Immune Regulation

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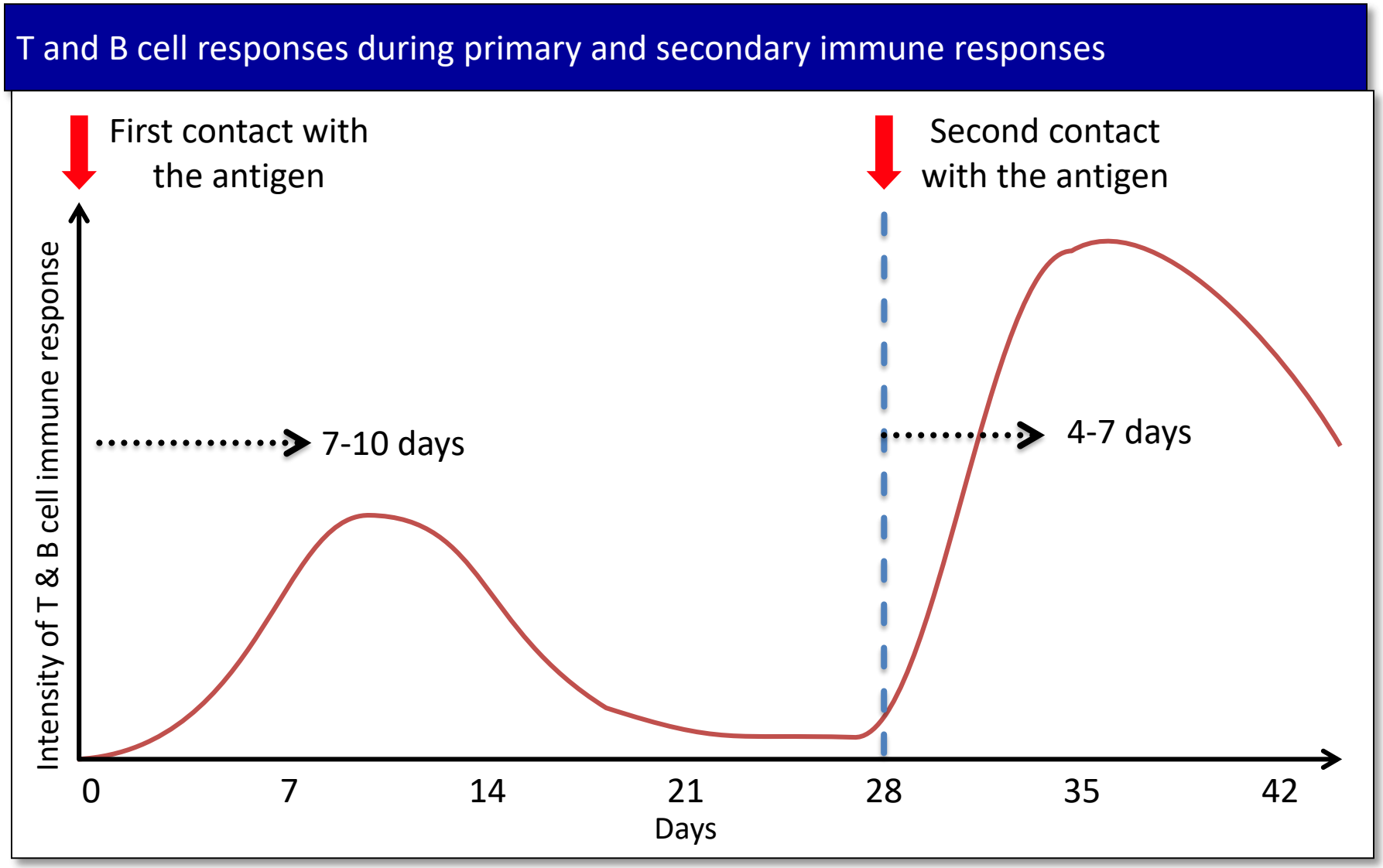
Molecular Immunology

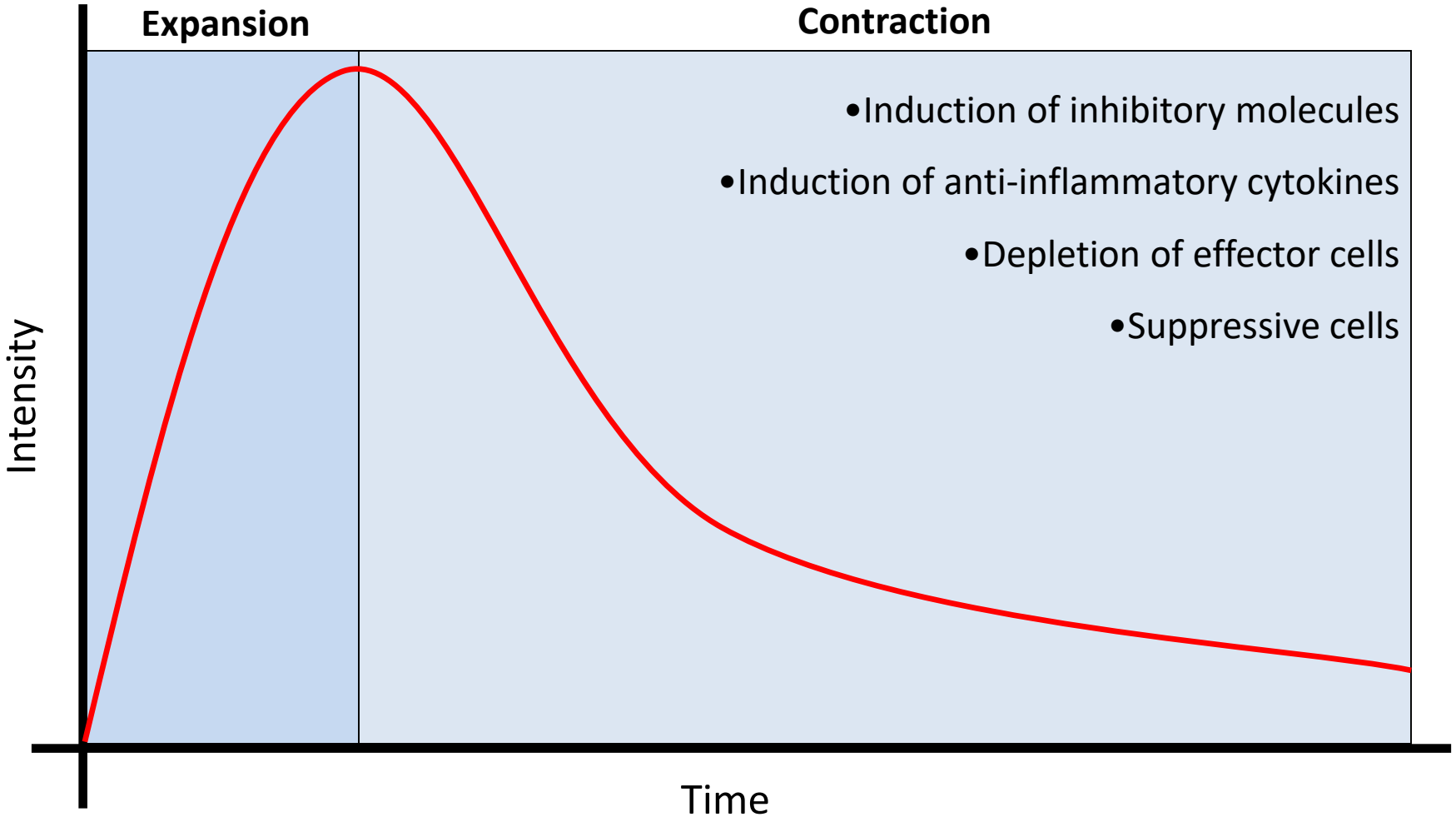
Index

- Introduction
- Tolerance
- Regulatory (Treg) cells
- Immunosuppressive cytokine: TGF-β
- Inhibitory molecules: CTLA-4 & PD-1 / PD-L1
- Depletion of effector cells: Apoptosis

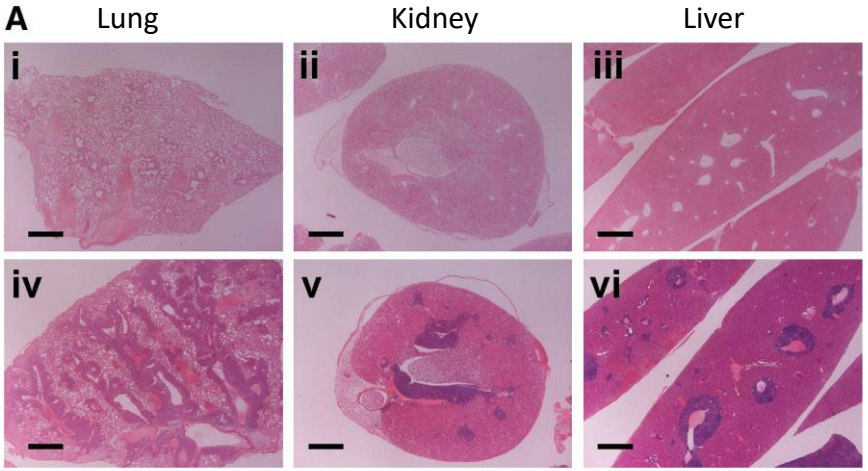
Primary and secondary immune response



Mechanisms of immune response

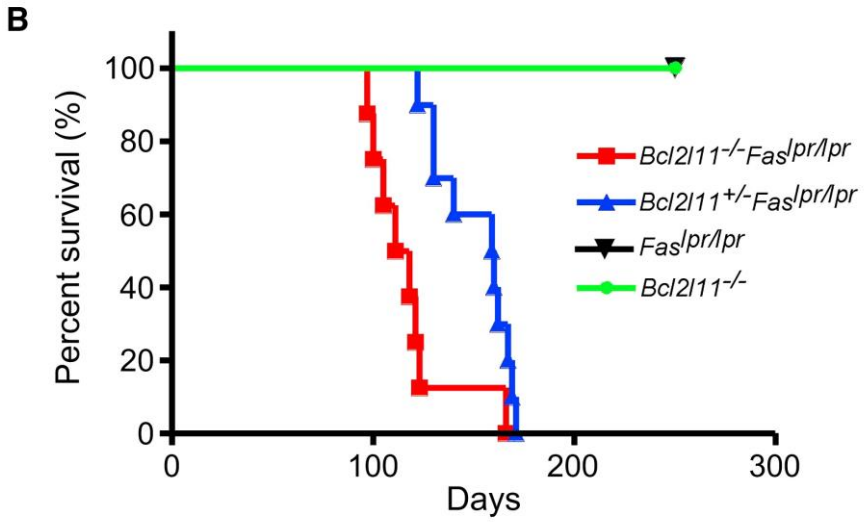


Apoptosis defect leads to lethal lymphoproliferation and a tolerance break



$Bcl2l11^{+/+}Fas^{lpr/lpr}$

$Bcl2l11^{-/-}Fas^{lpr/lpr}$



Hughes et al. (2008) Immunity 28, 197-205

Tolerance

Tolerance

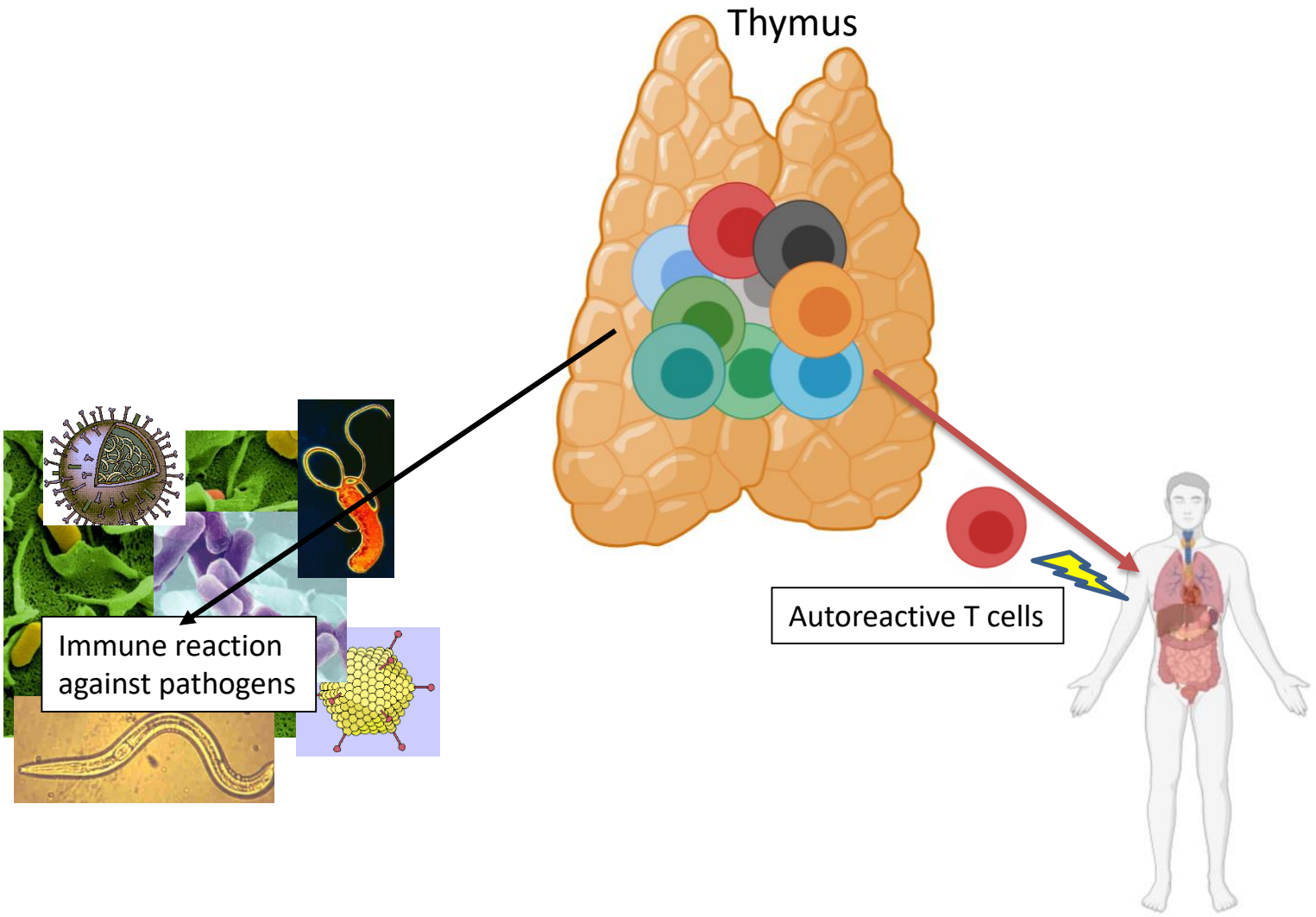
- Property of the immune system not to respond to self-antigens
- Differentiation between “self” and “foreign”

Tolerance break → **Autoimmune diseases**

Tolerance

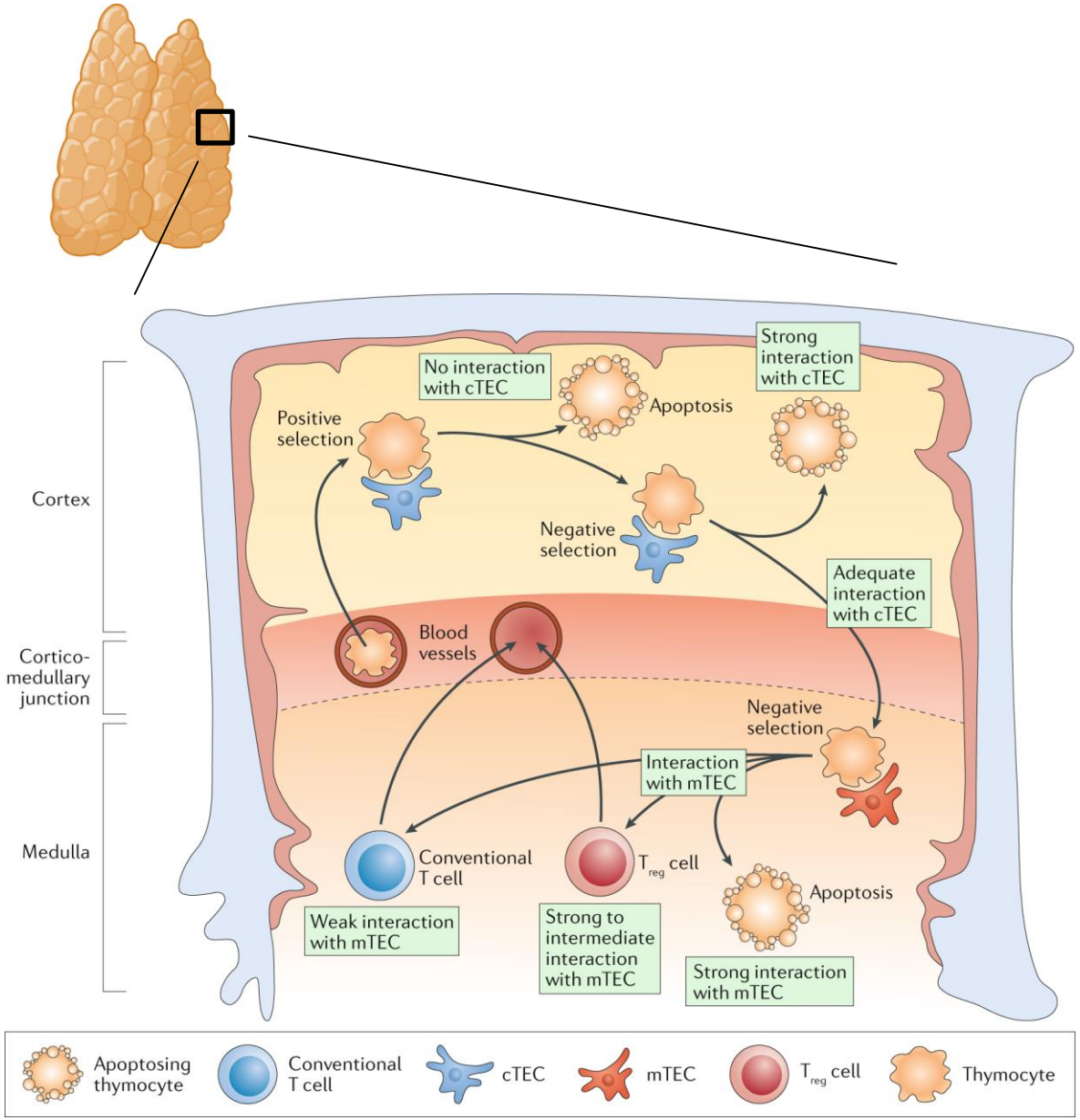
- 2 Levels of immunological tolerance:
  - Central tolerance
  - Peripheral tolerance

