Hôpitaux Universitaires de Genève

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UNIVERSITÉ DE GENÈVE

Geneva University Hospitals and University of Geneva

ESMO Preceptorship program

Basic Immunology for Oncologists

The basics….

what you need to know about immunology…
to make sense of tumor immunology

The key cells and molecules of innate and adaptive immunity

- Granulocytes
- Natural Killer Cells
- Dendritic Cells and APCs
- CD4 and CD8 T cells
- B cells, Plasma Cells and Antibodies

How immune cells and molecules recognise tumors…sometimes

- Recognition of infection, stress and danger by innate immune cells
- Recognition of peptides and MHC molecules by T cells

How innate and adaptive immunity function together

- Antigen presentation and co-stimulation

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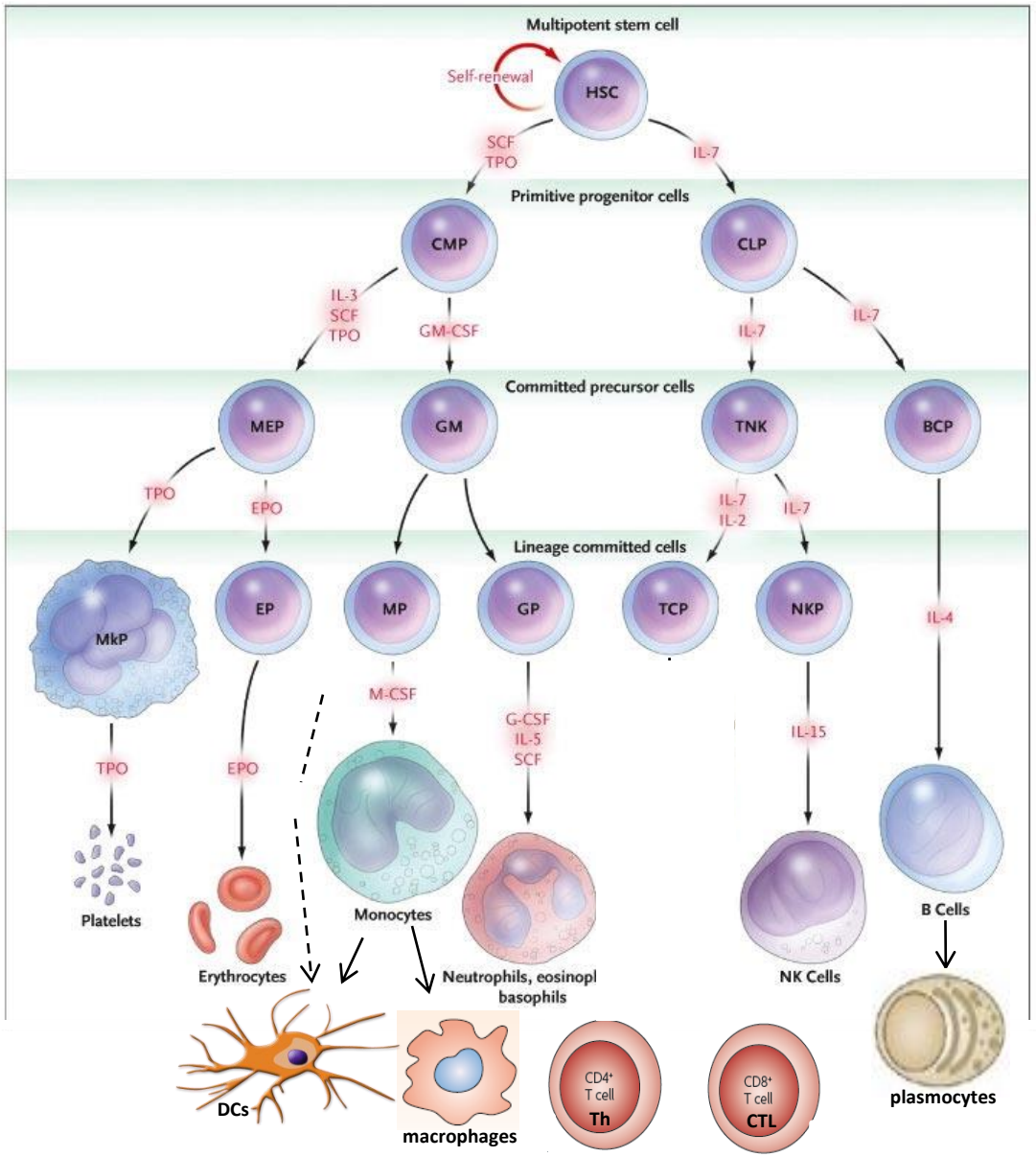
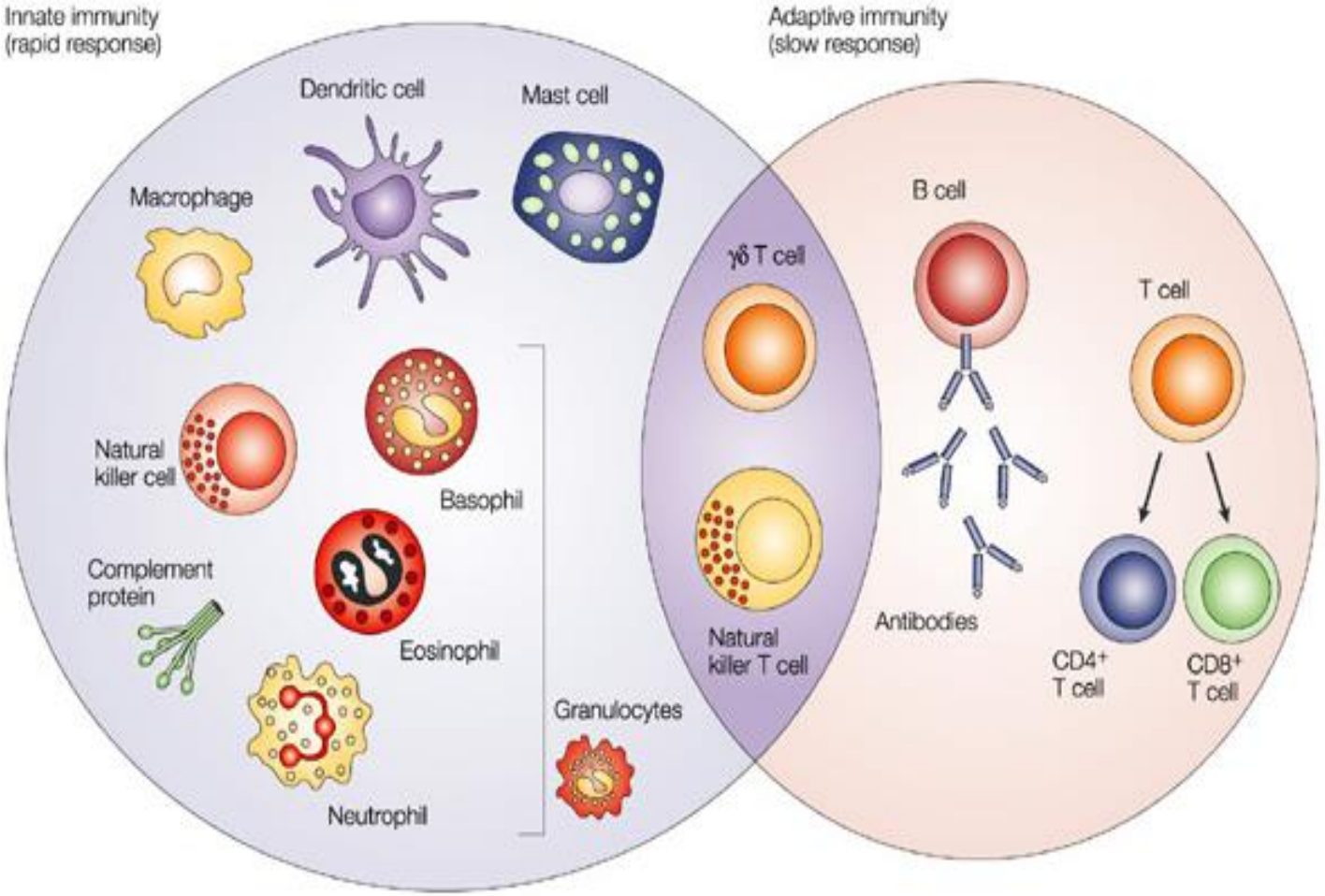
The key cells of innate and adaptive immunity are leukocytes (wbc) that derive from bone marrow



