



Society for Immunotherapy of Cancer

Innate Immunity: Cellular mechanisms and signaling

Monday, February 22, 2021 9:35-10:10 am ET

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Scientific Advisory Boards 2021

Alector

Atreca

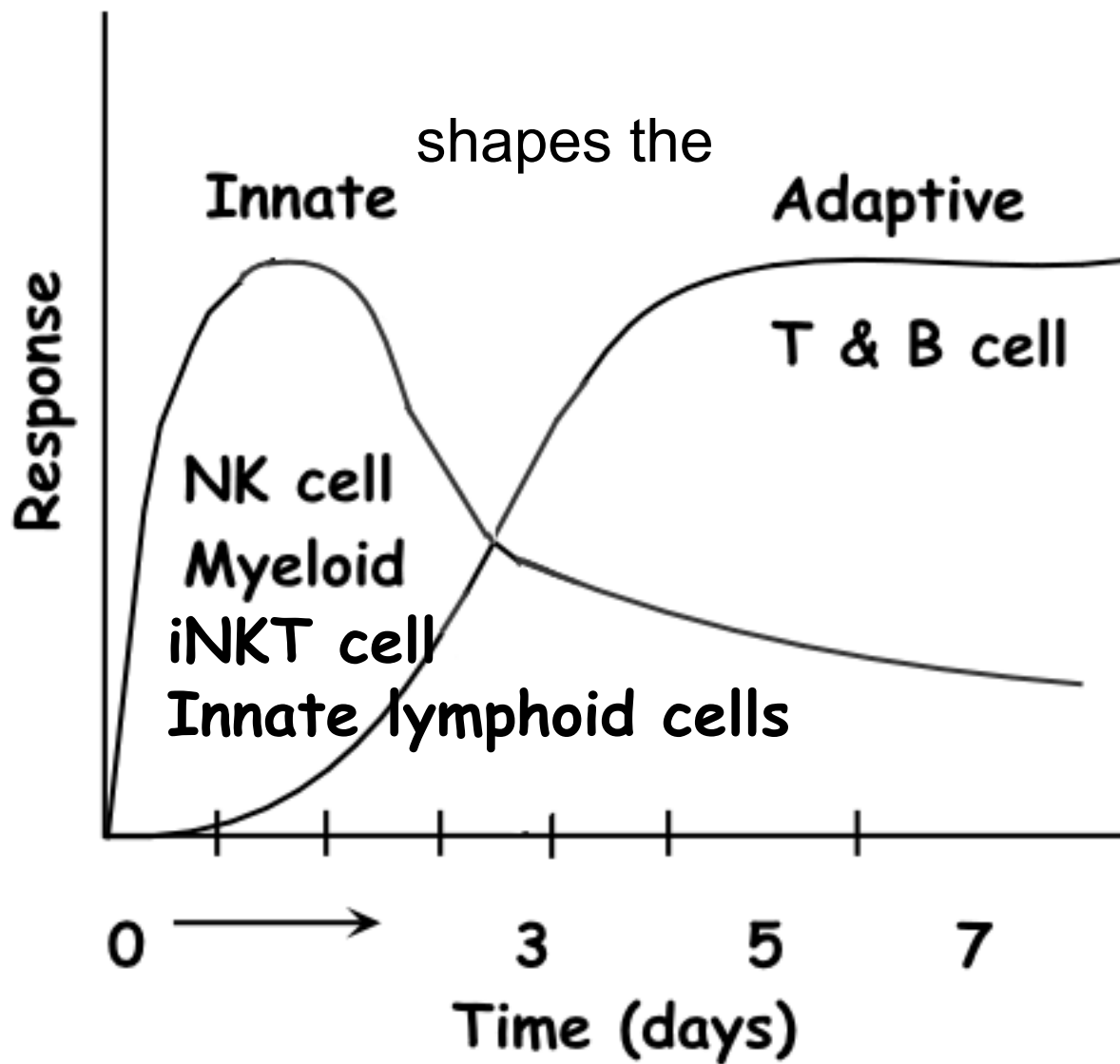
Dragonfly

DrenBio

Nkarta

Obsidian

SBI



What discriminates the innate and adaptive immune systems?

Innate immune cells use germline-encoded receptors

Adaptive immune cells somatically rearrange receptors (T cell receptors and Immunoglobulins)

Adaptive immune cells usually start from very low precursor frequencies and expand after encountering cognate antigens

Innate Immunity

- *Physical barriers and soluble factors in sera and tissues*
 - Some always present (protease inhibitors, complement)
 - Others induced by infection or inflammation (interferons, acute phase proteins, cytokines, & chemokines)
- *Cell intrinsic pathogen sensors*
 - In all cell types – Toll-like receptors, NODs, STING, RIG-I
- *Cells of the Innate Immune System*
 - Myeloid cells – phagocytes and antigen-presenting cells
 - Natural Killer cells - kill virus-infected cells and tumors

Soluble factors

- Blood clotting system (physical barrier)
Bradykinin (vasodilation – allow cell entry)
- Protease inhibitors
 - α 2-macroglobulin
- Defensins
- Acute phase proteins
 - C-reactive protein, mannose-binding lectin
- Complement
- Cytokines
- Chemokines
- Interferons

Defensins produced
by epithelial cells in gut, lung, reproductive tract
by neutrophils recruited to site of infection

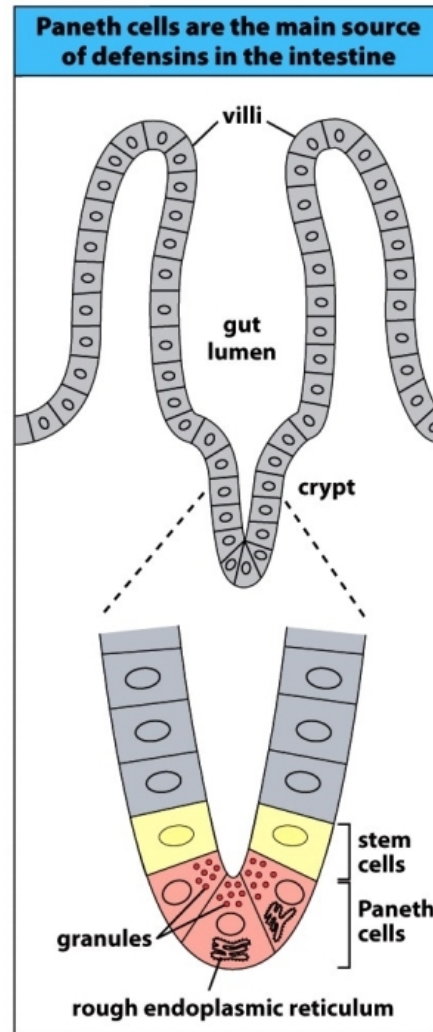


Figure 2.17 The Immune System, 3ed. (© Garland Science 2009)

Humans Have Several Defensins

Defensin		Site of synthesis	Tissues defended	Regulation of synthesis
Class	Name			
α	HNP1	Neutrophils > monocytes, macrophages, NK cells, B cells, and some T cells	Intestinal epithelium, placenta, and cervical mucus plug	Constitutive
α	HNP2			
α	HNP3			
α	HNP4	Neutrophils	Not determined	Constitutive
α	HD5	Paneth cells > vaginal epithelial cells	Salivary glands, gastrointestinal tract, eyes, female genital tract, and breast milk	Constitutive and induced by sexually transmitted infection
α	HD6	Paneth cells	Salivary glands, gastrointestinal tract, eyes, and breast milk	
β	HBD1	Epithelial cells > monocytes, macrophages, dendritic cells, and keratinocytes	Gastrointestinal tract, respiratory tract, urogenital tract, skin, eyes, salivary glands, kidneys, and blood plasma	Constitutive and induced by infection
β	HBD2			
β	HBD3			
β	HBD4	Epithelial cells	Stomach (gastric antrum) and testes	

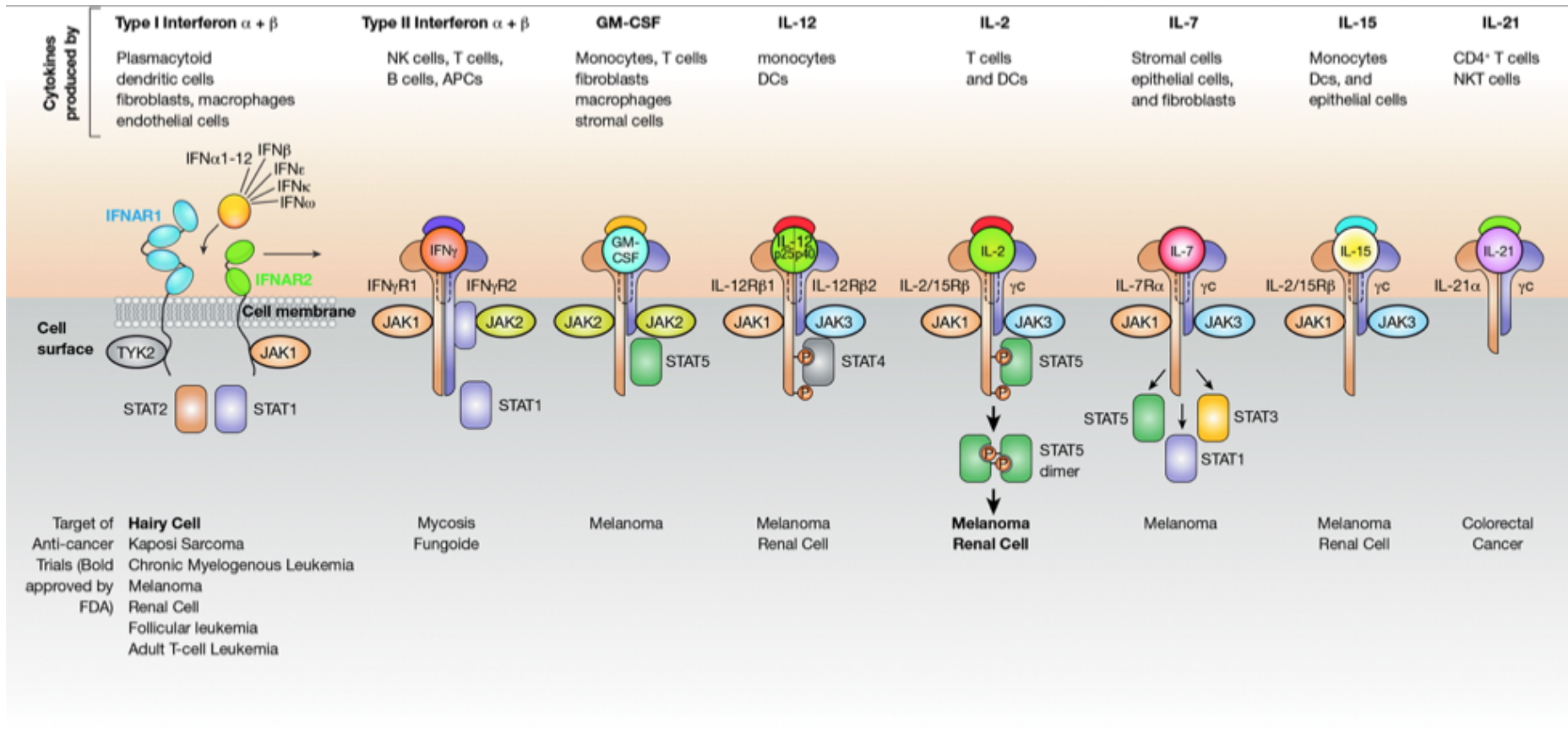
Figure 2.18 The Immune System, 3ed. (© Garland Science 2009)