Central Tolerance & T cell development



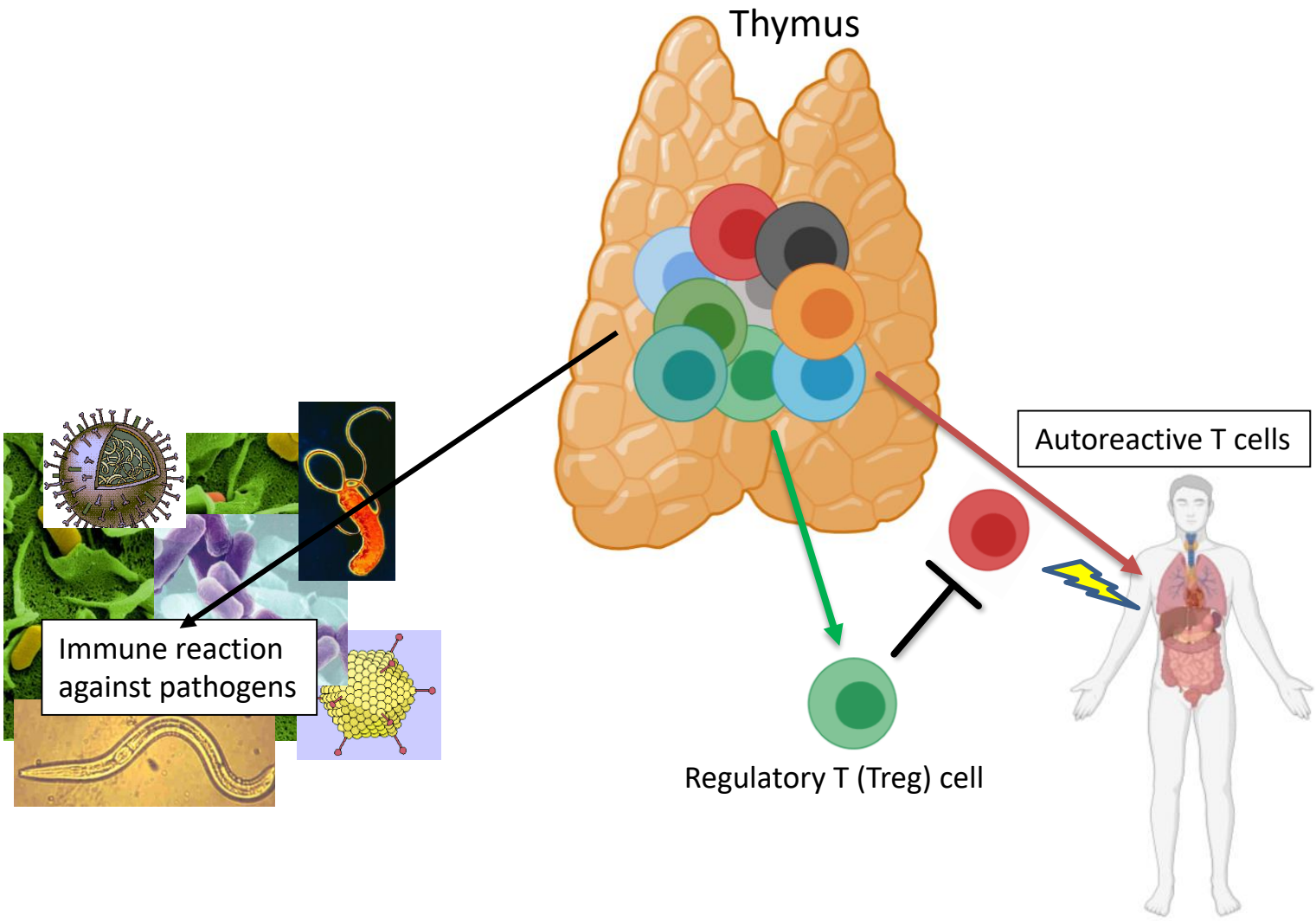
Central Tolerance & T cell development

J. Nikolic-Zugic (1991)
Immunology Today; Vol.12 No.2

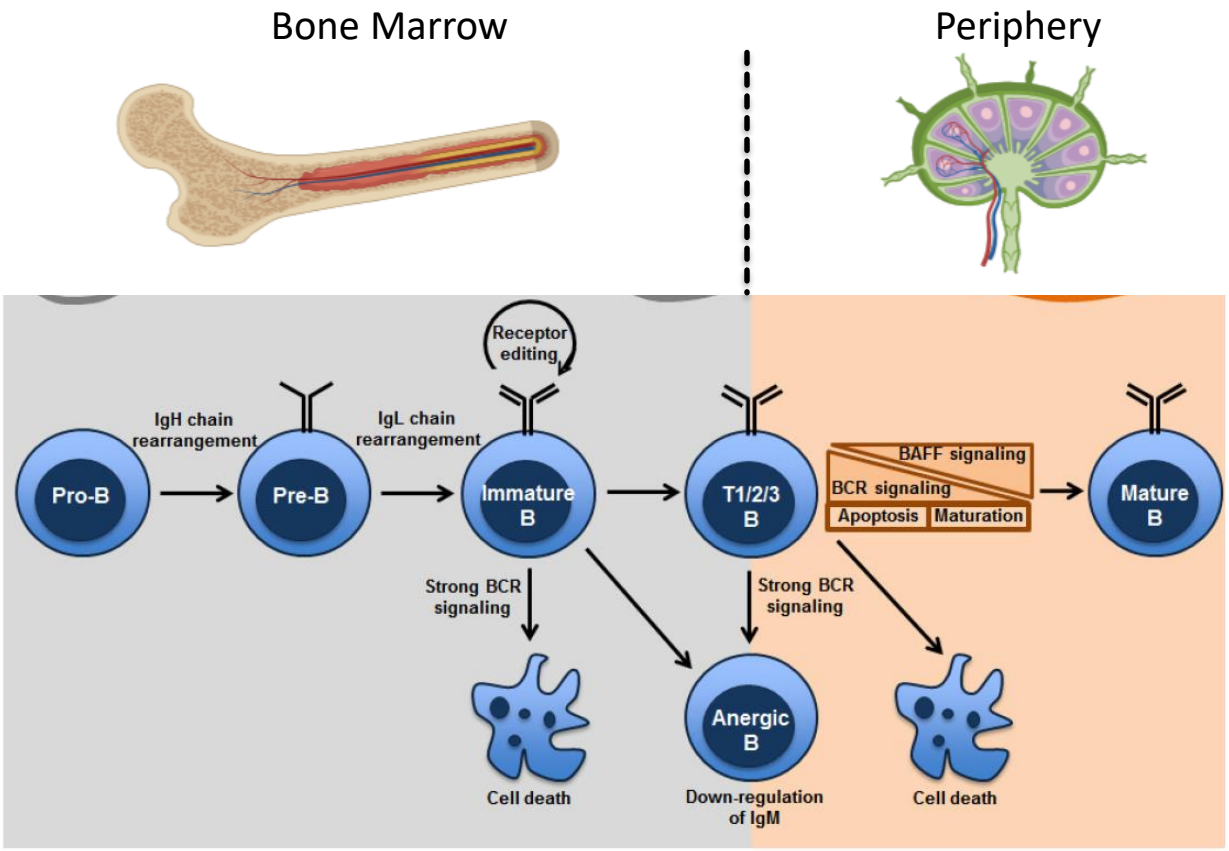


Handel.2018

Peripheral Tolerance & T cell development



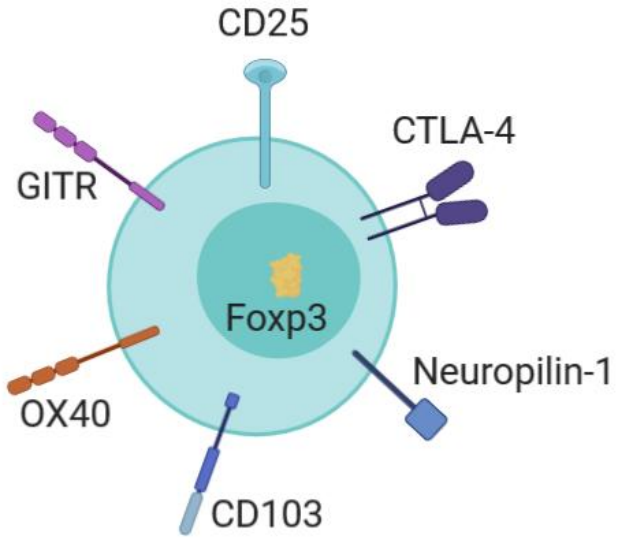
B cell selection

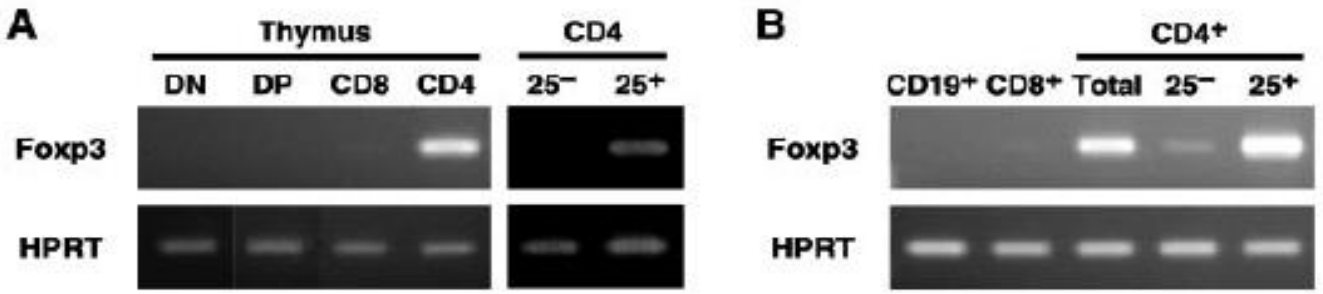


Gururajan. 2014

Regulatory T (Treg) cells

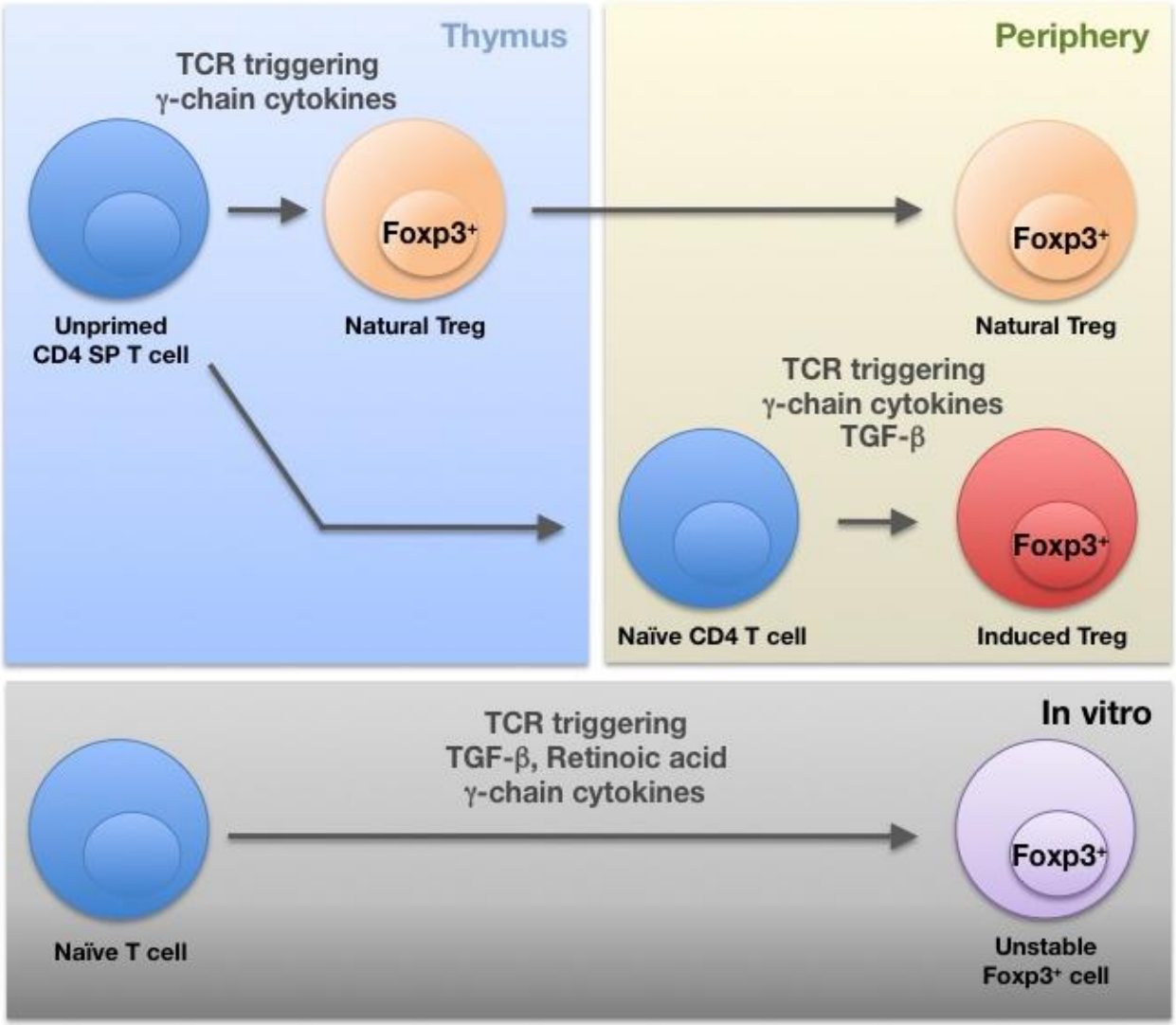
Treg cell markers





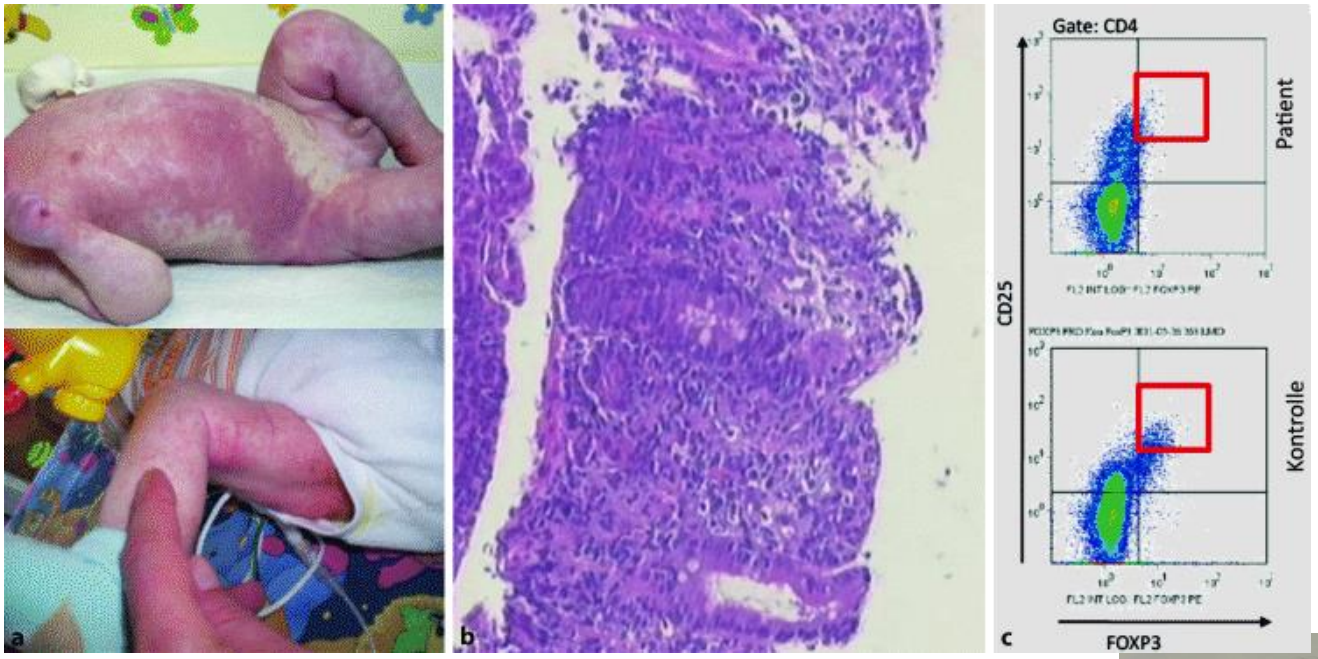
Hori et al. Science (2003) 299:1057

Treg cell sources



FoxP3 mutation causes autoimmune syndrome

IPEX = immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome



Weber et al., Pädiatrische Gastroenterologie, Hepatologie und Ernährung, pp 731-744, Springer 2013

