Introduction to Innate Immunity

Vincenzo Bronte
Verona University Hospital
Italy

References and suggested readings

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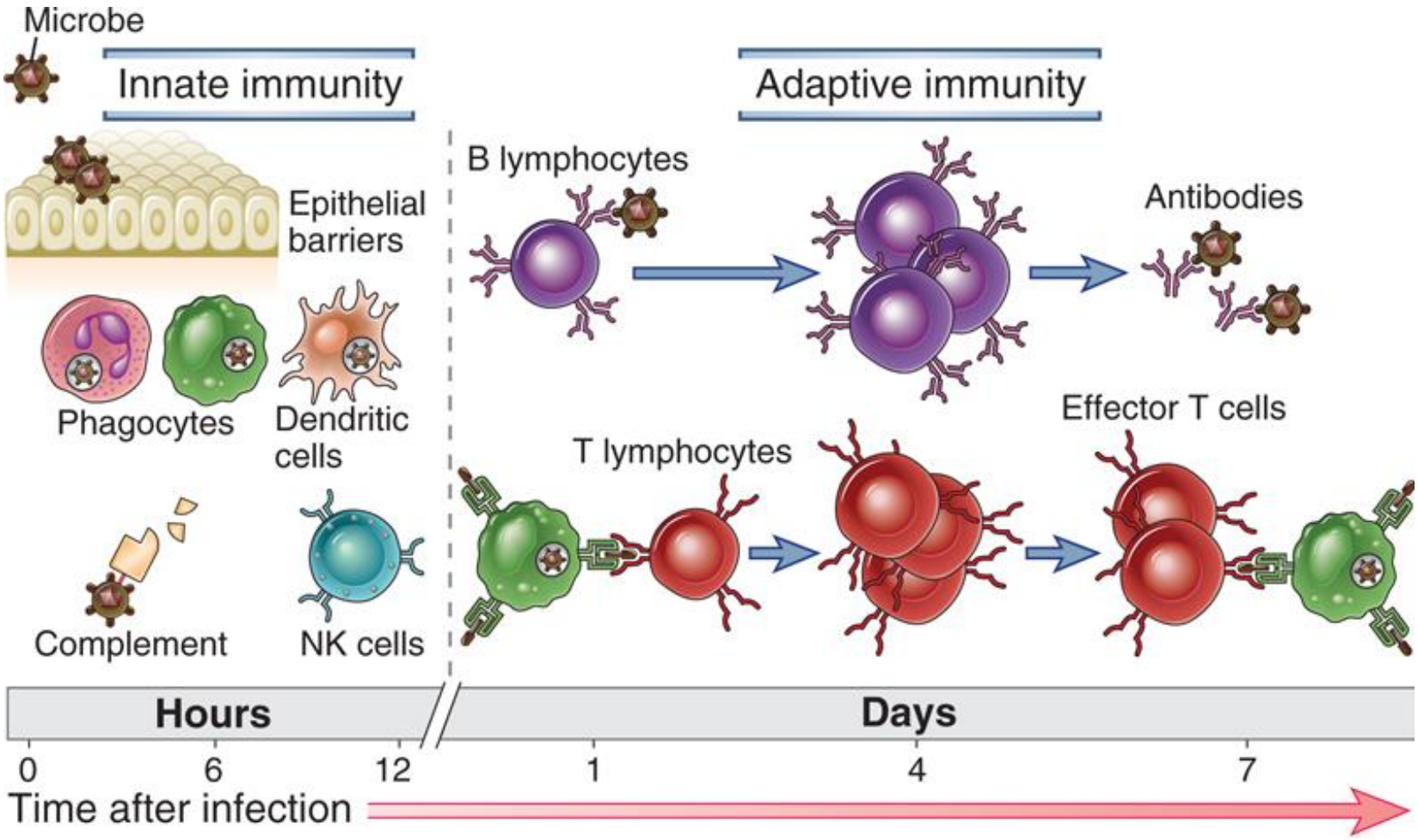
Innate immunity

- **Properties of innate immunity**
- **Components of innate immunity**
  - Epithelial barriers
  - Cellular mechanisms
  - Humoral mechanisms
- **Role of innate immunity in inducing adaptive immune responses**
- **Role of innate immunity in immune suppression**

Innate and adaptive immunity



Properties of innate immunity

- phylogenetically older

- preformed and immediately reacting to the encounter with pathogens

- repetead contacts with pathogen do not leave memory

- first line of defense

- archetypal discrimination between self and non self

- stimulates and shapes adaptive imunity

Principal components of innate immunity

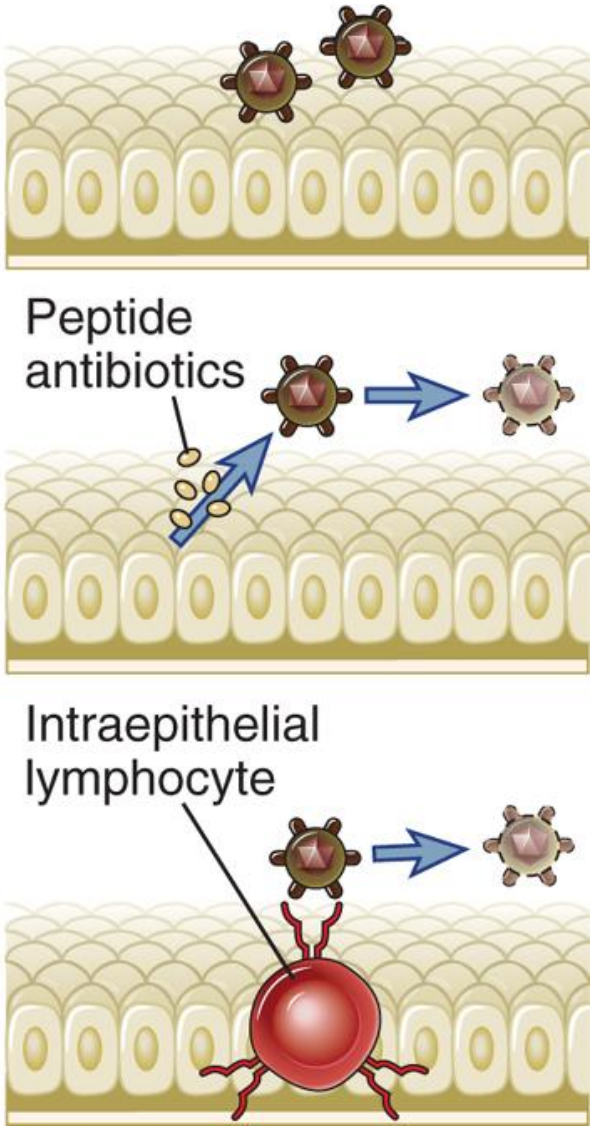
- epithelial barriers (skin and mucosal membranes)

- pattern recognition receptors (TLR, scavanger receptors…)

- cells (phagocytes, innate lymphoid cells…)

- humoral components (collectins, complement, cytokines etc.)