- CD4 and CD8 **T cells** are formed in the thymus and differentiate into **CTL** and **Th** in SLO
- Monocytes enter tissues and differentiate into **macrophages**
- B cells terminally differentiate into antibody secreting **plasmocytes** in SLO
- **Dendritic Cells** are a family of cells of BM origin from various precursors

The immune system functions at two levels

Innate and adaptive immunity – with corresponding cells and molecules



G. Dranoff Nat Rev Cancer, 4:11-22, 2004

The immune system functions at two levels

Innate and adaptive immunity – general characteristics

Innate

• preformed cells and molecules –**react immediately**

• detects pathogens directly (**specific receptors** – *cell bound, soluble*) with excellent self-tolerance

• also **detects tissue damage / cellular stress / "danger"** (*infection, malignancy*)

• response is similar after each infection **-no memory**

• essential to launch ***adaptive immunity*** →

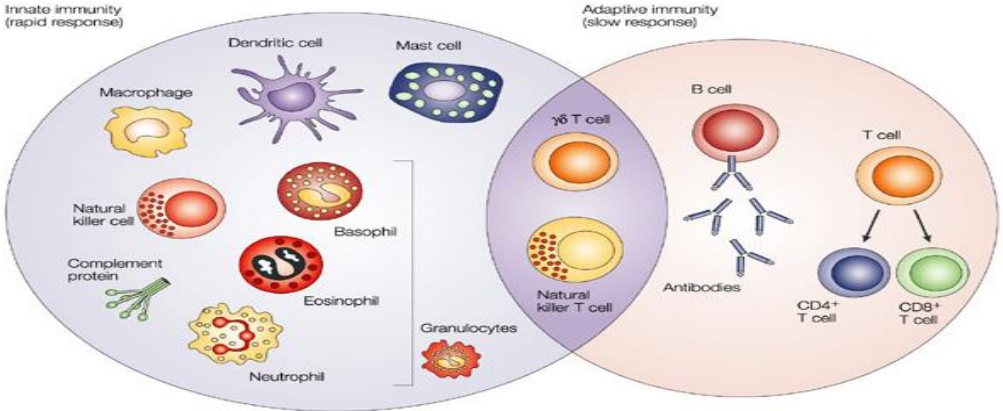
Adaptive

• **T cells and B cells** require **coordinated activation and cell interactions** to proliferate and acquire effector functions

• Use **antigen receptors** to detect unique structures (antigens) either cell associated (T cells) or soluble/extracellular (B cells)

• **Exquisite fine specificity** – but for structures not uniquely pathogen associated (*complex but imperfect mechanisms of self tolerance)*

• **Memory response** – more rapid and efficacious



The immune system functions at two levels

Innate and adaptive immunity – general characteristics

Principle innate immune cells/functions

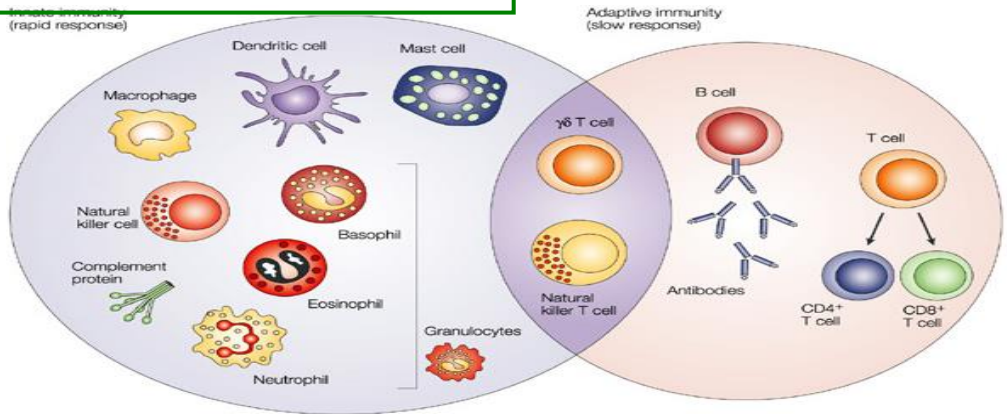
*(**complement** : inflammation, lysis, opsonisation and promotion of phagocytosis)*

- **Granulocytes**: phagocytosis , cytotoxic granules- pathogen destruction, inflammation
- **NK cells**: cytotoxicity, inflammation
- **Macrophages**: phagocytosis, cytokines /inflammation*, antigen presentation
- **Dendritic Cells** : phagocytosis, cytokines / inflammation, antigen presentation→

* major element in shaping tumor microenvironment

Principle adaptive immune cell functions

- **CD4 Th cells:** cytokine release and "helper" functions – cooperating with B cells, macrophages, DCs and CD8 T cells
- **CD4 Treg cells** : "regulation" (suppression) of immune response
- **CD8 CTLs** : cytotoxicity, cytokine release
- **B cells** : antigen presentation to Th cells, differentiation to antibody secreting **plasmocytes**
- **Memory T and B cells**: long-lived Ag-specific cells for rapid reactivation by Ag/pathogen



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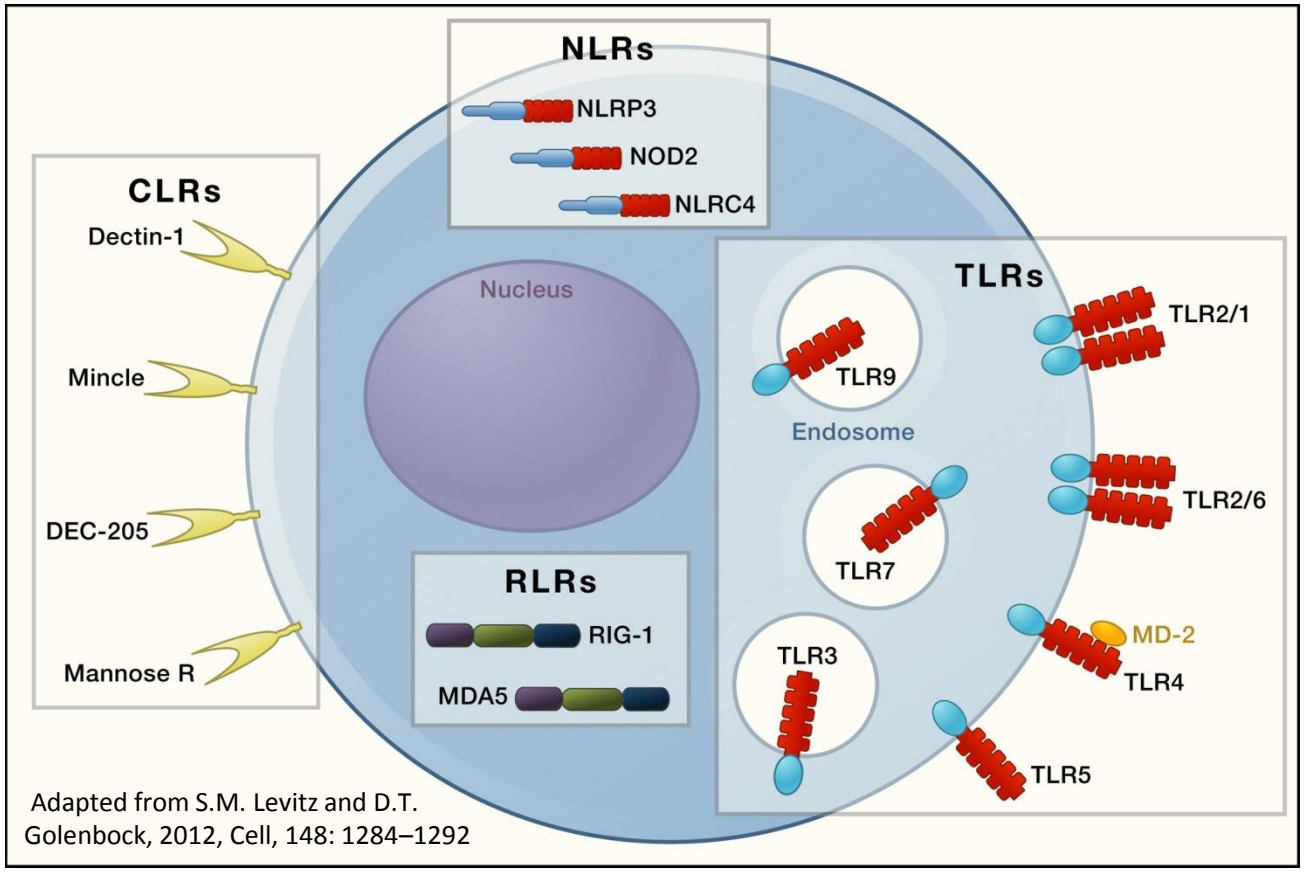
Sensing of infection stress and danger by Pathogen Recognition Receptors – PRRs