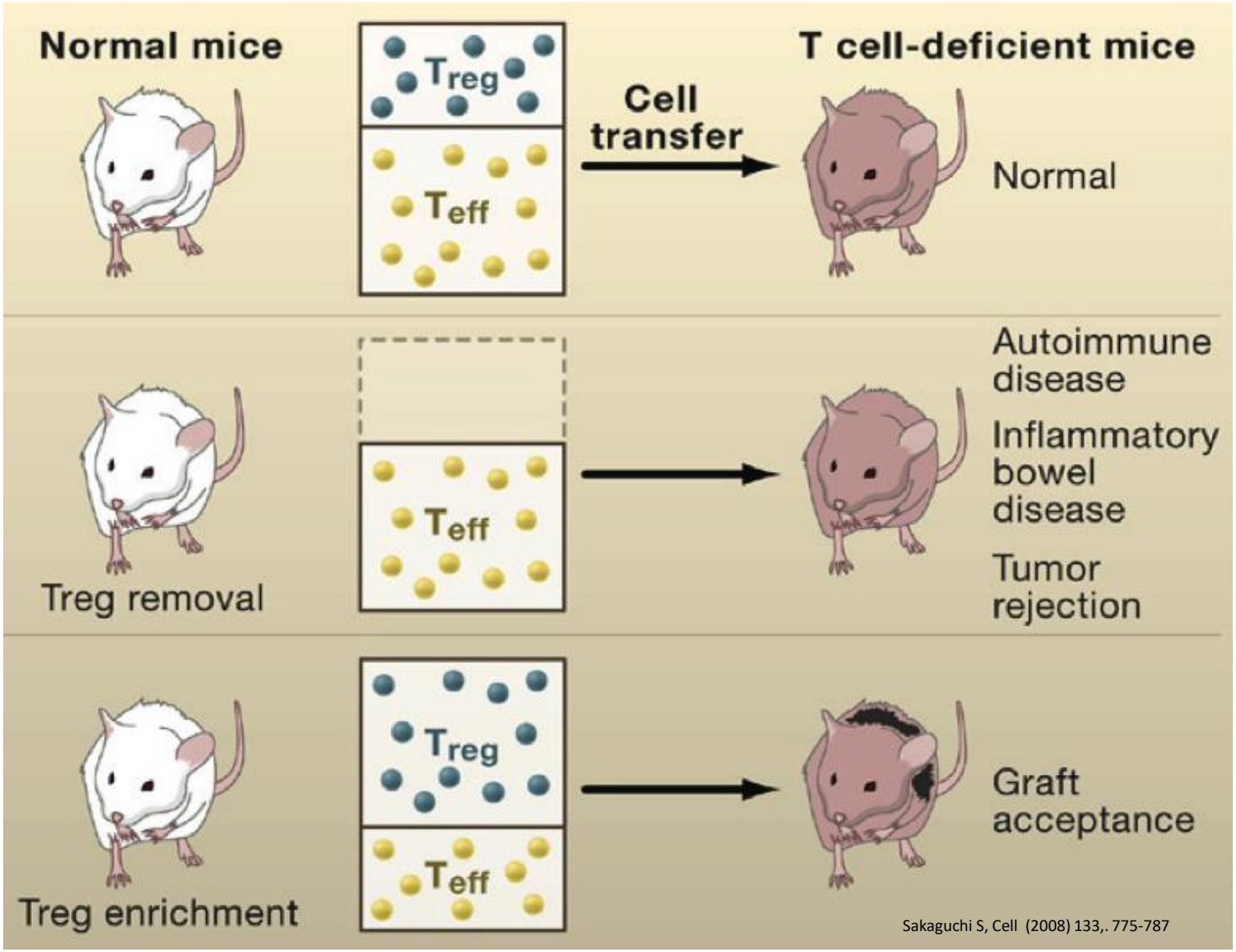
***Scurfy* mouse (spontaneous mutation)**

Bennett et al., *Nat Genet* 2001

Brunkow et al., *Nat Genet* 2001

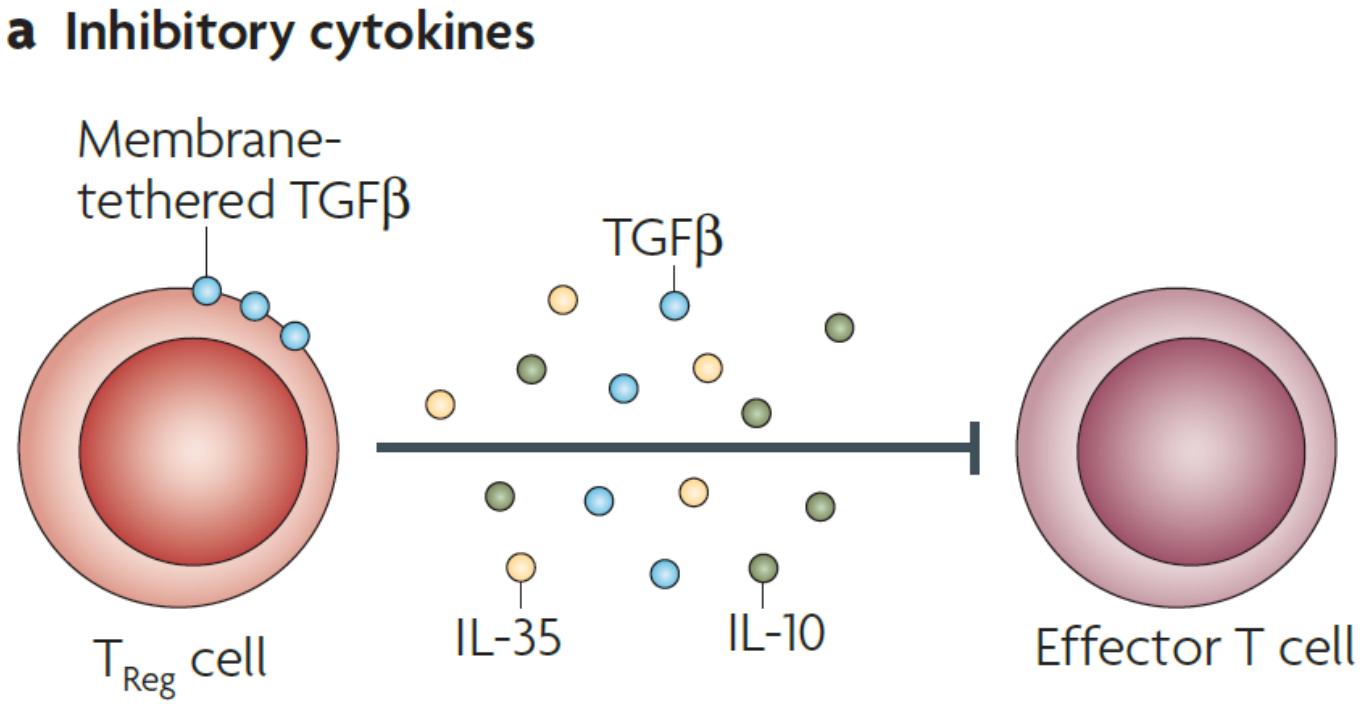
Chatila et al., *J Clin Inv* 2000

Effects of Treg cell deficiency / enrichment



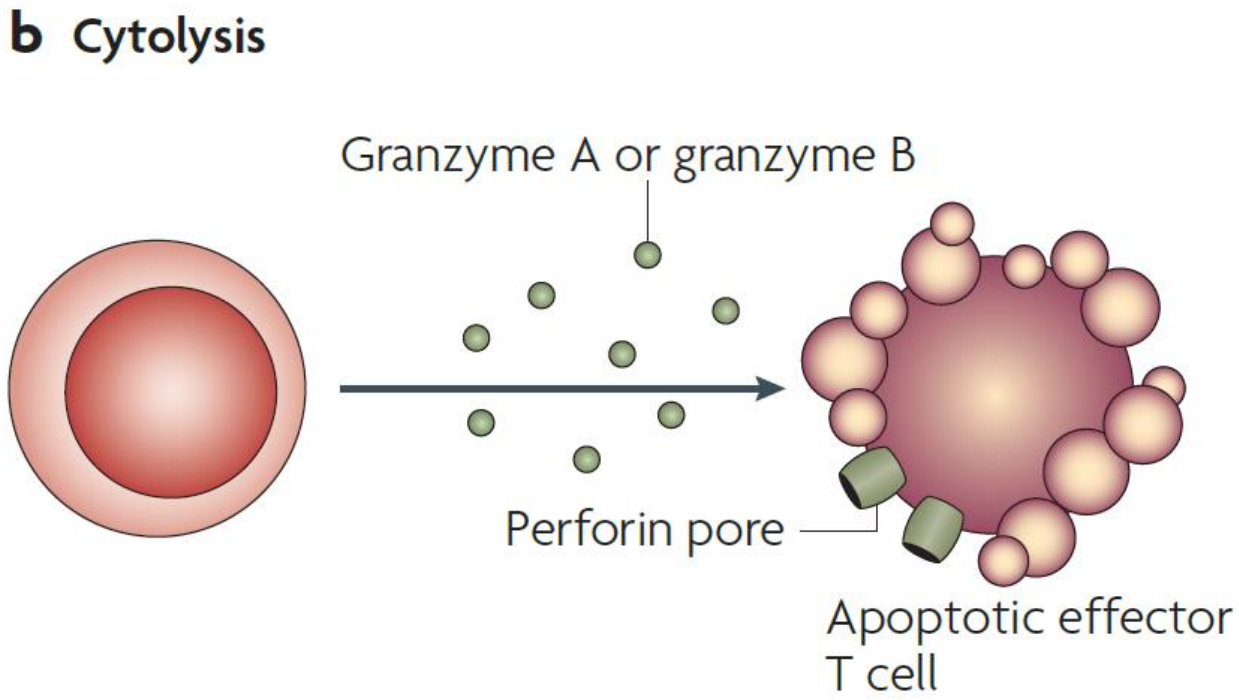
Sakaguchi S, Cell (2008) 133,. 775-787

Treg cell-mediated mechanisims of immunosupression



Vignali DAA, Nat. Rev Immunol (2008) 8, 523-532

Treg cell-mediated mechanisims of immunosupression



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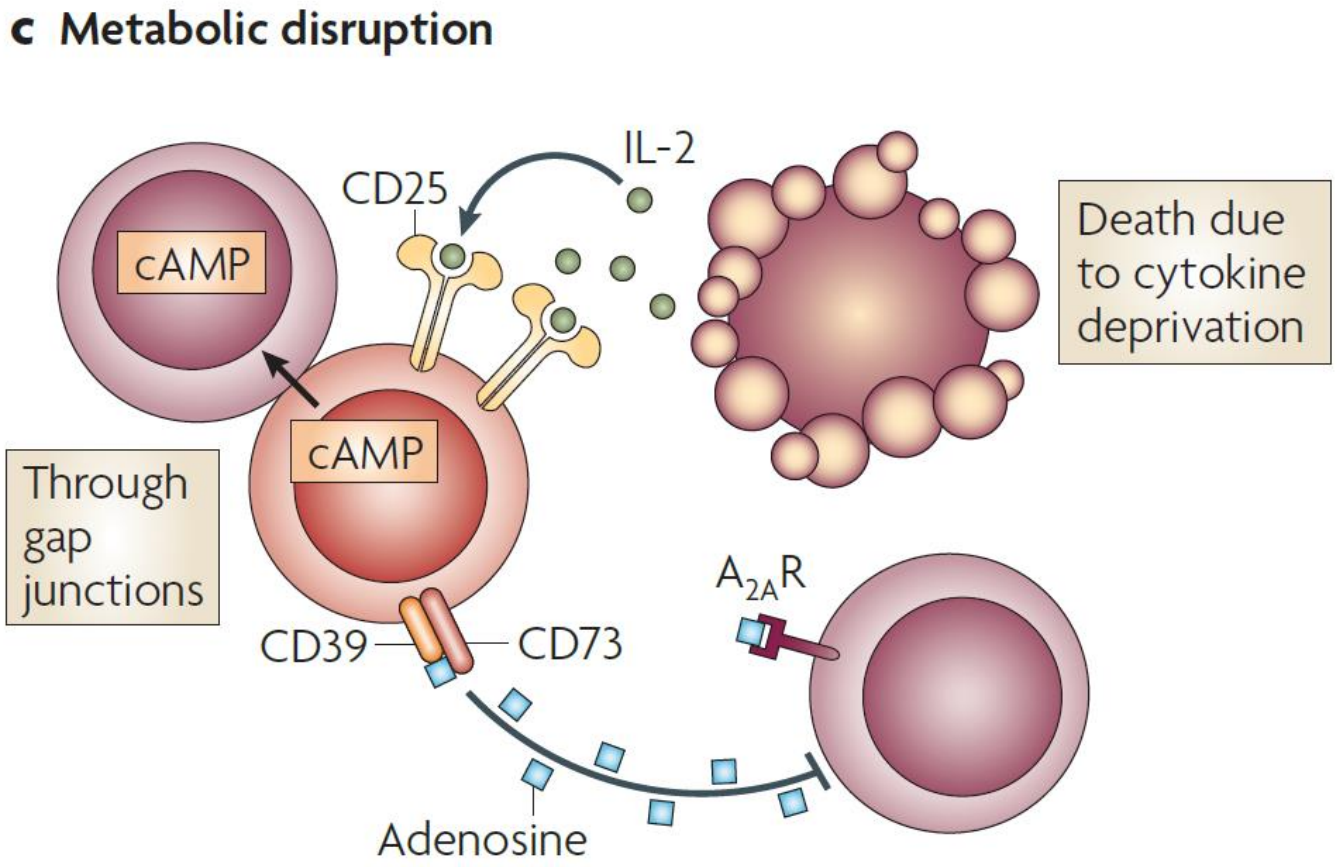
Treg cell-mediated mechanisims of immunosupression



