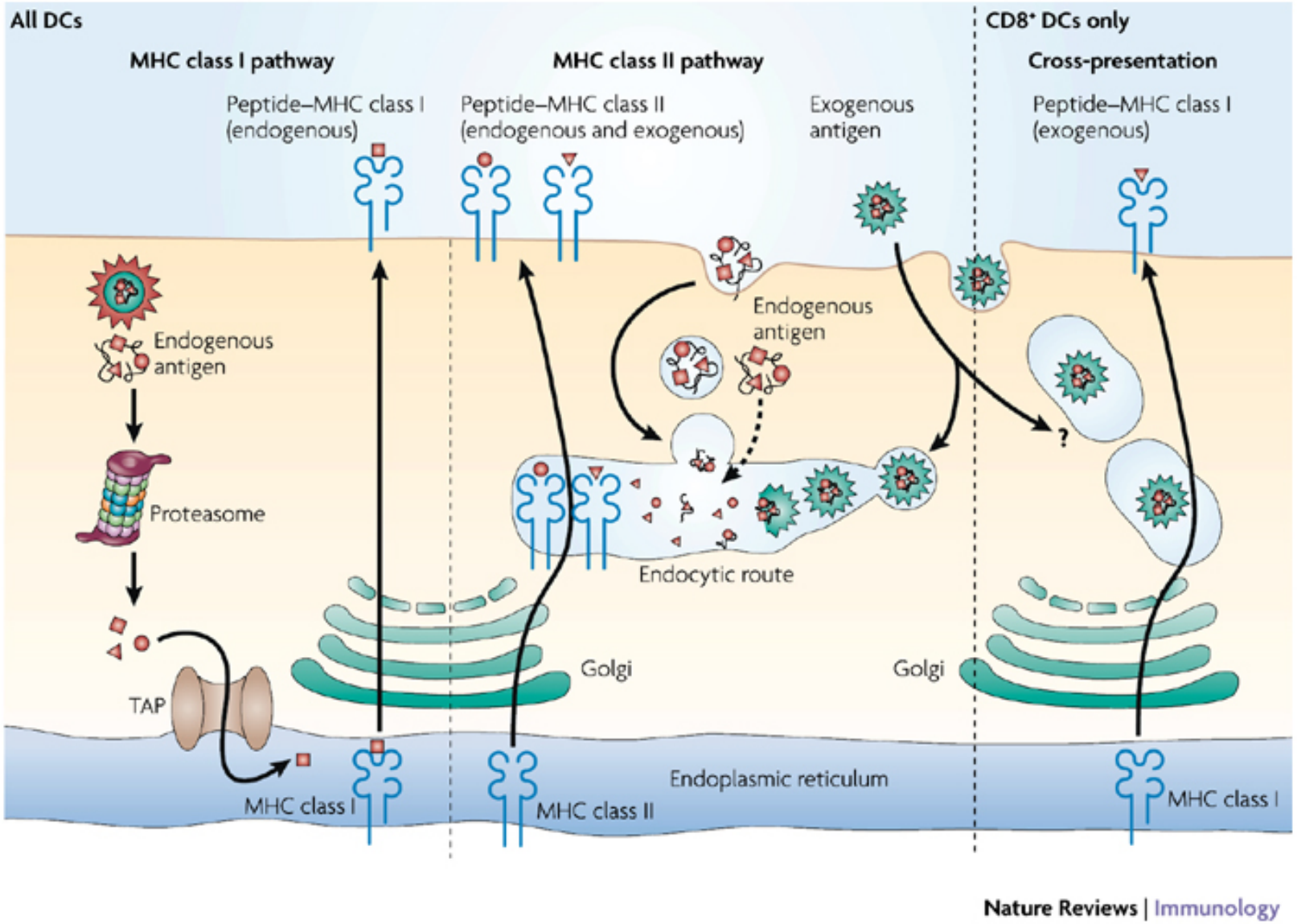
The class II MHC pathway of processing of internalized protein antigens



Endocytosed proteins are cleaved into peptides in vesicles

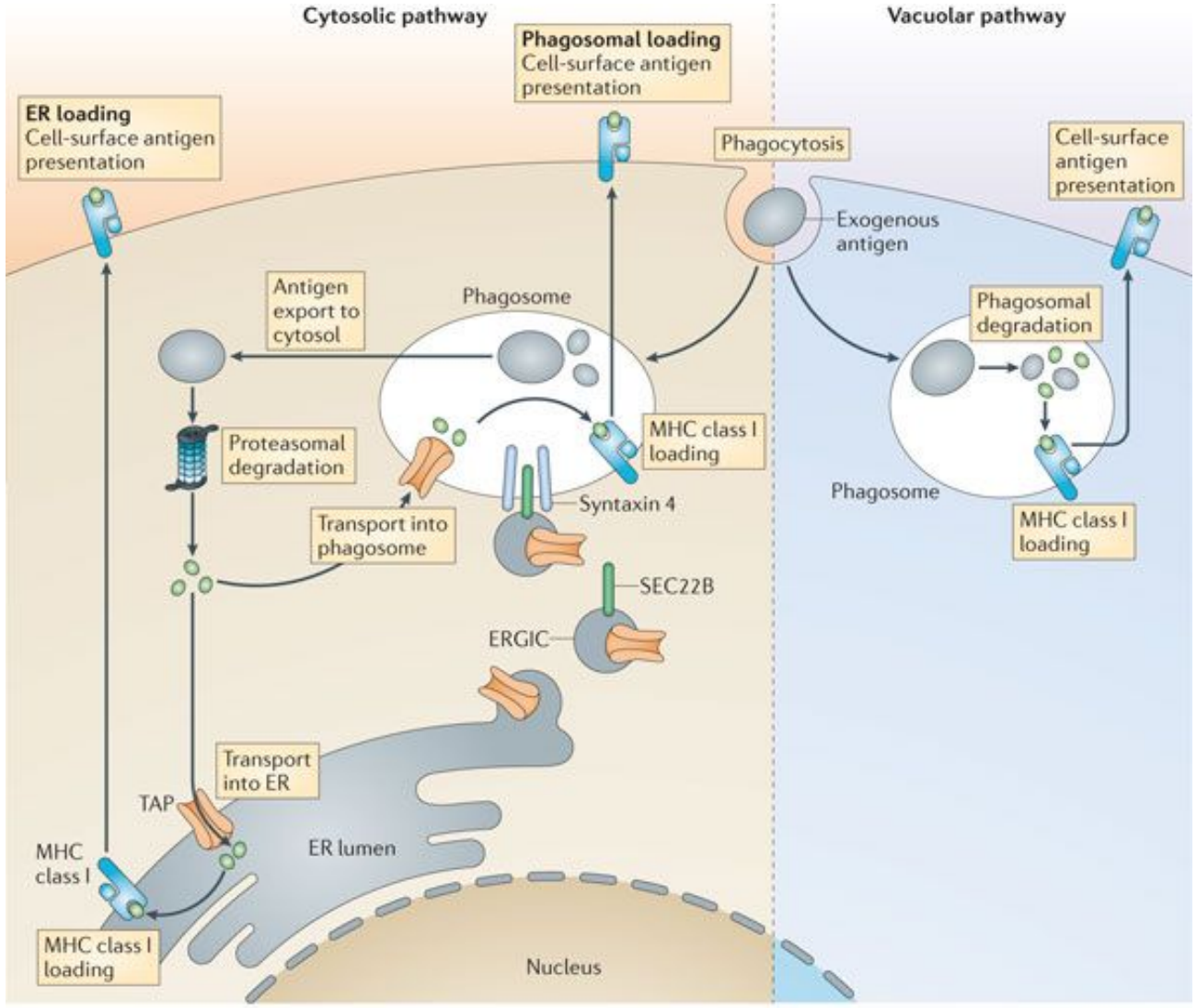
Class II MHC molecules are available to bind the peptides in the same vesicles