Abundantly expressed on innate immune cells e.g. DCs

- **PRRs:** Germline encoded, e.g. Toll-Like Receptors, Nod-like Receptors, C-type Lectin receptors, RIG-I-like receptors, Mannose-binding lectin – MBL (soluble)

- **PRRs:** recognise conserved microbial structures **P**athogen **A**ssociated **M**olecular **P**atterns - **PAMPs**



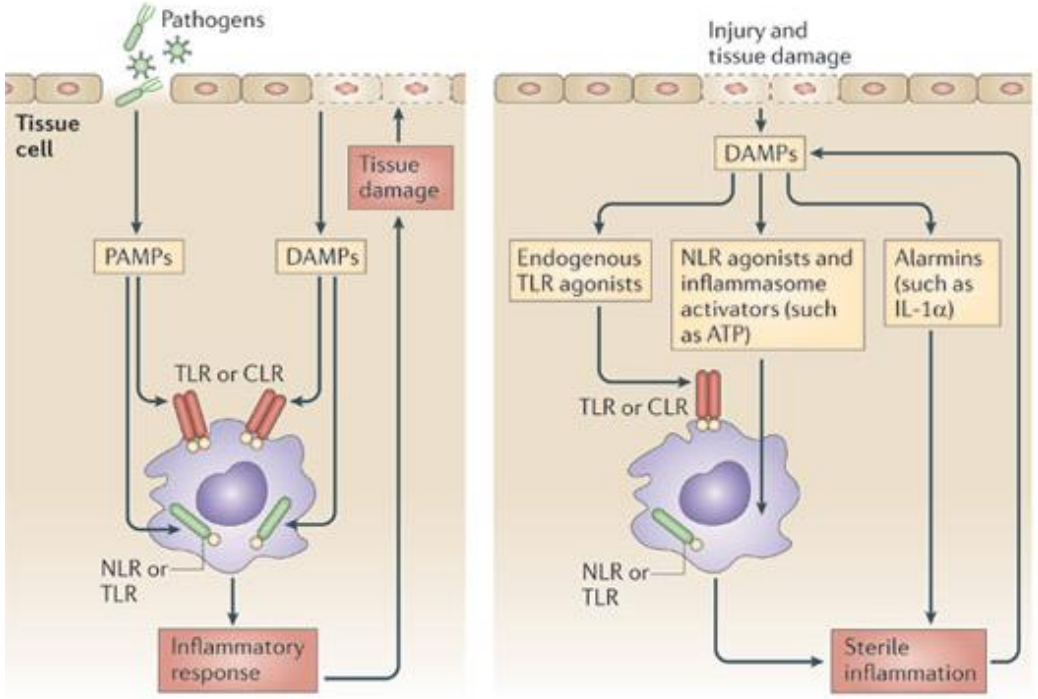
Adapted from S.M. Levitz and D.T. Golenbock, 2012, Cell, 148: 1284–1292

Sensing of infection stress and danger by Pathogen Recognition Receptors – PRRs

Abundantly expressed on innate immune cells e.g. DCs

- **Some** innate responses (e.g. NK cells) can be indirect - recognition of "missing self"
  - *downregulated MHC expression through infection…or malignancy*

- **Some PRRs**: recognition of **D**amage **A**ssociated **M**olecular **P**atterns - **DAMPs**

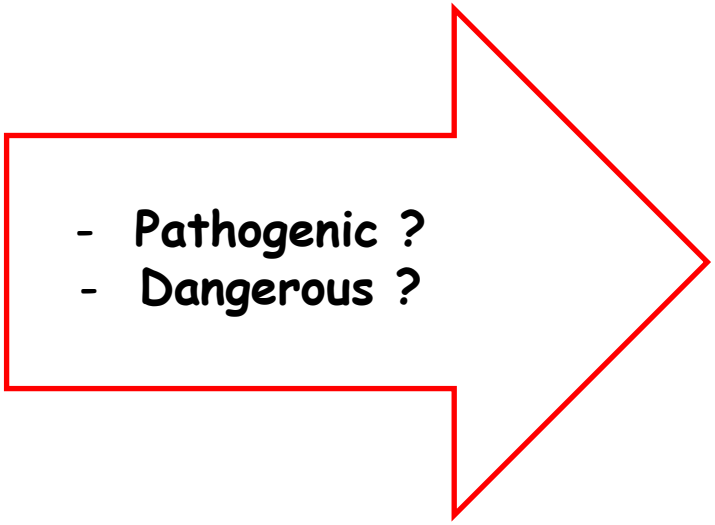


Adapted from K. H. G. Mills 2011, Nature Reviews Immunology 11:807-822

- **Dendritic Cell Maturation to become efficient APC**
- **Promotion of Adaptive Immunity**

Adaptive Immune Cells express Receptors that Recognise Structures *– pathogen derived or not*

- Innate Immune Reaction provide the context



- For T cells - peptides and MHC molecules
- For B cells* – any protein or non-protein structure…

**B cells require T cell help to make high-affinity IgG*

T cell receptors recognise peptides bound to MHC molecules

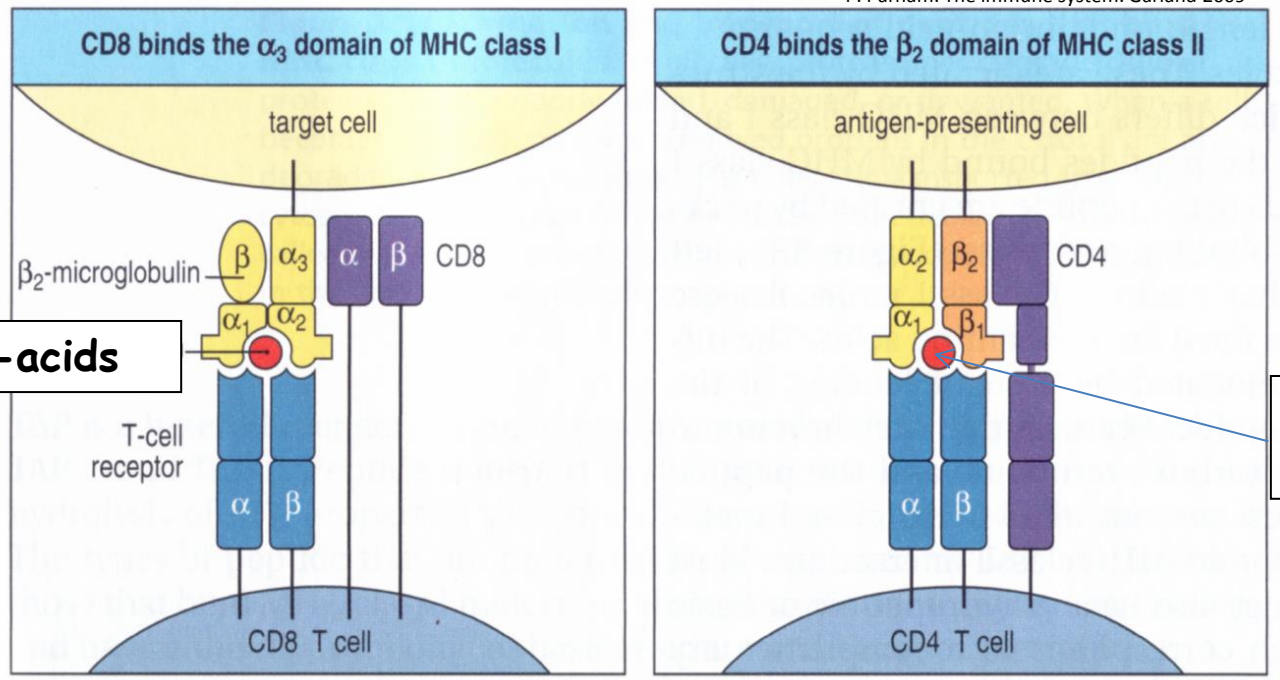
Clonally expressed on CD4 and CD8 T cells

CD4 and CD8 T cells recognise a complex of peptide antigen bound to a **M**ajor **H**istocompatibility **M**olecule (MHC)

Human MHC = HLA **Mouse MHC = H-2**

Groove on MHC molecules accommodates peptide antigens

P. Parham. The immune system. Garland 2009



8-11 amino-acids

MHC Class I

12-25 amino-acids

MHC Class II

How do we generate sufficient receptors to react with ANY antigen encountered in future?