Vignali DAA, Nat. Rev Immunol (2008) 8, 523-532

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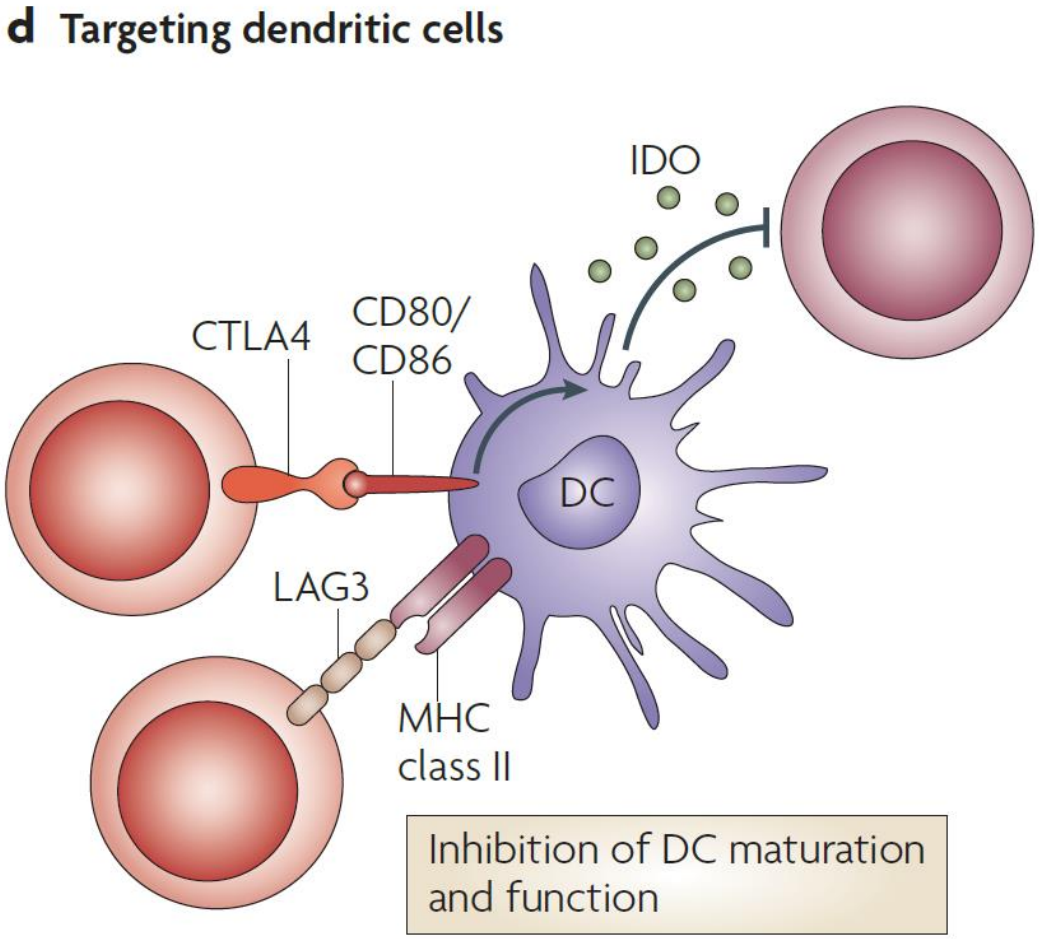
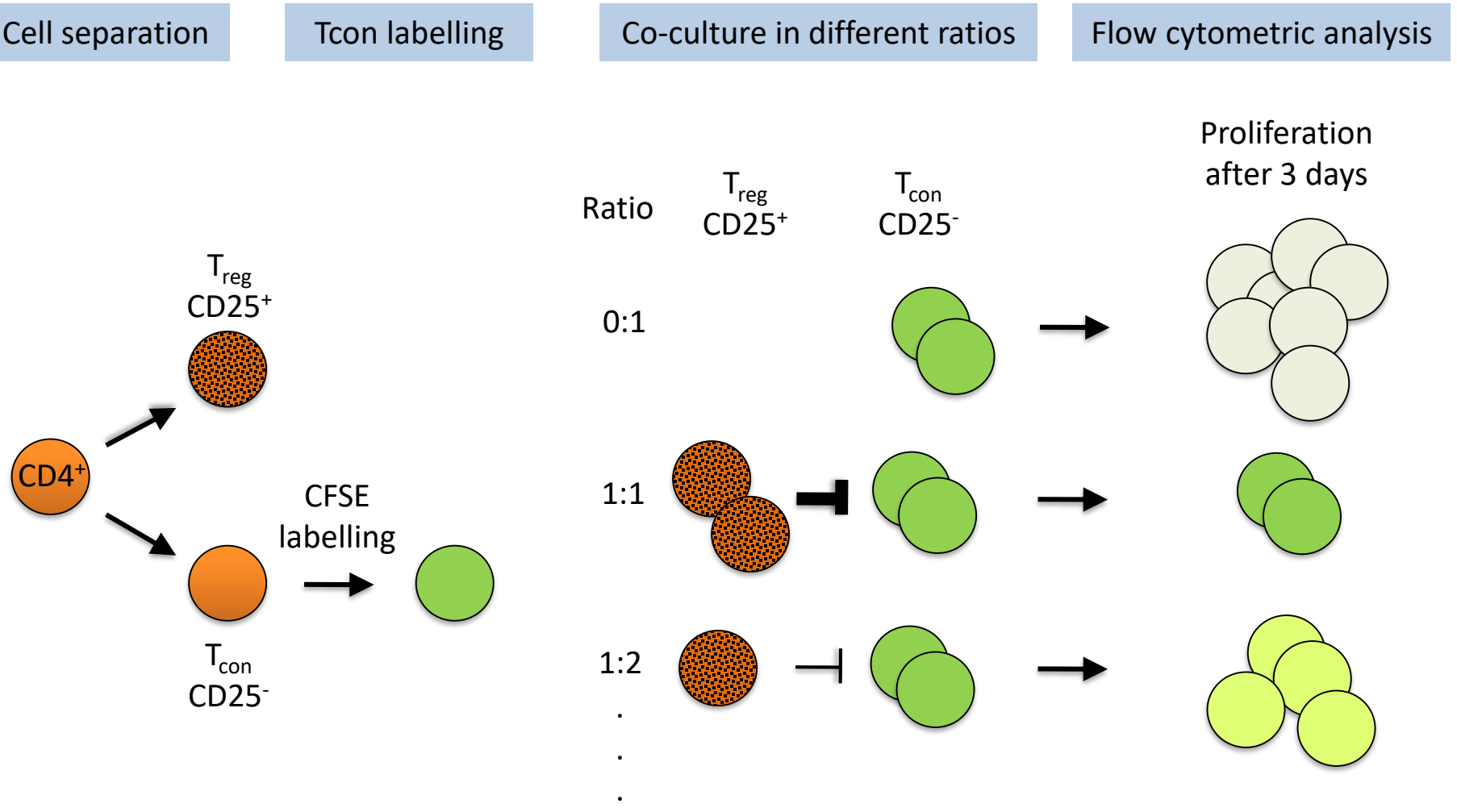
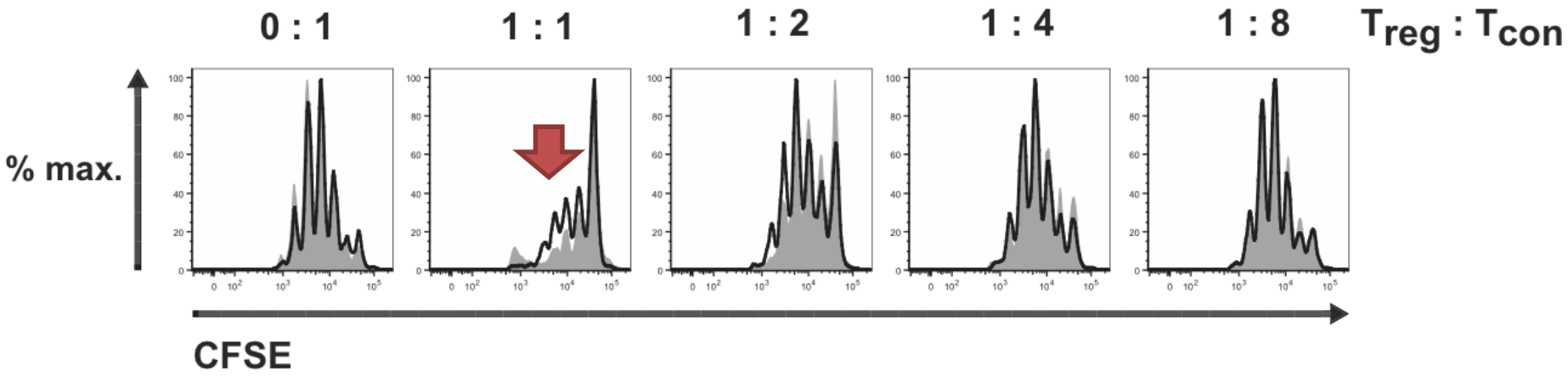


Vignali DAA, Nat. Rev Immunol (2008) 8, 523-532

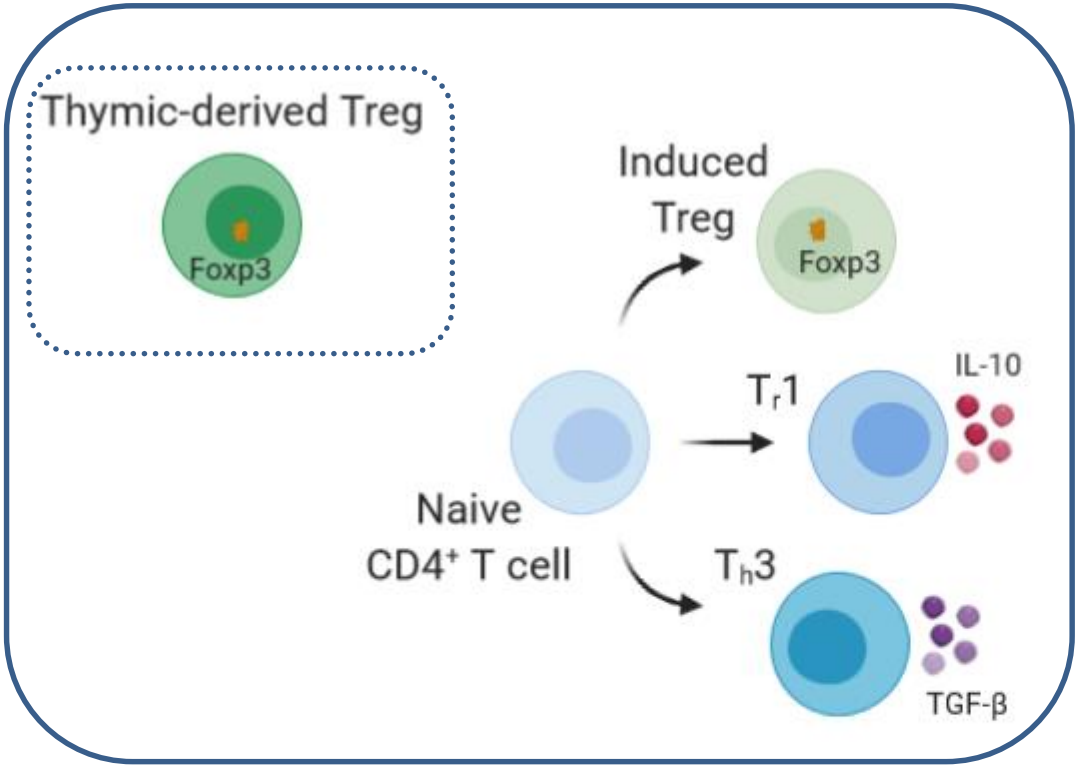
Treg cells inhibit T cell proliferation: *in vitro* suppression assay

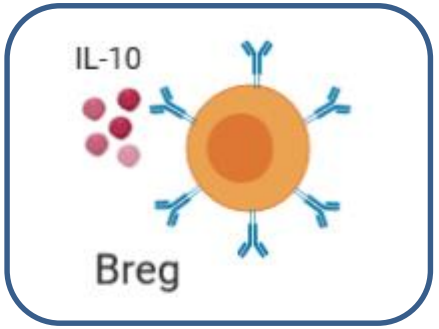


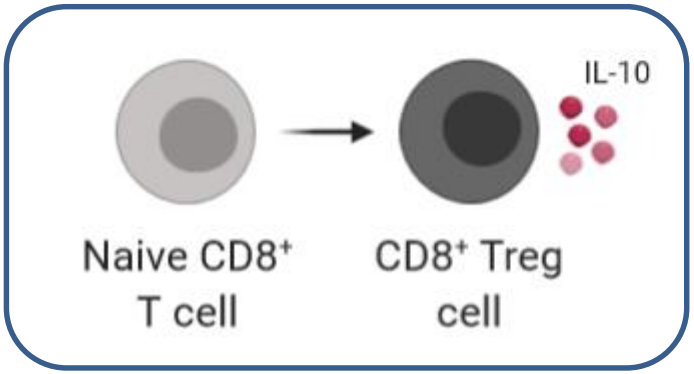
Treg cells inhibit T cell proliferation: *in vitro* suppression assay

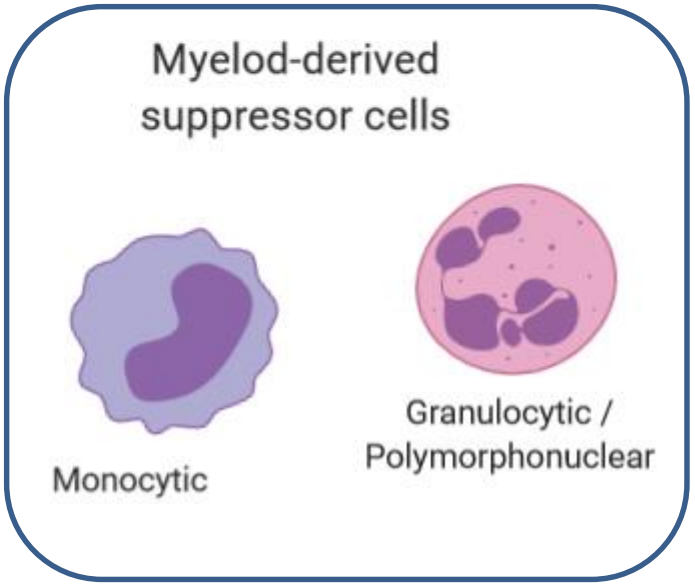


Supressive immune cells









Immunosuppressive cytokine: TGF-β

Immunosuppressive Cytokine: TGF-β

“TGF-ß: Brake of the immune system.”

“TGF-ß influences the life and death of T lymphocytes.”
S.M. Wahl: Cytokine Growth Factor Rev. 11, 71-79 (2000)

TGF-β family:

- TGF-β1 (predominant in the immune system)
- TGF-β2
- TGF-β3

Involved in embryogenesis, carcinogenesis and the immune response

TGF-β1 deficient mouse

TGF-β1$^{-/-}$ mouse

Leukocyte adherence

MHC I, II

Inflammation

Multi-organ failure

Death

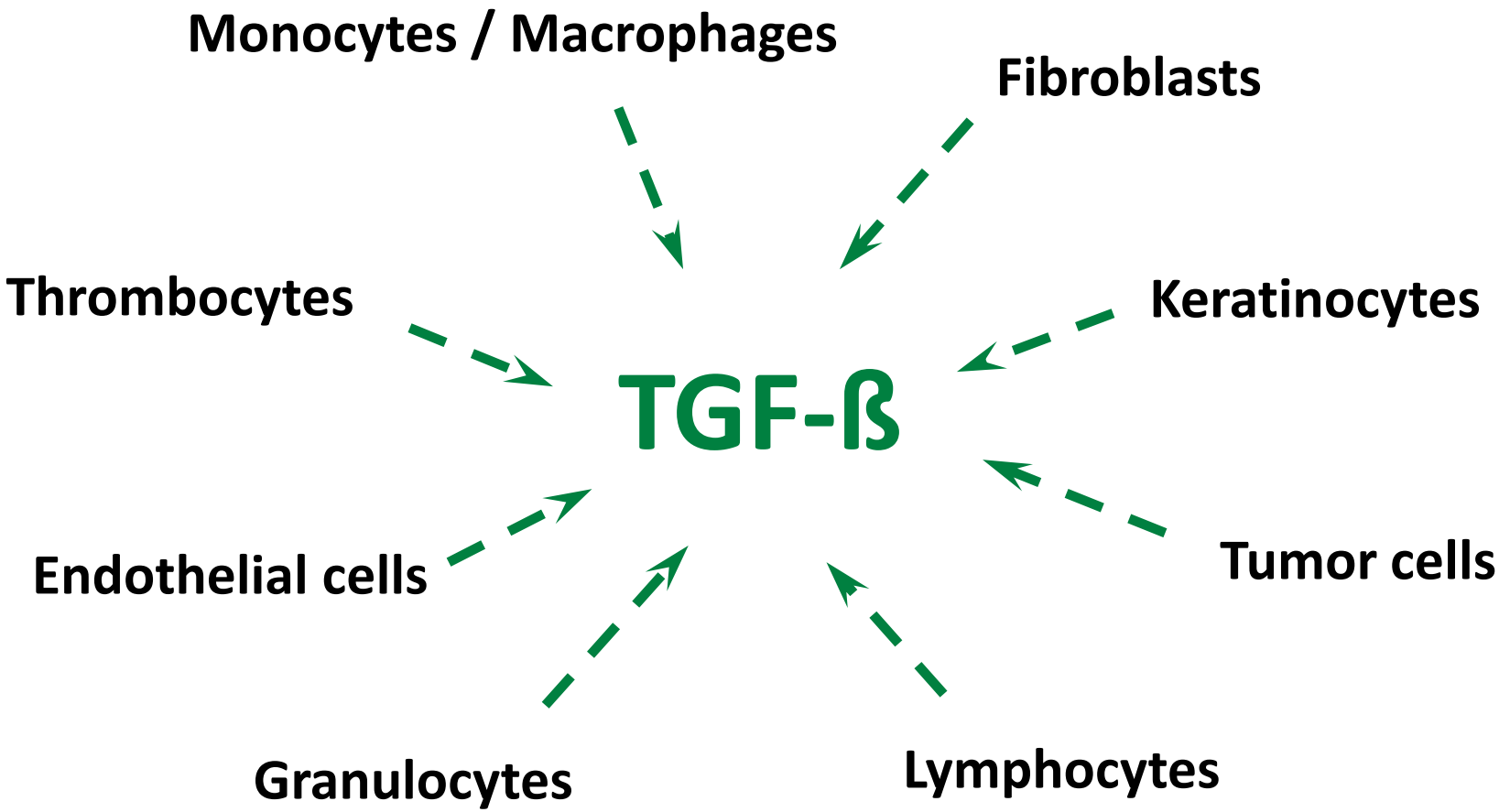
0 7 14 21 28

Age (Days)

