Immune Tolerance I

How the immune system distinguishes self from non-self

Lernziele

- Sie verstehen die grundsätzlichen Mechanismen der zentralen und periphären Toleranz.
- Sie können die Entwicklung von T Zellen im Thymus erklären
- Sie können die prinzipien der positiven und negativen Selektion erklären
- Die können die wichtigsten Mechanismen der selbst-Antigen Expression im Thymus beschreiben.
- Sie verstehen die Rolle von Adjuvanz und infektionen bei der Entstehung einer adaptiven Immunantwort.

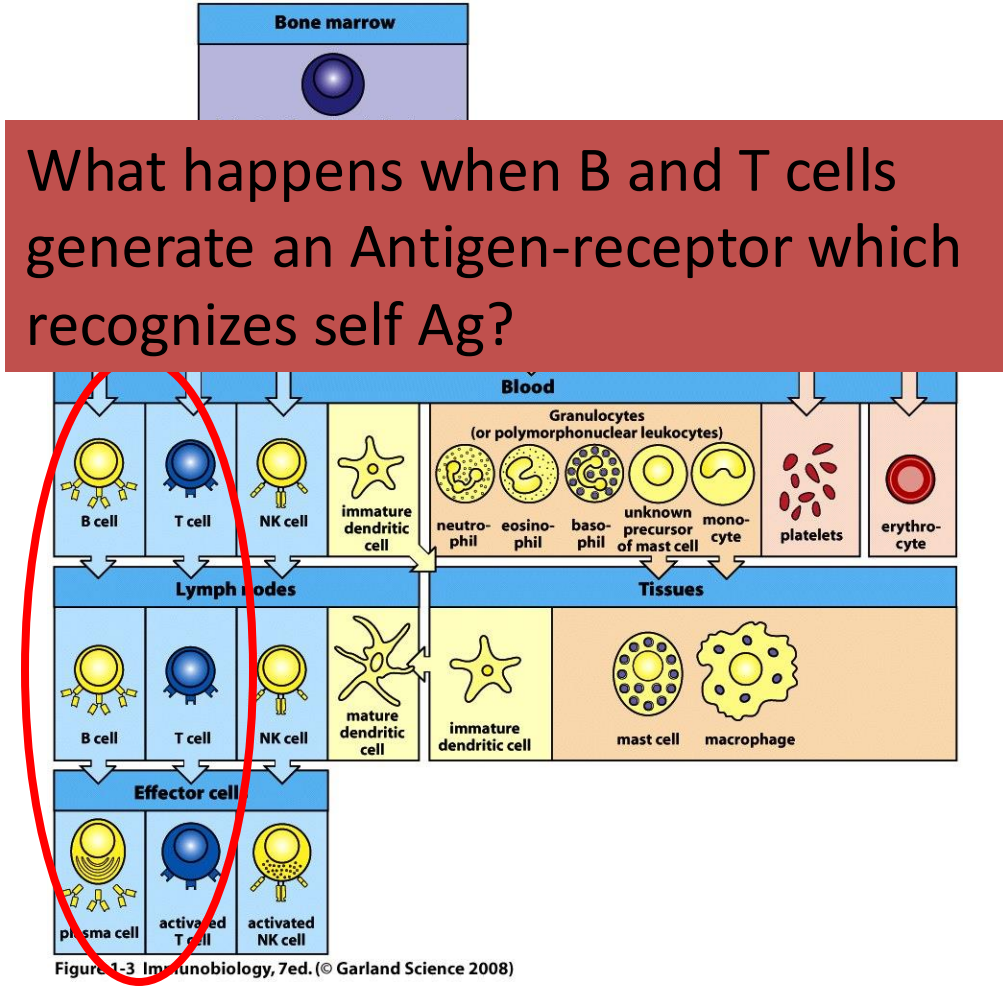


Figure 1-3 Immunobiology, 7ed. (© Garland Science 2008)