Epithelial barriers and innate immunty



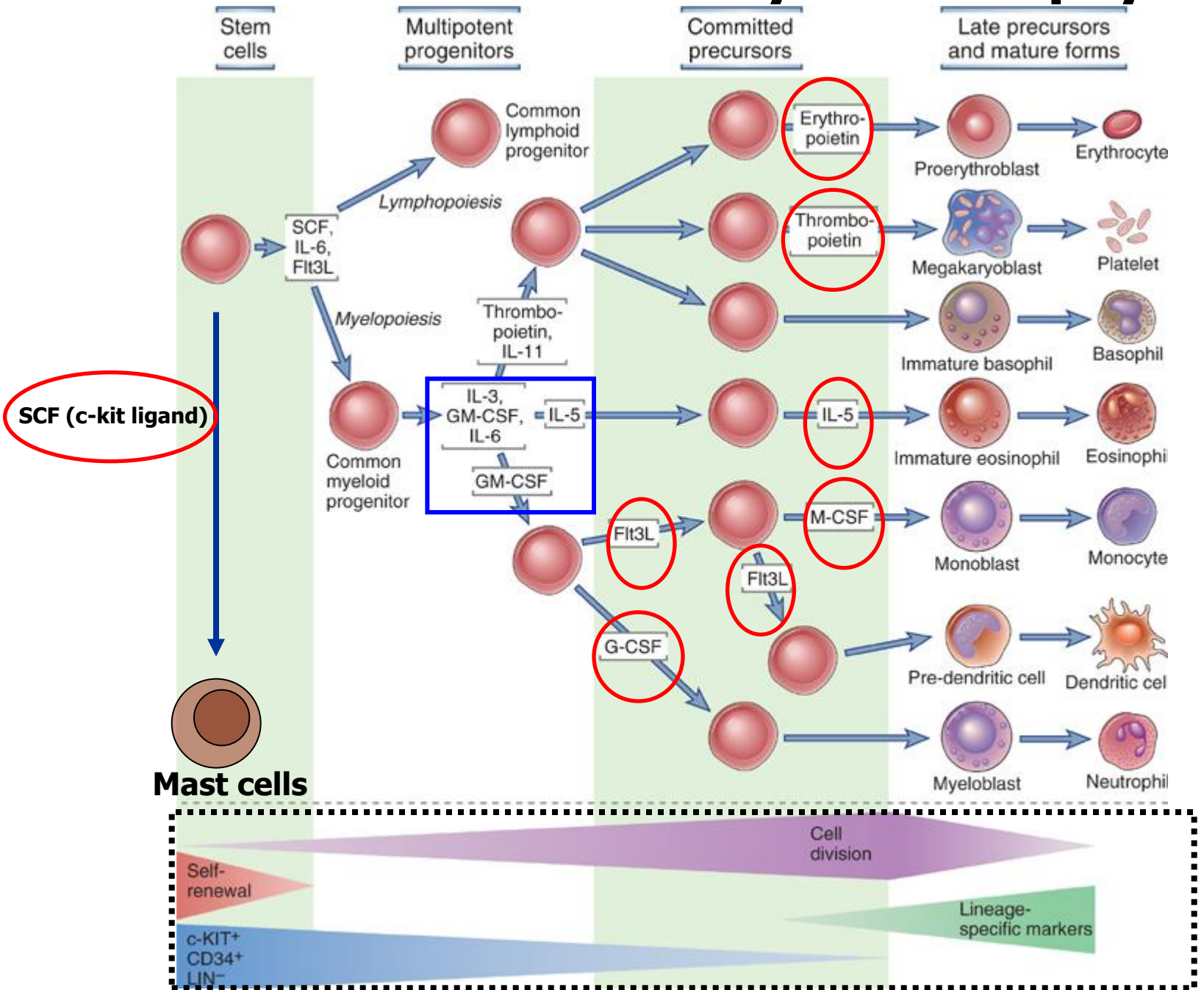
- **physical barrier**

- **normal bacterial flora (microbiota)**

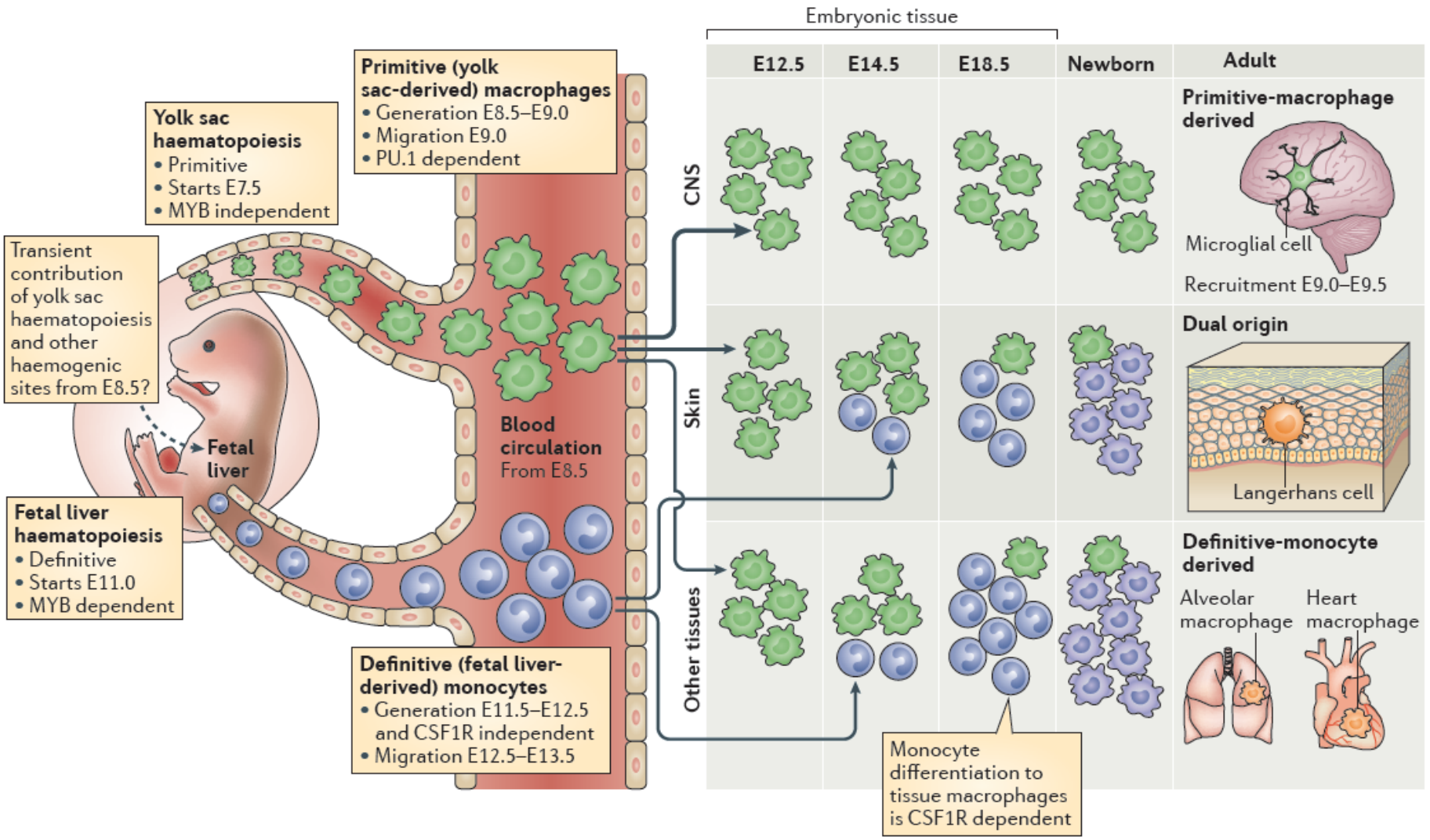
- **chemical/molecular barrier (production of antimicrobial peptides)**

- **direct elimination (intraepithelial lymphocytes)**

Cells of innate immunity: Hematopoyesis



Monocyte and macrophage developmental pathways



Cells of innate immunity

Cell type	*Main function*
Monocytes/Macrophages	**Phagocytosis, inflammation, tissue repair**
Neutrophils	**Phagocytosis, inflammation, antimicrobial peptide production**
NK cells	**Elimination of infected or tumor cells, macrophage activation**
Dendritic cells	**Activation of naïve T cells**
Mast cells	**Inflammation, vascular permeability**
Eosinophils	**Defense against parasites**

Pathogen Associated Molecular Patterns (PAMP)

Molecules shared by groups/classes of pathogens (i.e. Gram+ and Gram- bacteria)

- essential for their life cycle, replication and/or infectivity

- not present in mammalian cells

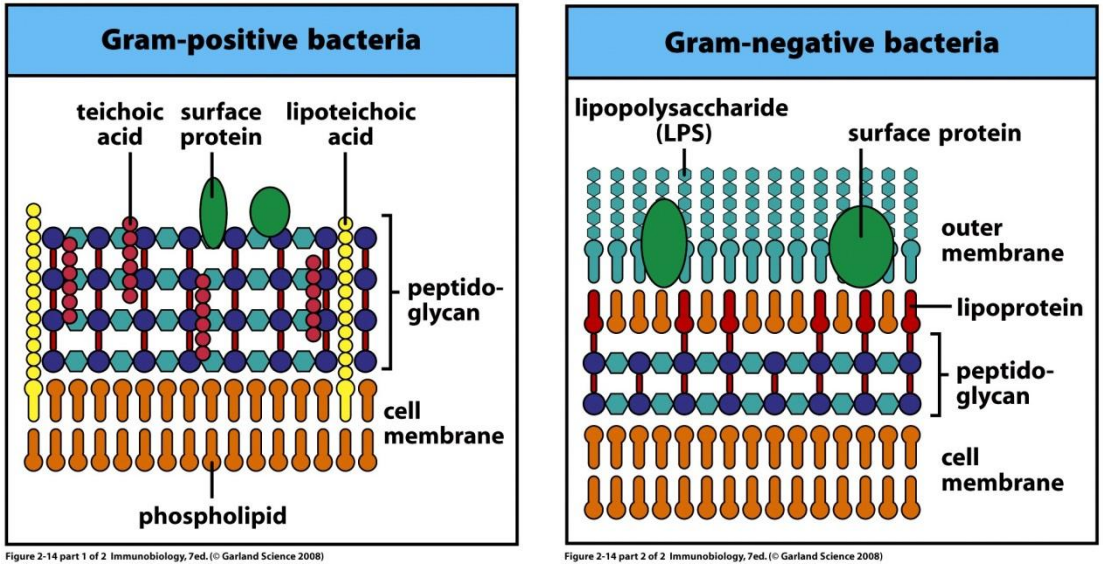


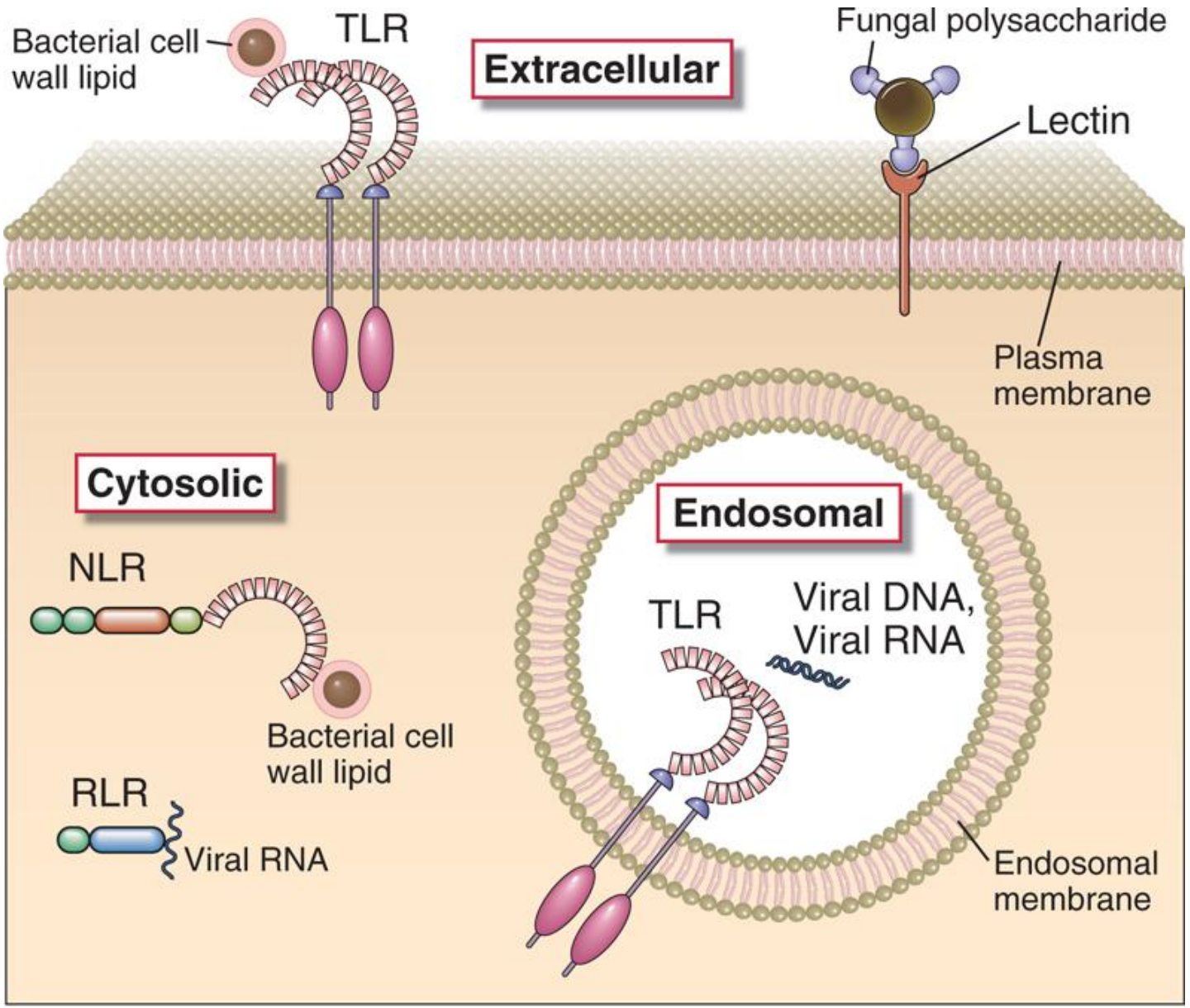
Figure 2-14 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Figure 2-14 part 2 of 2 Immunobiology, 7ed. (© Garland Science 2008)

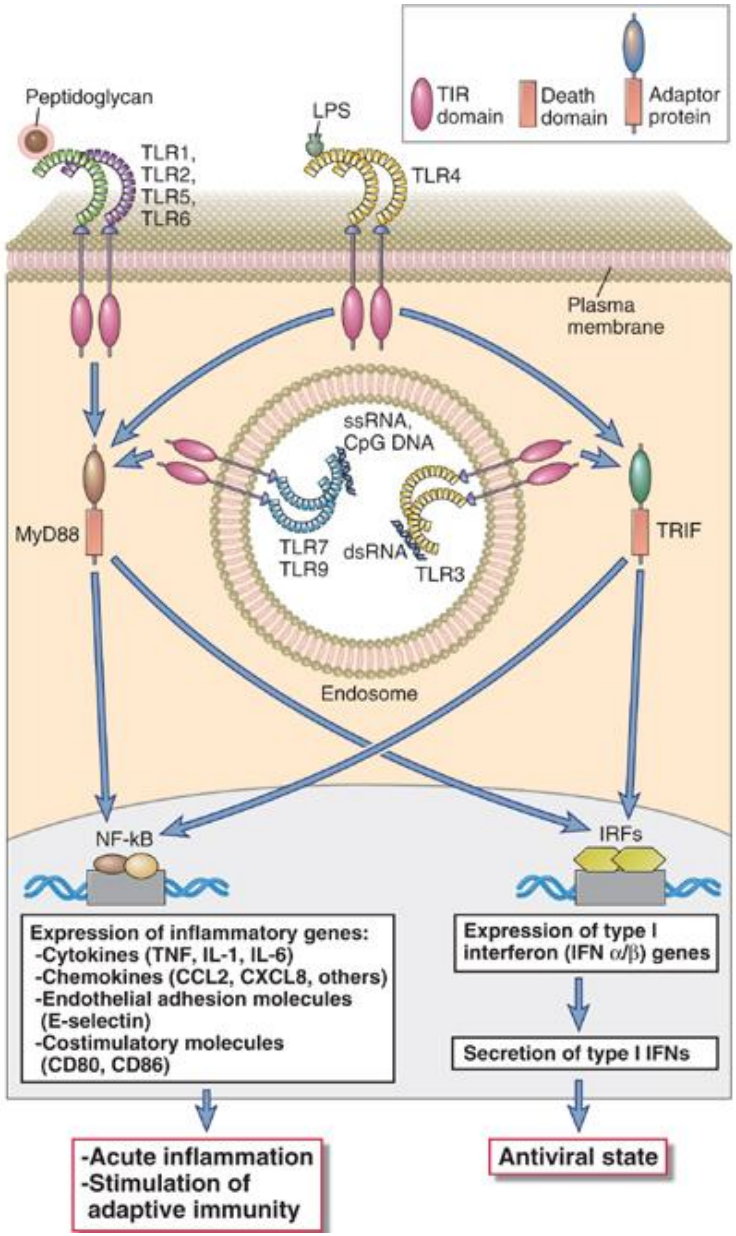
structures of bacterial cell wall (LPS, peptidoglycan, flagellin...)

nucleic acids of pathogens (dsRNA, unmethylated CpG dinucleotides...)