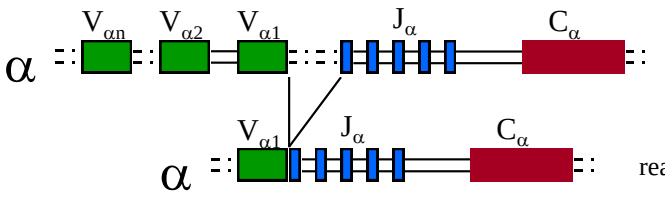
T cell receptors are not germline encoded

they are not selected to bind to pathogens

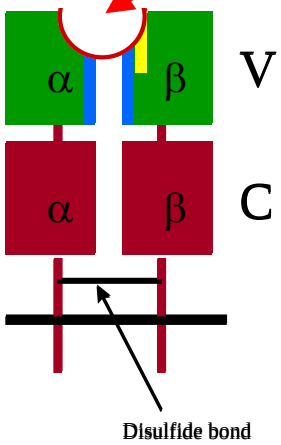
αβ T Cell Receptor
a disulphide linked heterodimer comprised of an **α** and a **β** chain with variable (V) regions and constant (C) regions

TCR diversity generated by somatic recombination of gene segments **(V, D, J, C)** during T cell development in thymus

Further diversity at the V(D)J junctions by nucleotide addition



αβ TCR



Diversity concentrated in antigen binding site

	α chains
Variable segments	~70
Diversity segments	0
Joining segments	61

Number of TCR estimated in periphery up to ~10^8

What about QC?

The role of the thymus

T cell education and central tolerance

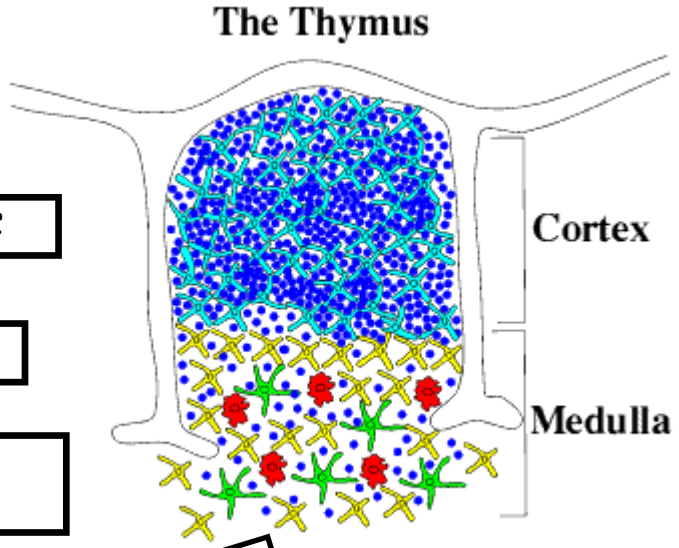
bone marrow derived T cell precursors enter thymus from blood

Generation of a functional TCR

Positive selection to ensure recognition of self MHC

Commitment to CD4 or CD8 lineage

Negative selection eliminates cells too highly reactive with self MHC + self peptides



>98% thymocytes die during selection

Exit of mature naïve T cells to blood

Mature CD4 and CD8 T cells

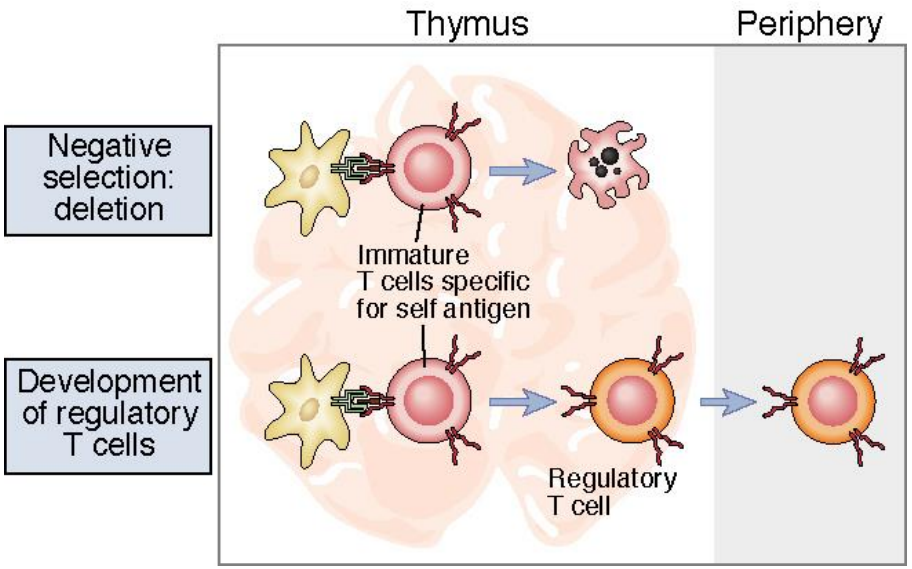
- should be able to react with any non-self protein antigen (+ self MHC) e.g. pathogen or tumor neoepitope

- should not react with self antigens or shared tumor/self antigens IF the antigen was presented in thymus for negative selection (central tolerance)

In biology, there is always an exception….

Regulatory T cells (Treg) can escape negative selection in thymus

- Some CD4 T cells express Foxp3 transcription factor
- TCR specific for self peptides + MHC



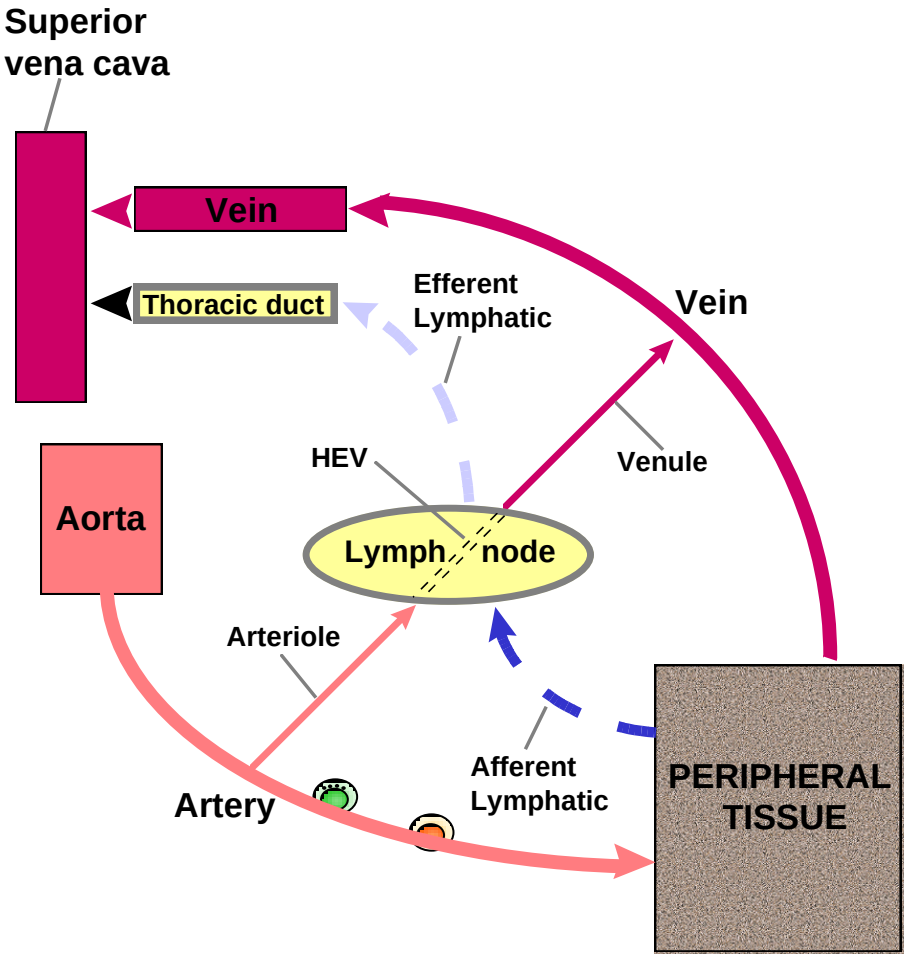
From: Abbas & Lichtman, Cellular & Molecular Immunology 5th ed 2003