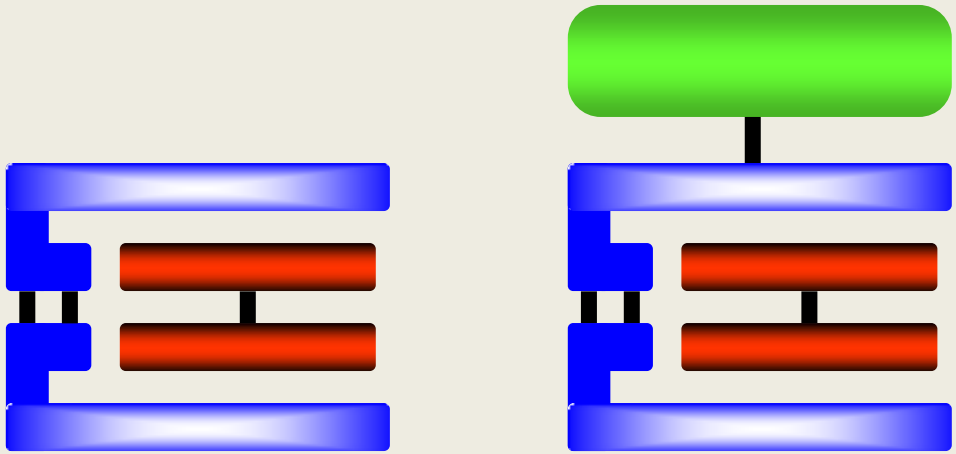
Maternal TGF-β1

Gorelik and Flavell 2000; Li et al. 2006a; Marie et al. 2006

TGF-β secreting cells



TGF-β structure



~ 100 kDa

~ 225 - 260 kDa

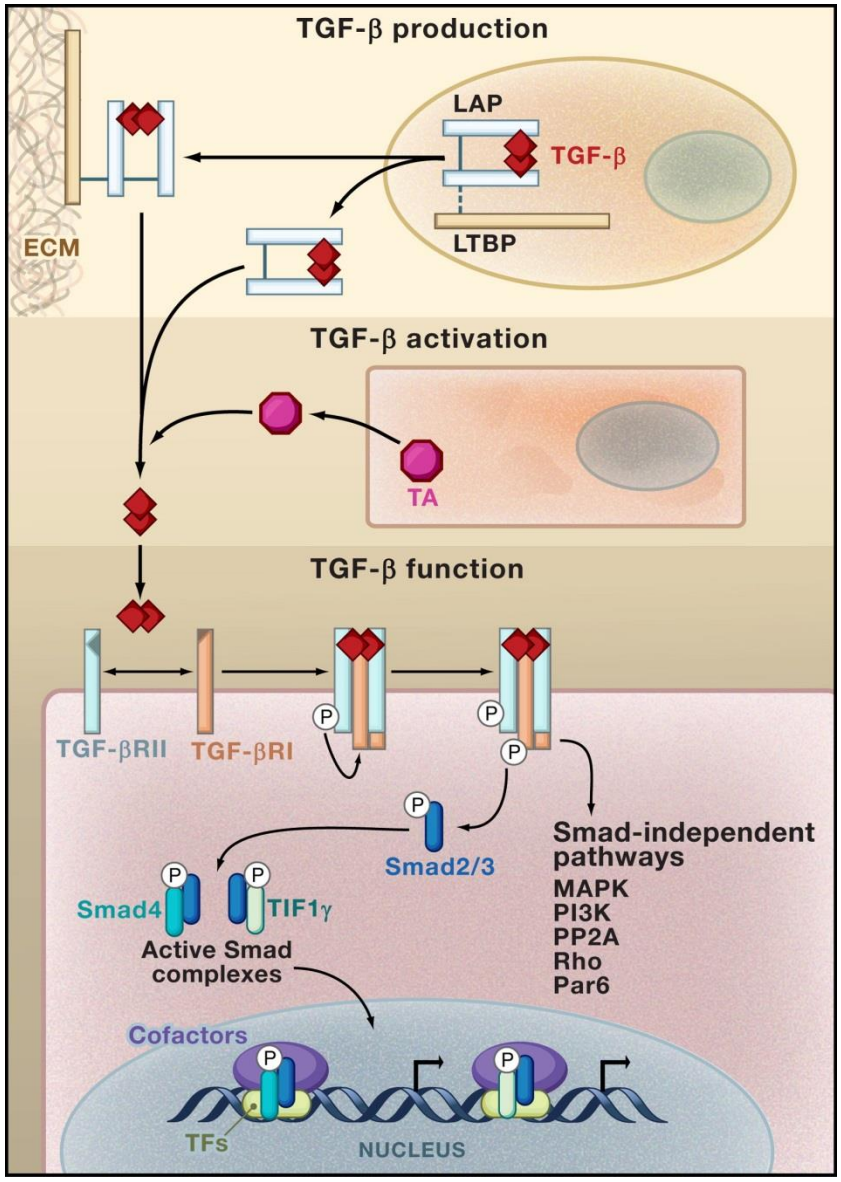
LTBP: 125 -160 kDa

LAP: 75 kDa

Active TGF-β: 25 kDa

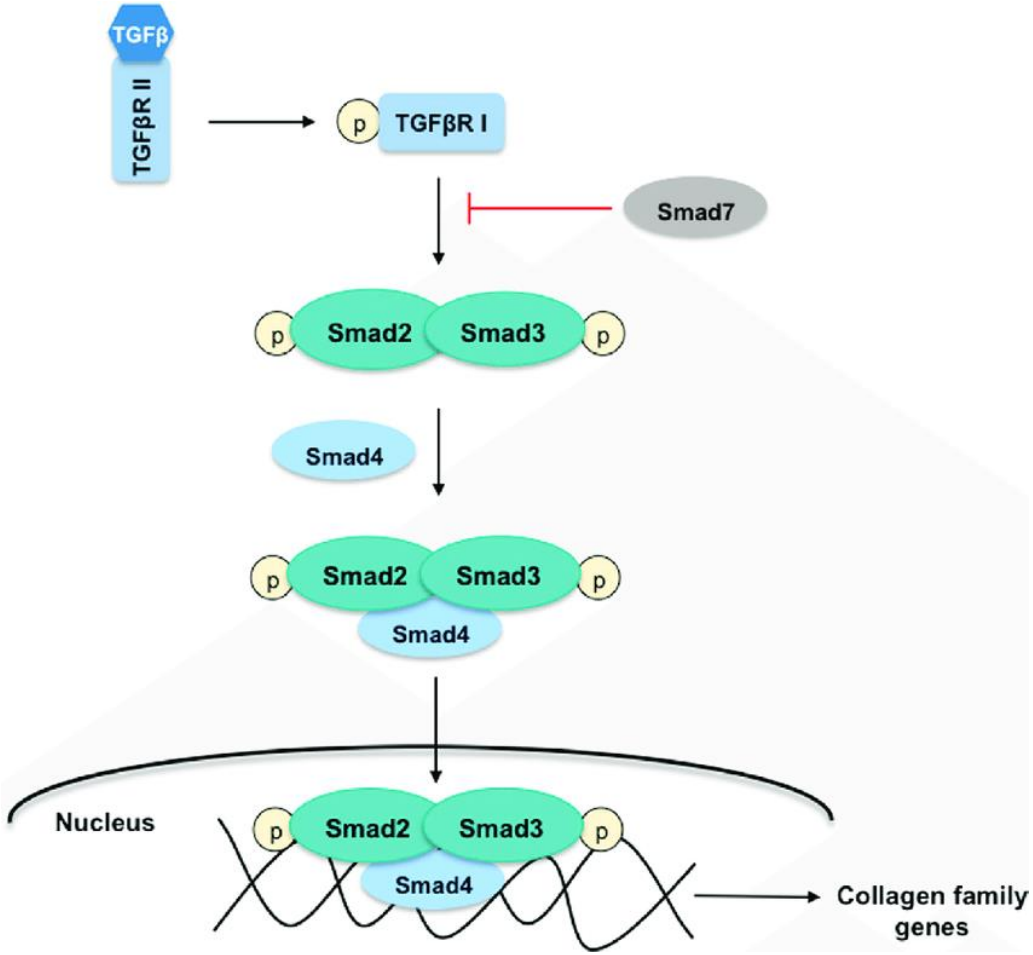
LAP = Latency-associated protein
LTBP = Latent TGF-β binding protein

TGF-β: from secretion to gene induction



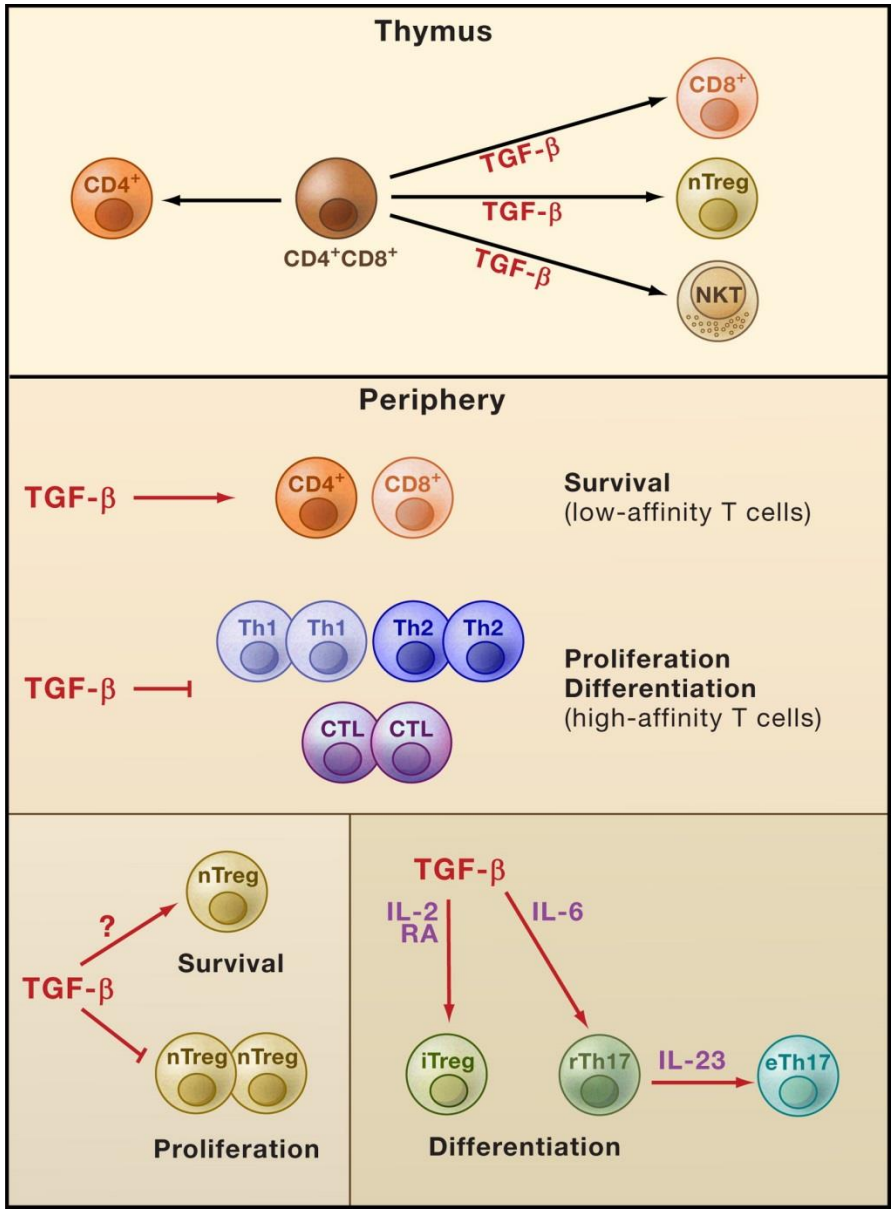
Li & Flavell, Cell. 2008 Aug 8;134(3):392-404.

TGF-β signaling



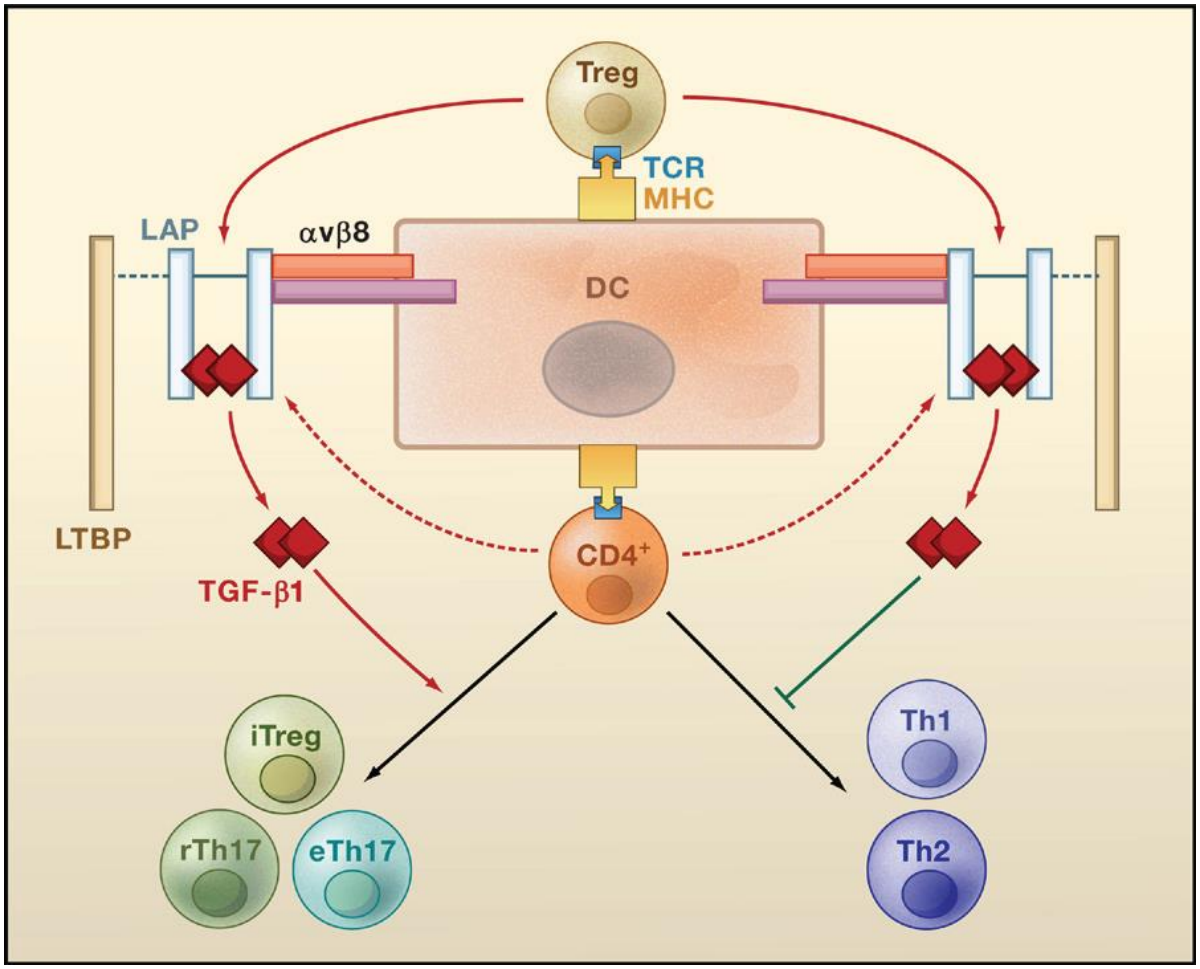
Fernández-Iglesias & Gracia-Sancho. 2017

TGF-β-mediated T cell regulation



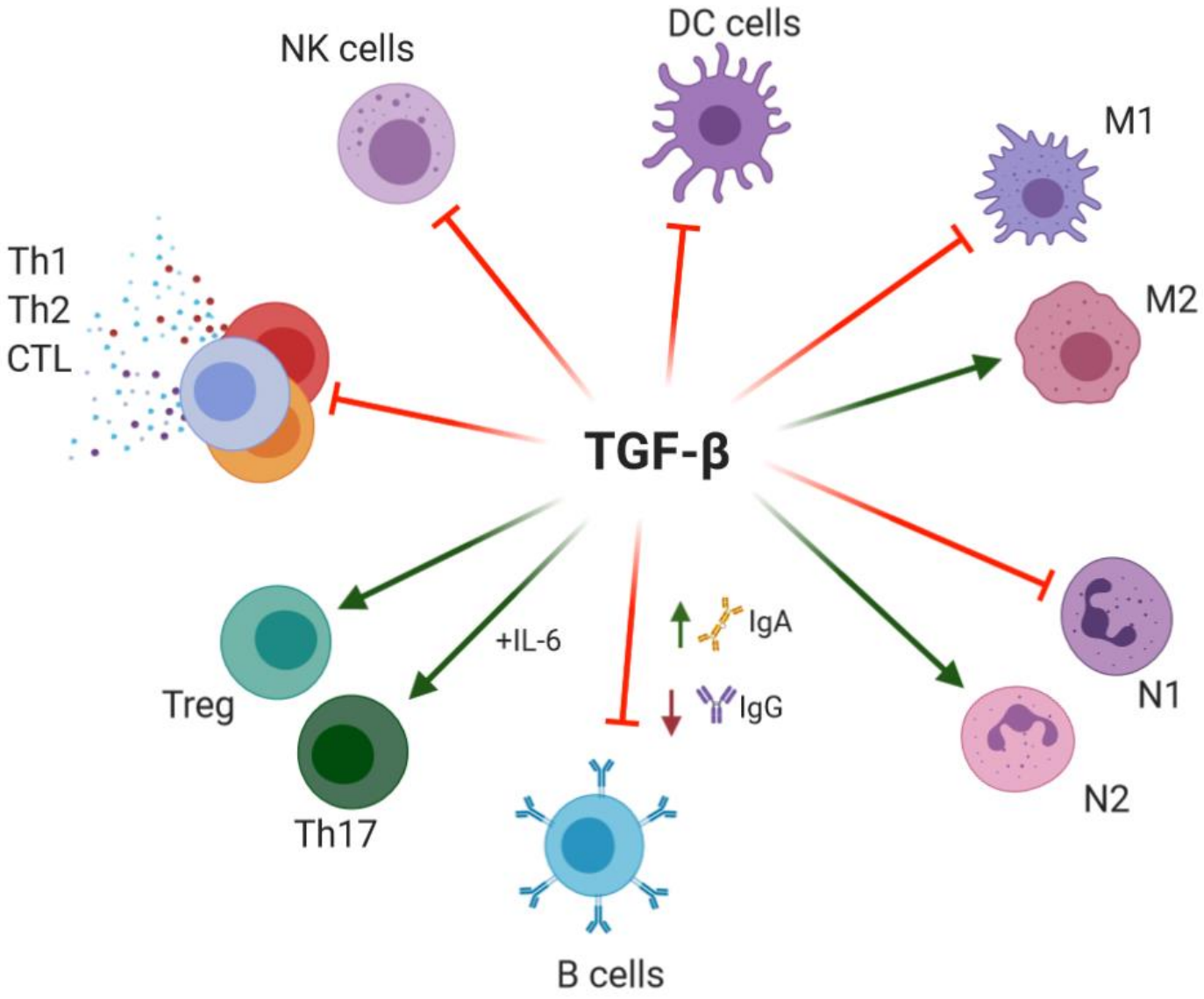
Li & Flavell, Cell. 2008 Aug 8;134(3):392-404.

TGF-β-mediated immune synapsis regulation



Li & Flavell, Cell. 2008 Aug 8;134(3):392-404.