Granulysin – unique to humans – expressed in NK and T cells

Cytokines – hormones of the immune system

- Soluble proteins produced by immune cells and epithelial cells that can activate or suppress the immune system
- **“Pro-inflammatory cytokines”** – induced during infection or inflammation to activate immune system – e.g. Tumor Necrosis Factor- α (TNF), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-17 (IL-17), etc.
- **“Regulatory cytokines”** – suppress immune responses – e.g. Interleukin-10 or skew the adaptive immune system, e.g. IL-12 drives Th1 responses, IL-4 drives Th2 responses, TGF- β drives Treg cells, etc.
- **Growth factors** – e.g. IL-2, IL-7, IL-15 – for proliferation and survival

Cytokines and Cancer Immunotherapy

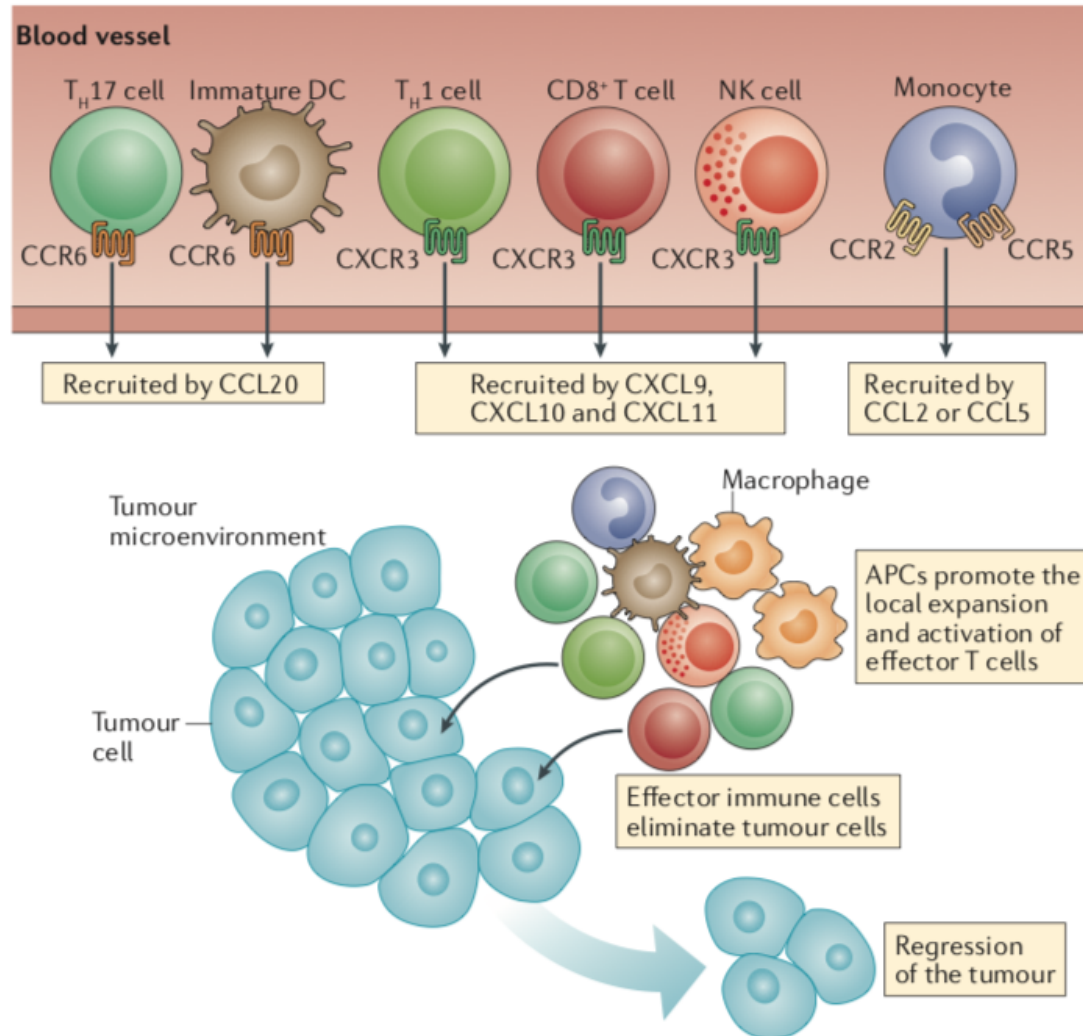


Issues – systemic toxicity IL-2, IL-12, IL-15, IFN
IL-2 expands Tregs

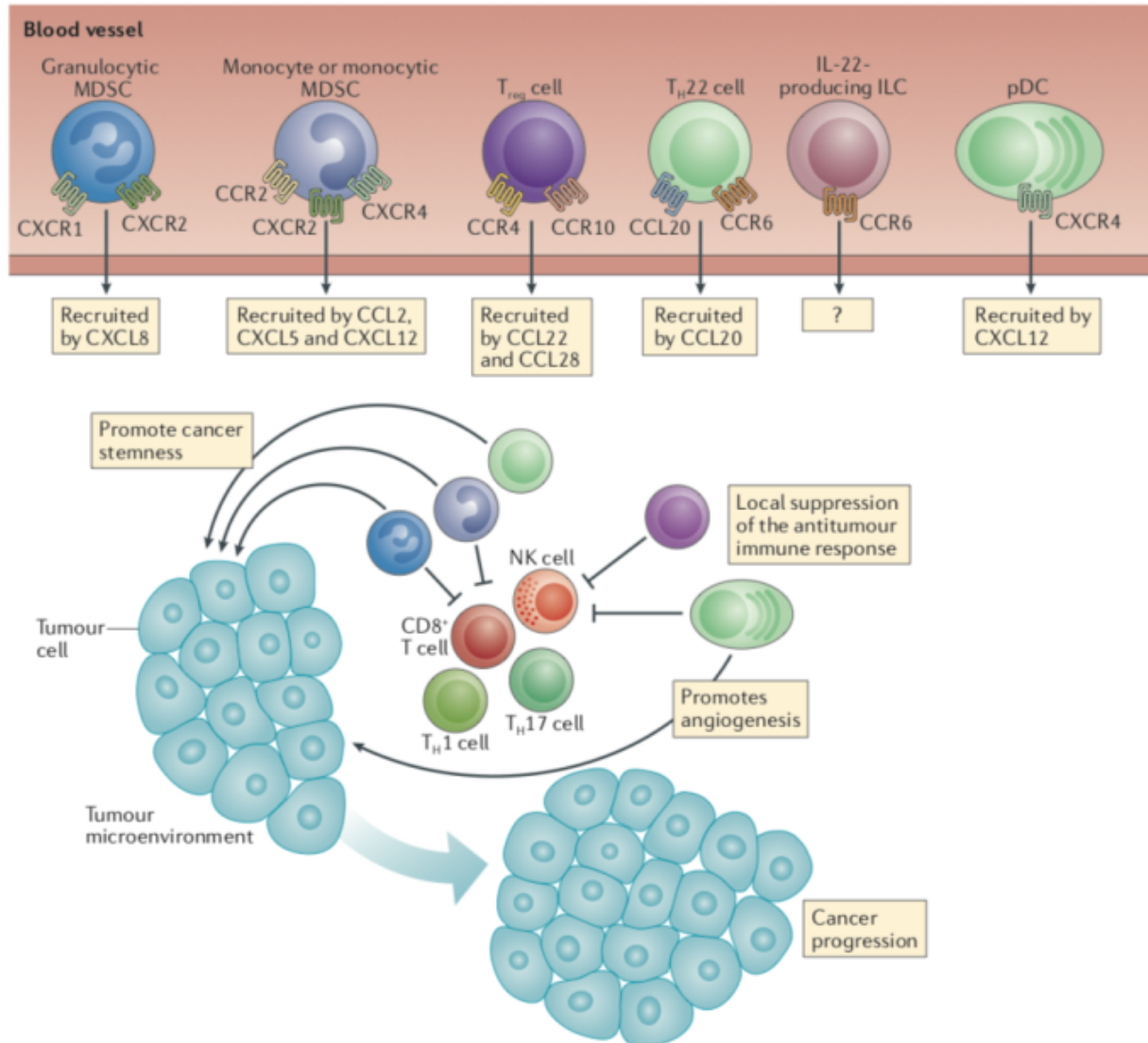
Chemokines – traffic directors of the immune system

- Family of more than 50 soluble factors that induce the migration of cells, including CXC, CC, CX3C and XC chemokines
- Leukocytes expressing chemokine receptors (G-coupled protein receptors) migrate due to density gradients of chemokines
- Some chemokines are produced constitutively in tissues (e.g. lymph nodes) to organize cells within the tissue
- Chemokines are secreted by immune cells, epithelial cells, or endothelial cells in response to infection or inflammation to recruit granulocytes, myeloid cells, and lymphocytes to the site

How do effector cells get out of the blood or lymphatic vessels and into infected tissues or tumors?