Ag trafficking in cross-presentation



Nature Reviews | Immunology

Ag trafficking in cross-presentation



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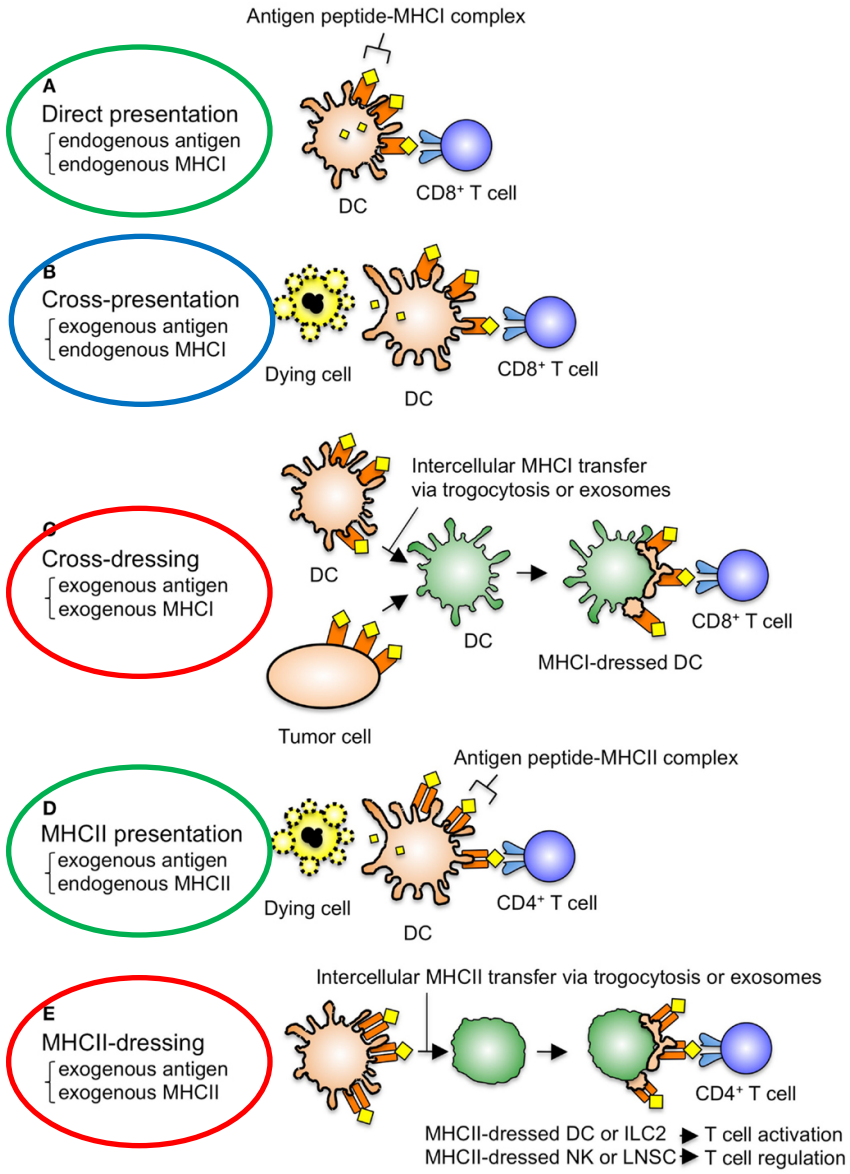
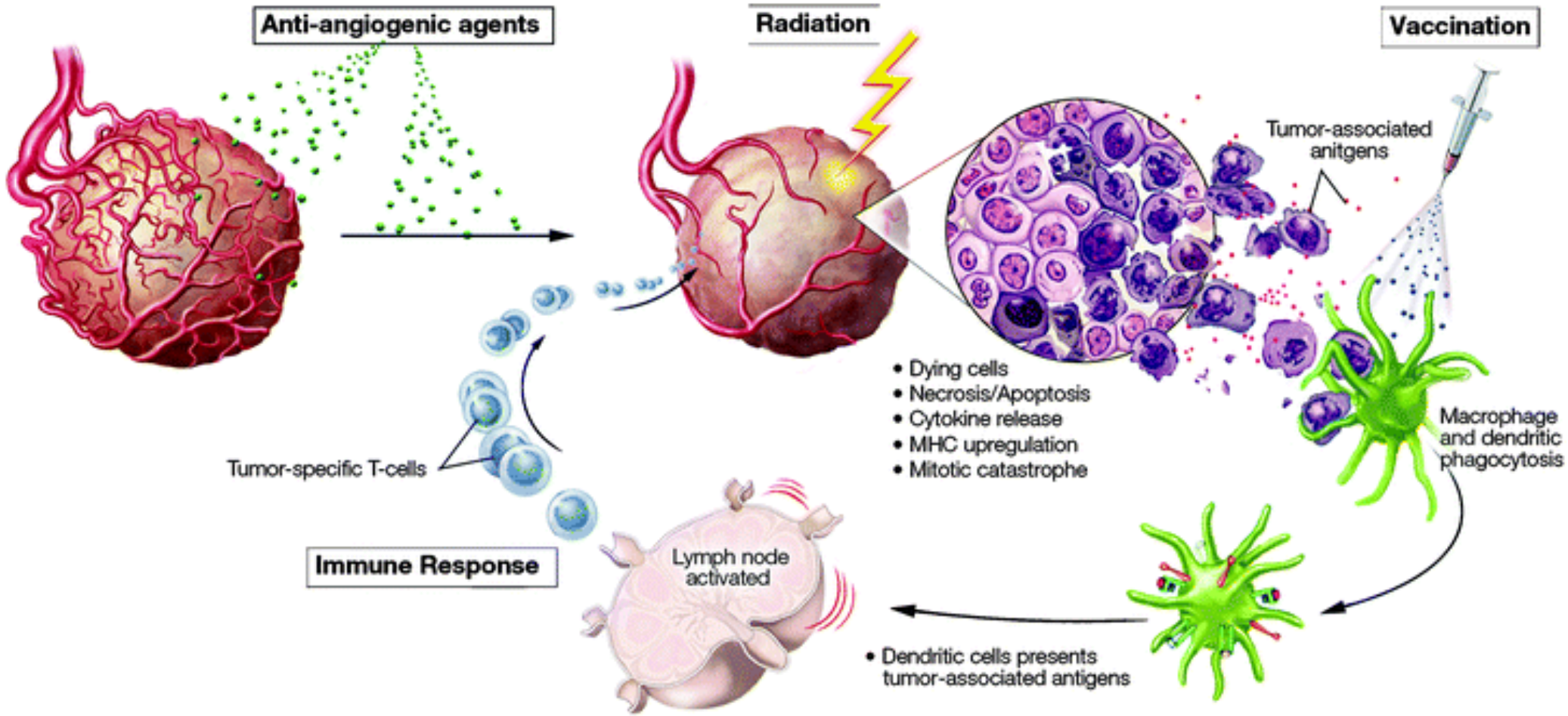
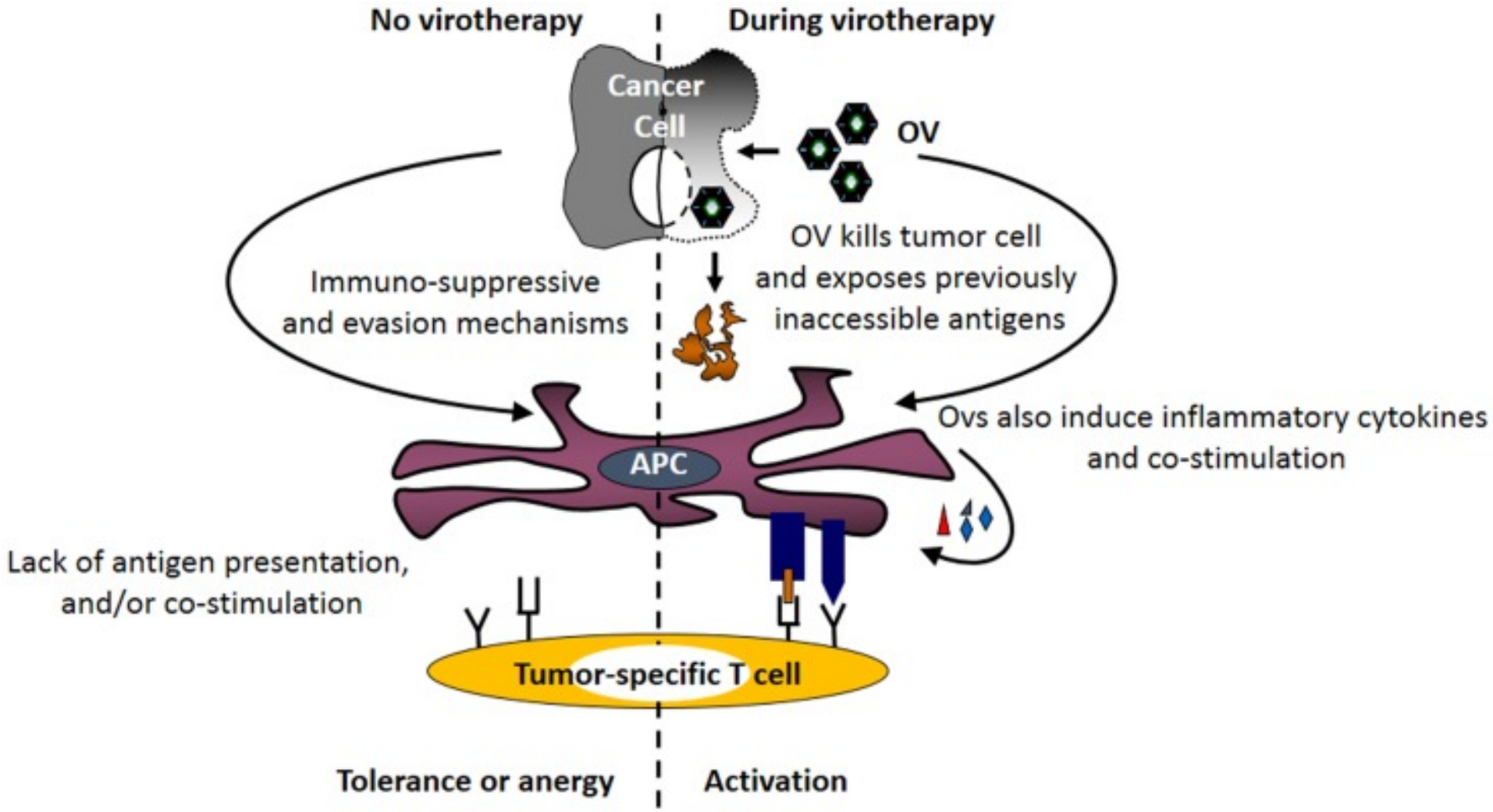
Modes of presentation for peptide/MHC complexes