Effects of TGF-β on immune cells



Inhibitory molecules

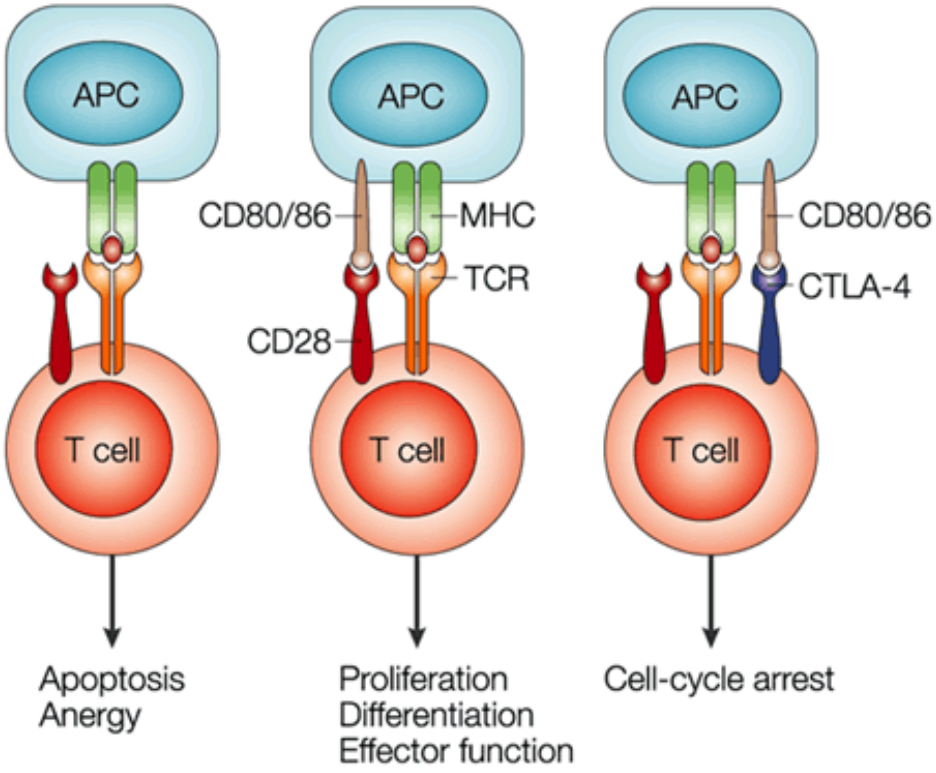
CTLA-4

PD-1 / PD-L1

CTLA-4

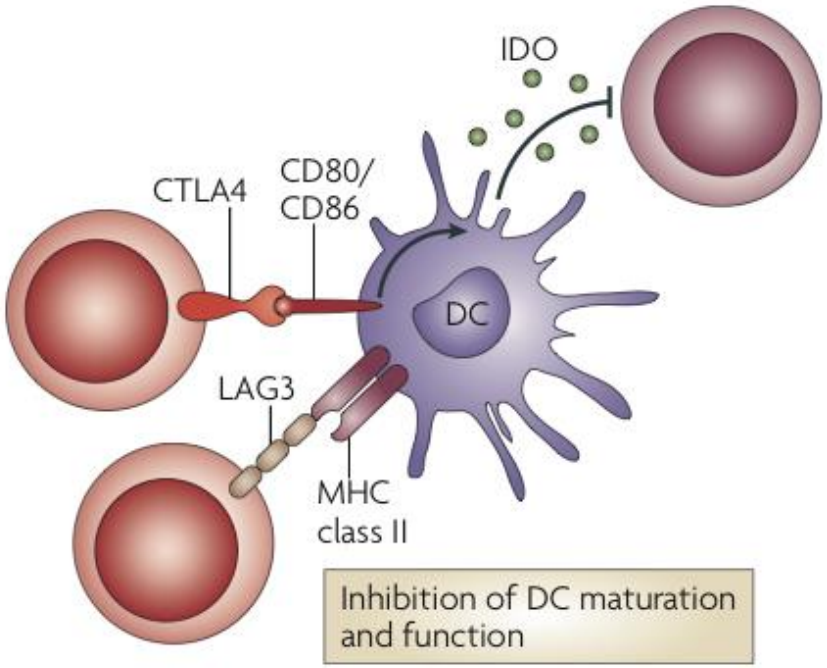
- **CTLA-4**: cytotoxic T-lymphocyte antigen-4 (CD152)
- **CD28 homologue**: immunoglobulin family
- **Inhibitory receptor**: binds to CD80 and CD86 with higher affinity than CD28. Inhibits T cell activity and causes cell anergy.
- **Expression:** Treg cells and activated T effector cells (few days after activation)
- **CTLA-4$^{-/-}$ (KO)-mause**: massive lymphocyte expansion and lymphocyte infiltration into many tissues, uncontrolled lymphocyte proliferation, generalized autoimmune disease, death at about 6 weeks.

CTLA-4 intrinsic effect



Nature Reviews | Immunology

CTLA-4 extrinsic effect



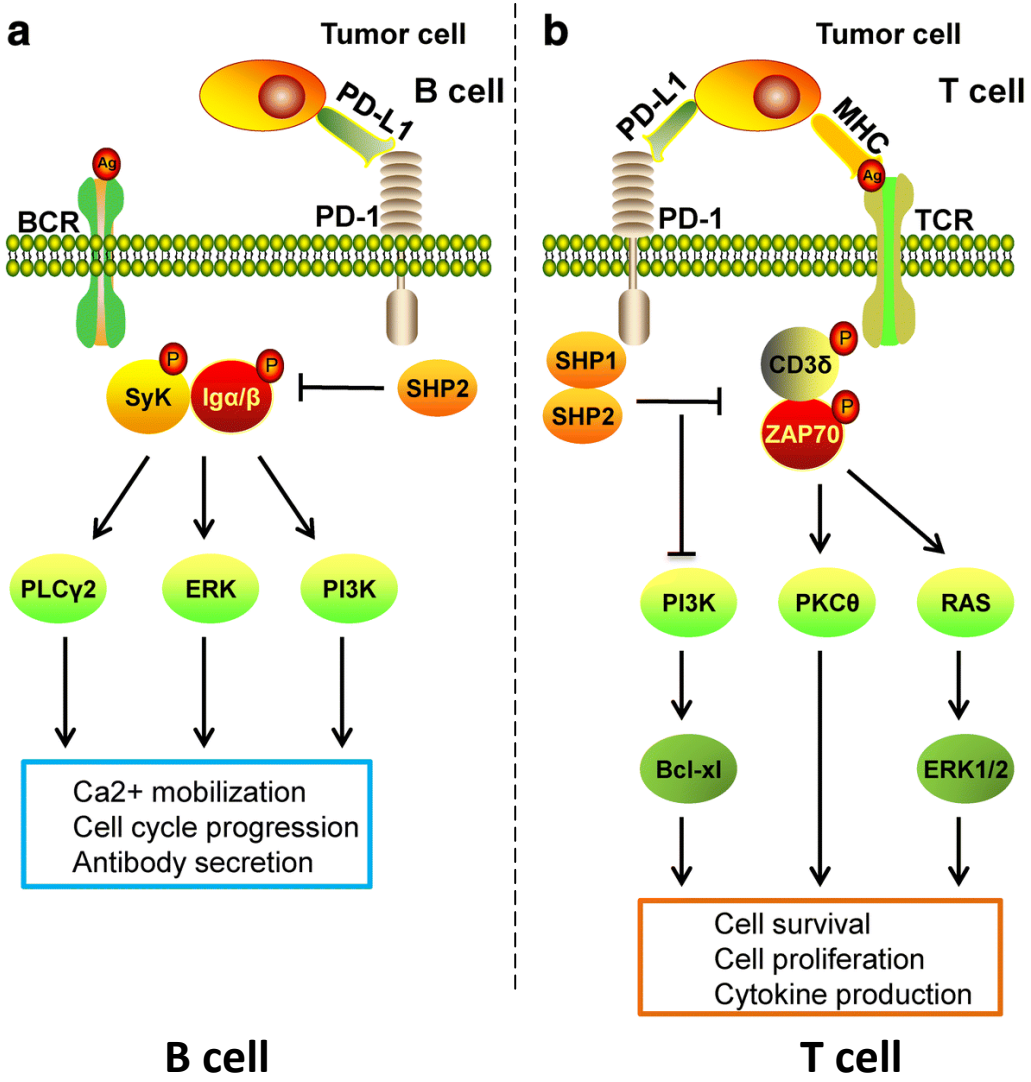
Vignali DAA, Nat. Rev Immunol (2008) 8, 523-532

- CTLA-4 binds to CD80/86 on dendritic cells (DC)
- Induction of indolamine-2,3-dioxygenase (IDO) – immunosuppressive molecule
- Reduction of CD80/80 availability
- Possible: inhibition of DC maturation

PD-1

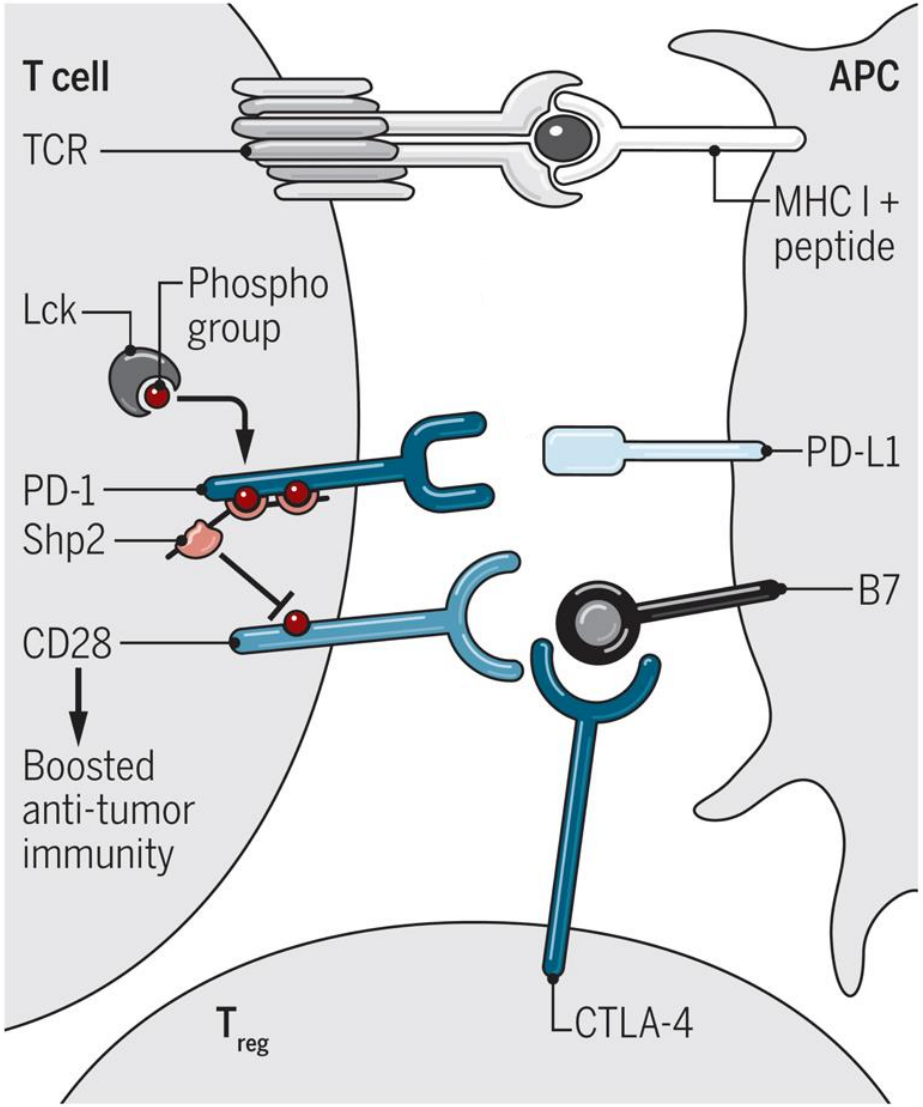
- **PD-1:** Programmed cell death protein 1 (CD279)
- Immunoglobulin family
- **Inhibitory receptor**: inhibits TCR- and BCR-mediated cell activation
- **Expression:** activated T cells, B cells, monocytes, NK cells, and certain DCs.
- PD-L1
  - PD-L1 (B7-H1 or CD274): B7 family
  - Abnormal high expression of PD-L1 in tumor cells

PD-1/PD-L1 inhibitory mechanism



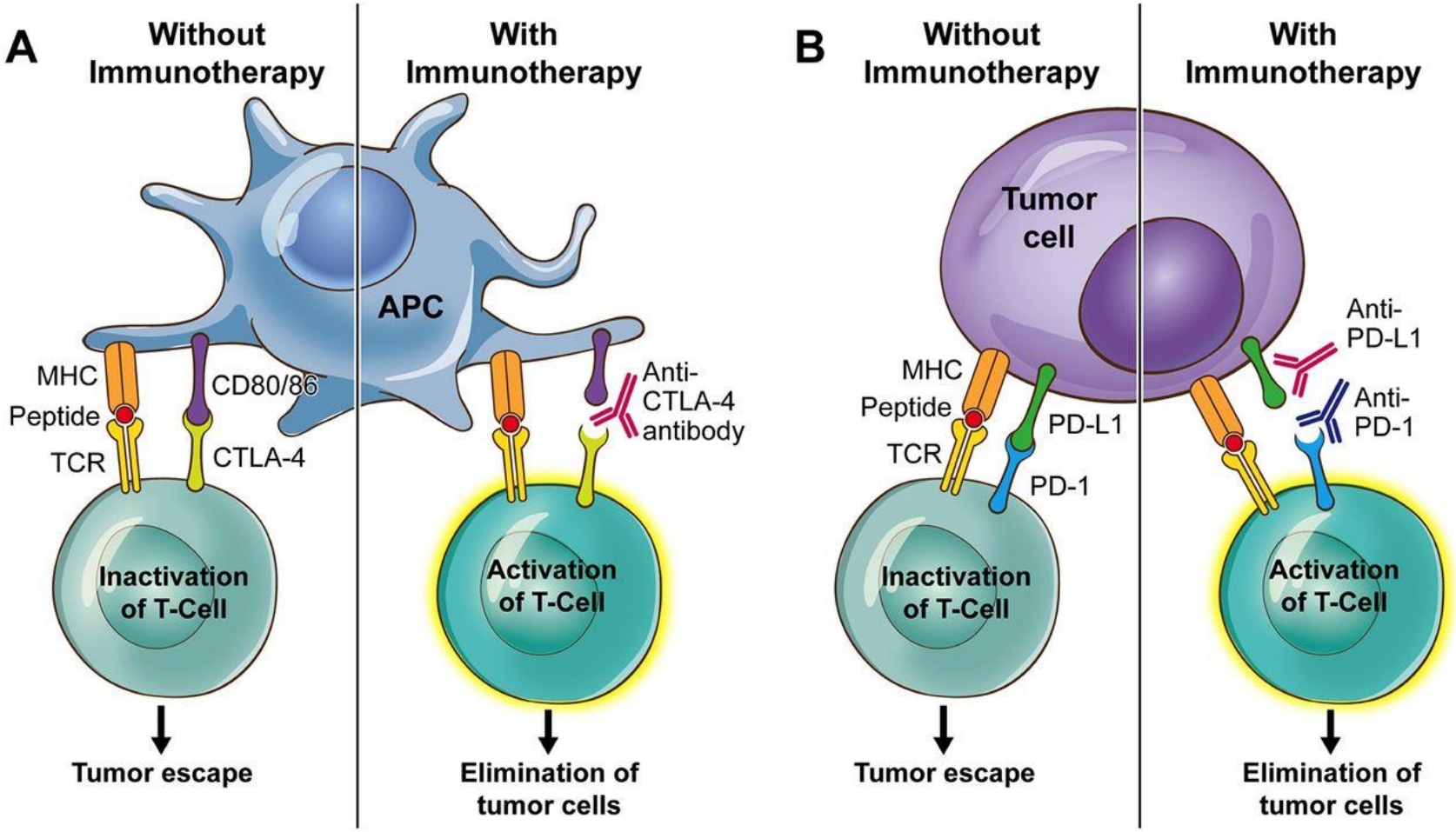
Jiang, X., Wang, J., Deng, X. *et al.* Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. *Mol Cancer*