Pattern Recognition Receptors (PRR)



Toll-like receptors



Sensing of Damage Associated Molecular Patterns

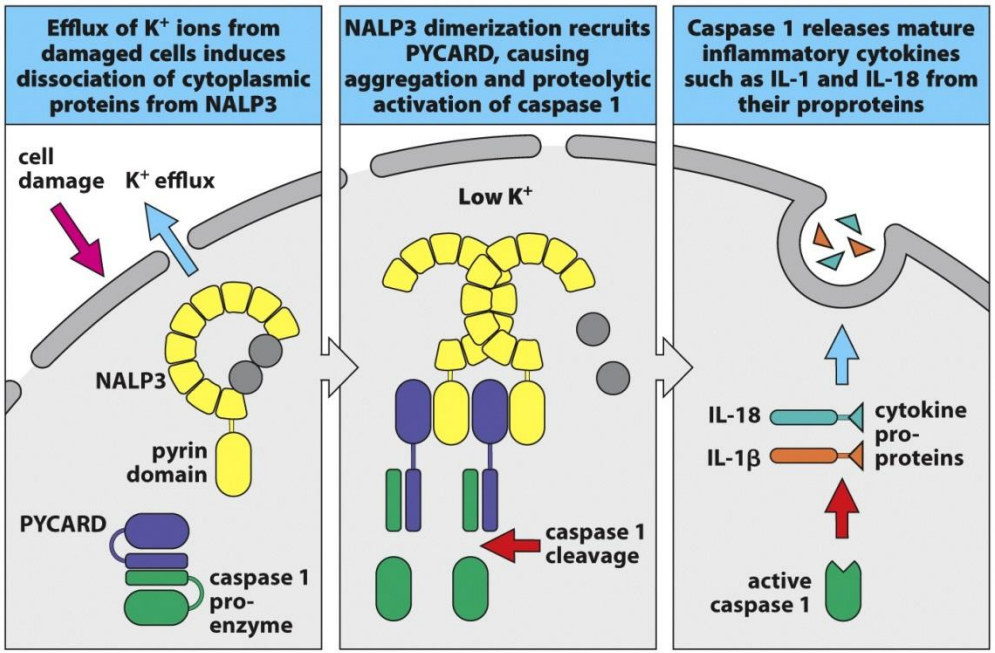
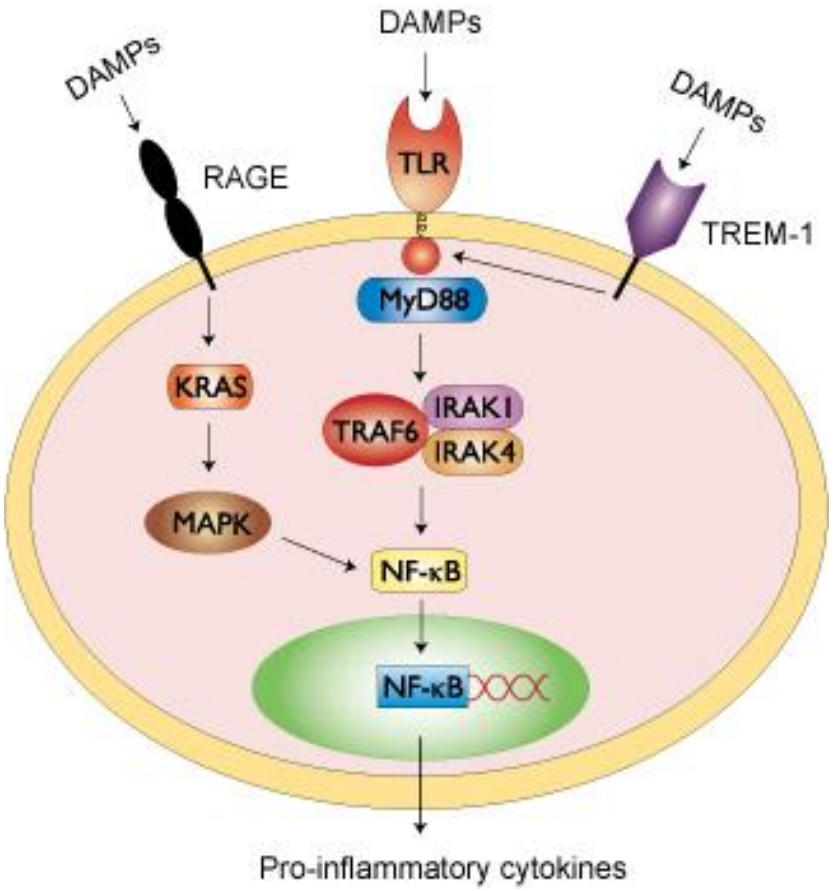


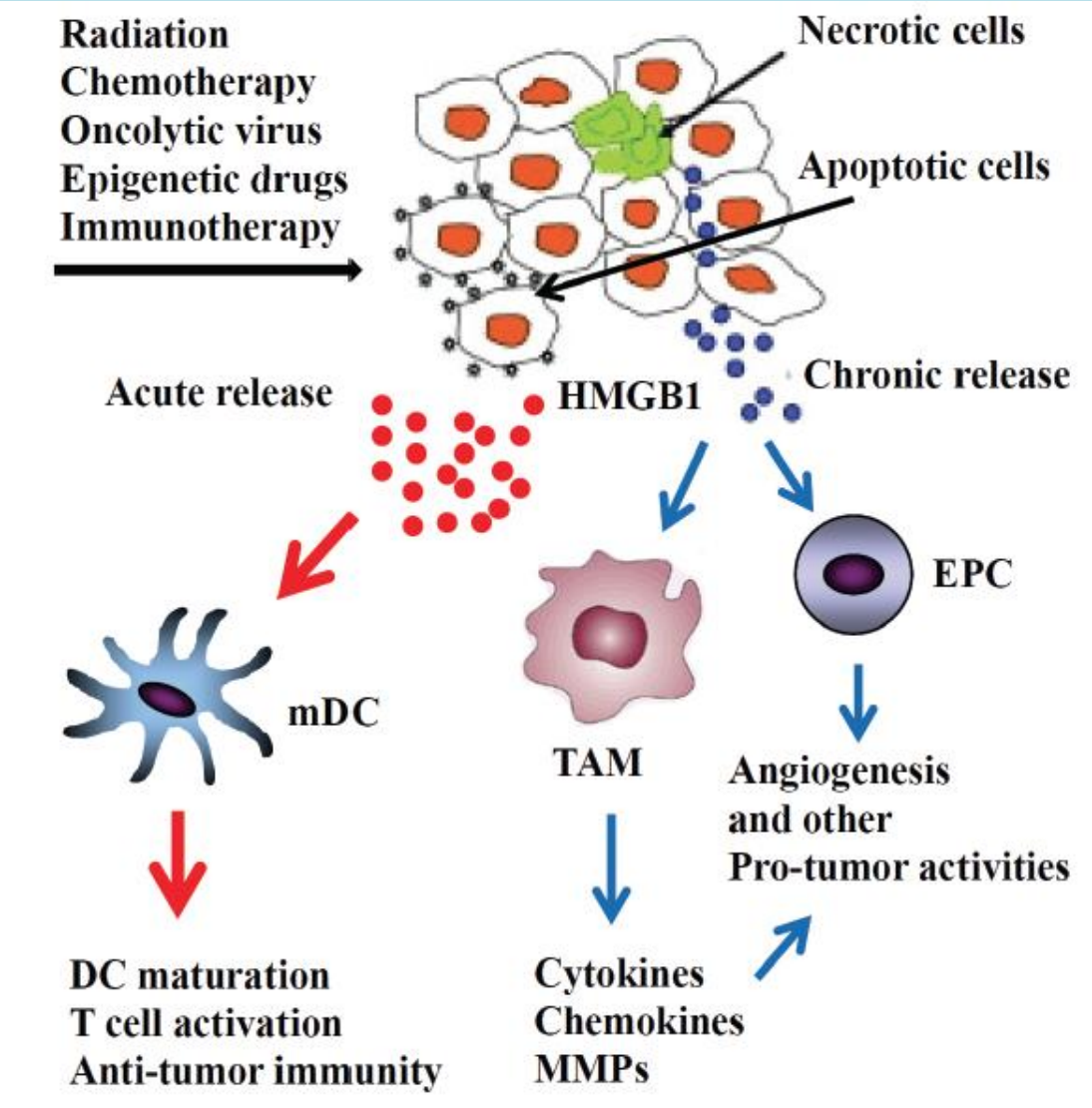
Figure 3.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Inflammasome



HSP (Heat Shock Proteins)
HMGB1 (high-mobility group box 1)
S100A8
S100A9
ATP
Sodium urate crystals

DAMPs in the response to chemo-radiotherapy treatment of tumors. The example of HMGB1



From: Guo SZ et al, Am J Cancer Res 2013; 3: 1-20

Acute release of HMGB1

Cancer therapies induce apoptosis of cancer cells, with acute release of DAMPs, e.g. HMGB1, promoting maturation of DCs through interaction with TLRs, presentation of tumor antigens, activaion of anti-tumor T cell immunity