Chemokines in tumor microenvironment can also promote cancer



Severe systemic inflammation


>>cytokines →






Letter | Published: 28 May 2018

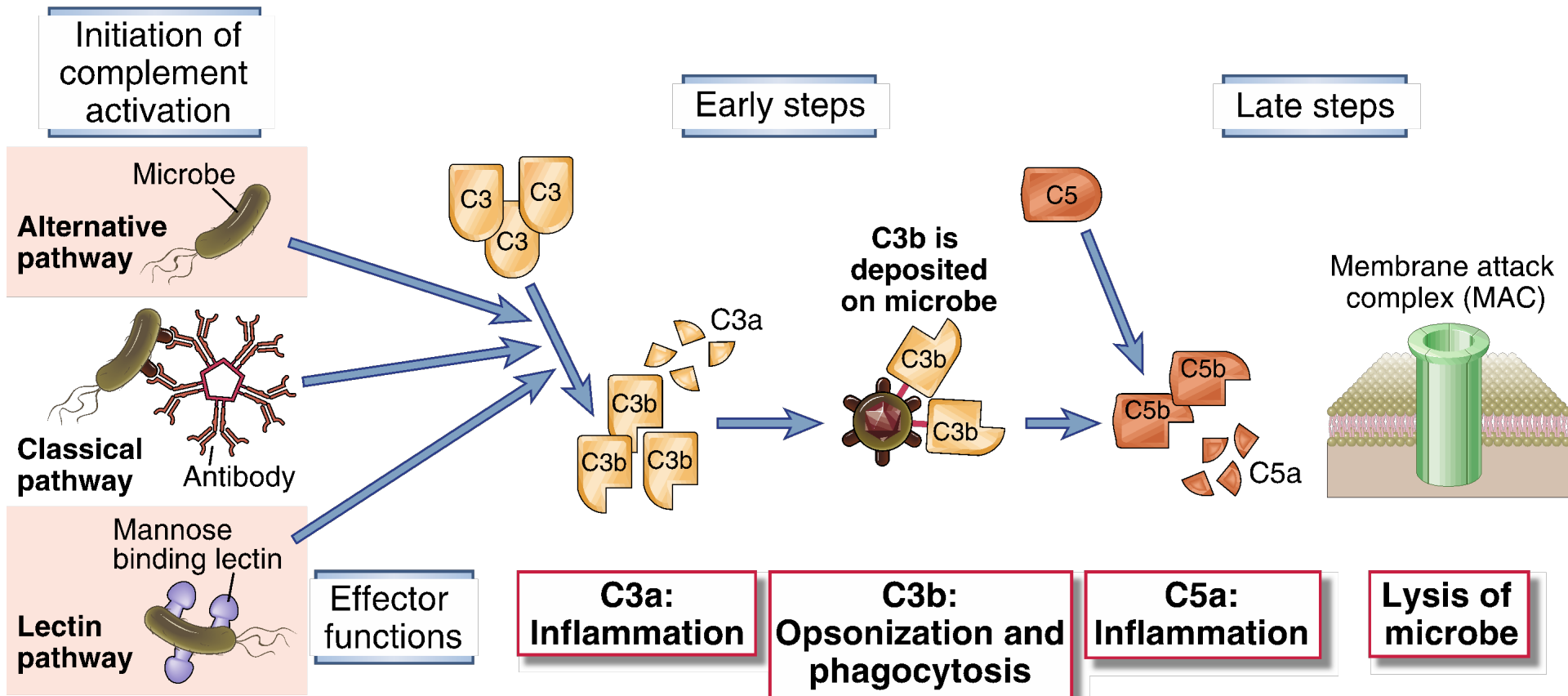
CAR T cell–induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade

Theodoros Giavridis, Sjoukje J. C. van der Stegen, Justin Eyquem, Mohamad Hamieh, Alessandra Piersigilli & Michel Sadelain 

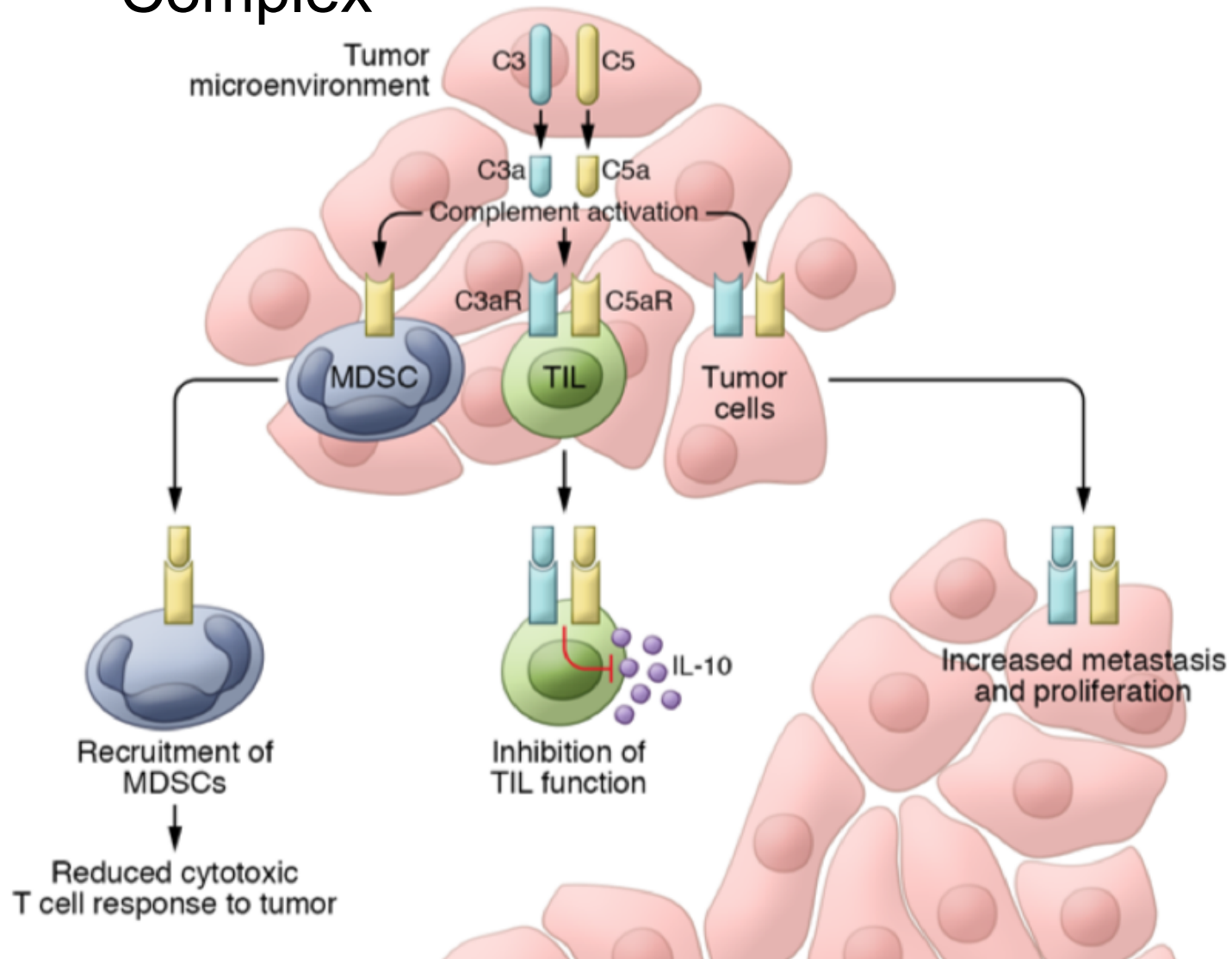
Nature Medicine **24**, 731–738 (2018) | [Download Citation](#) 

Complement

- Circulating inactive serine protease enzymes
- Cascade of sequential activation



Role of Complement in Cancer – Complex



Interferons

- Soluble proteins with anti-viral activity

Type I interferons

α14 genes

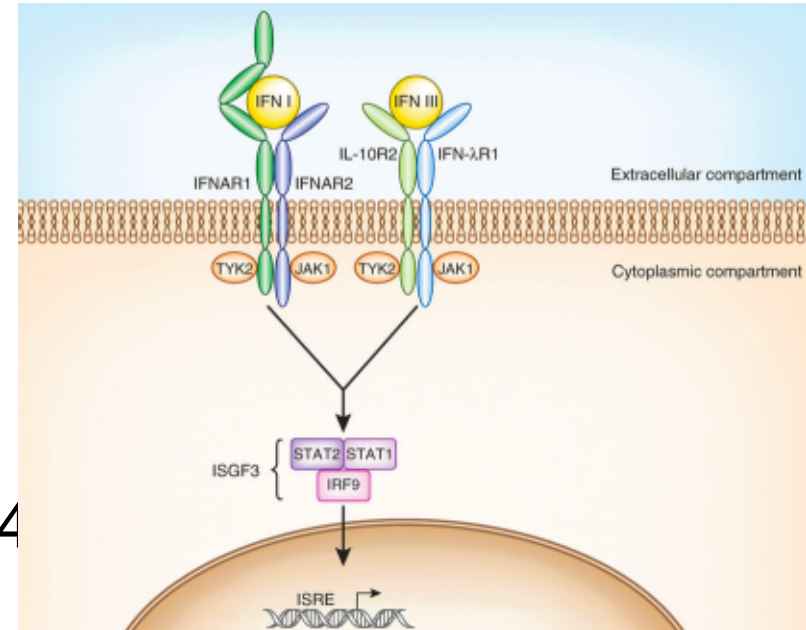
β1 gene

Type II interferon

γ1 gene

Type III interferons

λ(IL-28A, IL-28B, IL-29, $\lambda 4$)



- α and β interferons made by most virus-infected cells, high levels are made by specialized dendritic cells (plasmacytoid dendritic cells)
- γ interferon made by activated Natural Killer cells & T cells
- λ interferons made by myeloid and epithelial cells