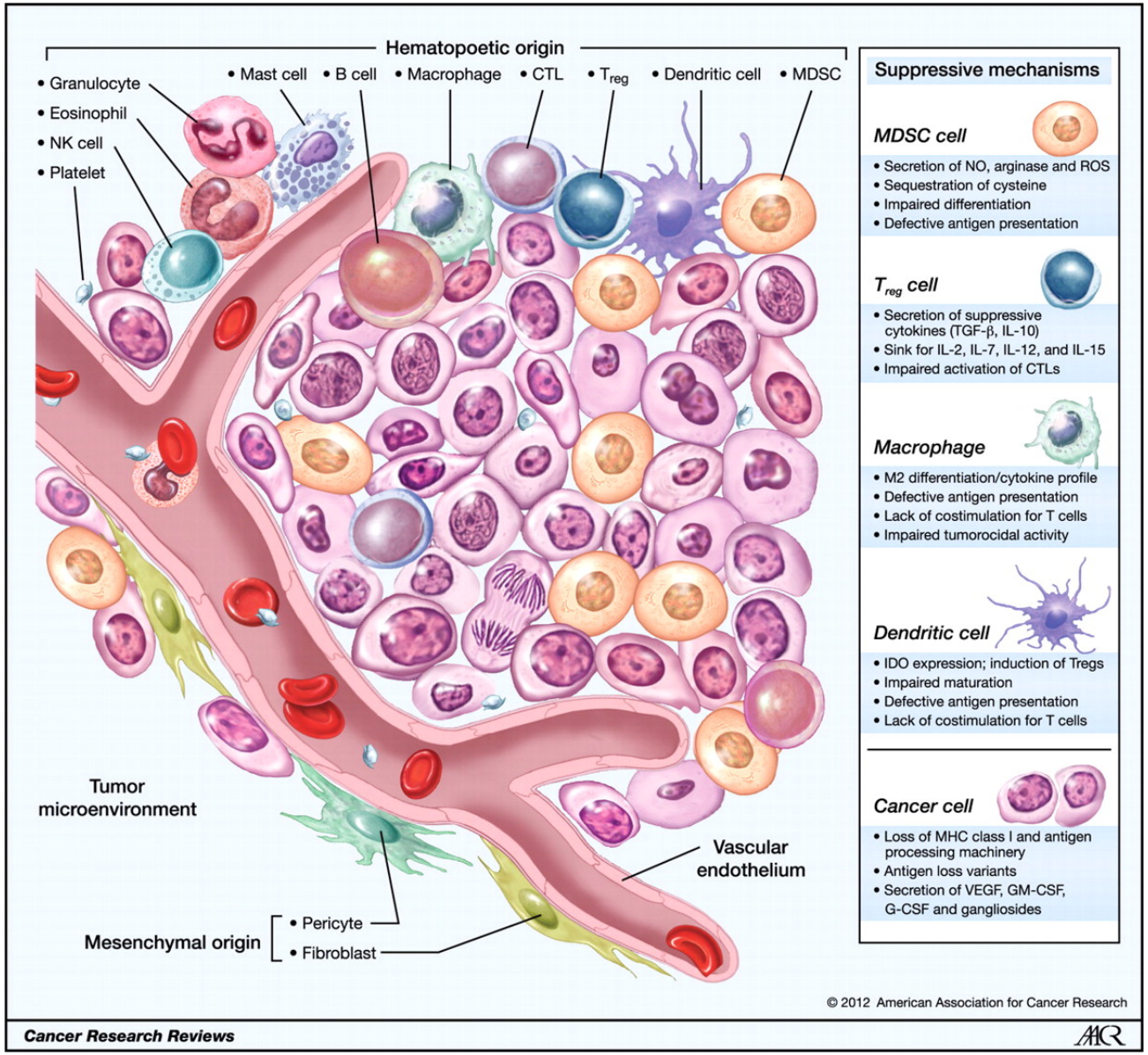
Pathways of enhancing tumor Ag presentation: radio-immunotherapy