Cells exit thymus and can maintain peripheral tolerance to:

- self antigens (control autoimmunity)…
- shared self/tumor associated antigens (limit anti-tumor immunity)

Naïve T Cells Survey SLO for their specific antigen

Mature, naive T cells recirculate between the blood and secondary lymphoid organs



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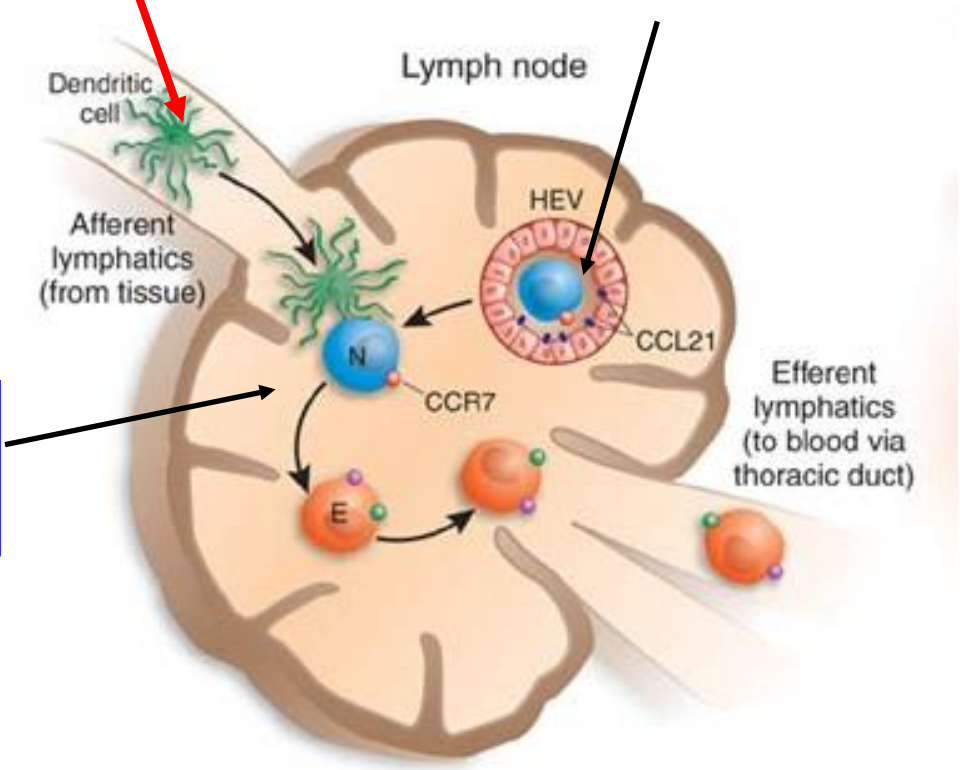
Dendritic Cells can transport antigens to T cells in LN

DCs activated through PRR migrate to LN and will efficiently activate naive T cells

- Naïve T cells (N) leave blood through (HEV) of lymph nodes LN), and enter T cell zones

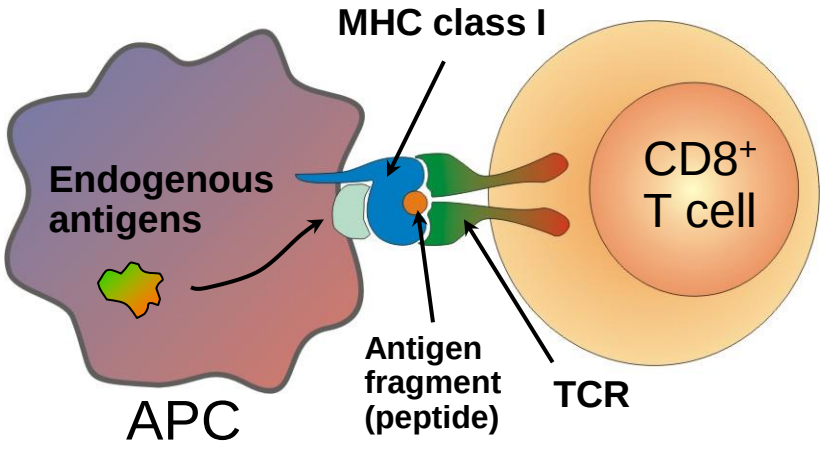


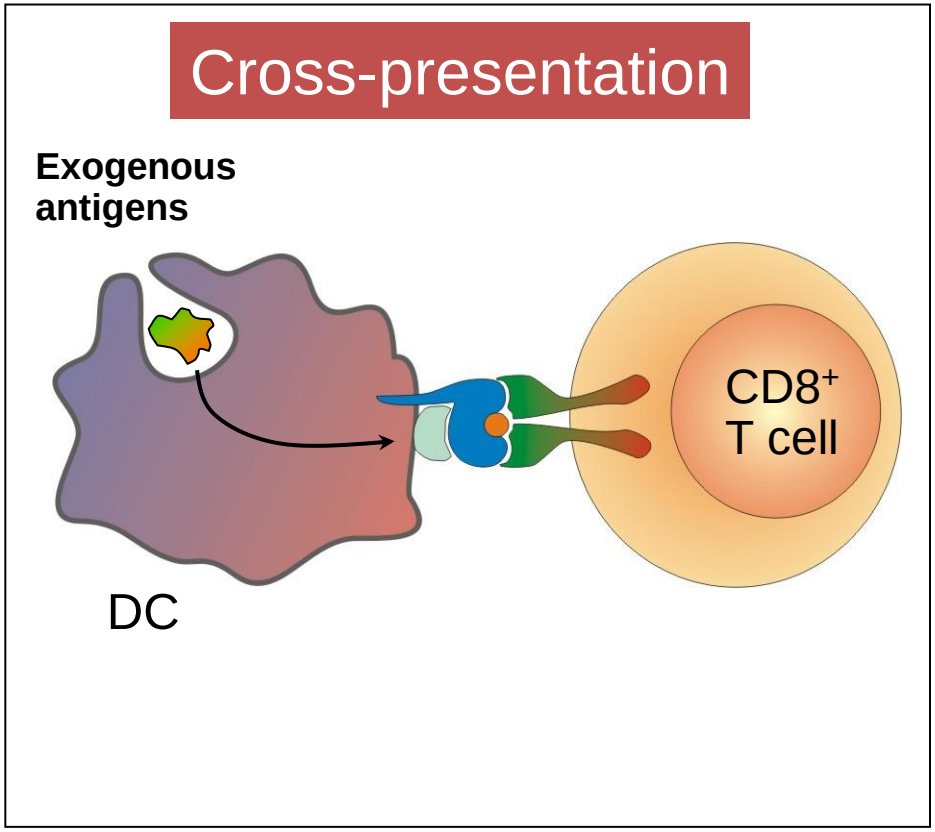
-Chemokine gradients guide the T cell – DC encounter

Nature Immunology **6**, 866 - 868 (2005)