Pattern recognition receptors - cell intrinsic sensors

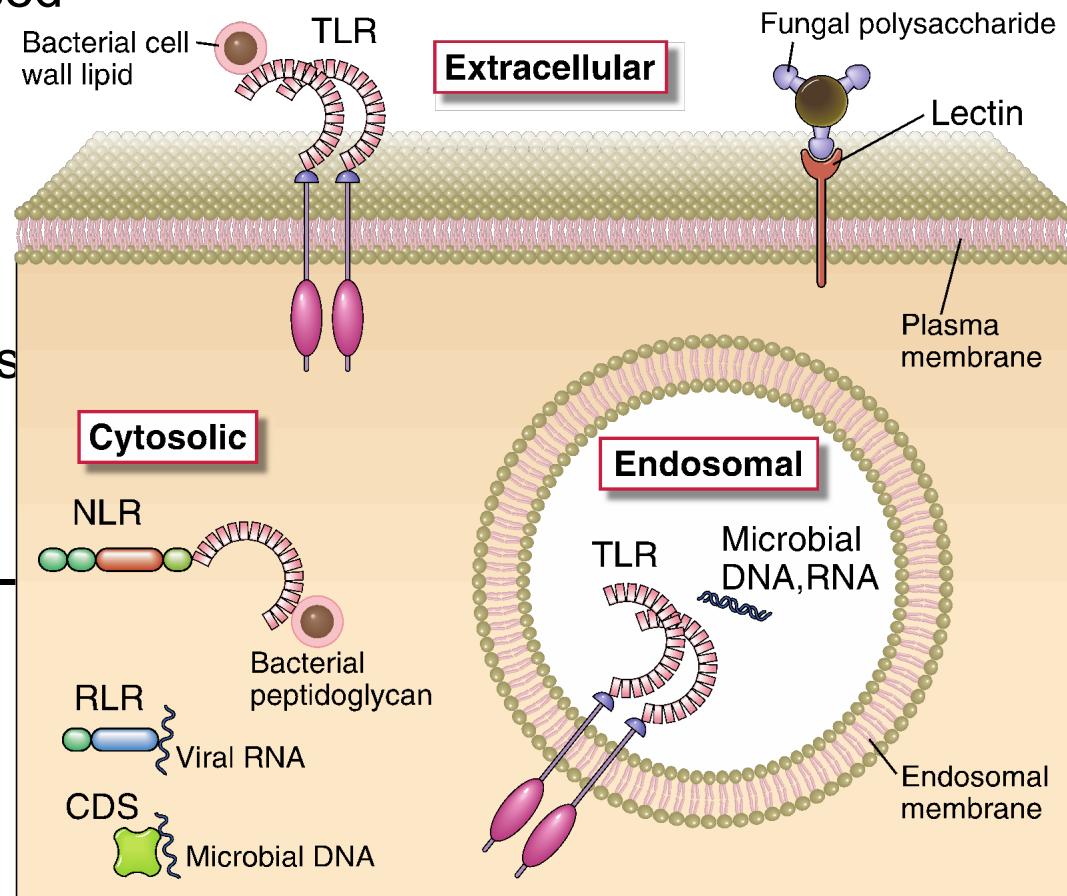
TLR (Toll-like Receptors) - PAMPs
extracellular or phagocytosed
ligands

CLR (C-type Lectins) –
Carbohydrates

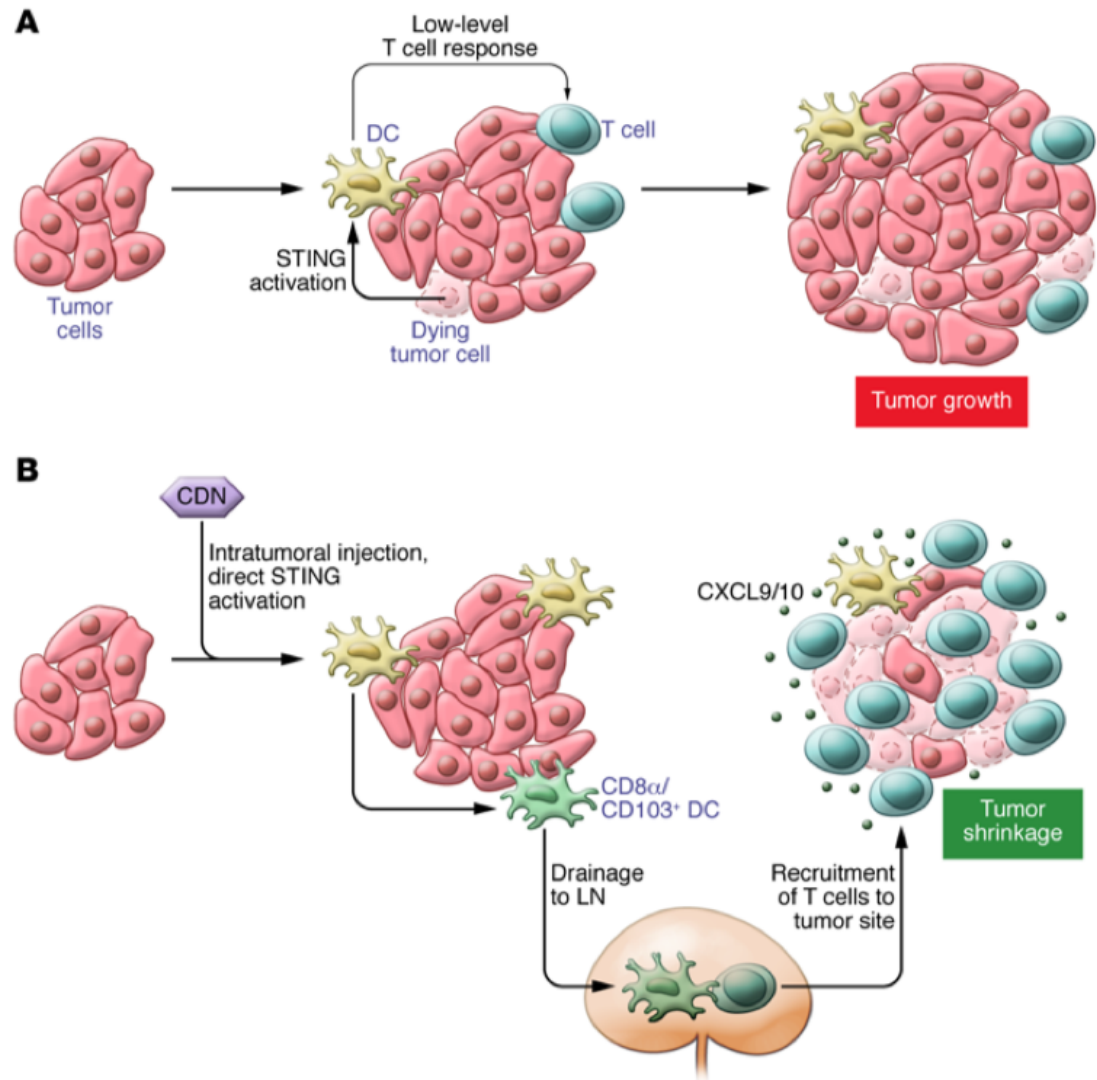
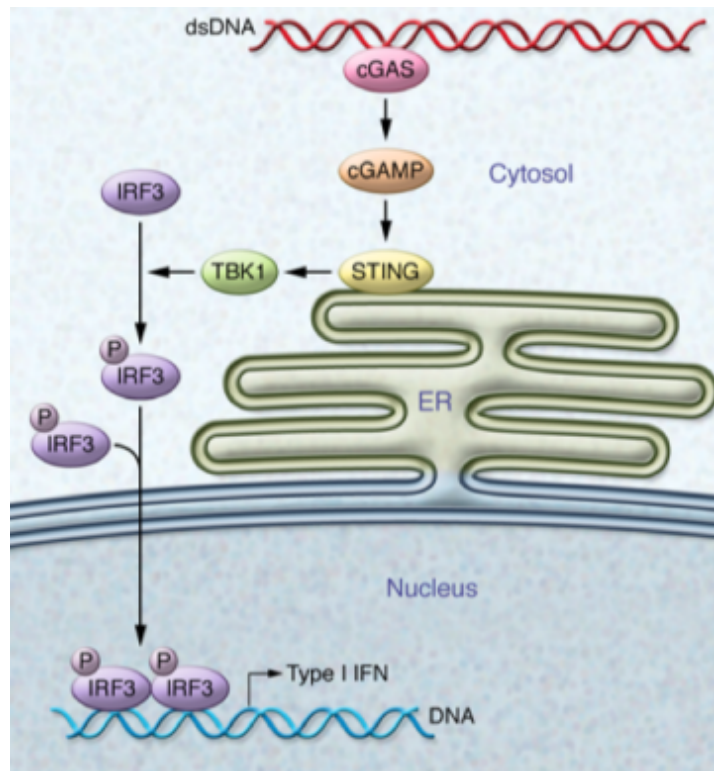
NLR (NOD-like Receptors) –
Cytosolic PAMPs & DAMPs

RLR (RIG-I-like Receptors) –
Cytosolic Viral RNA

CDS (Cytosolic DNA Sensors) –
Cytosolic nucleotides



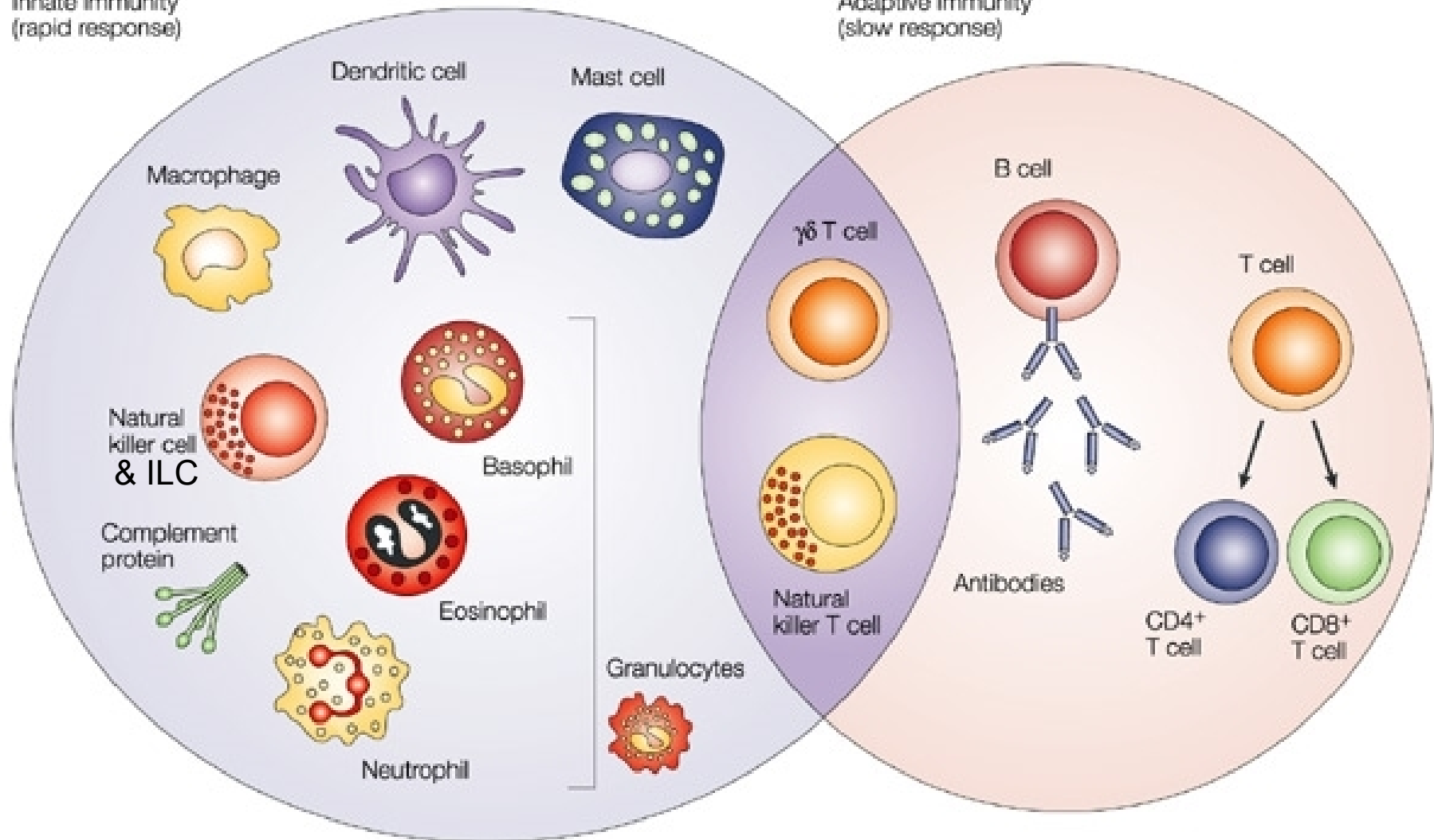
STING Agonist as Cancer Immunotherapeutics