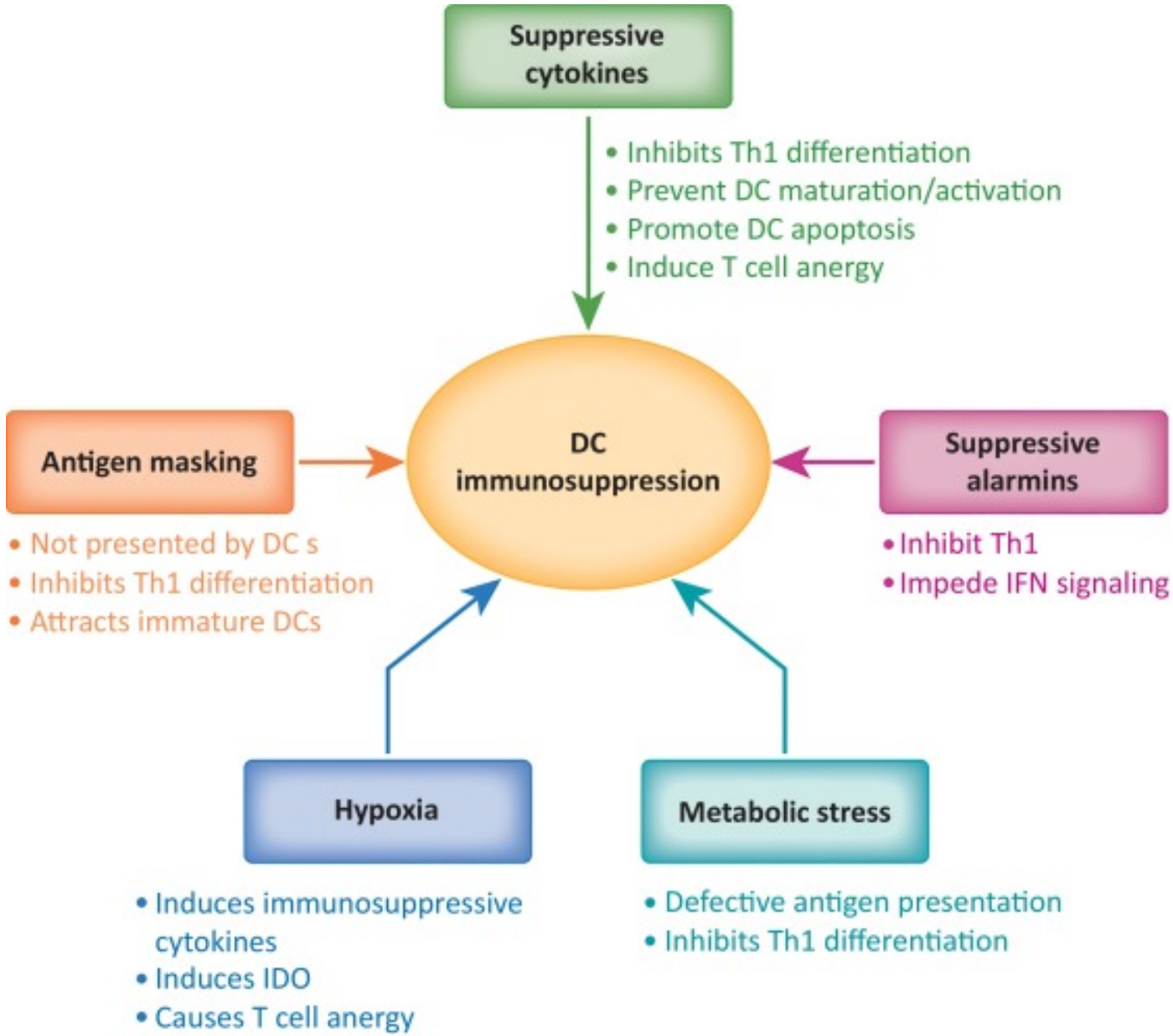


Pathways of enhancing tumor Ag presentation: oncolytic virotherapy

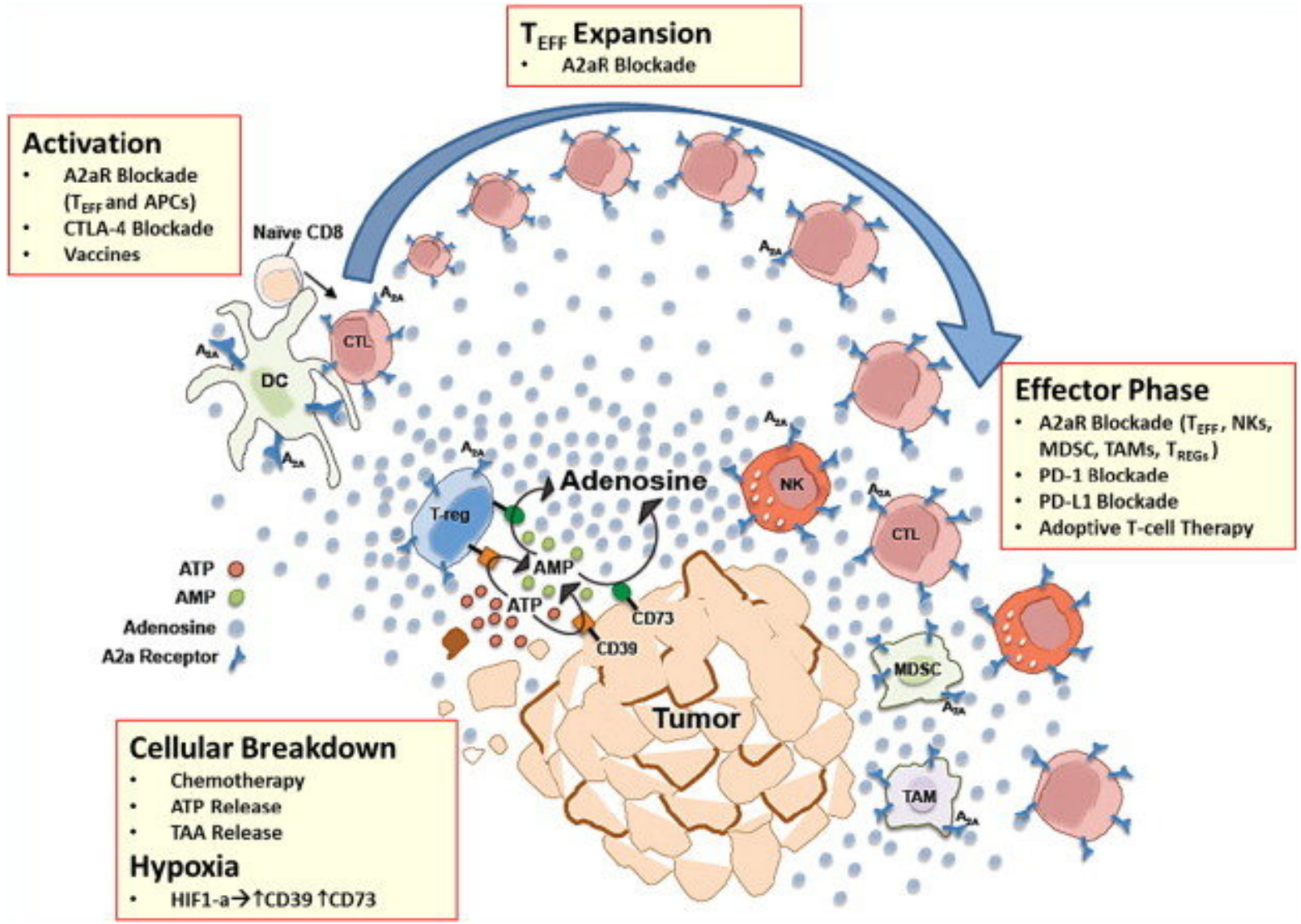


Pathways of APC-mediated immune suppression

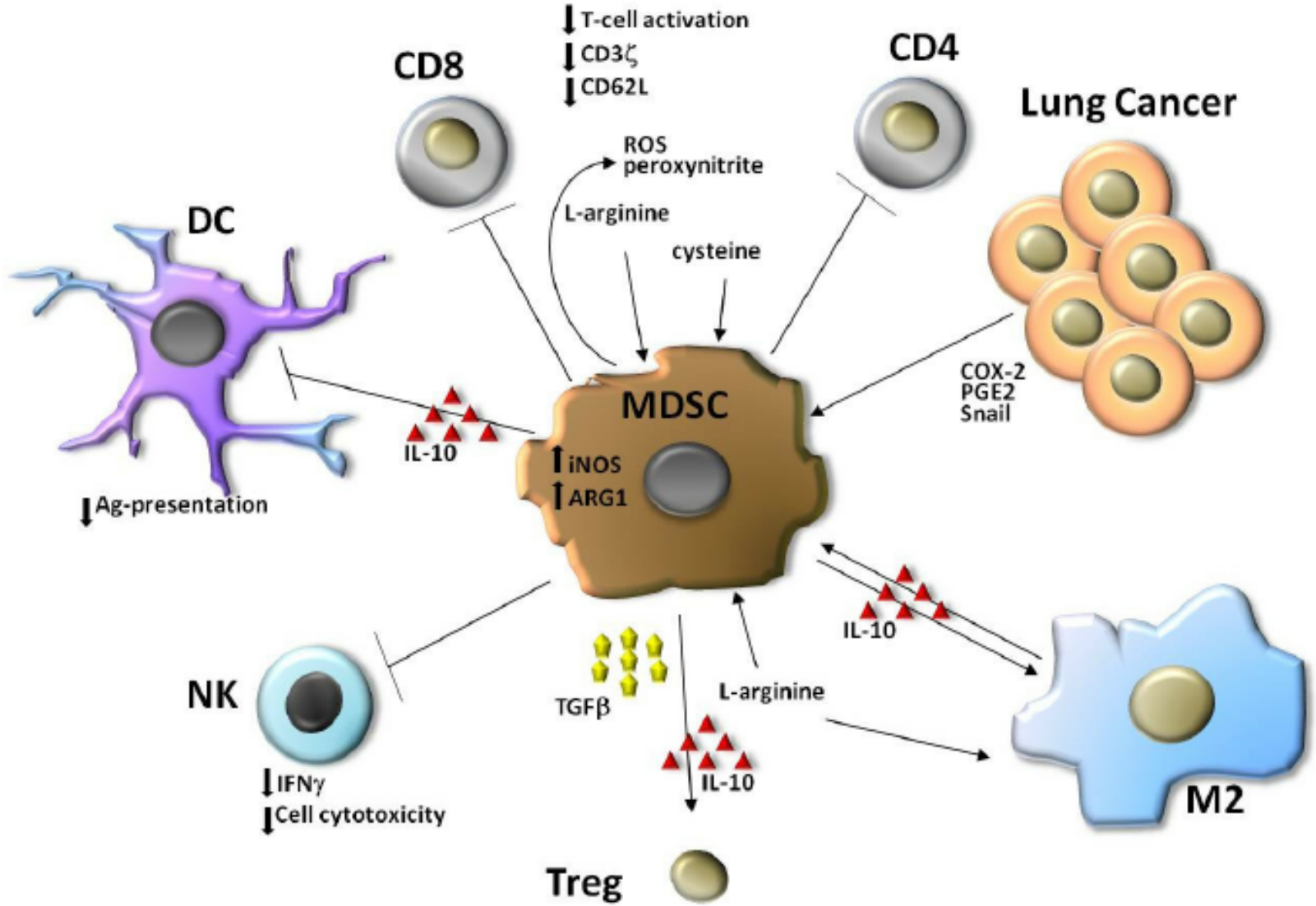



Suppressive cytokines
• Inhibits Th1 differentiation
• Prevent DC maturation/activation
• Promote DC apoptosis
• Induce T cell anergy
Antigen masking
• Not presented by DC s