CTLA-4 and PD-1 checkpoint inhibitors



Walker. 2017

CTLA-4 and PD-1 checkpoint inhibitors



Soularue. 2018

Depletion of effector cells
-Apoptosis-

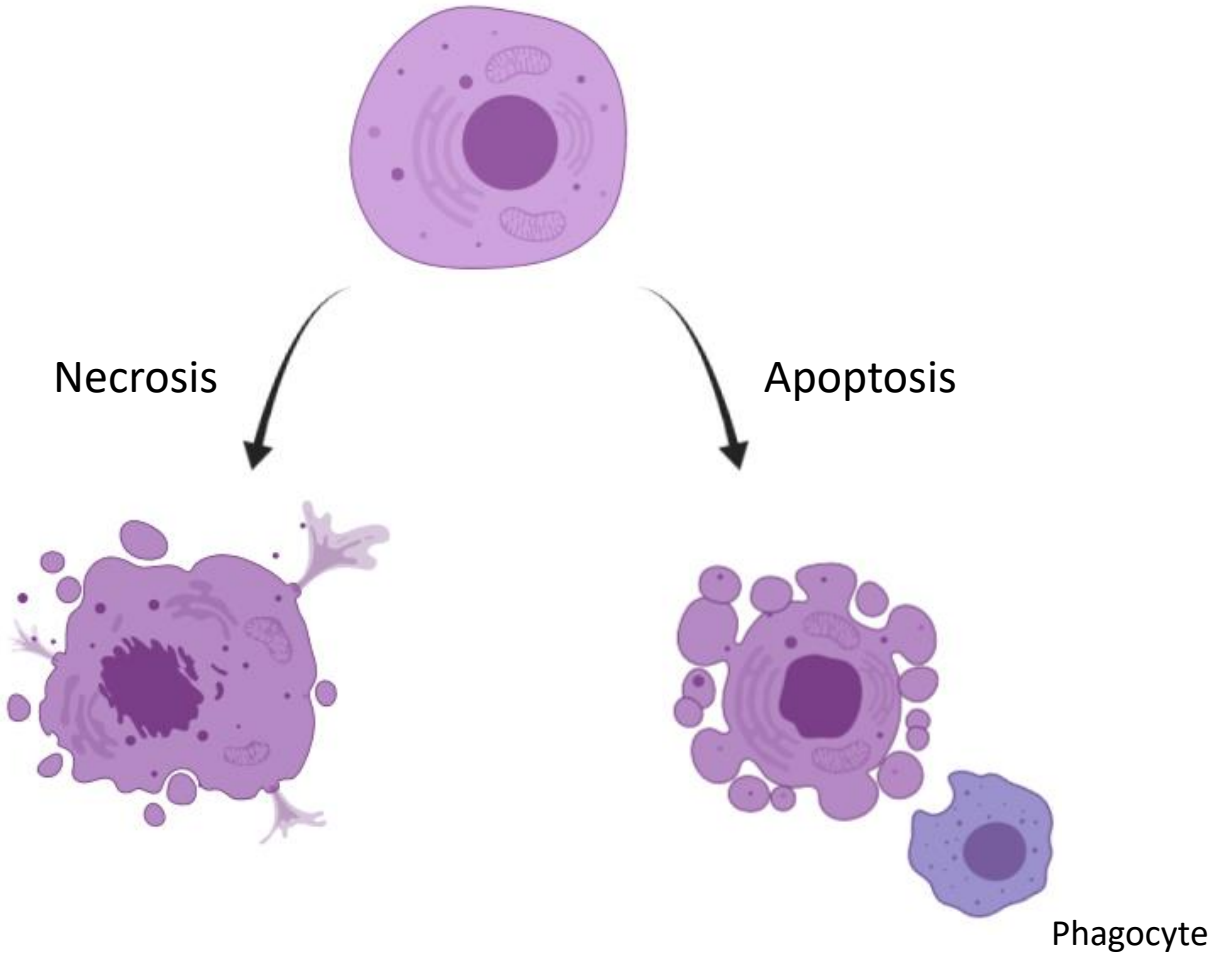
Apoptosis

ΑΠΟΠΤΩΣΙΣ (Greek)

- = Fall off petals or tree leaves

- Cell biology (immunology):
  - Apoptosis = "programmed cell death"

Necrosis vs. Apoptosis



Apoptosis

Programmed cell death

The Nobel Prize in Physiology or Medicine 2002 was awarded jointly to Sydney Brenner, H. Robert Horvitz and John E. Sulston "for their discoveries concerning genetic regulation of organ development and programmed cell death'."

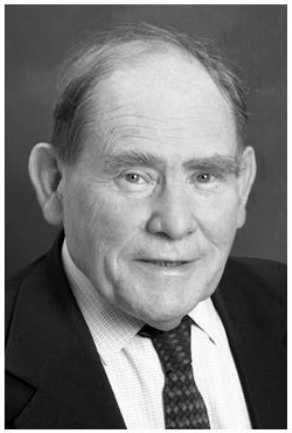


Photo from the Nobel Foundation archive.
Sydney Brenner

Photo from the Nobel Foundation archive.
H. Robert Horvitz

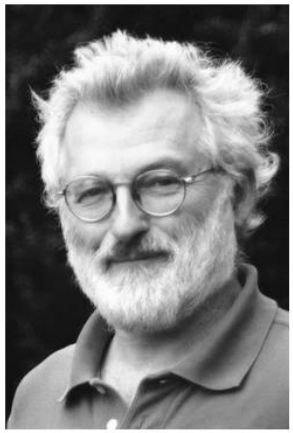
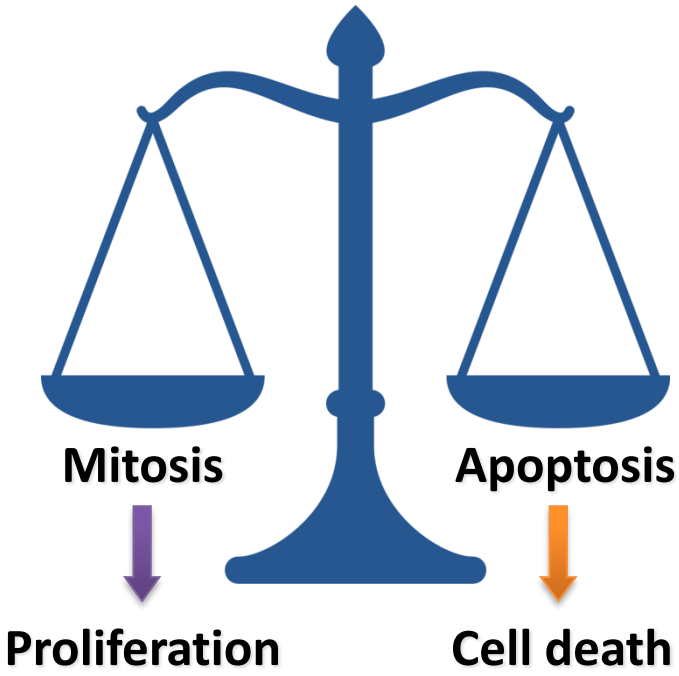


Photo from the Nobel Foundation archive.
John E. Sulston

Apoptosis as an essential part of organogenesis

- Tissue homeostasis: balance between renewal (mitosis) and elimination of disused cells (apoptosis)

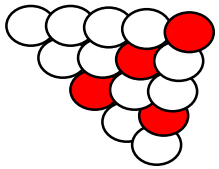
Life and death balance



10 billion (10^{10}) of our body cells (10^{14}) have to die every day to compensate for the new cells created by mitosis. (M. T. Heemels: Nature 2000 407:769)

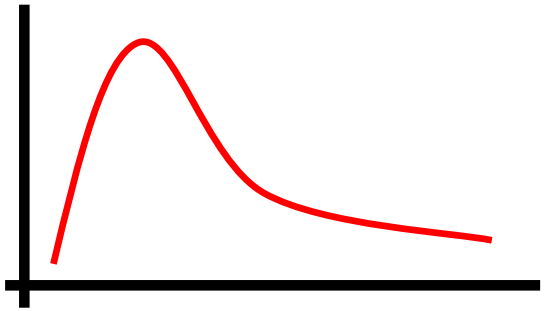
Without cell death, an 80-year-old person would have 2 tons of bone marrow and lymph nodes and 16 km of intestines (Gerry Melino: The siren's song Nature 2001 412:23)

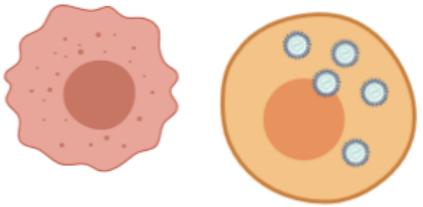
Physiological role of apoptosis



- Preservation of tissue structure in vertebrates

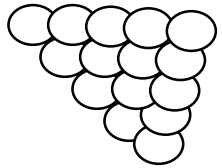
- In the immune system:
  - Negative selection
  - Regulation of the immune response
  - Deletion of infected and abnormal cells

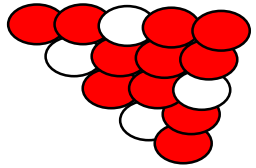




Pathophysiological role of apoptosis

- Insufficient apoptosis:
  - Autoimmune diseases
  - Cancer
  - Virus infection

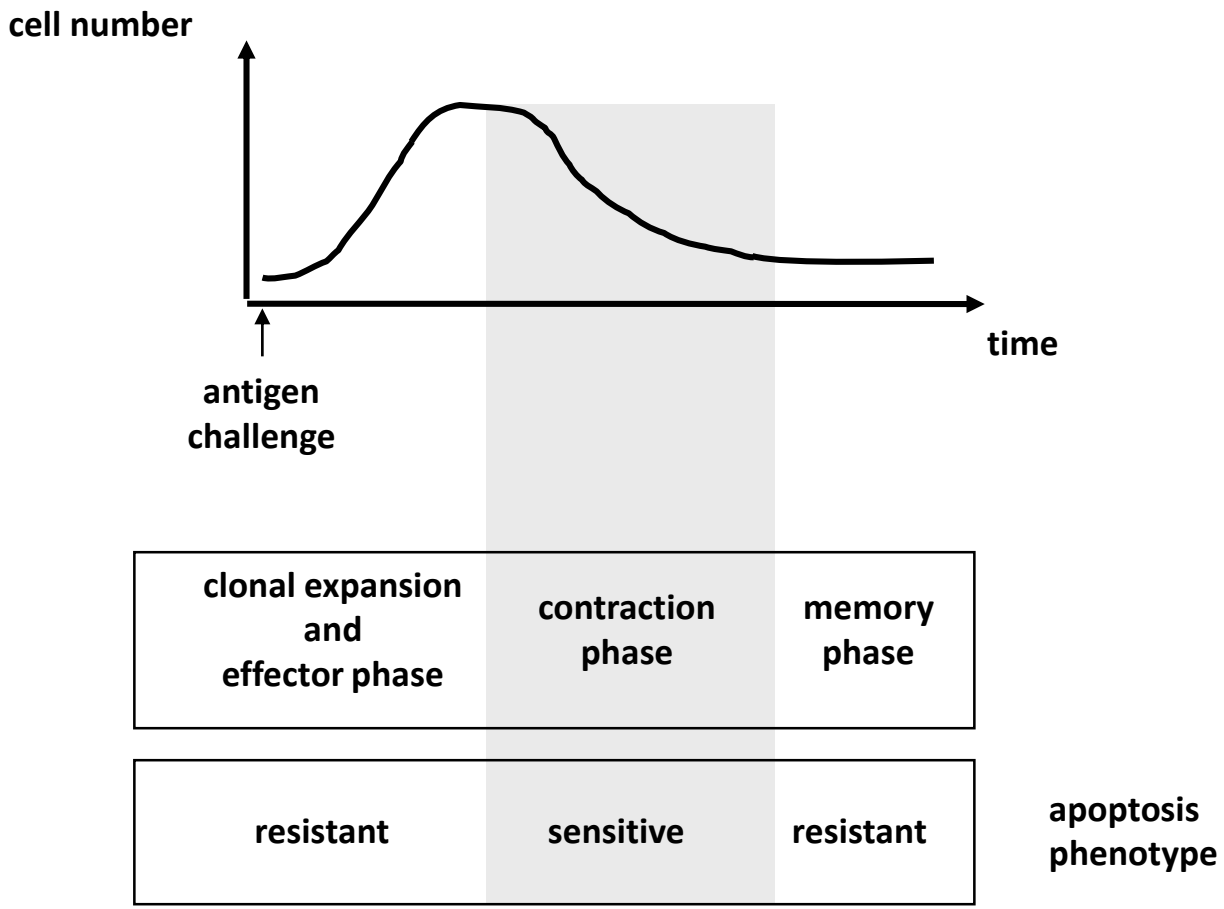




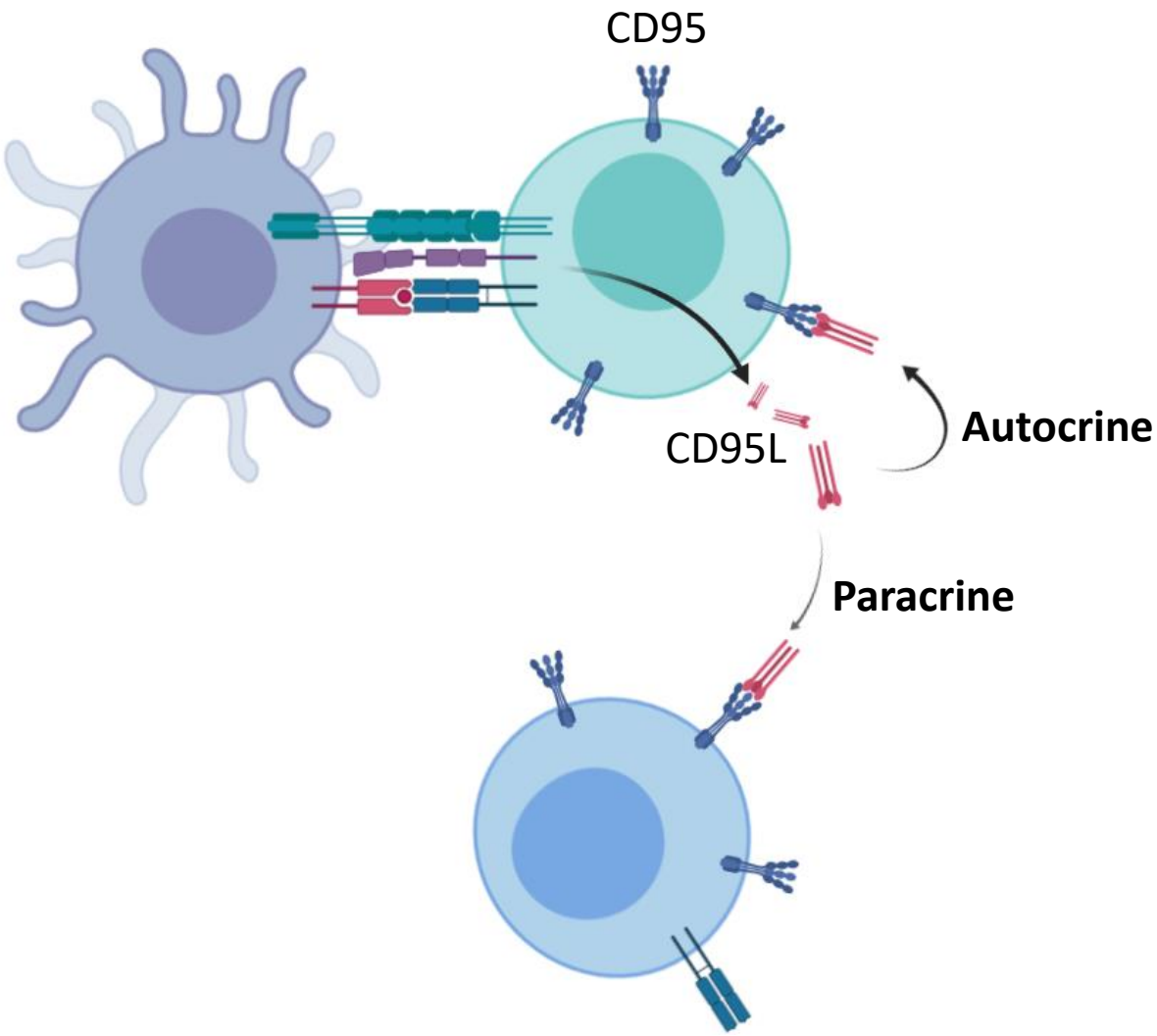
- Excessive apoptosis:
  - AIDS
  - Stroke

  - Neurodegenerative diseases:
    - Alzheimer´s, Parkinson´s, Retinitis pigmentosa