Chronic release of HMGB1

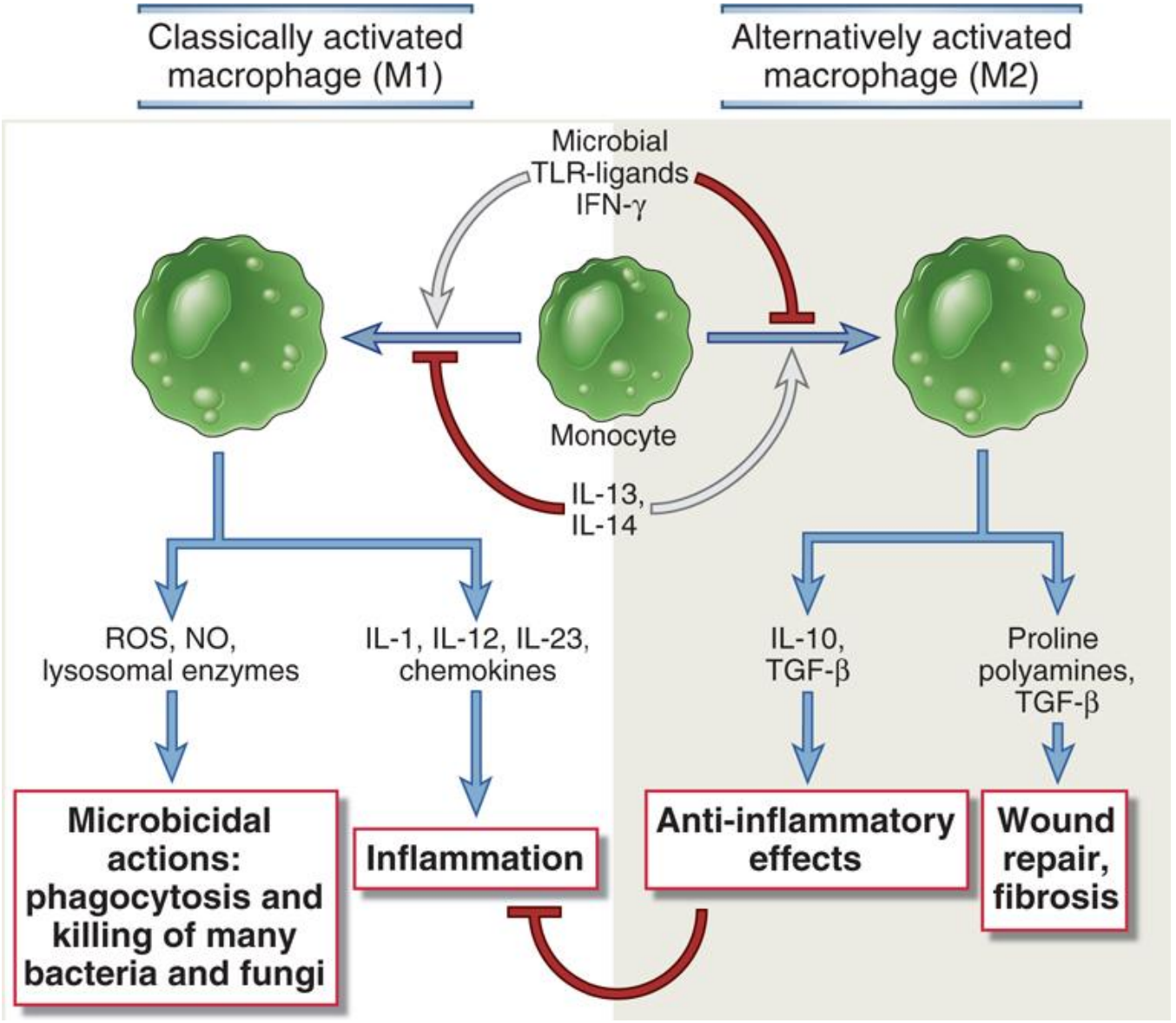
In contrast, persistent hypoxia in growing tumors leads to necrosis, causing chronic release of HMGB1, which promotes angiogenesis and tumor growth through the recruitment oftumor associated macrophages (TAM) and endothelial precursor cells (EPC).

Role of phagocytes in innate immunity

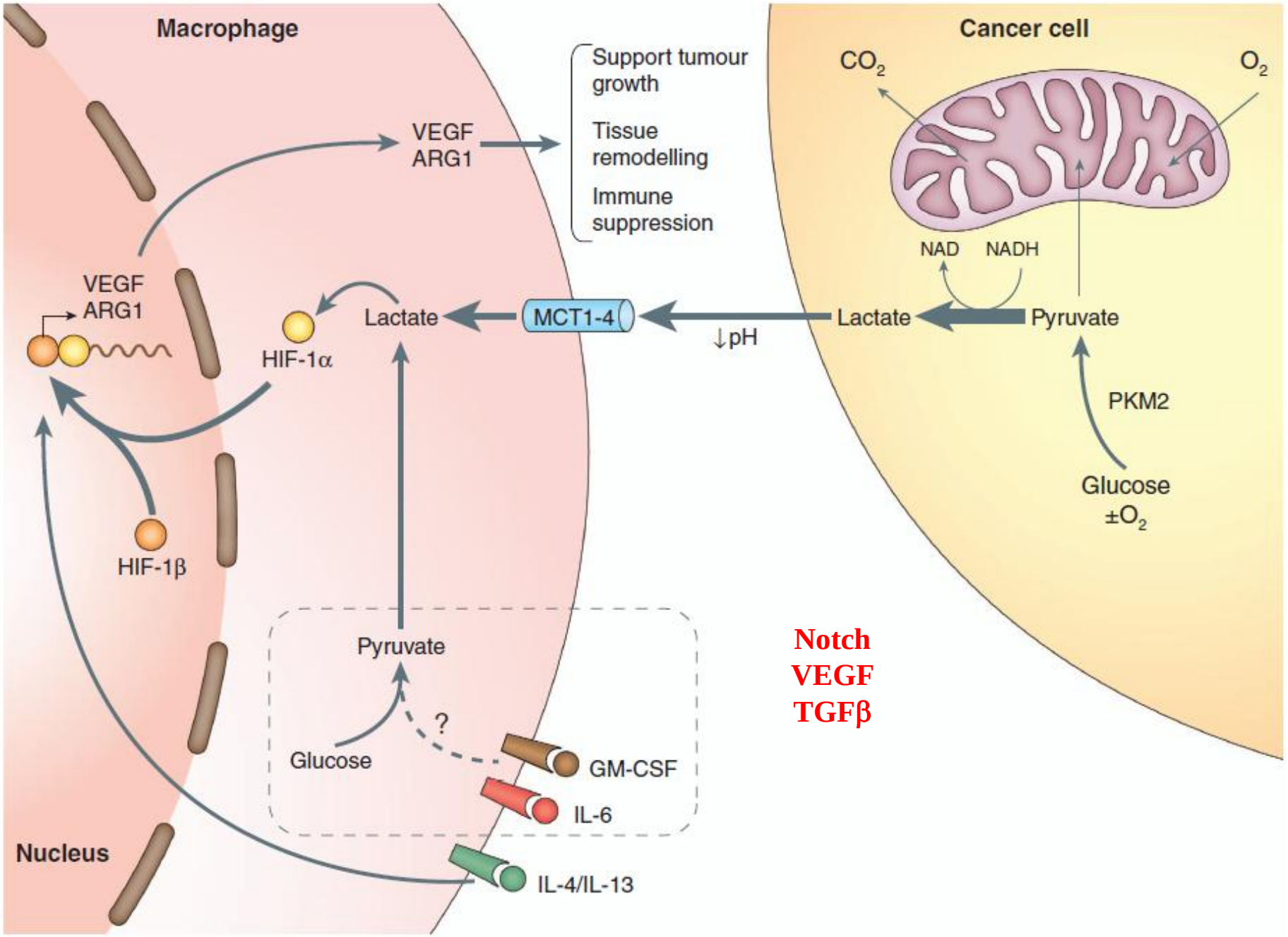
Order of events following infection

1. **Entry of pathogen**
2. **Recognition of pathogen**
3. **Phagocytosis and killing of pathogen**
4. **Inflammation induction**
5. **Chemoattraction of other cells to the infection site**
6. **Pathogen elimination and/or adaptive immunity activation**
7. **Tissue repair and remodeling**

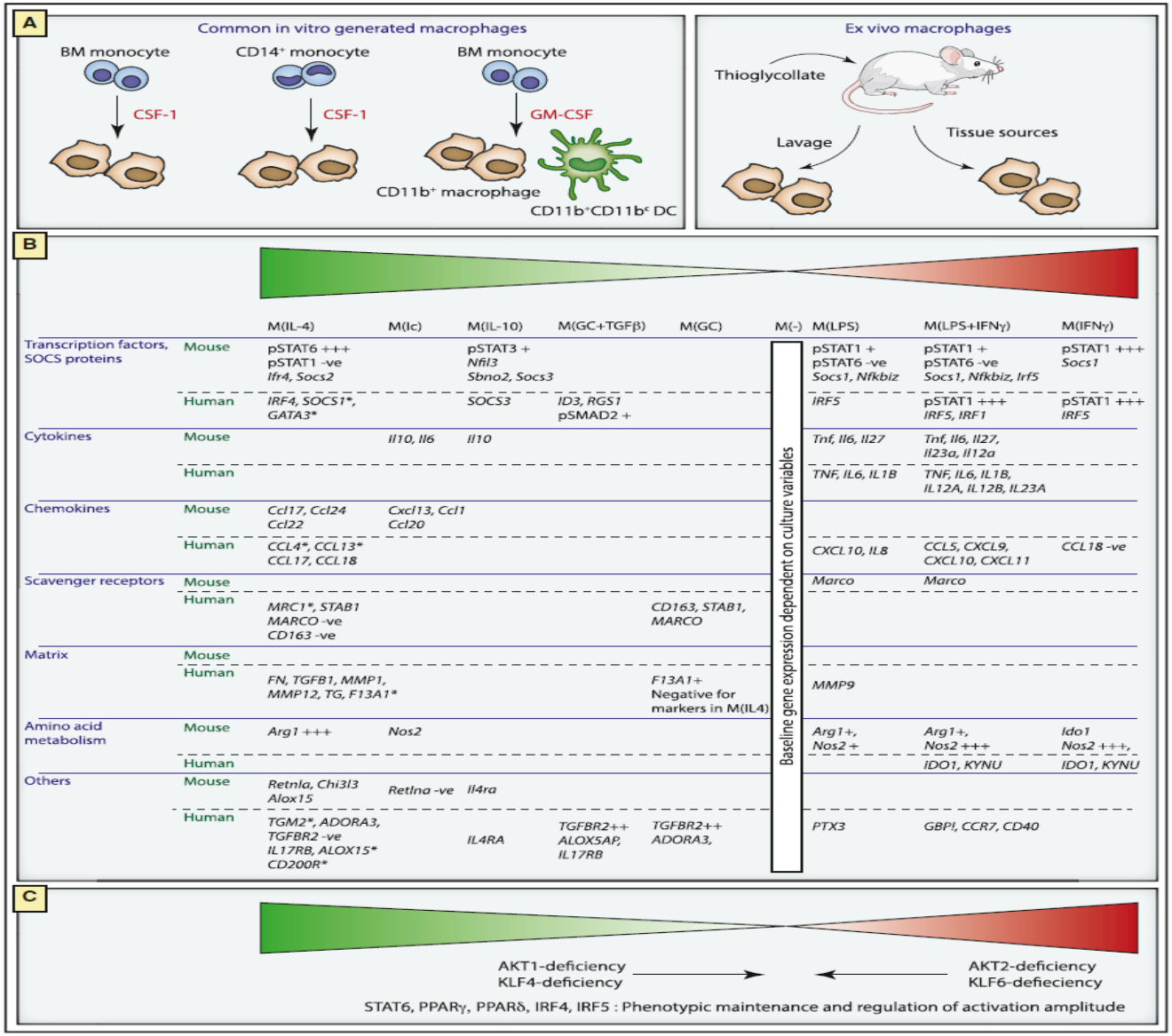
Classic and alternative activation of macrophages