• Inhibits Th1 differentiation
• Attracts immature DCs
DC immunosuppression
Suppressive alarmins
• Inhibit Th1
• Impede IFN signaling
Hypoxia
• Induces immunosuppressive cytokines
• Induces IDO
• Causes T cell anergy
Metabolic stress
• Defective antigen presentation
• Inhibits Th1 differentiation

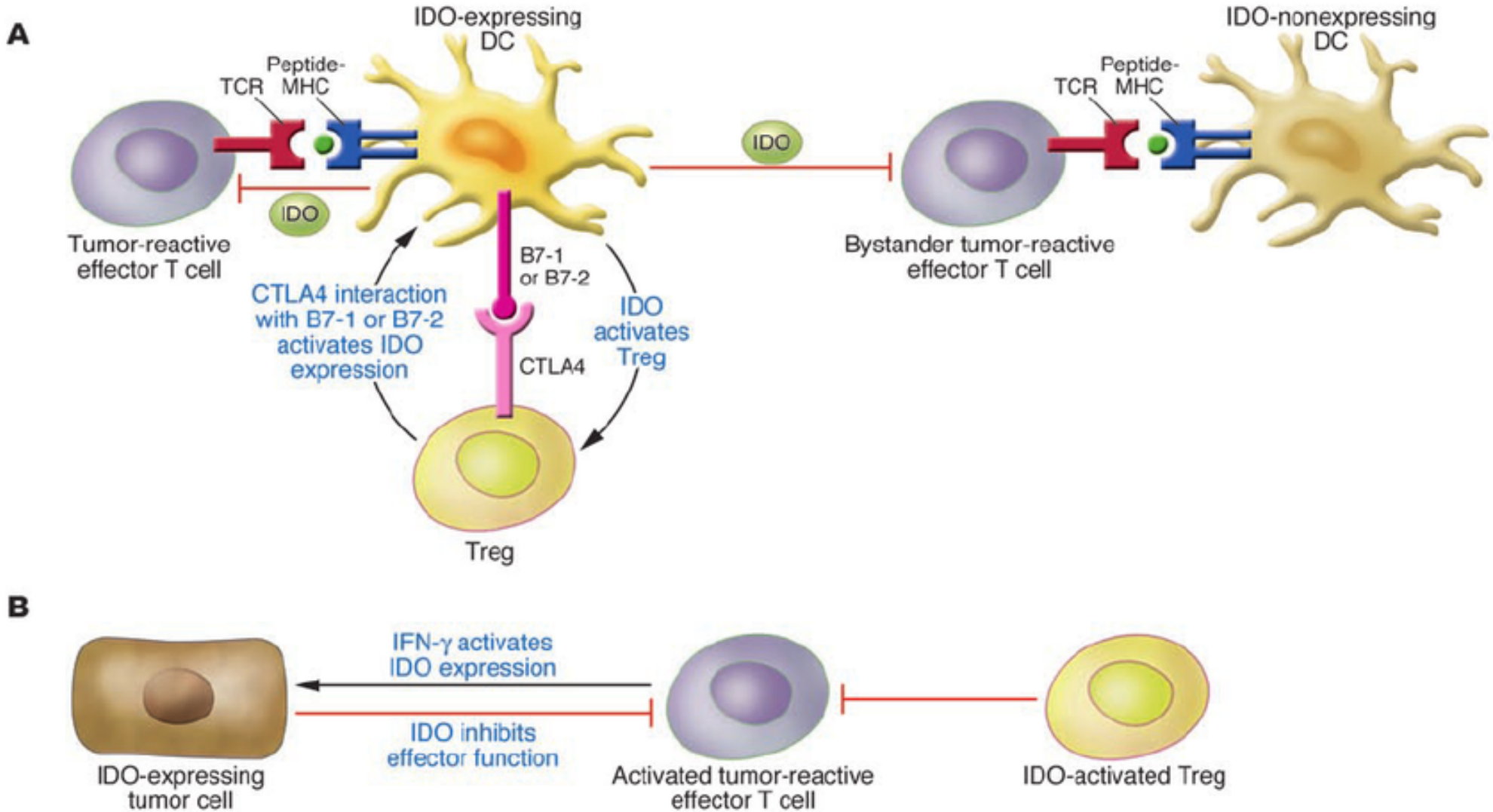
Pathways of APC-mediated immune suppression: Adenosine