Cells of the Immune System

Innate immunity
(rapid response)

Adaptive immunity
(slow response)




Myeloid Cells

- Granulocytes (Polymorphonuclear leukocytes)

-  – Neutrophils – most abundant in blood

-  - Eosinophils – less abundant (helminths, bacteria, IL-5, IL-13)

-  – Basophils – rare (parasites, IgE-allergic responses)

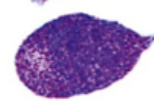
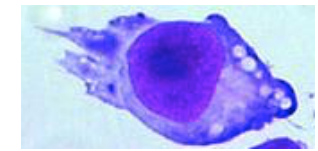
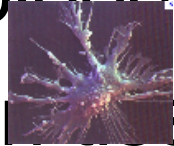
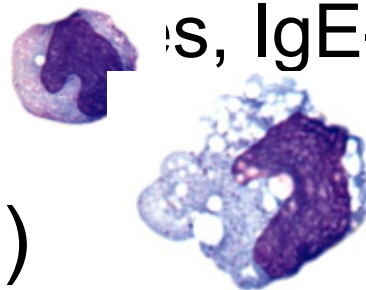
- Monocytes (in blood)

- Macrophages (in tissues)

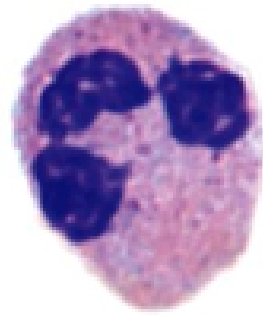
- Dendritic Cells

- Plasmacytoid dendritic cells (type I IFN)

- Mast cells (in tissues)

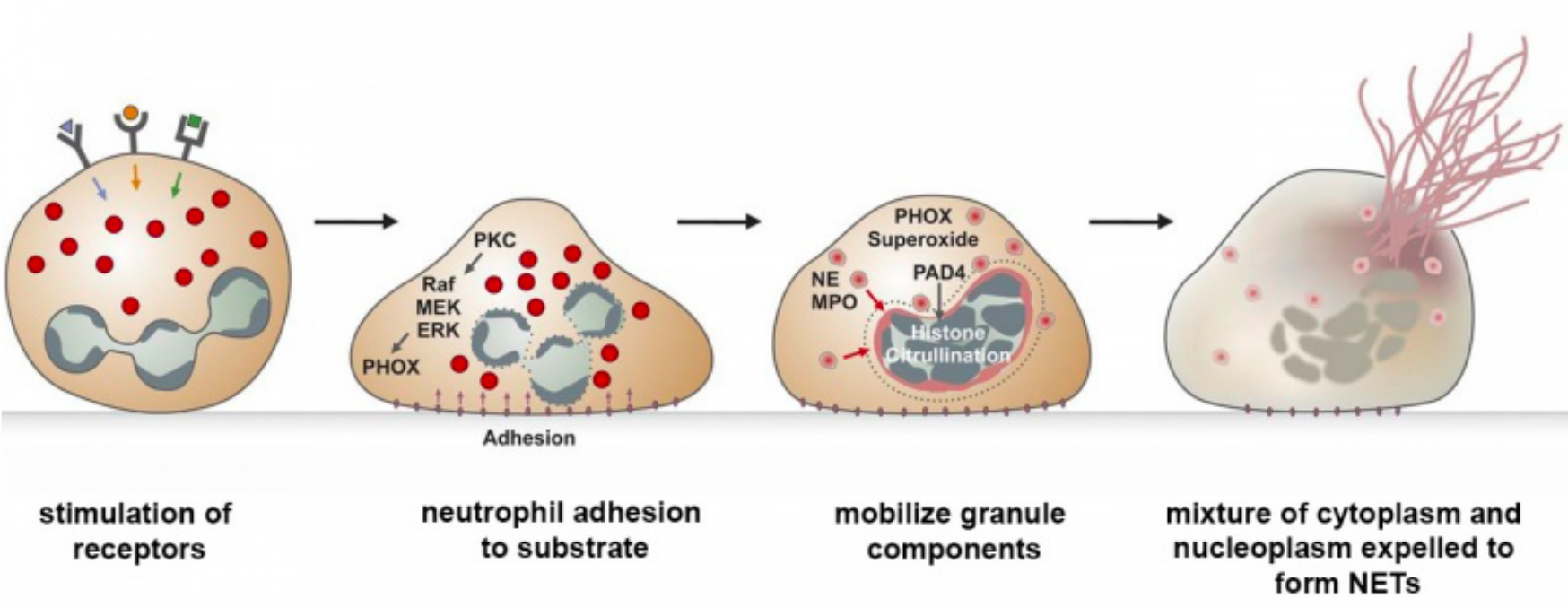


Innate Immunity - Neutrophils



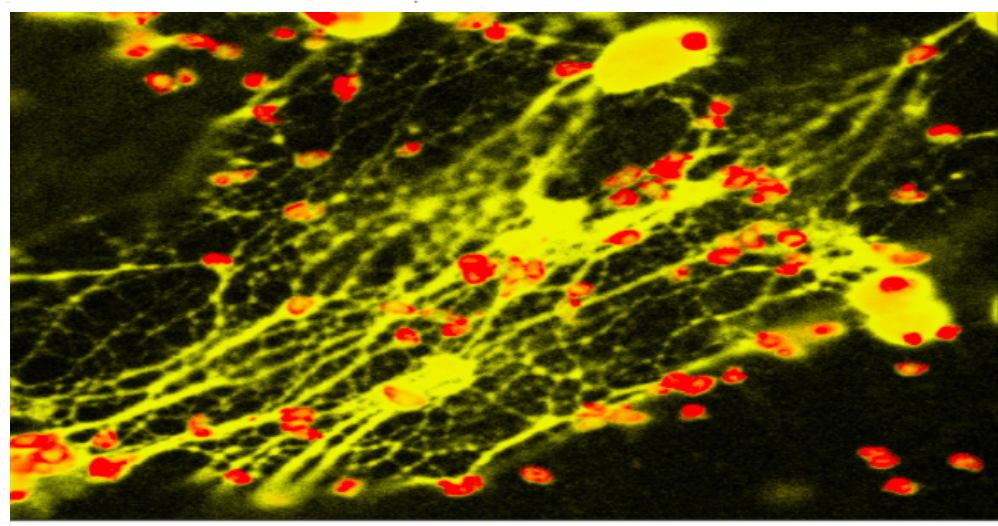
- Bone marrow-derived, short-lived (~ 5 days), rapid response - minutes!
- Increased production during infection - neutrophilia
- Cytoplasmic granules containing degradative enzymes, including lysozyme, collagenase, and elastase
- A type of MDSC (myeloid-derived suppressor cell)