Metabolic and molecular pathways for TAM programming

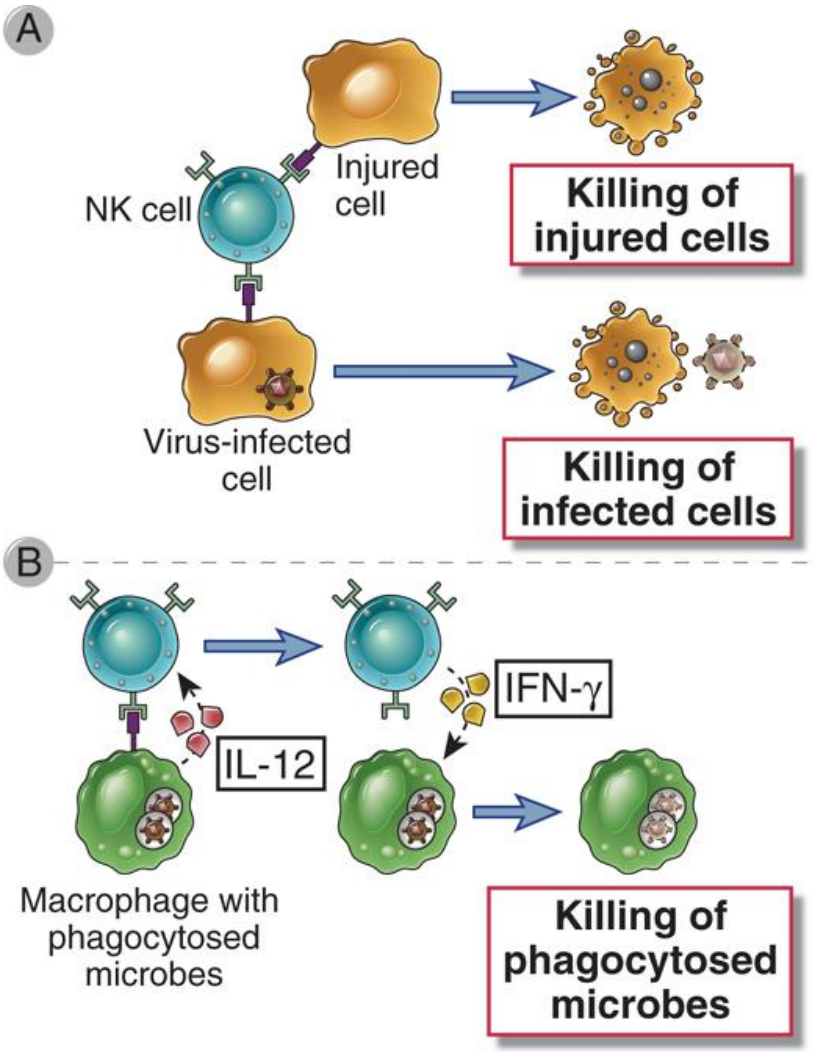


Macrophage plasticity



Murray J.P., et al., Immunity, 2014

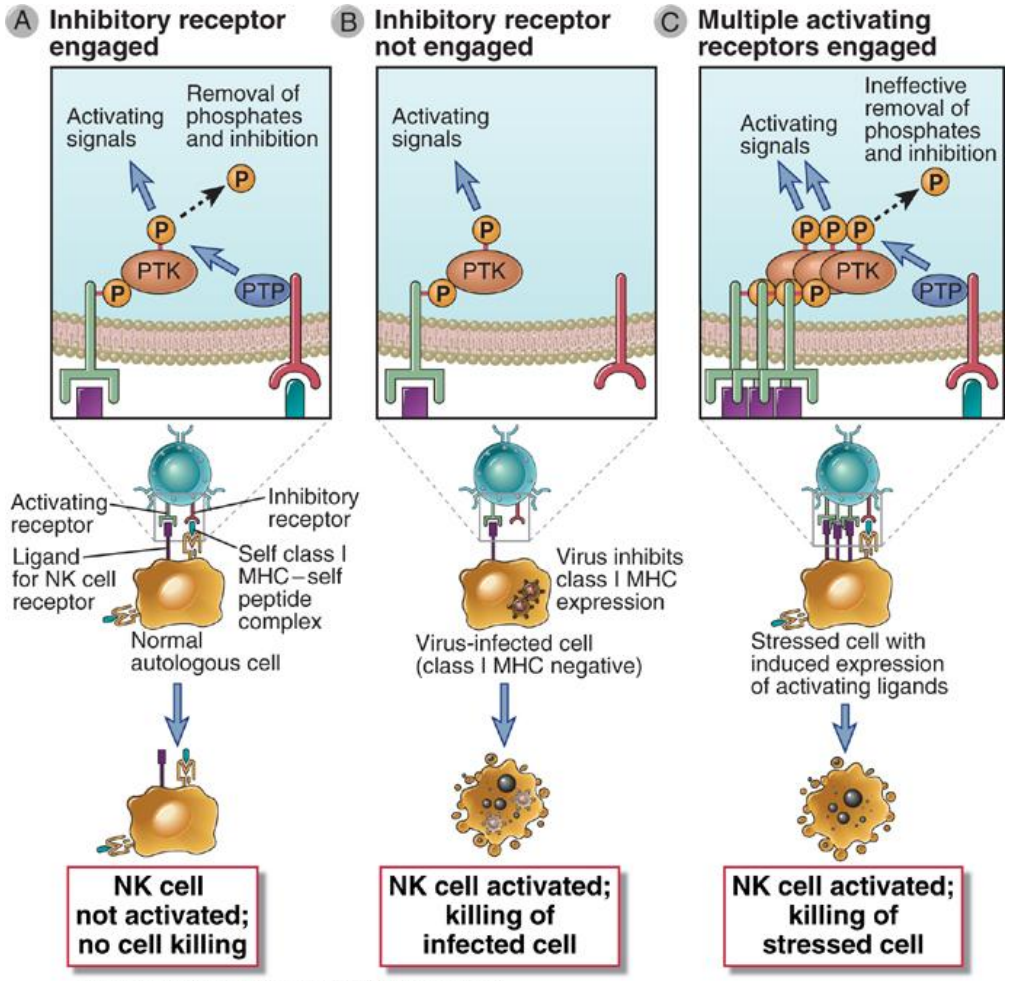
Role of Natural killer (NK) cells in innate immunity



Killing of cells infected by intracellular pathogens (eg. viruses) and tumor cells

Activation of macrophages (by IFN-γ)

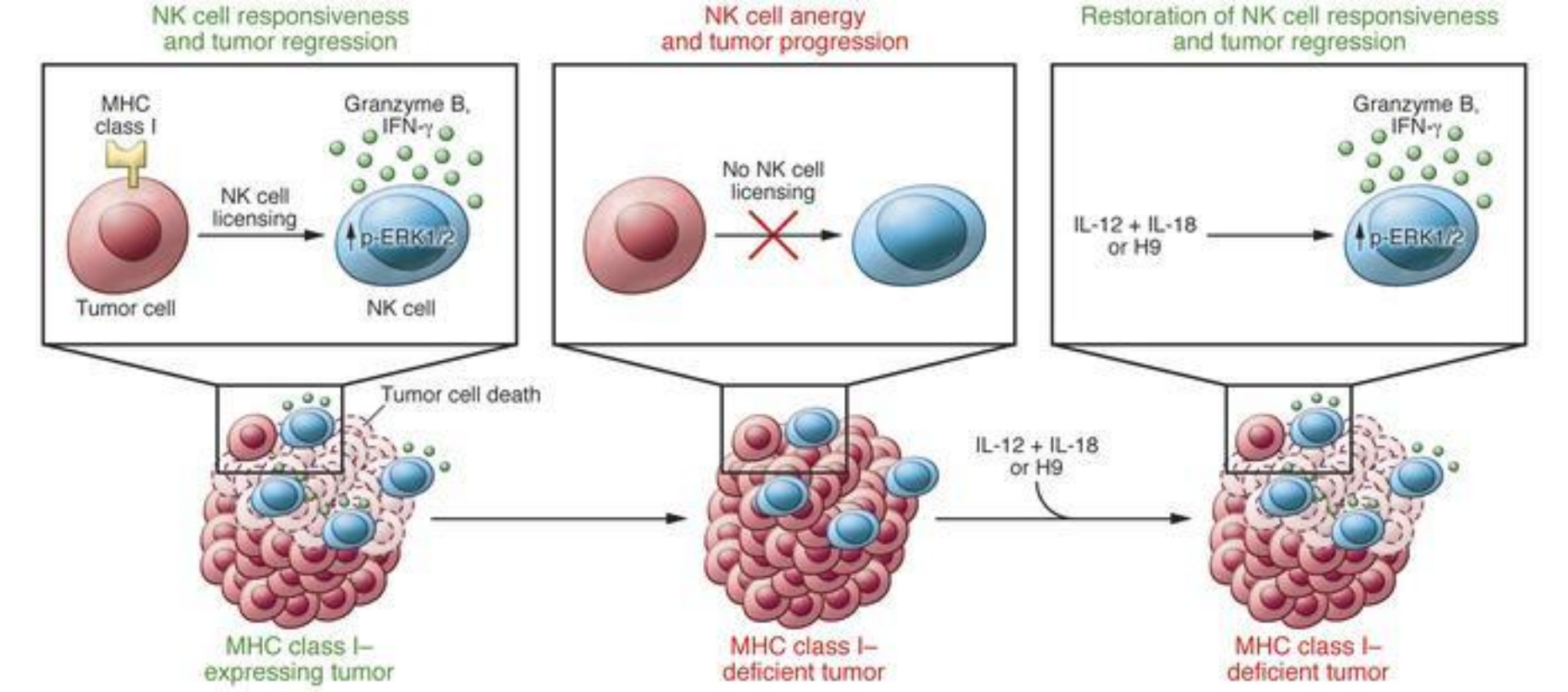
Mechanisms of NK cell activation



- **activating receptors recognize stress-induced molecules on cell surface (including virus infected and neoplastic)**