Sensing of infection stress and danger by Pathogen Recognition Receptors – PRRs

Promotes antigen presenting functions - especially by DCs

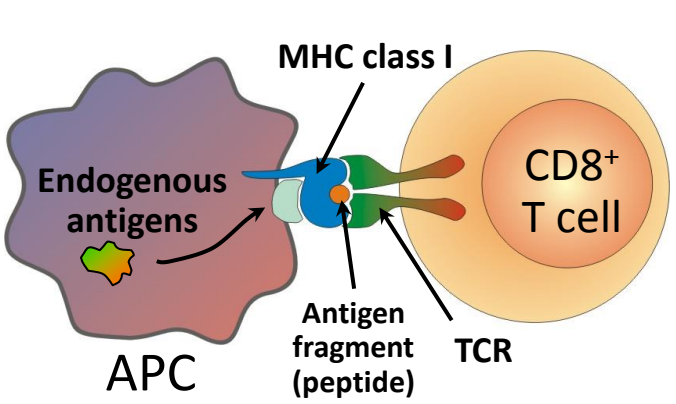


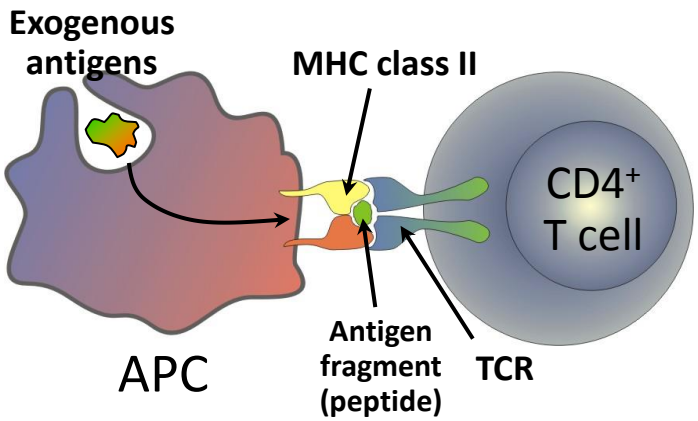


Activation of mature T cells in secondary lymphoid tissue

Minimum requirement: 2 SIGNALS

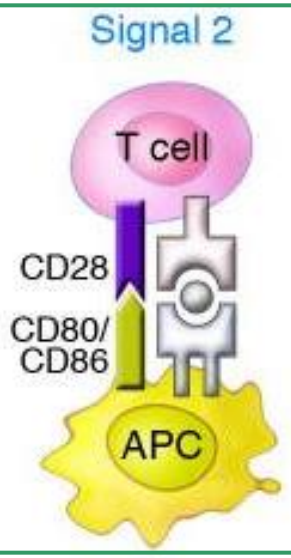
SIGNAL 1:
An antigen-presenting cell (APC) stimulating the TCR through peptide presented on an MHC molecule



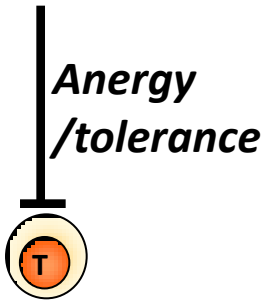


SIGNAL 2:
Co-stimulating signal through (e.g.) CD80/86* on the DC binding to CD28 on the T cell

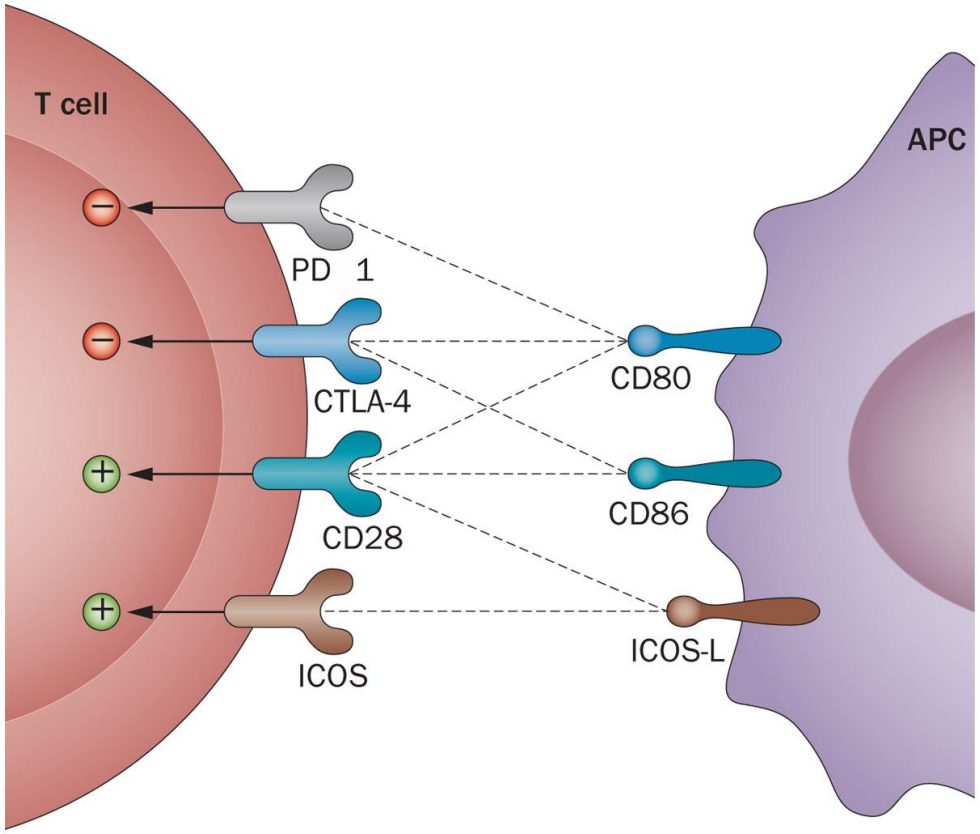
**** induced on DCs after PRR ligation***



NO SIGNAL 2 ?