Neutrophil Extracellular Traps

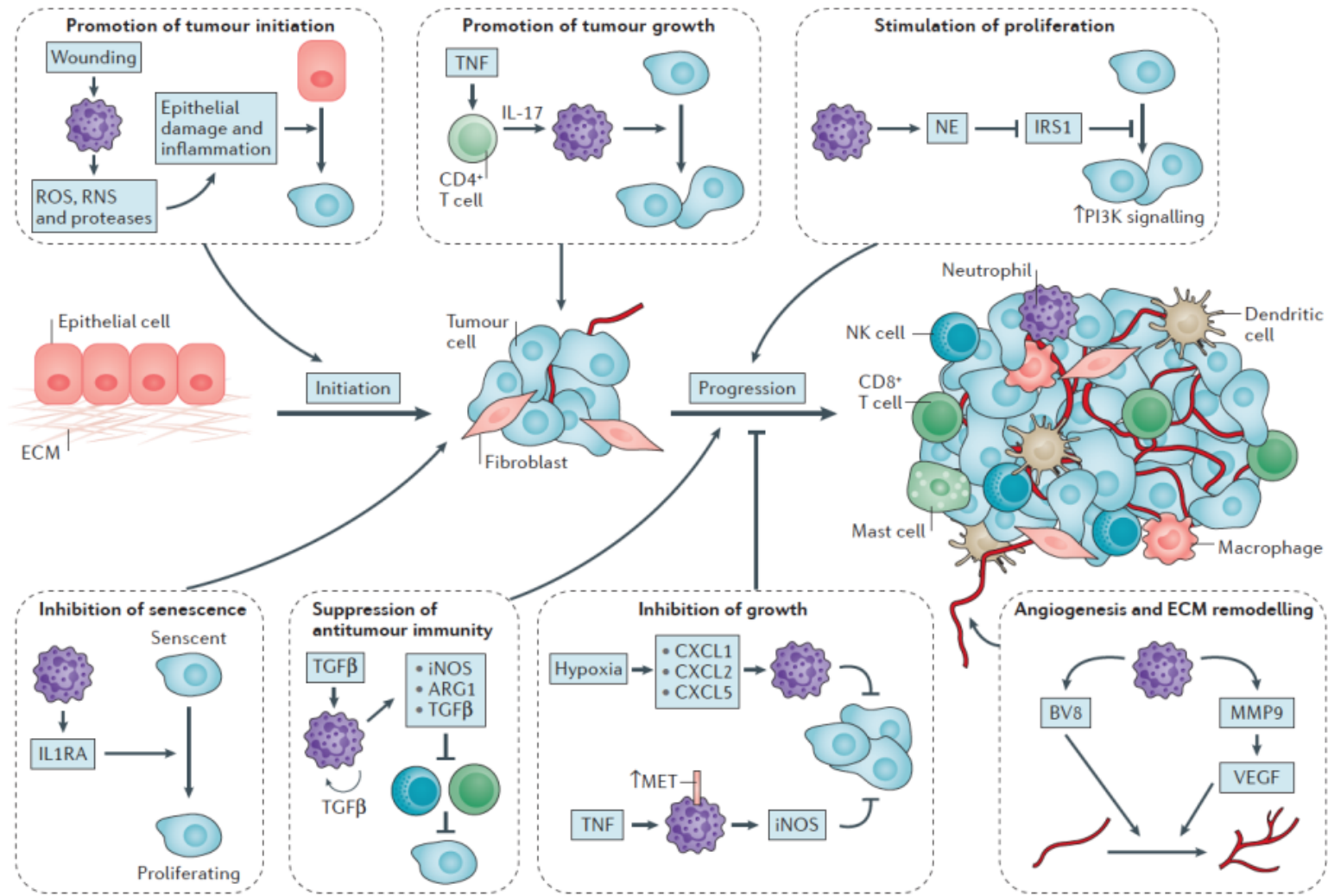


Modified from: Brinkmann, V and Zychlinsky, A., J. Cell Biol.: 2012, 198(5):773-83

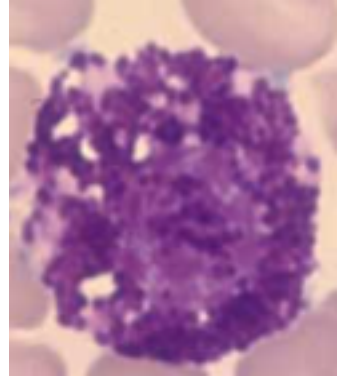
PMID: 22945932



Role of Neutrophils in Cancer - Complex

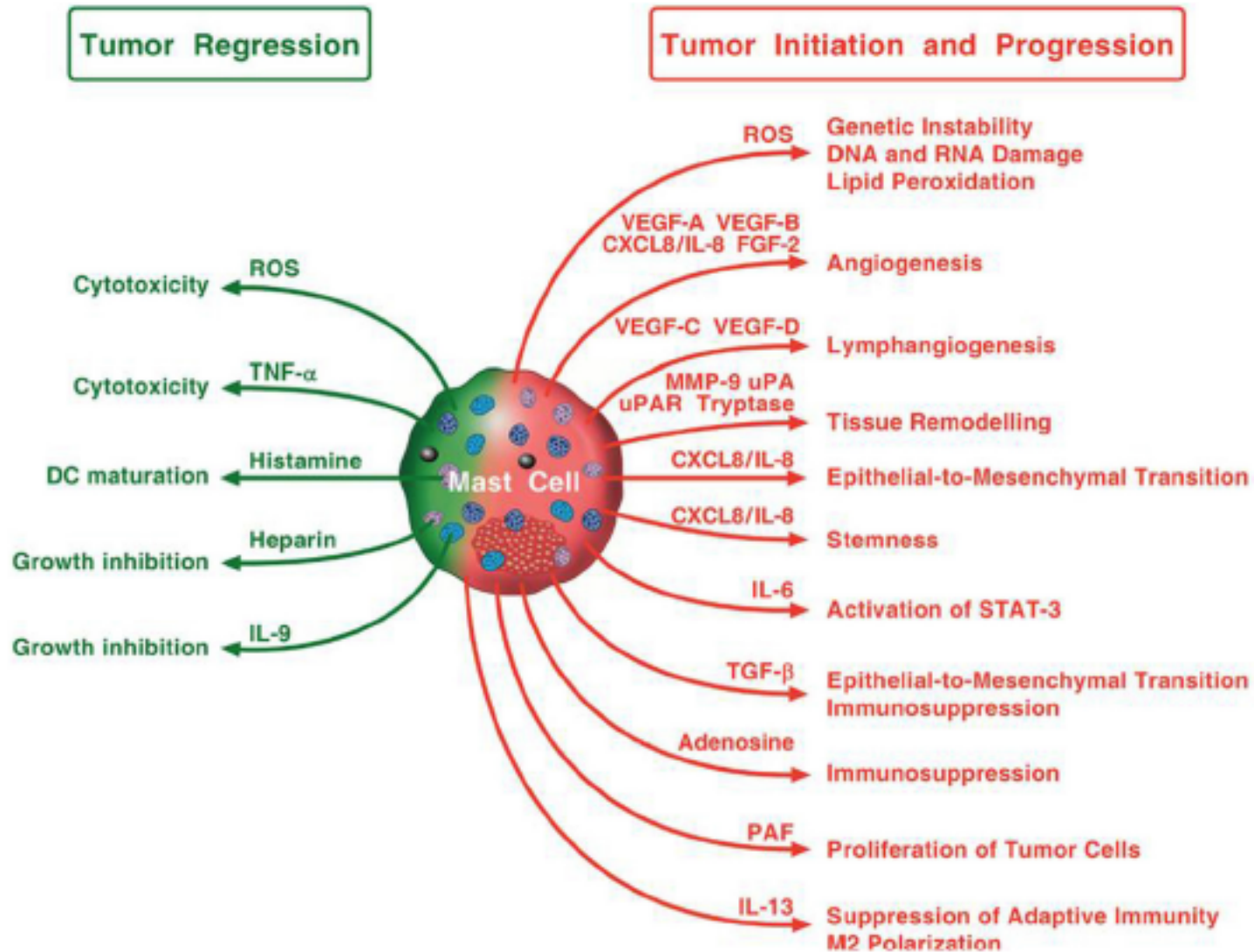


Innate Immunity – Mast Cells



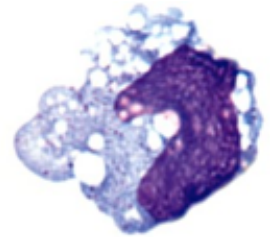
- Two types – connective tissue & mucosal
- Involved in defense against parasites and allergic reactions
- Connective tissue mast cell granules contain histamine, tryptase, chymase cathepsin G
- Mucosal mast cell granules contain chondroitin sulfate, tryptase, neutral protease
- Secrete IL-4, IL-13, leukotrienes
- Express high affinity receptors for IgE that can trigger release of histamine and other mediators

Role of Mast Cells in Cancer - Complex



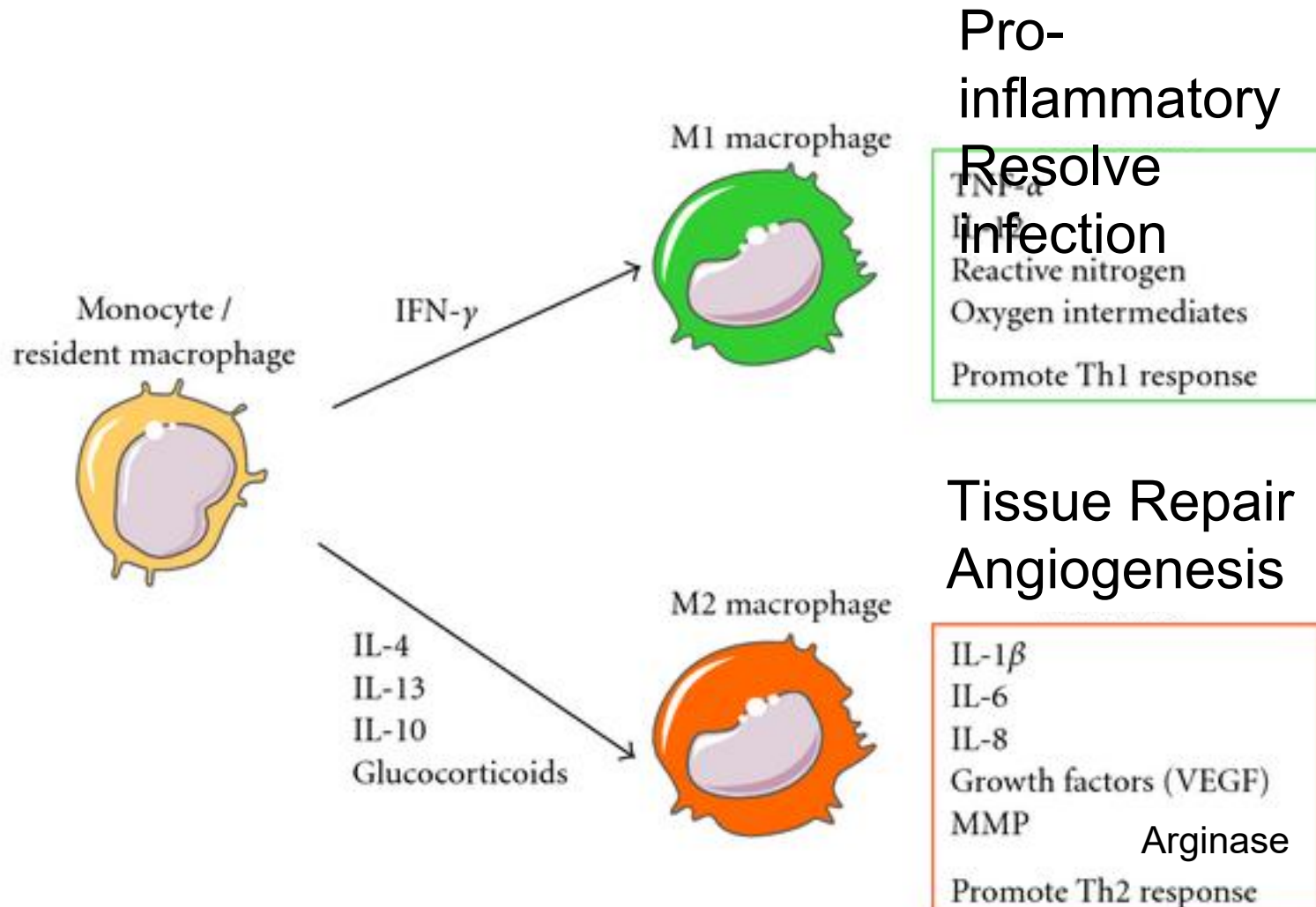
Innate Immunity - Monocytes and Macrophages

- Monocytes - bone-marrow derived, circulating mononuclear cells with kidney-shaped nucleus and abundant cytoplasm
- Tissue-resident macrophages
 - Kupffer cells in liver, microglial cells in brain, alveolar macrophages in lung, Langerhans cells in skin (some seed organs during fetal life, others replenished in adults from bone marrow)

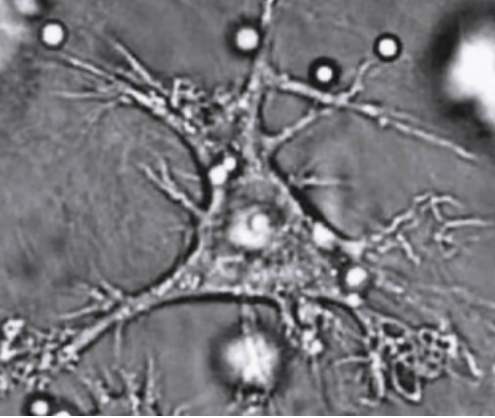


Flavors of Macrophages

“M1” – “M2” – a vast oversimplification!