- inhibitory receptors recognize MHC class I molecules

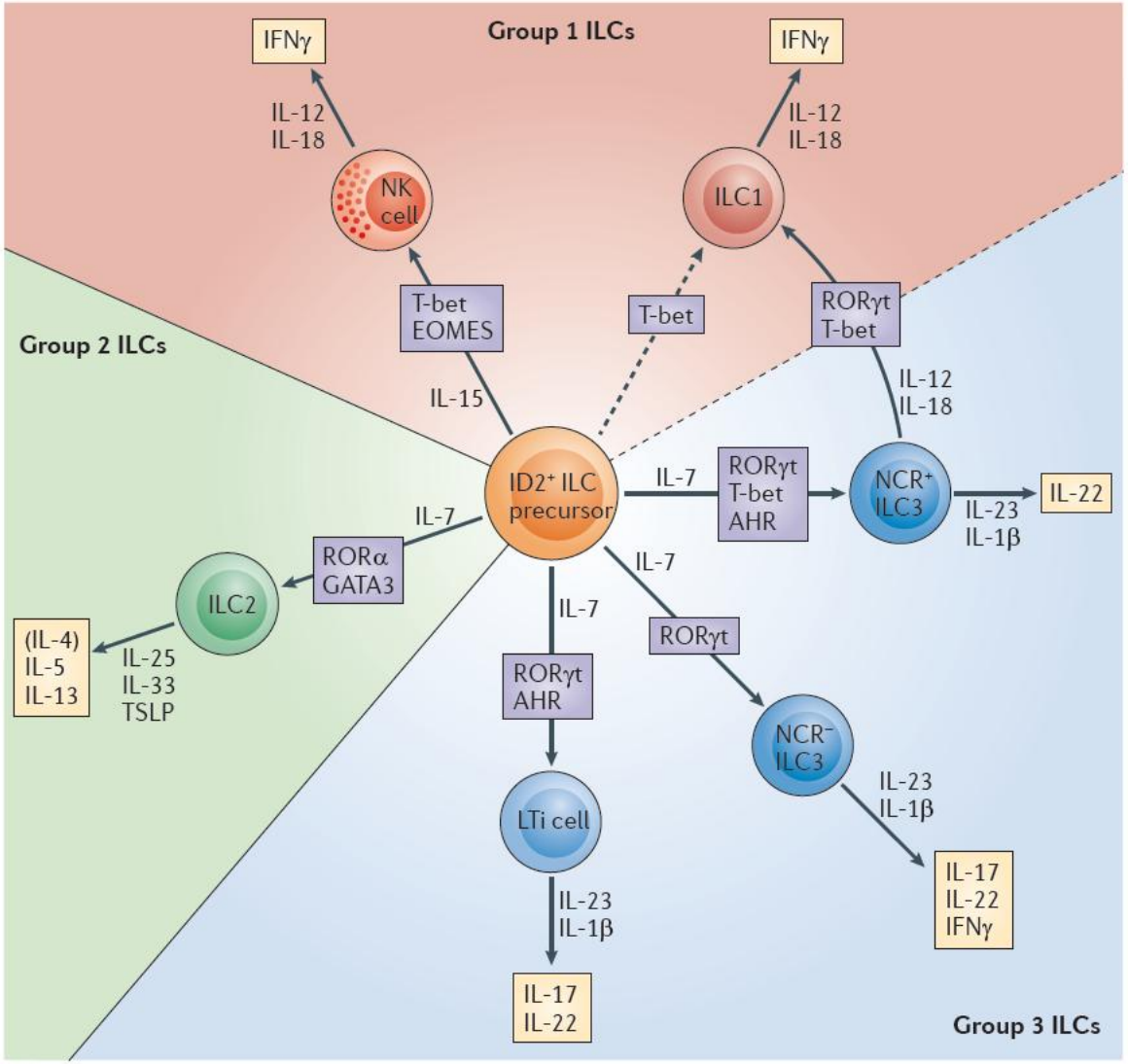
Restoring intratumoral NK cell functions with cytokines



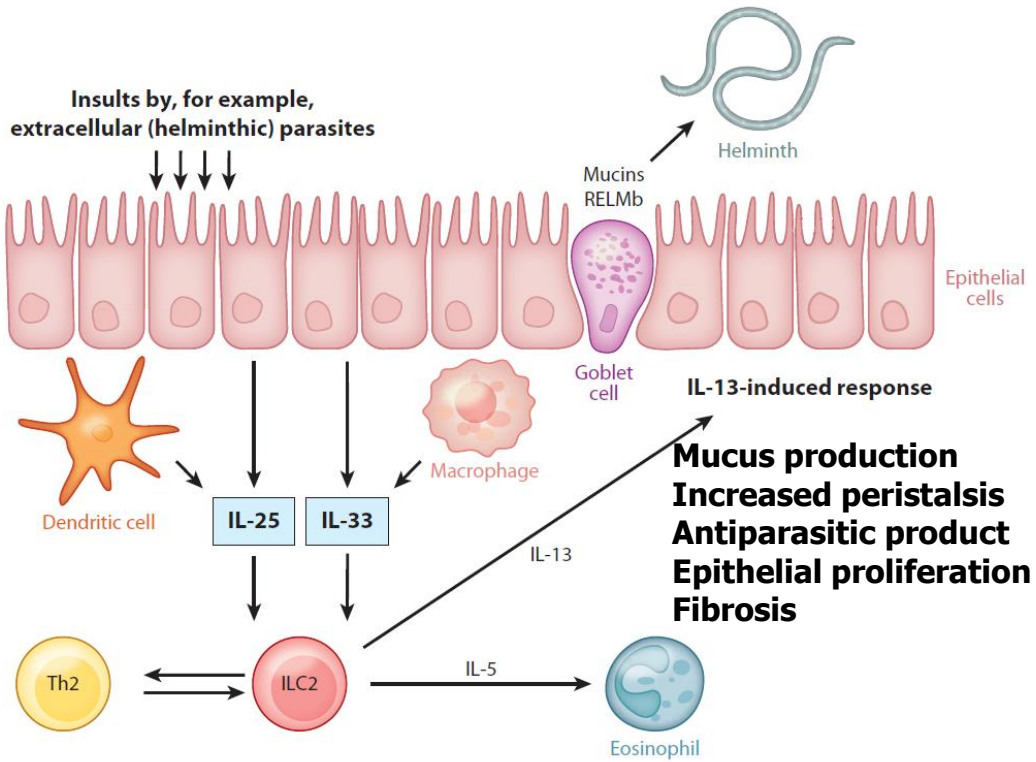
•Laurence Zitvogel and Guido Kroemer Cytokines reinstate NK cell–mediated cancer immunosurveillance J Clin Invest. 2014

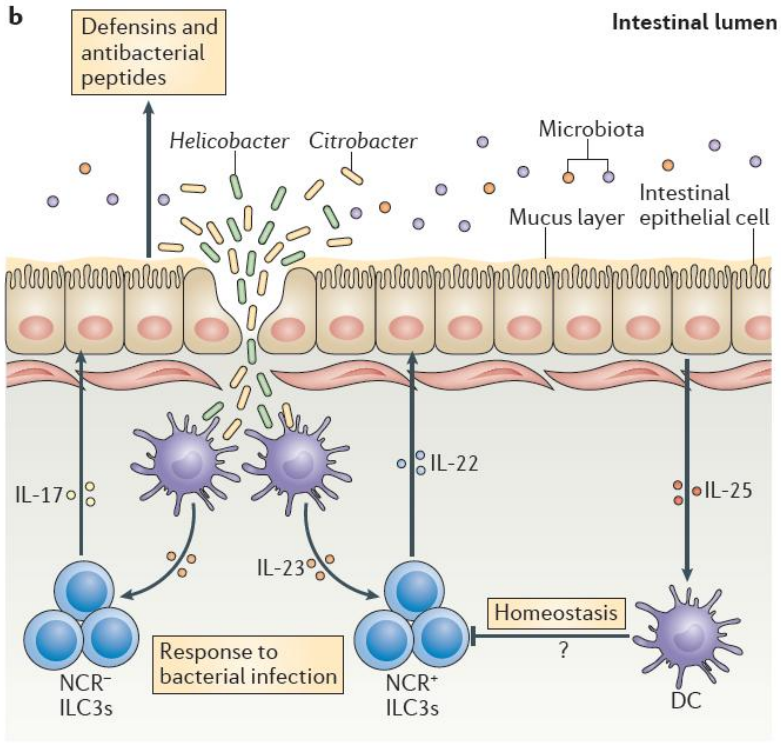
•Michele Ardolino et al., Cytokine therapy reverses NK cell anergy in MHC-deficient tumors. J Clin Invest 2014.

Innate Lymphoid Cells (ILC)