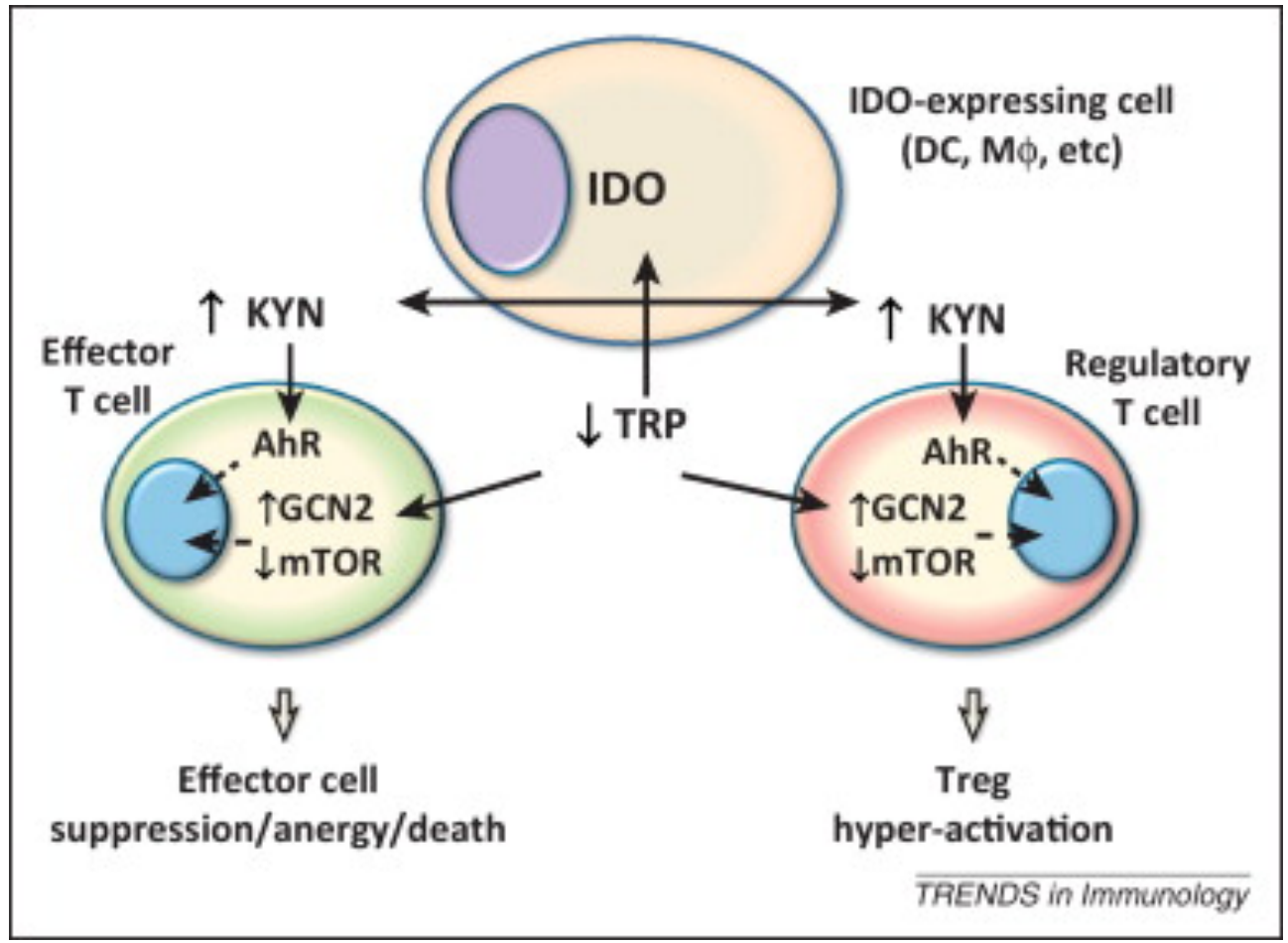
Pathways of APC-mediated immune suppression: Arginase



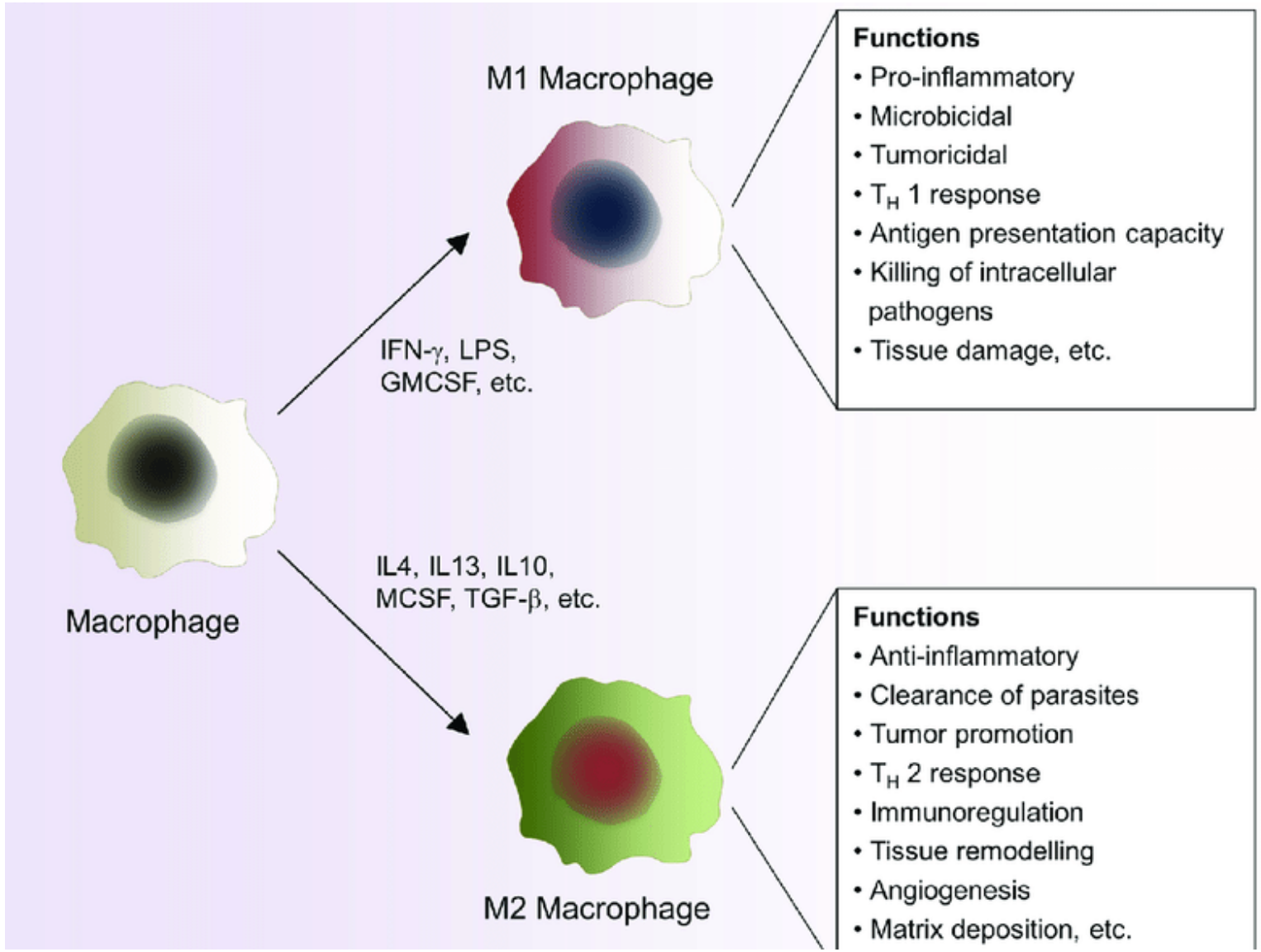
Pathways of APC-mediated immune suppression: IDO