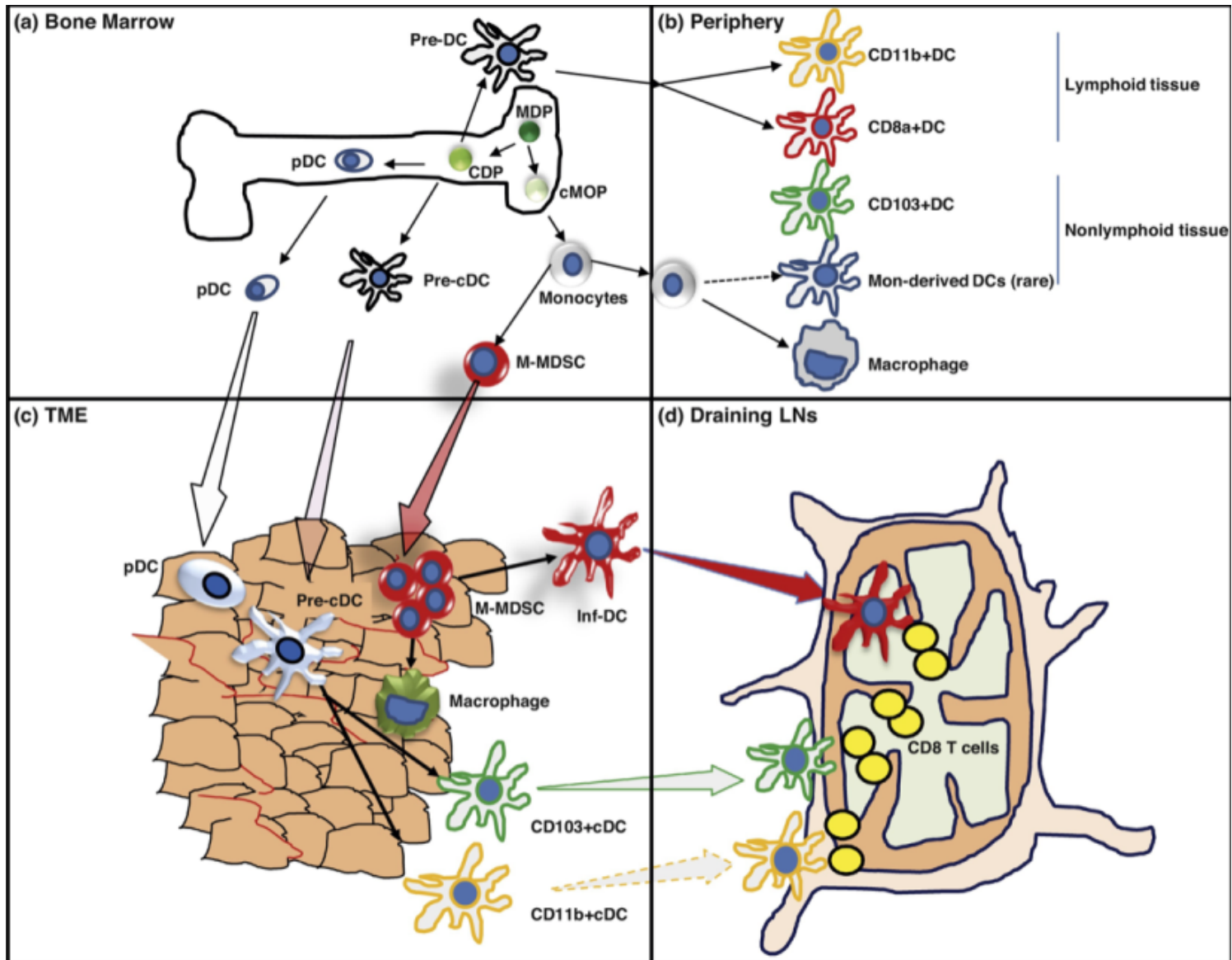
Myeloid-derived Suppressor Cells (MDSC) suppress T cells responses – promote tumor growth?



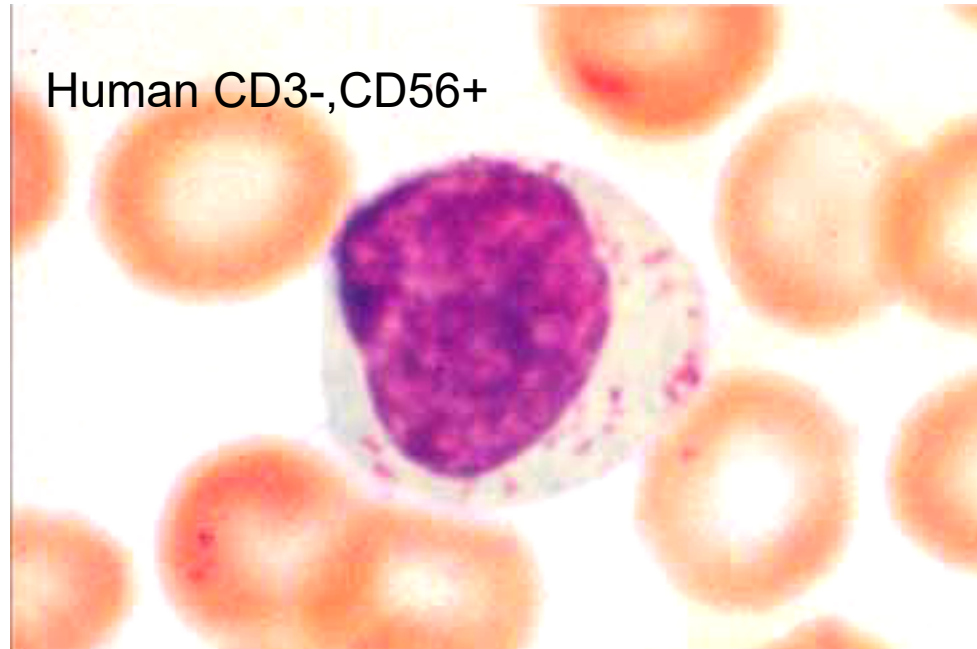
Innate Immunity - Dendritic Cells

- In mucosal tissues and skin, immature DC efficiently capture antigens
- Pro-inflammatory cytokines induces their maturation, up-regulation of MHC class II, and co-stimulatory molecules, and migration to lymph nodes
- Considered the most potent 'antigen-presenting cells' in the body – activate T cells