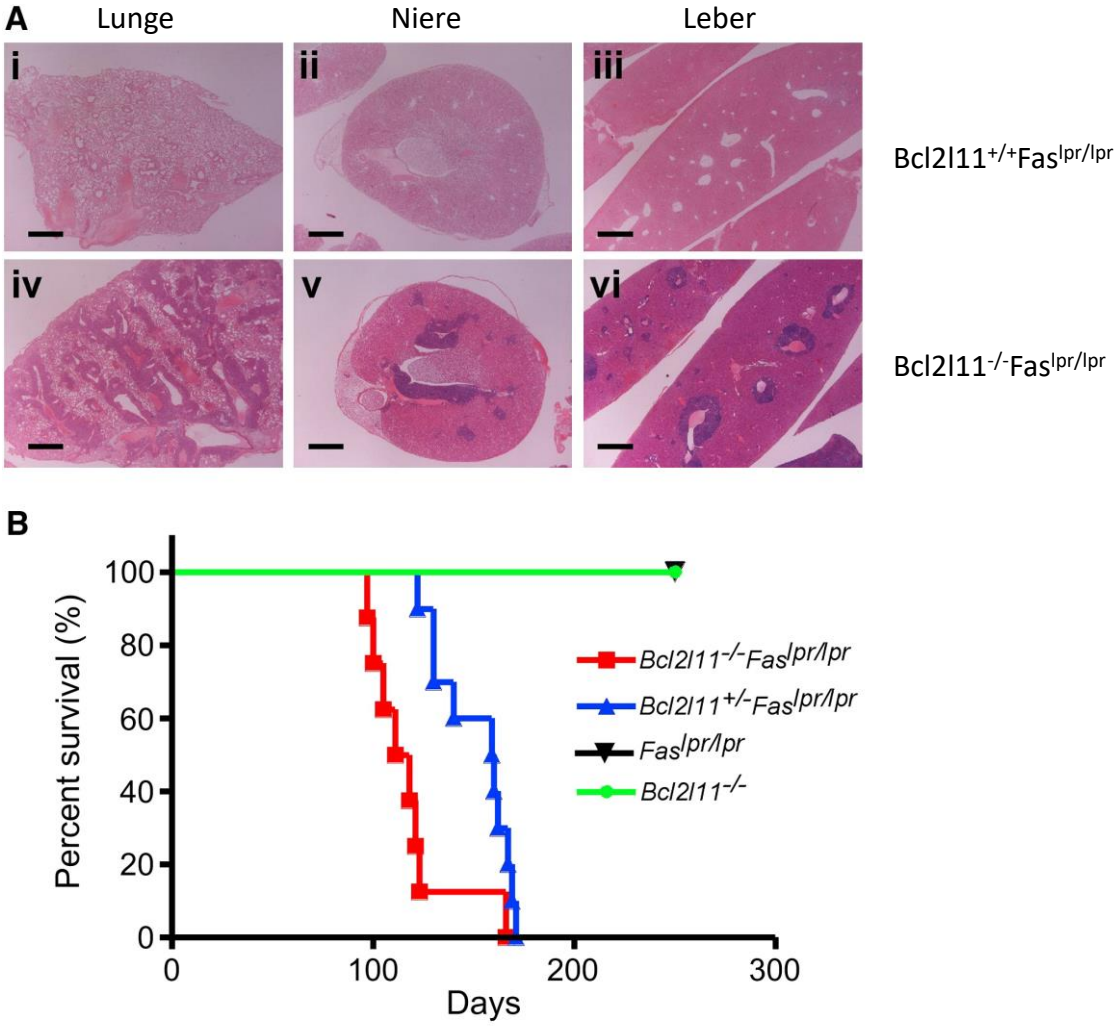
T cell mediated immune responses



AICD (activation-induced cell death) in T cells

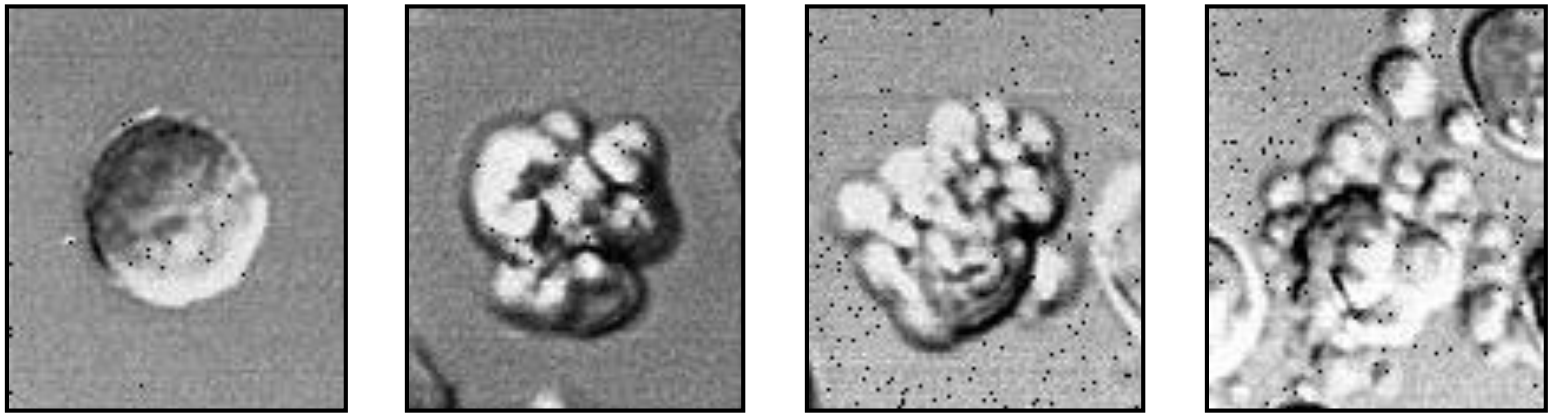


Reminder: Loss of apoptosis leads to lethal lymphoproliferation and a break in tolerance

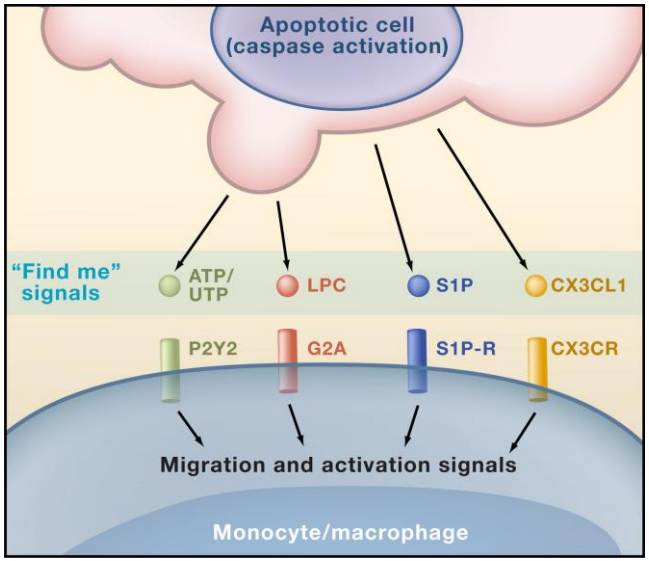


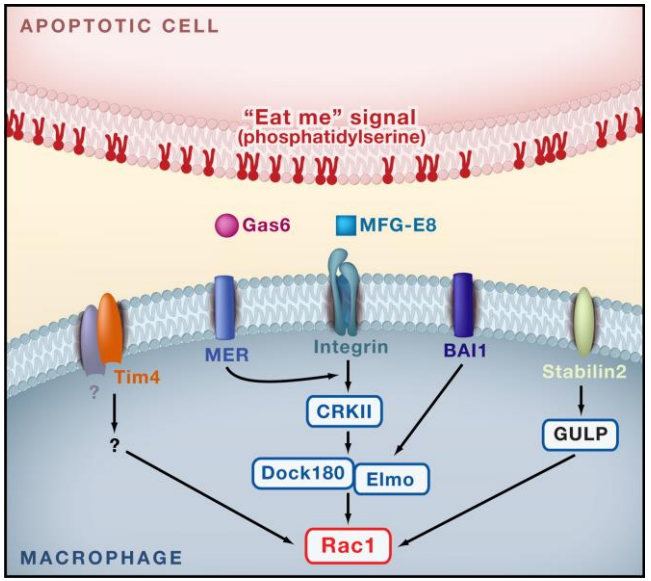
Hughes et al. (2008) Immunity 28, 197-205

Elimination of apoptotic cells



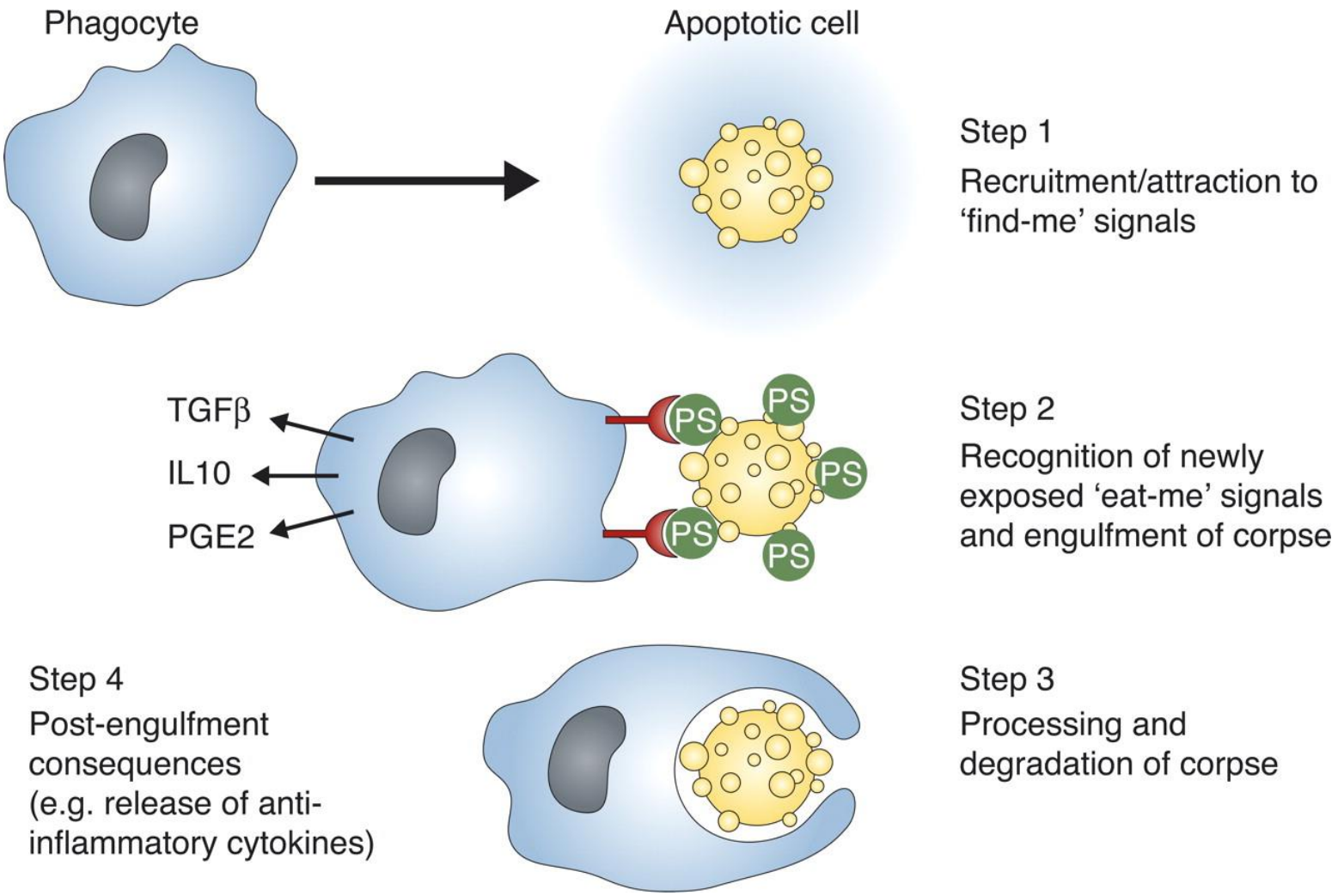
„Find me“ und „Eat me“ signals control the removal of apoptotic cells





Nagata et al., Cell. 2010 Mar 5;140(5):619-30.

Successive steps in the removal of apoptotic cells



Ravichandran K S J Exp Med 2010;207:1807-1817

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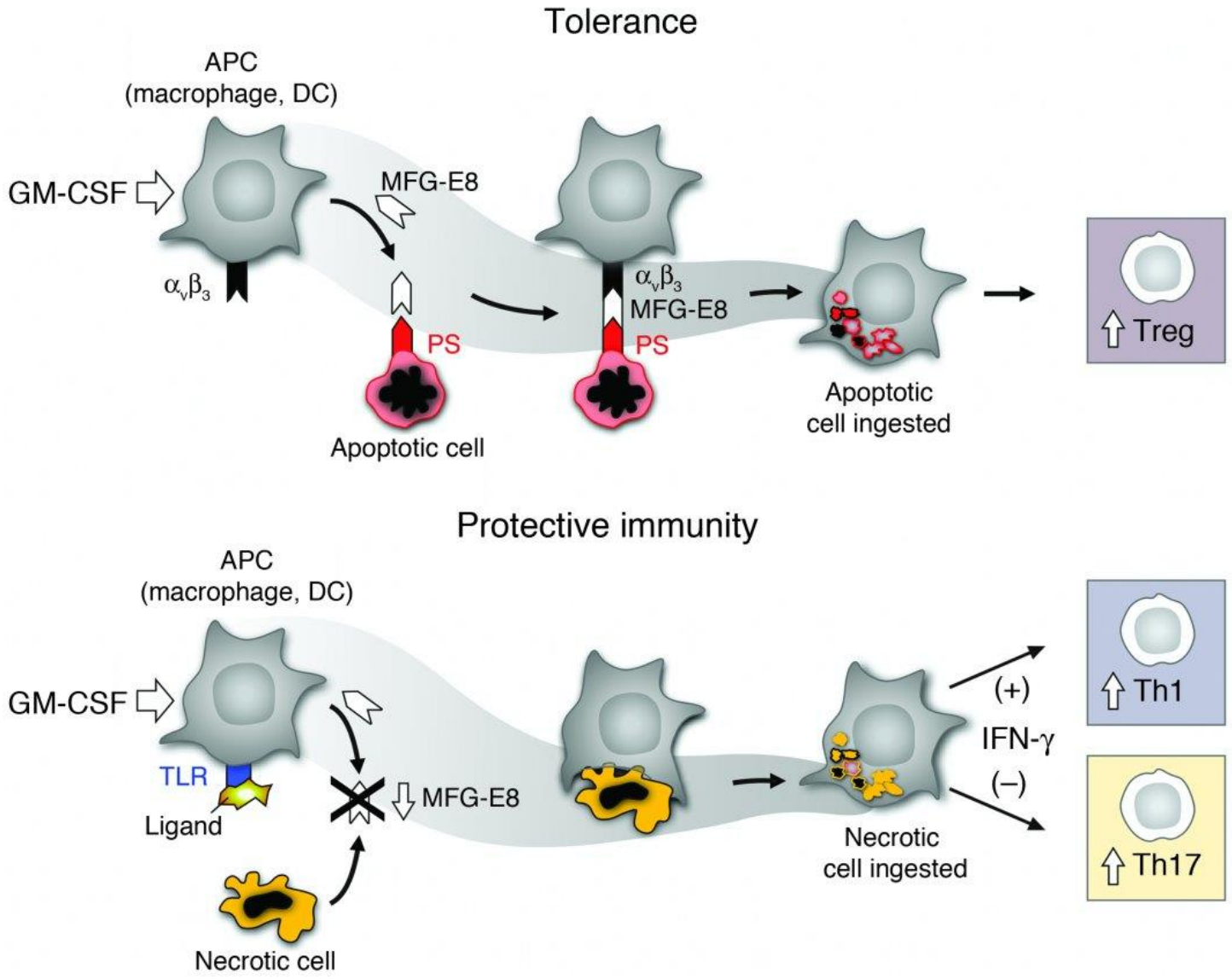
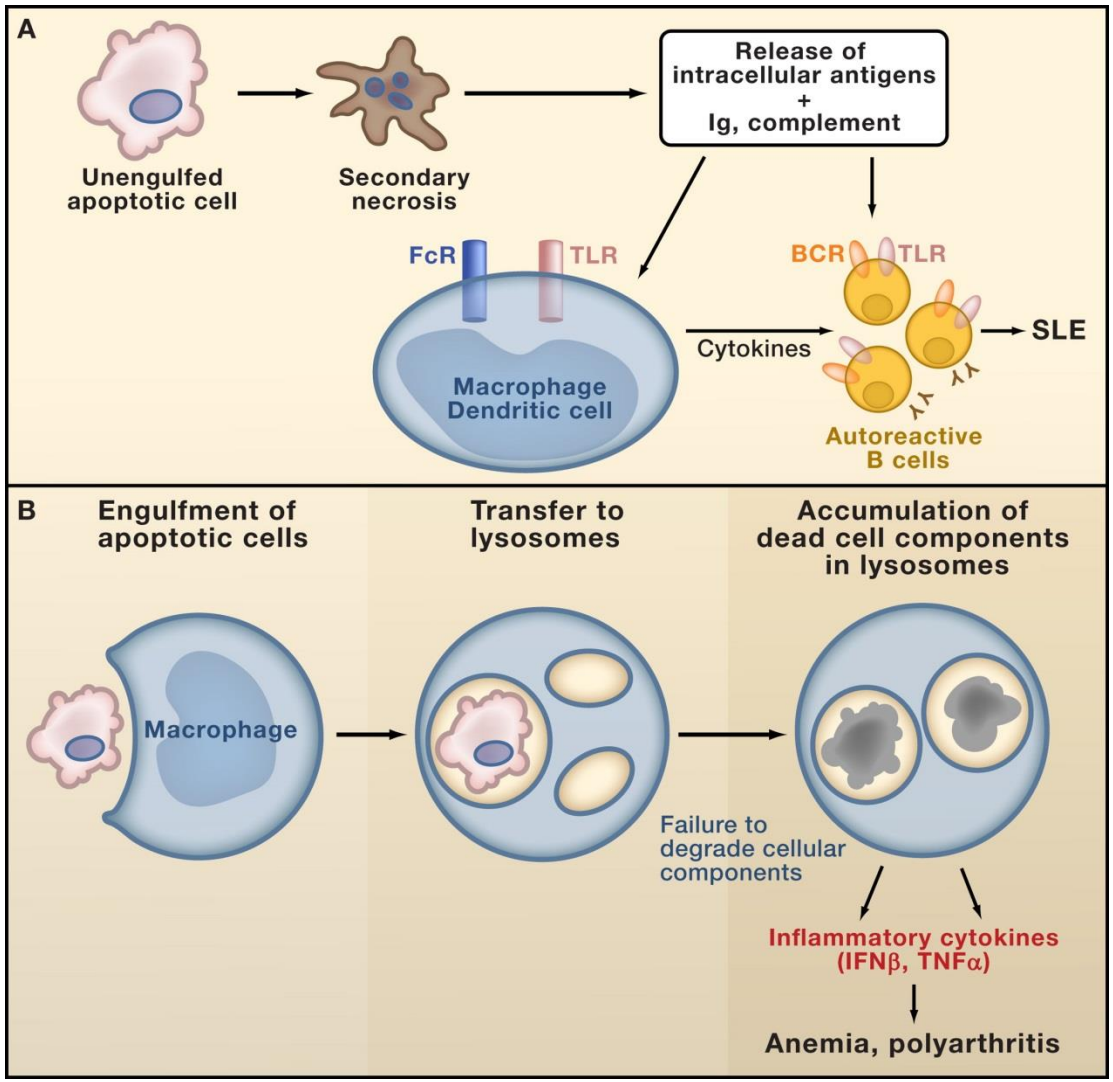
Influence of apoptotic vs. necrotic cells to the immune response



Defects in cell death elimination in pathophysiological conditions



Nagata et al., Cell. 2010 Mar 5;140(5):619-30.

Thanks for your attention

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