Pathways of APC-mediated immune suppression: IDO



Pathways of APC-mediated immune suppression: Macrophage polarization



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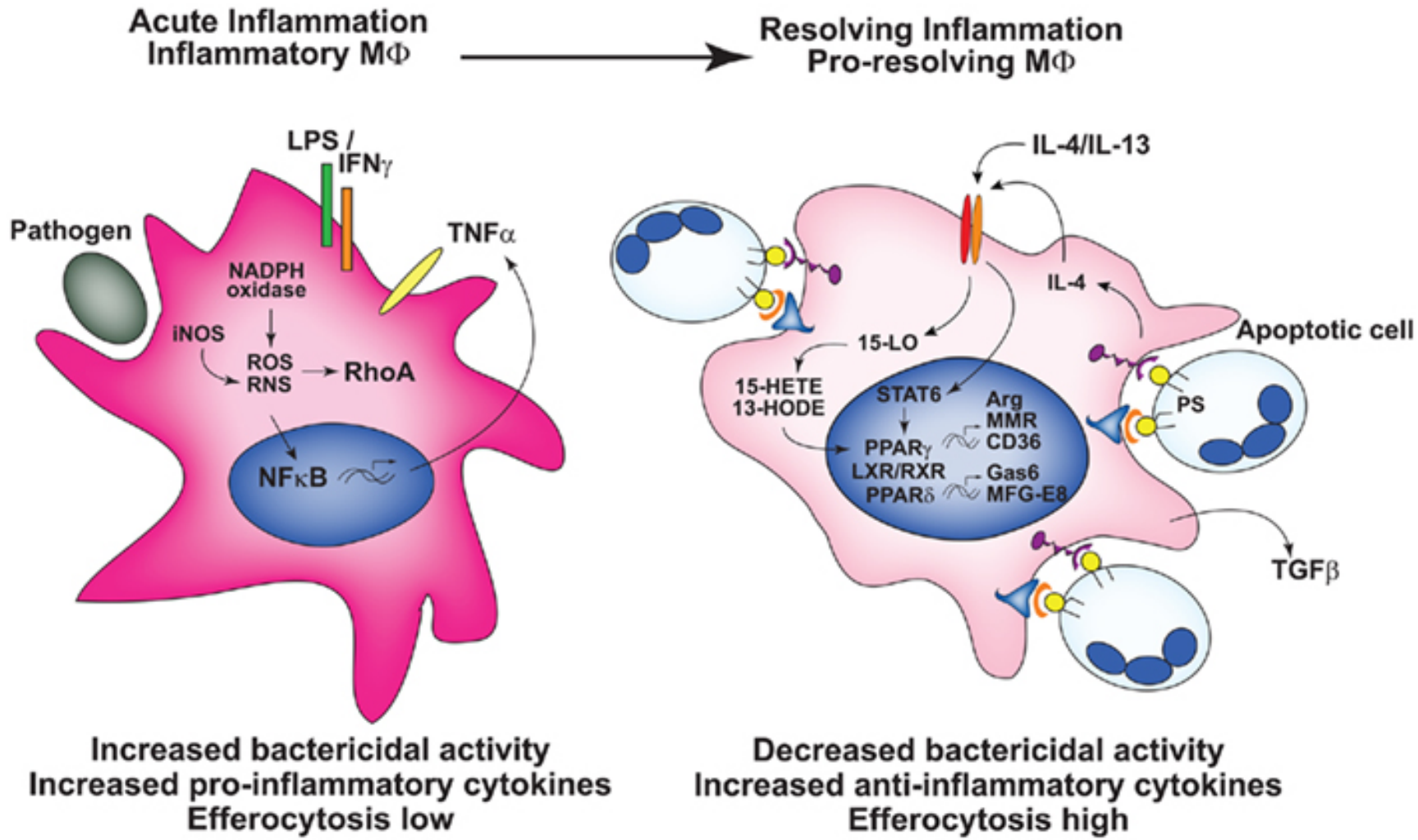

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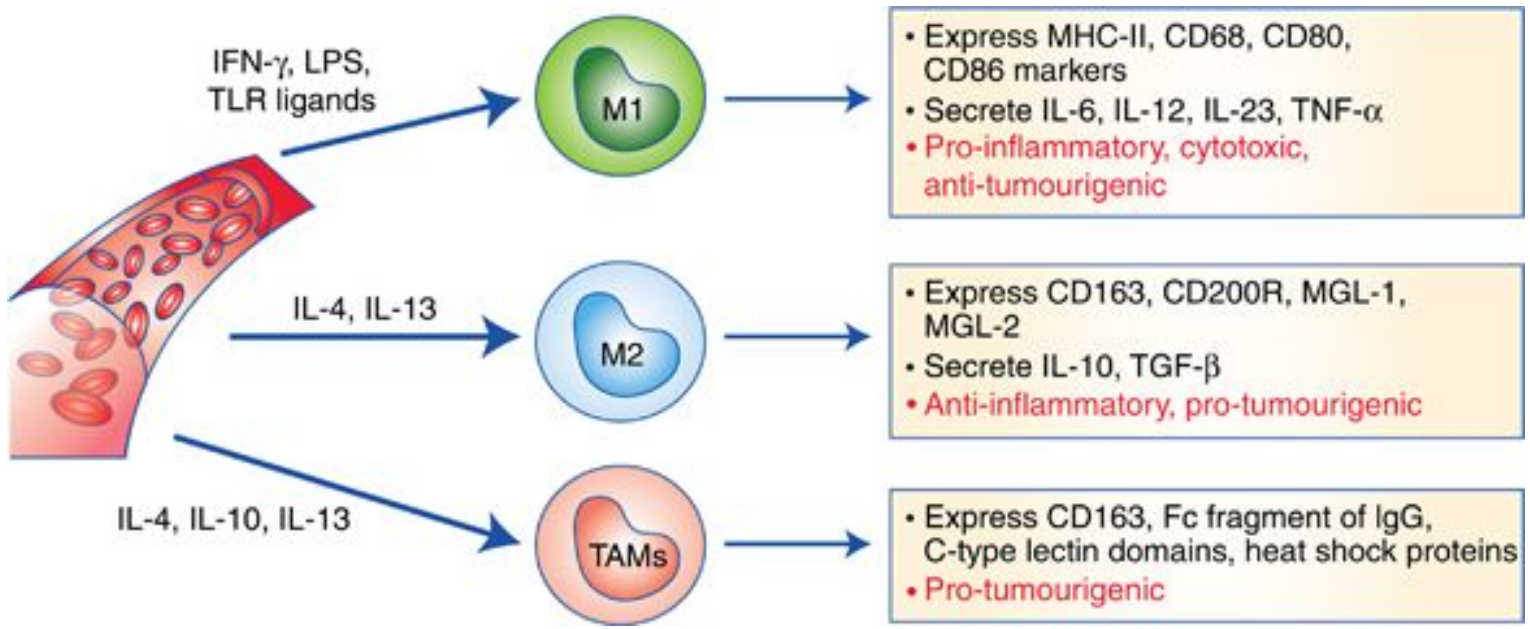
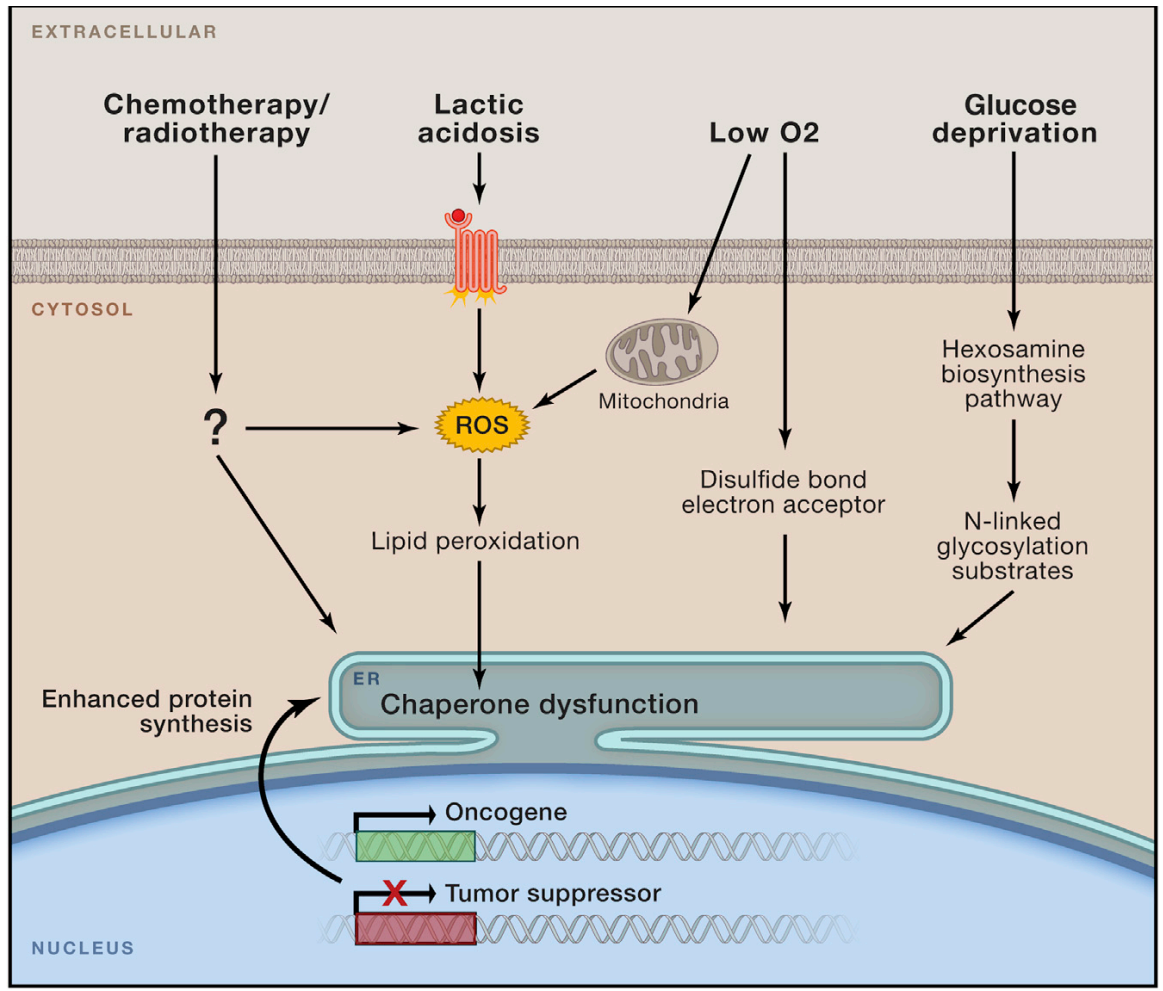
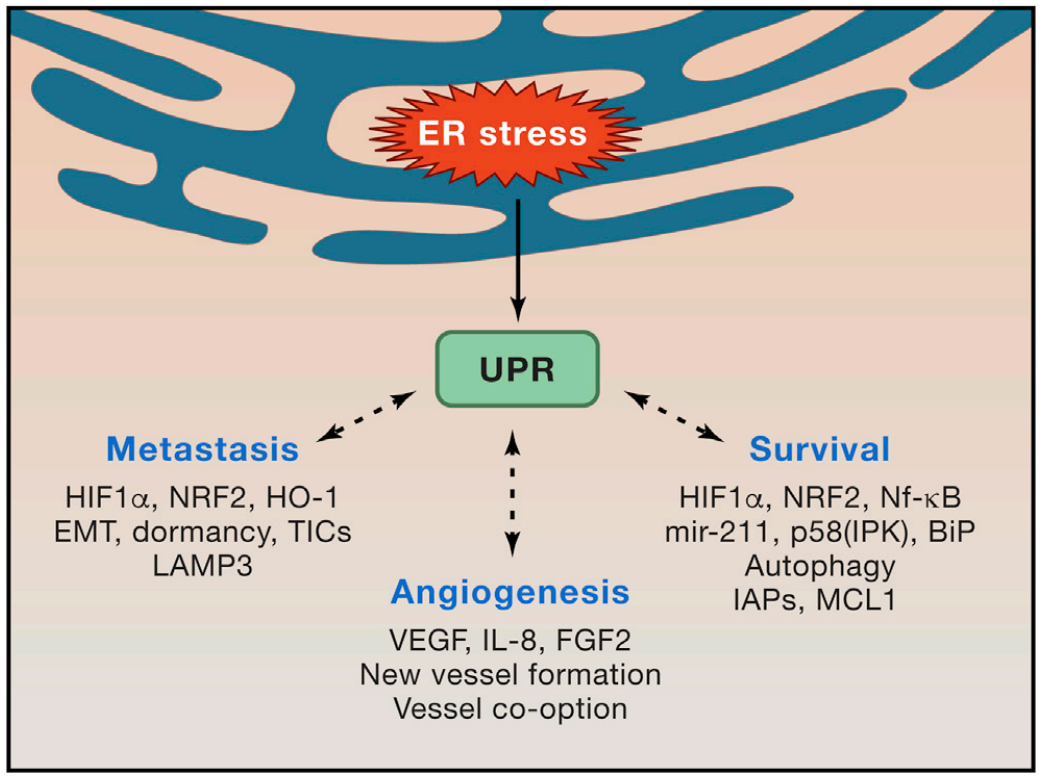