Dendritic cell subsets in cancer immunity



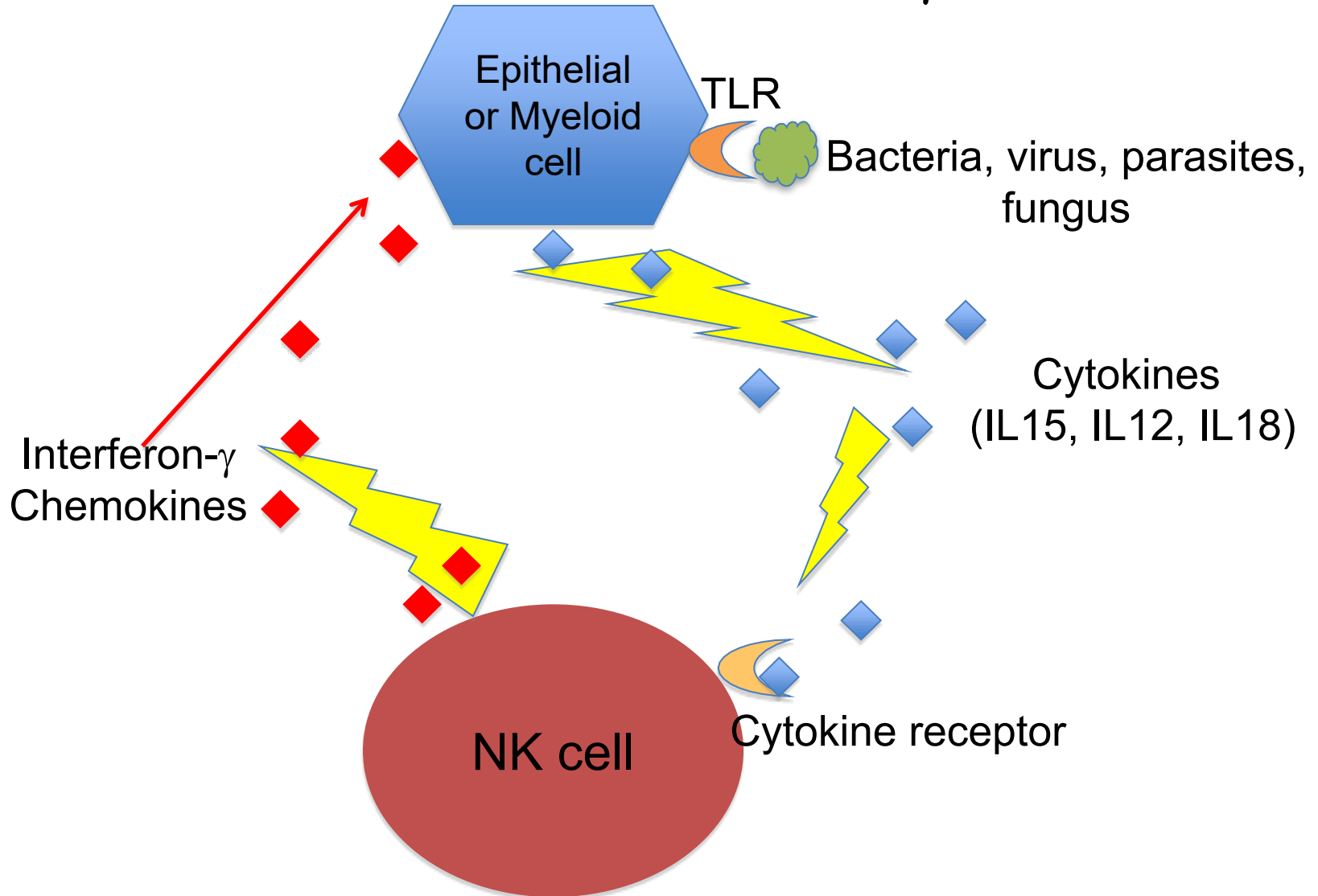
Natural Killer cells



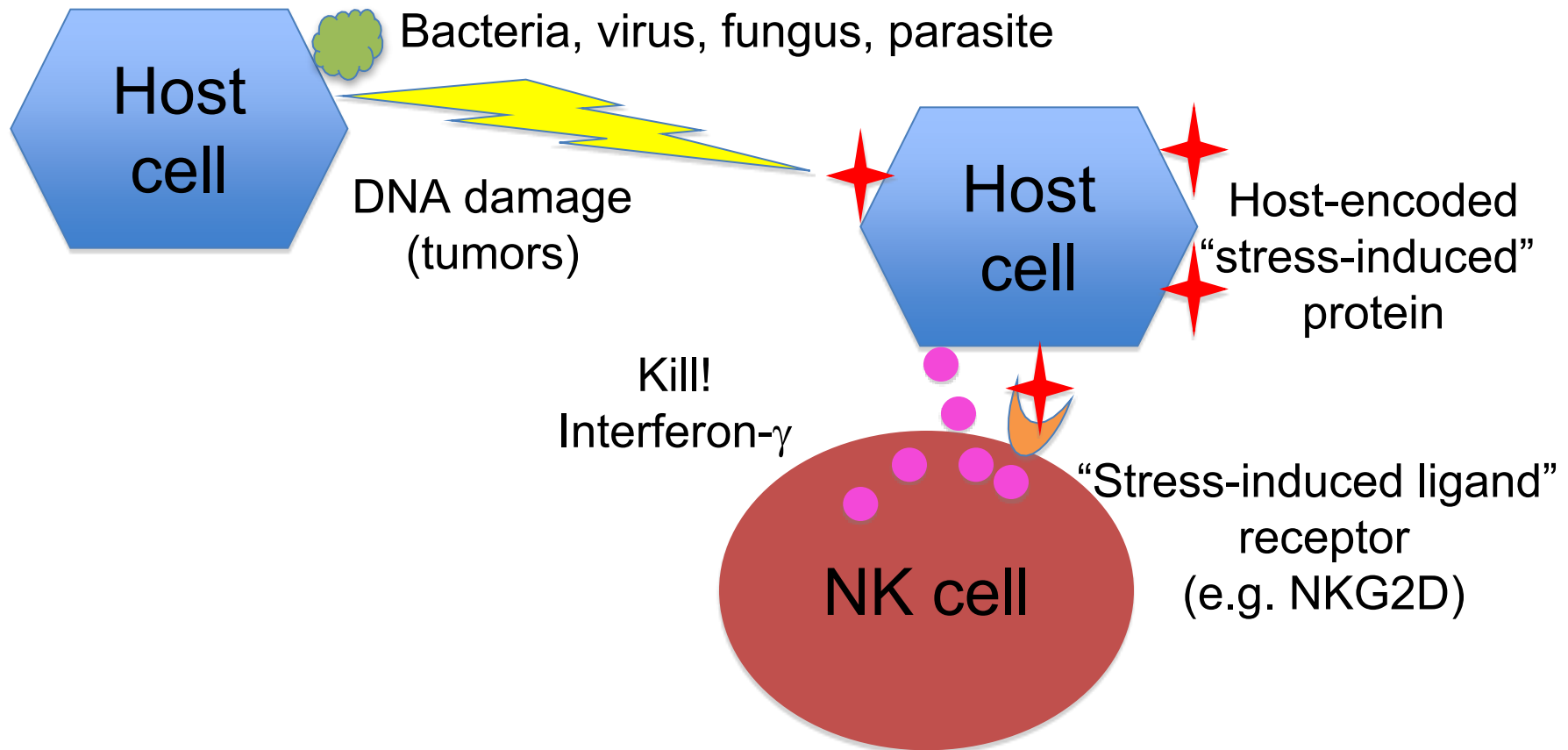
- Innate lymphocytes
- ~10-20% of blood lymphocytes
- Function in innate immunity to protect against viruses, bacteria, fungus, and tumors
- Produce cytokines & directly kill abnormal cells

Cytokines produced by infected epithelial or myeloid cells

activate NK cells to secrete Interferon- γ and chemokines



“Stressed” cells – upregulate host-encoded ligands for activating NK receptors



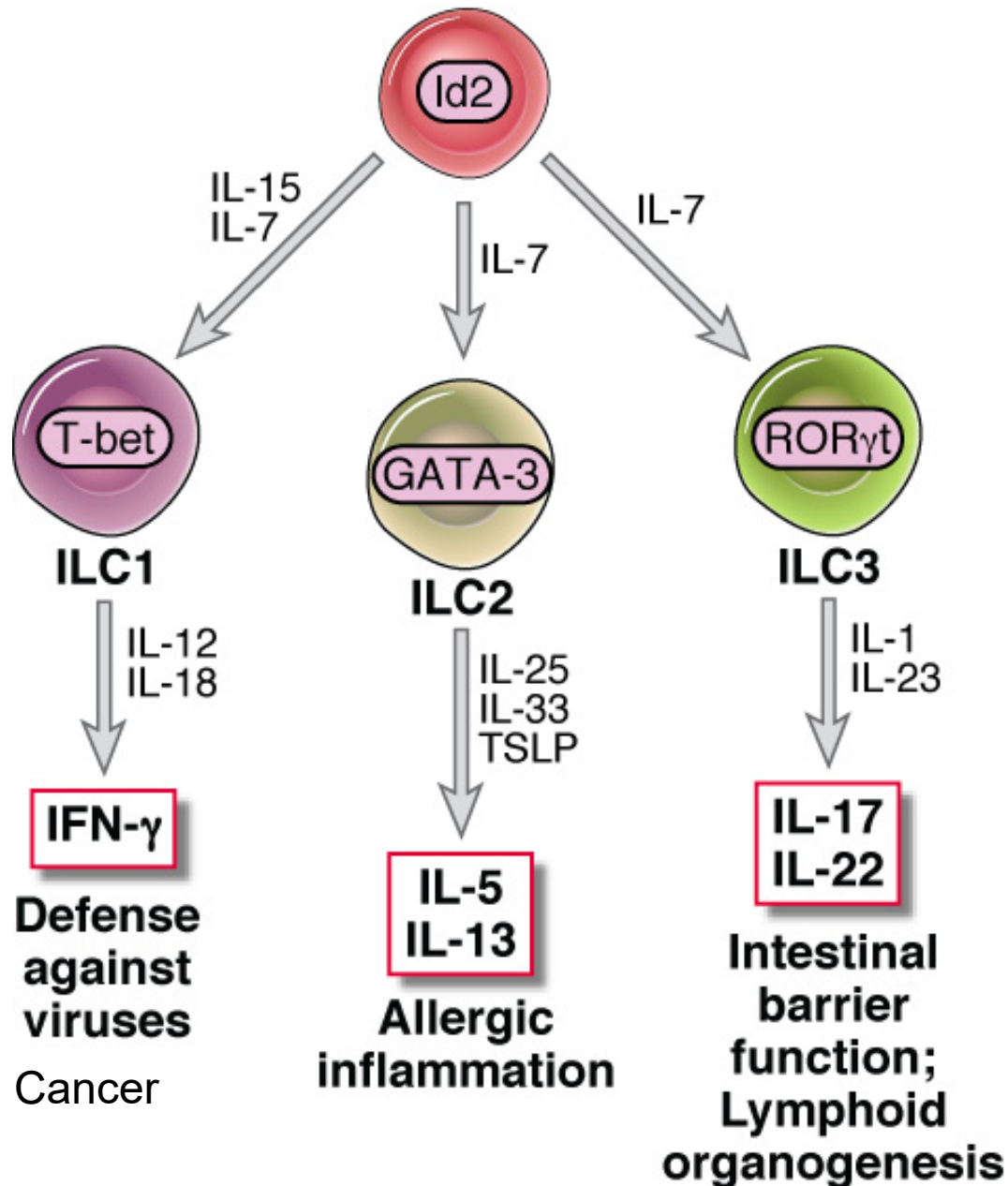
Immune regulatory role of NK cells

- *Kill cells that are proliferating too much
- *Kill T cells causing autoimmunity
- *Secrete pro-inflammatory cytokine – $\text{IFN}\gamma$
- *Secrete suppressive cytokines – IL-10

Innate Lymphoid Cells (ILC)

present in mucosal tissues to regulate immune responses by secreting cytokines

Innate lymphoid cells



ILCs make many of the same cytokines as T cells but lack TCRs

May contribute to early cytokine responses in host defense and inflammatory diseases

Useful Reviews – Innate Immunity in Cancer

Complement – Afshar-Kharghan J. Clin. Invest. 127:780, 2017

Interferons – Parker et al. Nat Reviews Cancer 16:131, 2016

Chemokines – Nagarsheth et al. Nat Reviews Immunology 17:559, 2017

Cytokines – Conlon et al. J. Interferon & Cytokine Research 39:6, 2019

Innate Immune Recognition of Cancer Woo et al. Ann Rev Imm 33:445, 2015

STING – Corrales et al. J. Clin. Invest. 126:2404, 2016

Neutrophils - Coffelt et al. Nature Reviews Cancer 16:431, 2016

Mast cells - Varricchi et al. Frontiers Immunology 2017

Macrophages – Poh & Matthias Frontiers Oncology 2018

Dendritic cells – Veglia & Garilovich Curr Op Immunol 45:43, 2017

NK cells – Miller & Lanier Ann Rev Cancer Biology 2019