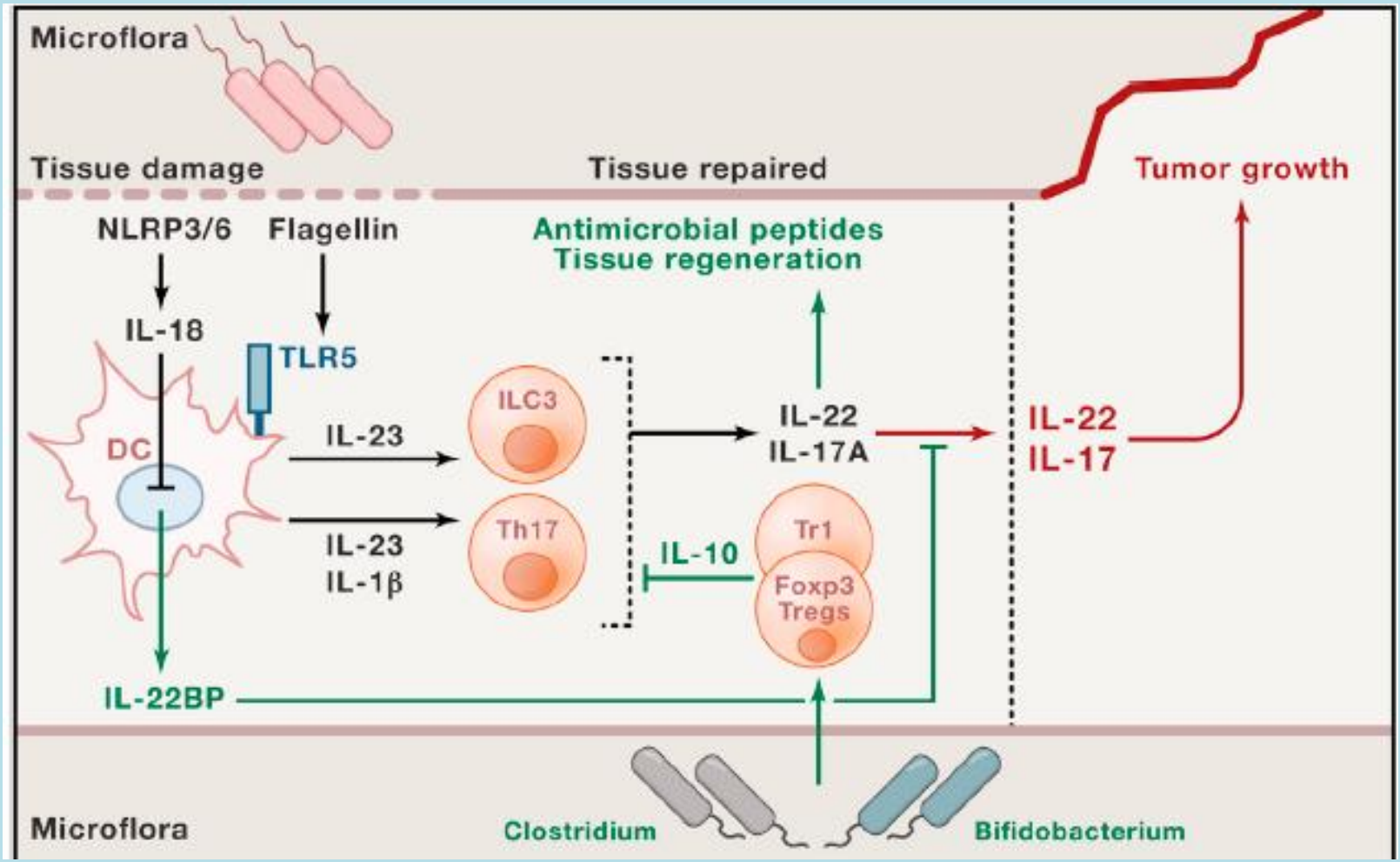


ILC2, ILC3 and regional immunity





Role of microbiota in inflammation, carcinogenesis and cancer therapy



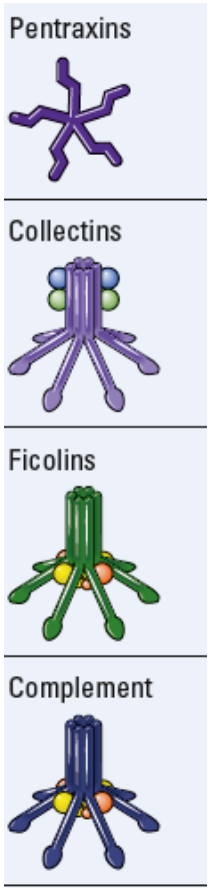
Gagliani N. et al., Cell 2014

Humoral mechanisms of innate immunity

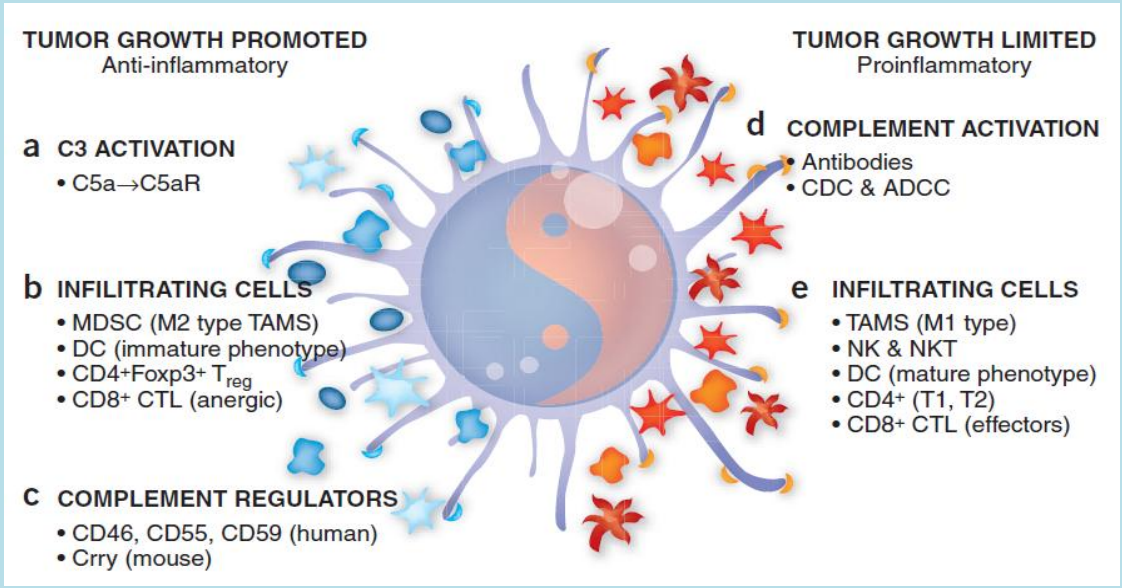
- complement proteins

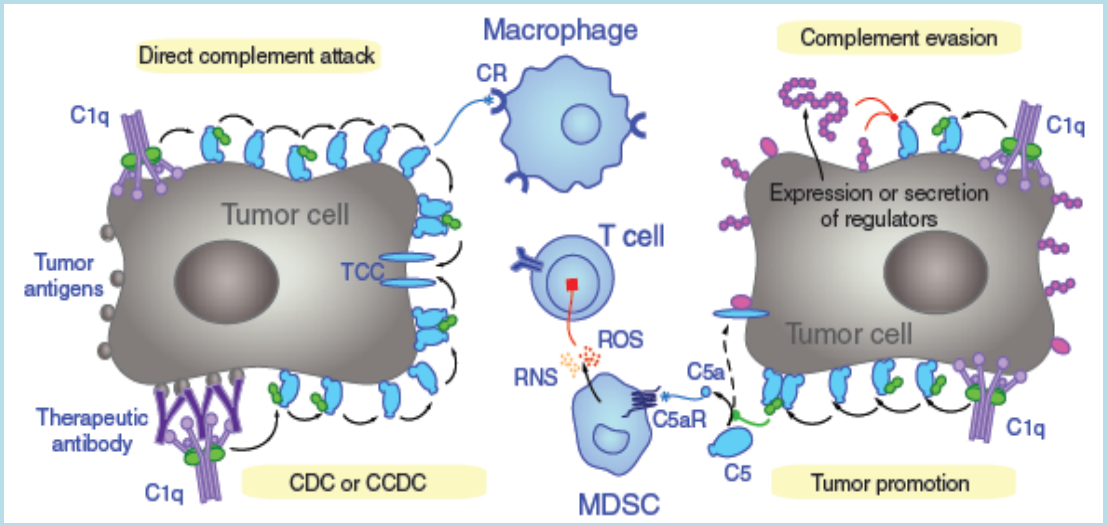
- cytokines

- other plasma proteins (collectins, ficolins, pentraxins, etc.)



The double-edged sword of complement action in cancer



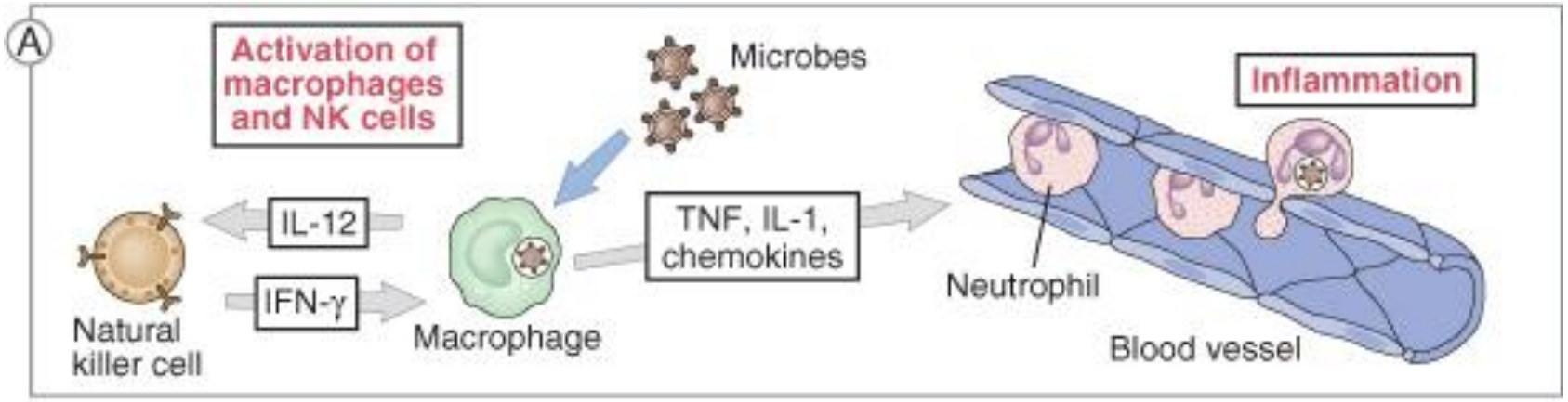


Complement is likely to have a dual role in cancer.

- It contributes to protection through direct activation of complement or as part of the complement-dependent cytotoxicity (CDC) of tumor-directed therapeutic antibodies.
- The generation of C5a in the tumor microenvironment can attract myeloid-derived suppressor cells (MDSC) and induce the generation of reactive oxygen and nitrogen species (ROS and RNS, respectively) through the C5a receptor (C5aR), which impairs the tumor-directed effect of T cells.

From:
Bruce E Loveland & Jonathan Cebon : Cancer exploiting complement: a clue or an exception? Nature Immunology 2008
Daniel Ricklin, George Hajishengallis, Kun Yang & John D Lambris Complement: a key system for immune surveillance and homeostasis surveillance and homeostasis Nature Immunology 2010

Cytokines in innate immunity



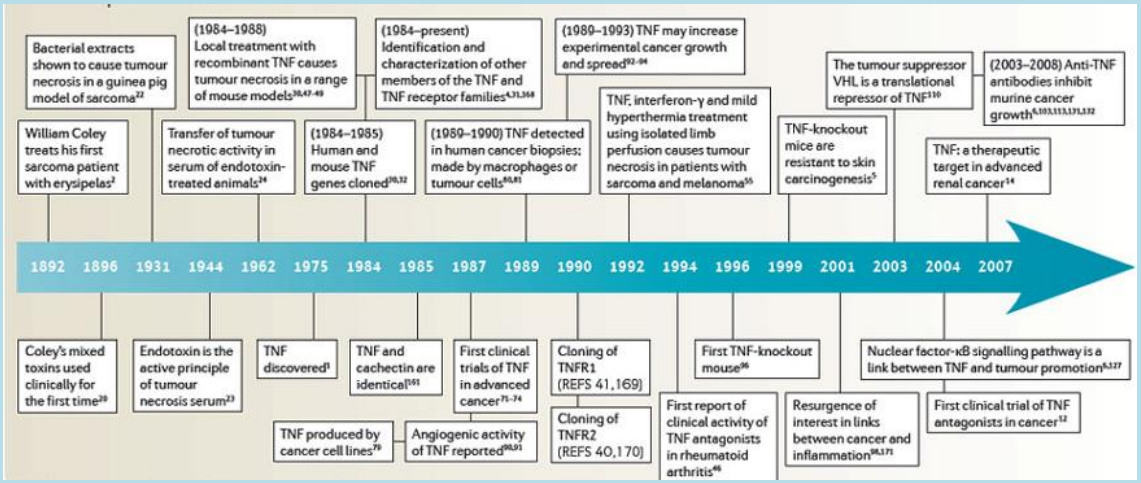
Macrophage and NK cell Activation (IL-12 and IFN-γ)

Inflammation induction (TNF, IL-1, chemokines...)

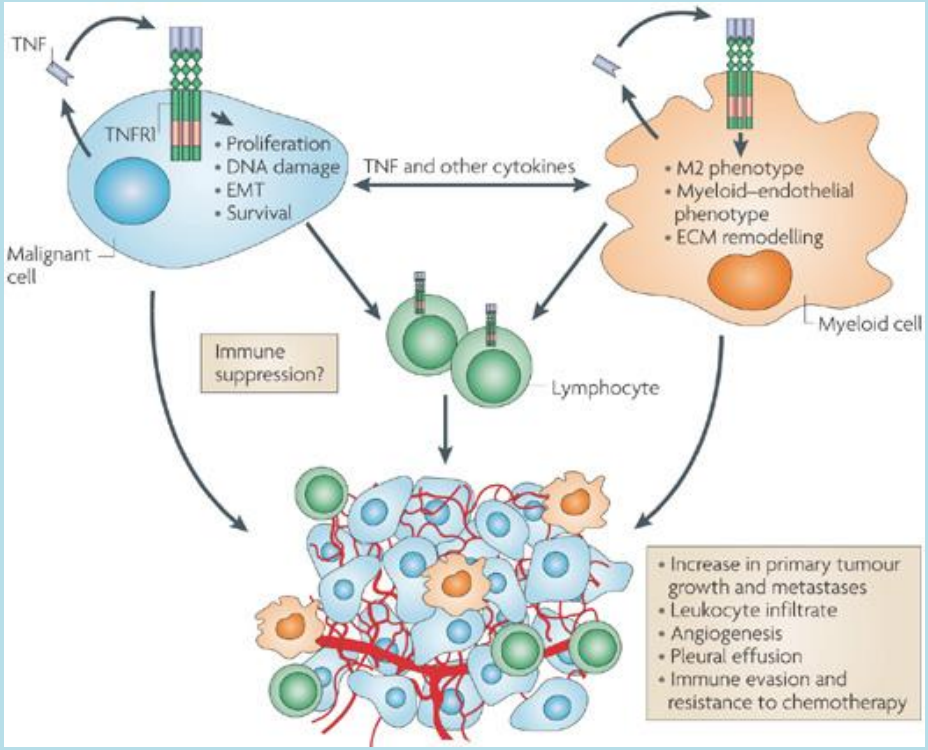
Antiviral effects (IFN type I, IFN-α and IFN-β)

Differentiation of T cell subpopulation (eg. IL-12, IL-4)

TNF in cancer: target or treatment?