Tumors have it rough:

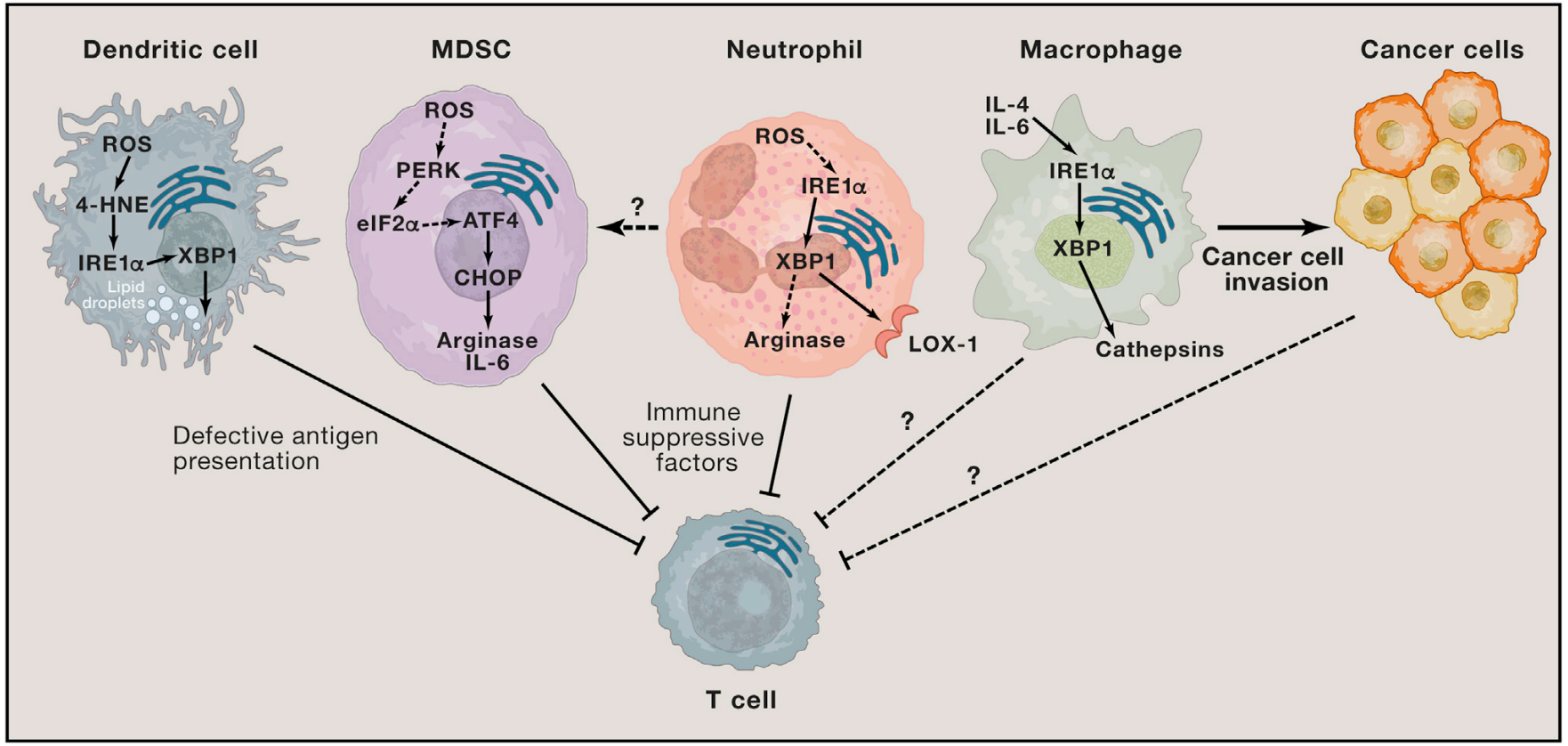
Hypoxia, oxidative stress, nutrient deprivation, etc cause “ER stress’



ER Stress and the Unfolder Protein Response in cancer cells



ER stress in tumor-associated myeloid cells leads to immunosuppression



Concluding remarks

1. Antigen presentation is crucial for adaptive immune responses to tumors and is therefore a superb control point for limiting them.

2. Professional APC exist in distinct functional states (promoting versus resolving inflammation), and tumors seek to leverage this

3. B cells can assume a regulatory role (like T cells)

4. Metabolites constitute a point of immune control leveraged by tumors

5. ER stress-mediated suppression appears to be transmissible.