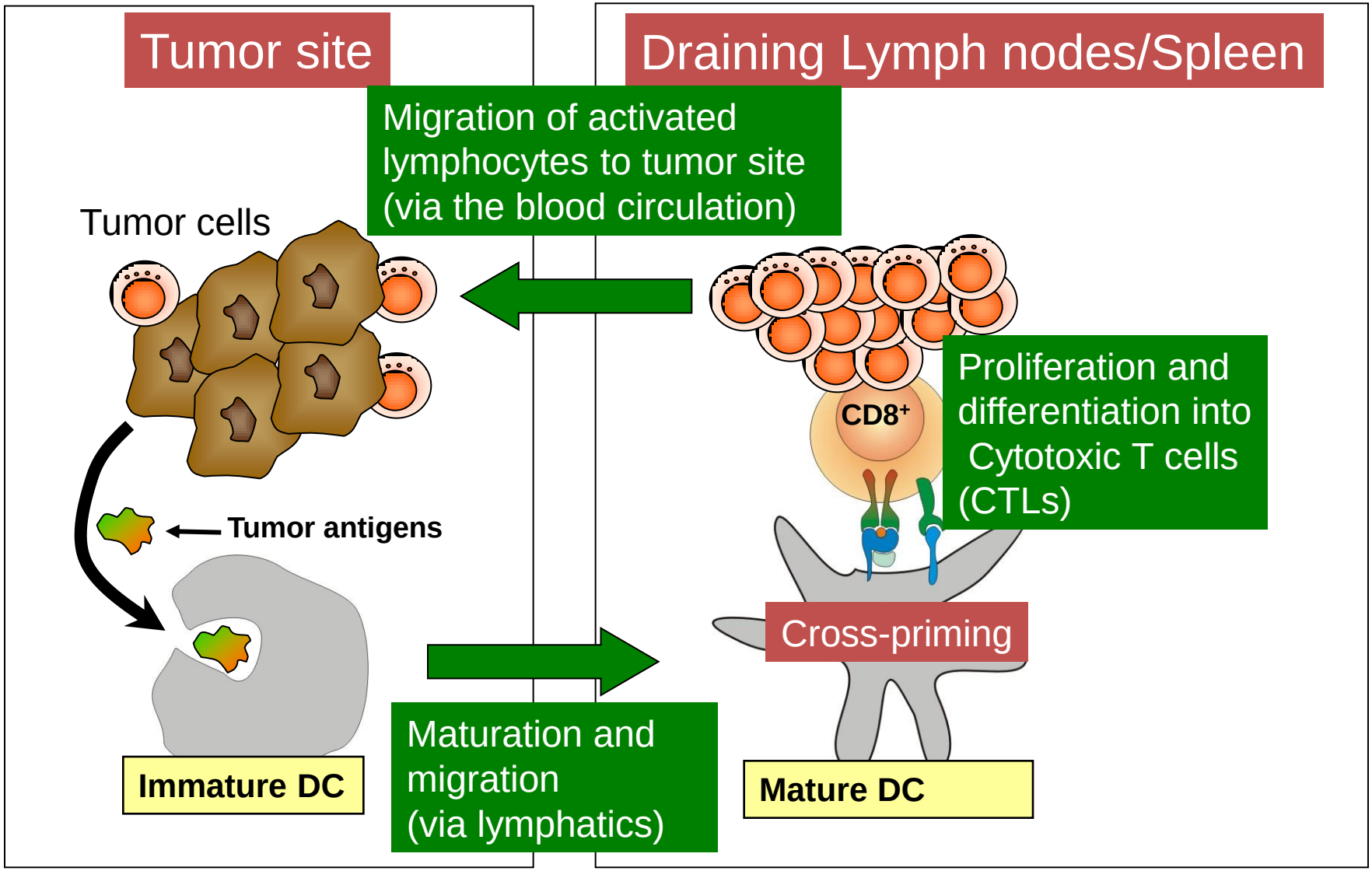


Complexities of the CD28 co-stimulatory pathway



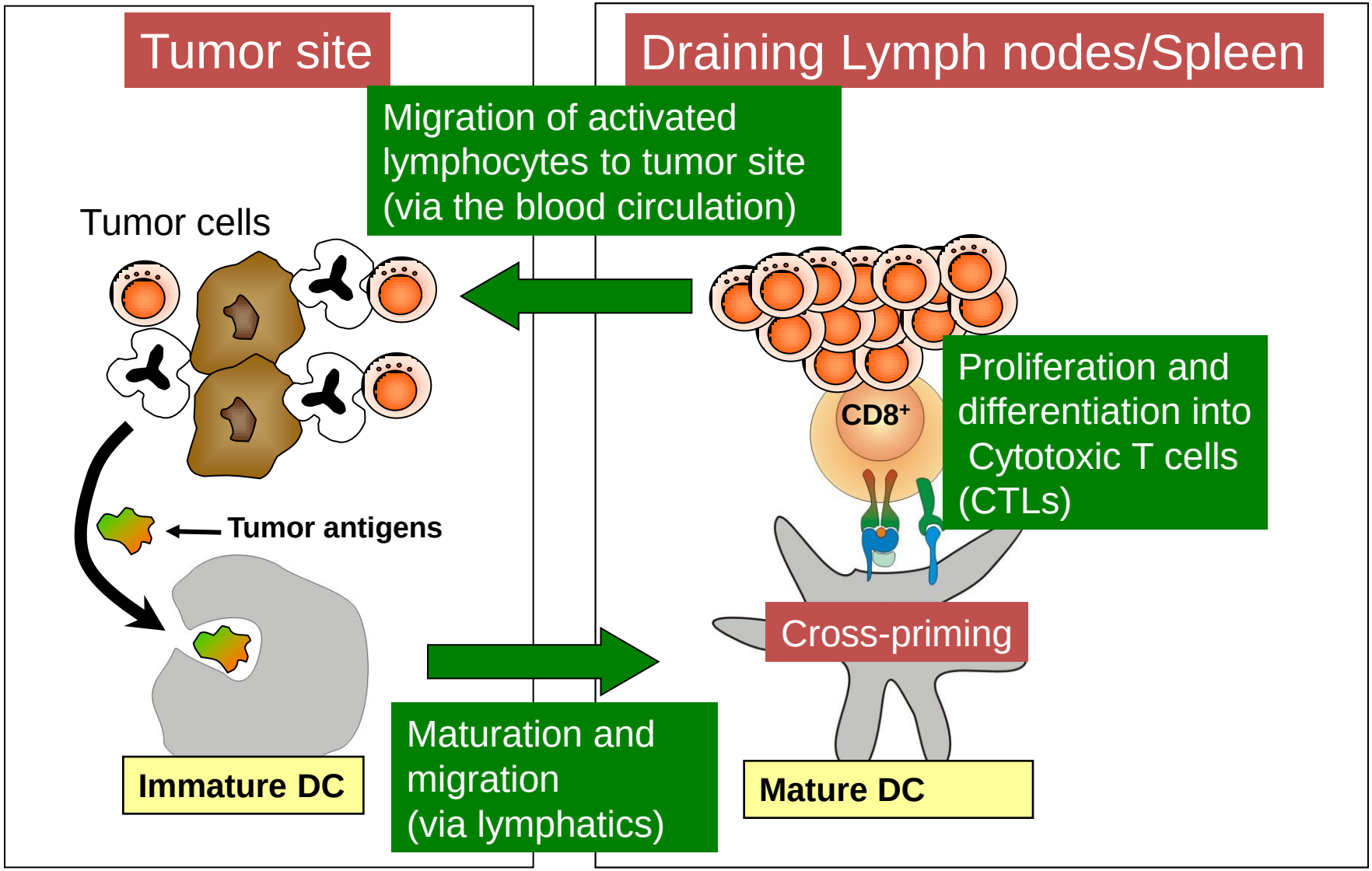
Ford, M. L. *et al.* (2013) Targeting co-stimulatory pathways: transplantation and autoimmunity *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2013.183

If co-stimulation>> co-inhibition…and if tumor + microenvironment permissive…
generation of an anti-tumor immune response
– leading to tumor regression by CD8 T cells