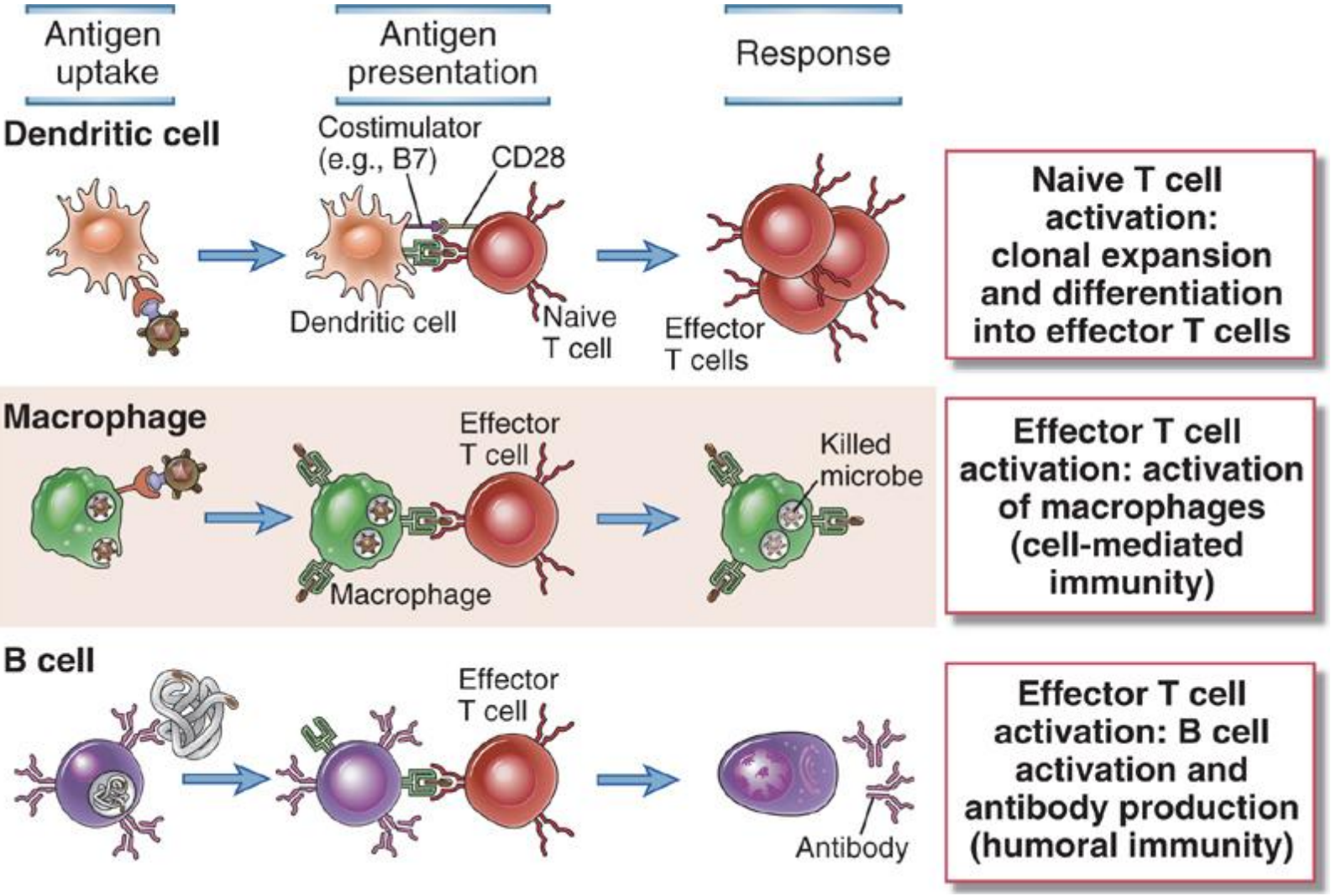


The history of TNF shows us how inflammation can have both positive and negative effects on cancer. Our challenge is to harness the helpful aspects of the inflammatory response in cancer while neutralizing its pro-tumour actions.

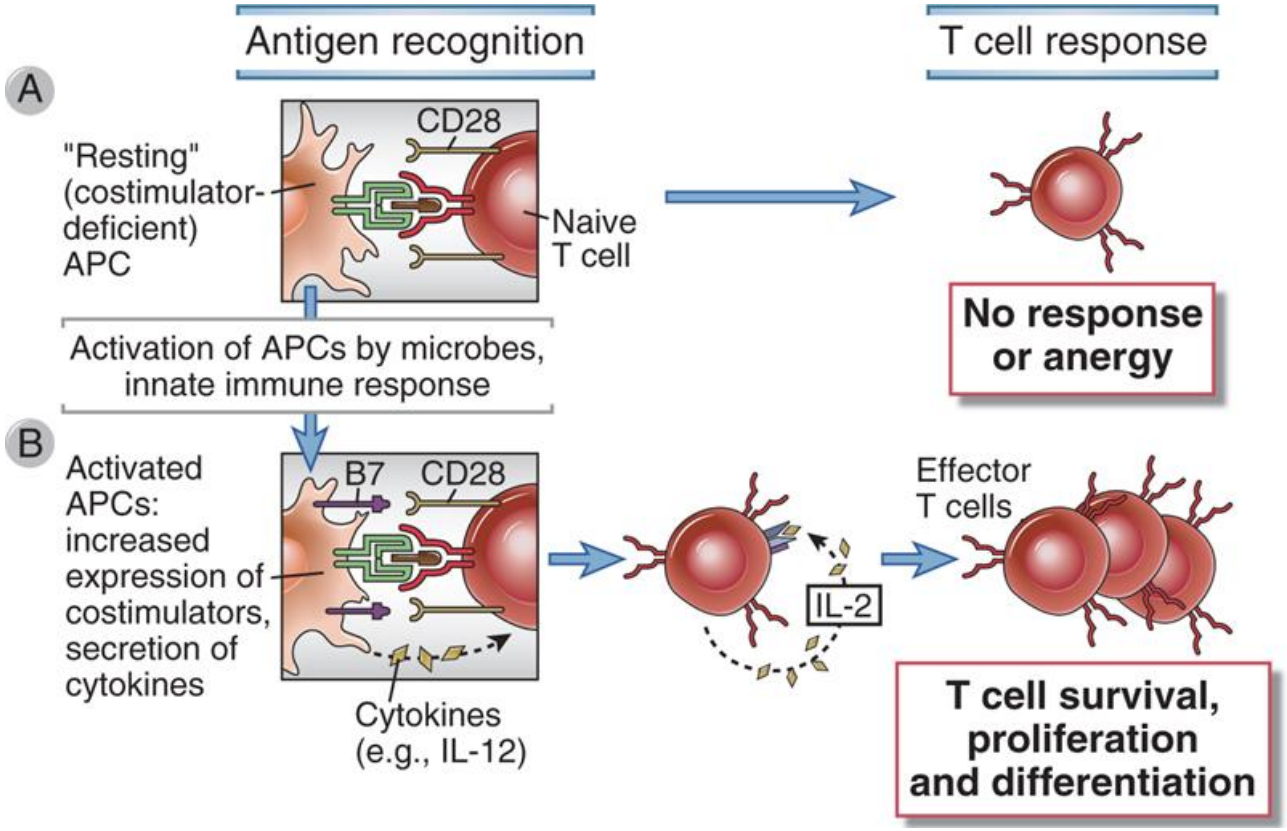


From: Frances Balkwil **Timeline: Tumour necrosis factor and cancer.** Nature Reviews Cancer, 2009

Functions of the different Antigen Presenting Cells (APCs)



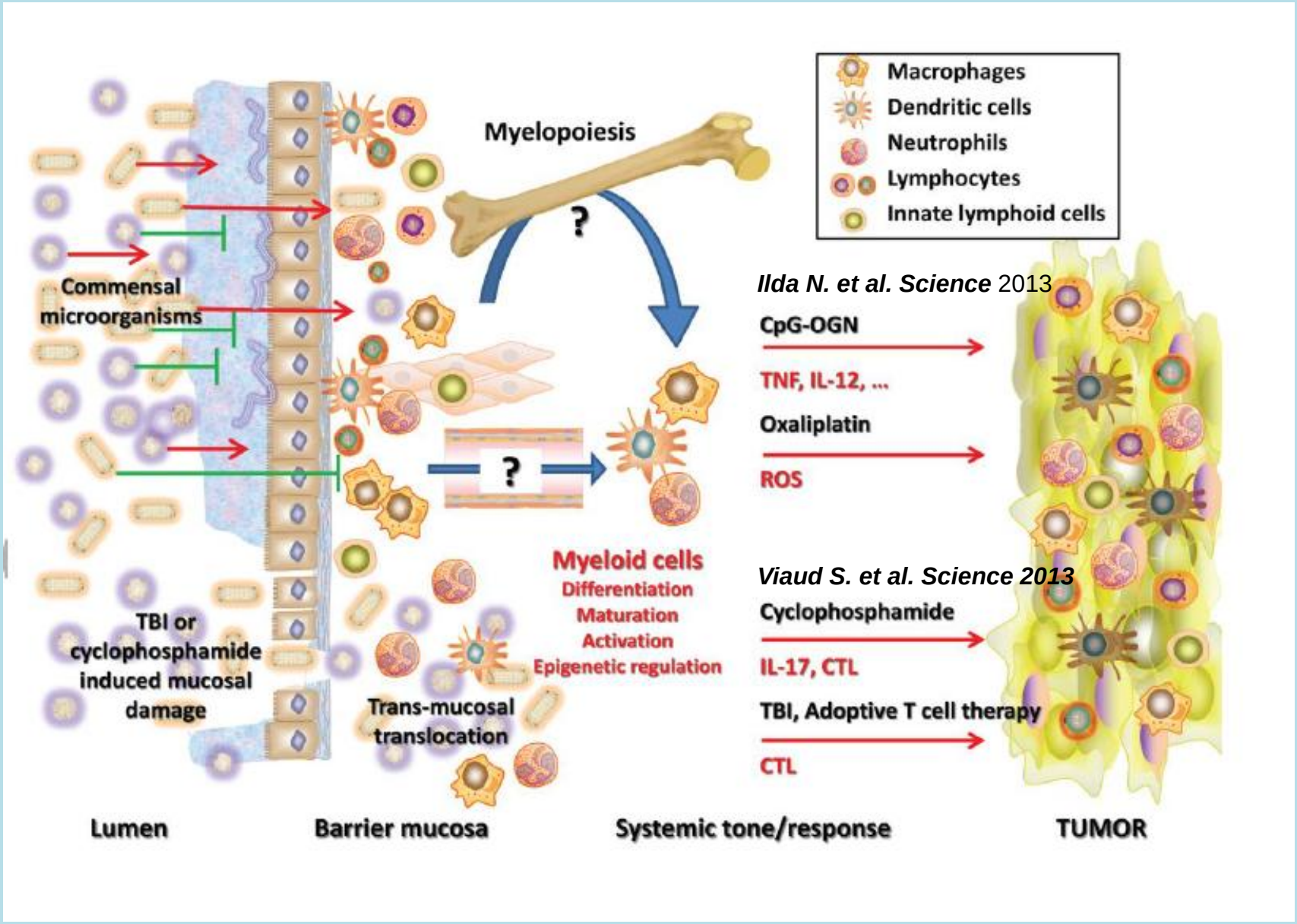
Role of innate immunity in stimulation of adaptive immune response



First signal: antigen recognition

Second and third signal: costimulation and cytokines

Microbiota control of response to cancer therapy



Dzutsev A . et al., Eur J. Immunol. 2014