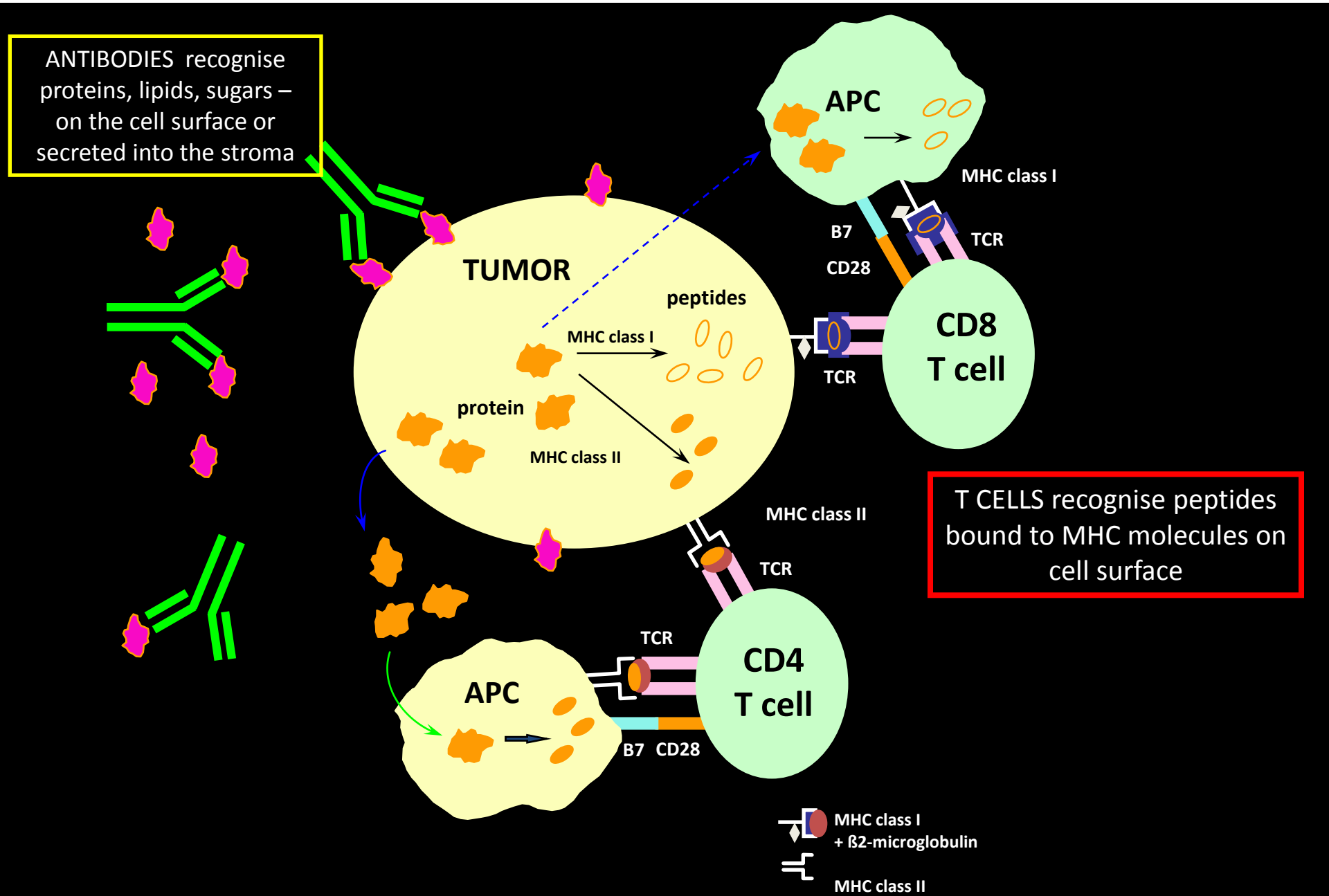
Idealised anti-tumor immune response

– *leading to tumor regression by CD8 T cells*



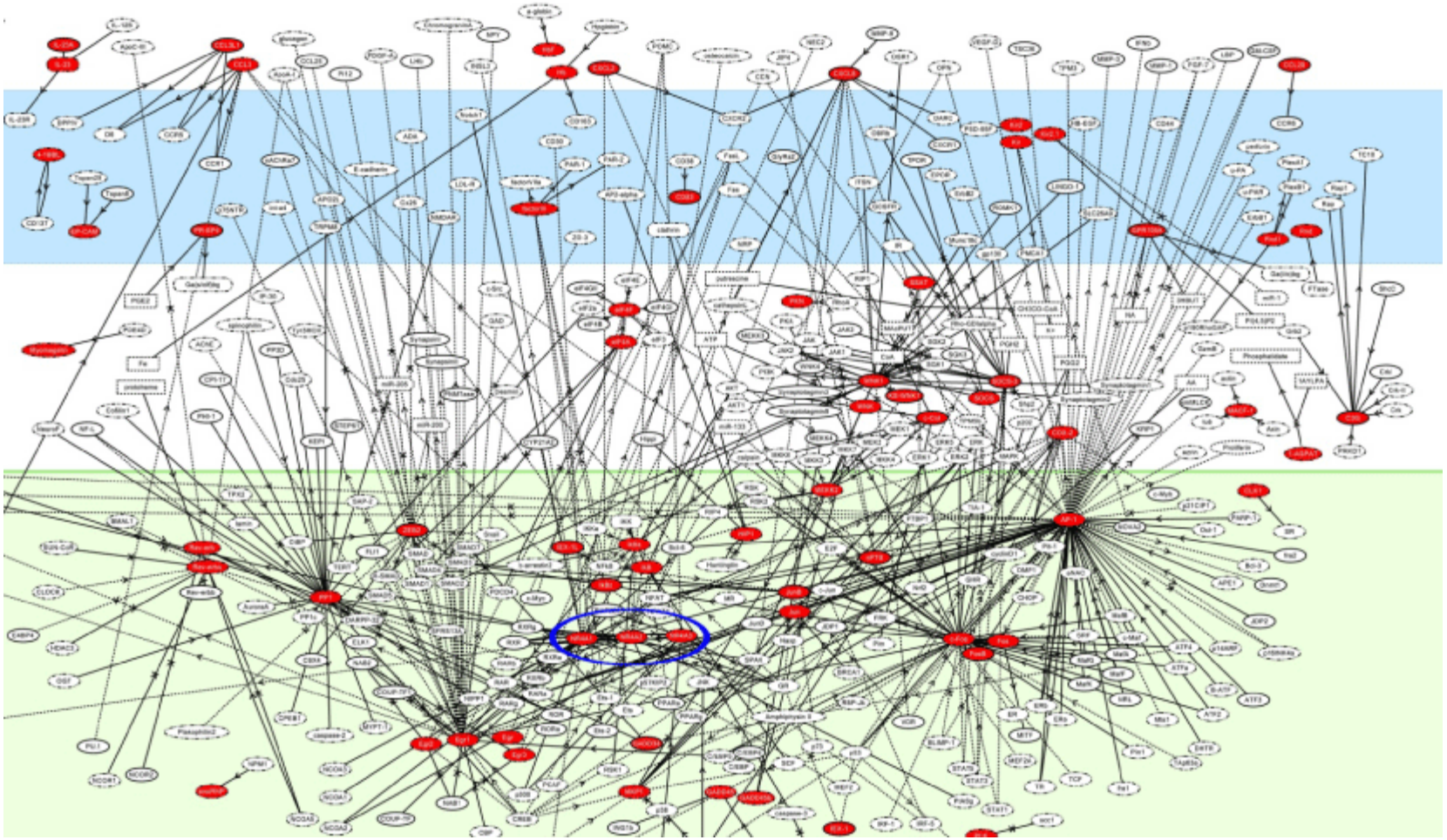
CD4 T cells and Antibodies also involved in tumor recognition

- but only T lymphocytes can detect INTRACELLULAR tumor antigens



Remember the basics…

and what follows will be easy to understand…

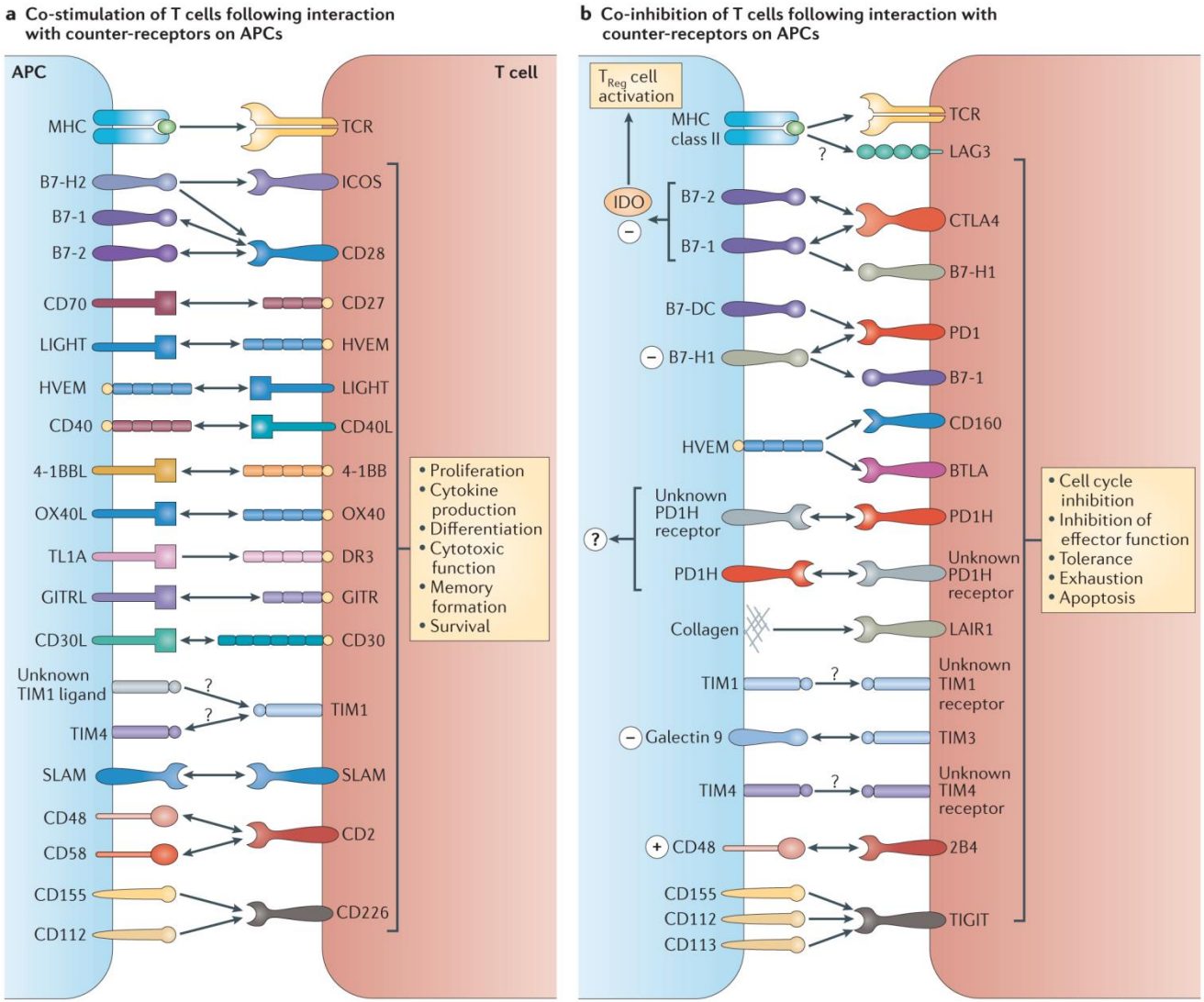


Adapted from Kawana N et al, Austin J et al, Clin Immunol. 2014;1(4): 10.

Thank you

Even more complexities of other co-stimulatory /inhibitory pathways

- Multiple possibilities for immune response regulation / fine tuning



L .Chen & D.B. Flies 2013, Nature Reviews Immunology 13, 227-242