Tolerance Mechanisms

Wichtig

Unwichtig

Wichtig

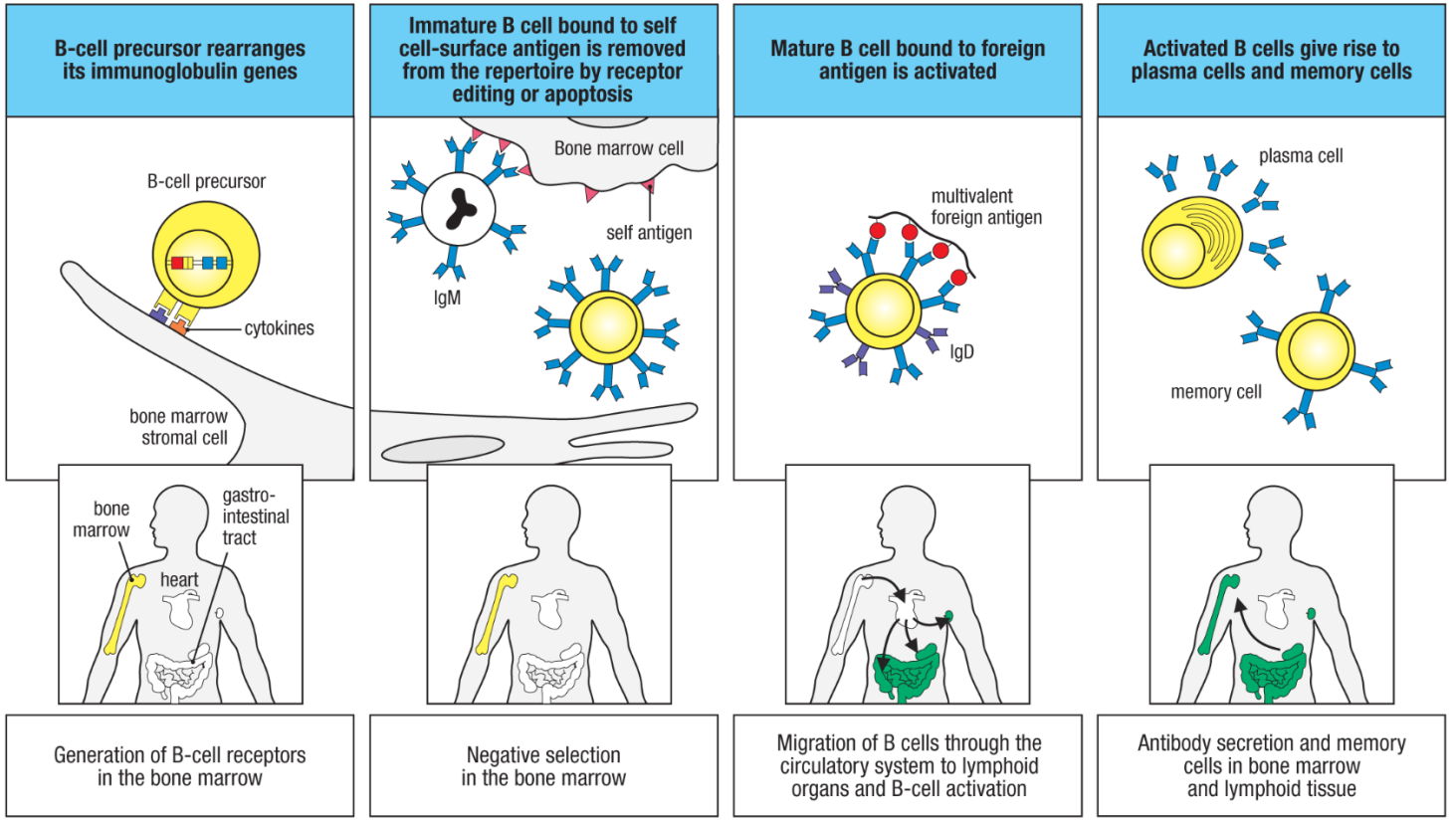
Layers of self-tolerance		
Type of tolerance	**Mechanism**	**Site of action**
Central tolerance	Deletion Editing	Thymus Bone marrow
Antigen segregation	Physical barrier to self-antigen access to lymphoid system	Peripheral organs (e.g. thyroid, pancreas)
Peripheral anergy	Cellular inactivation by weak signaling without co-stimulus	Secondary lymphoid tissue
Regulatory cells	Suppression by cytokines, intercellular signals	Secondary lymphoid tissue and sites of inflammation
Cytokine deviation	Differentiation to T_H2 cells, limiting inflammatory cytokine secretion	Secondary lymphoid tissue and sites of inflammation
Clonal deletion	Apoptosis post-activation	Secondary lymphoid tissue and sites of inflammation

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

Antigen receptors are randomly generated in B and T cells.

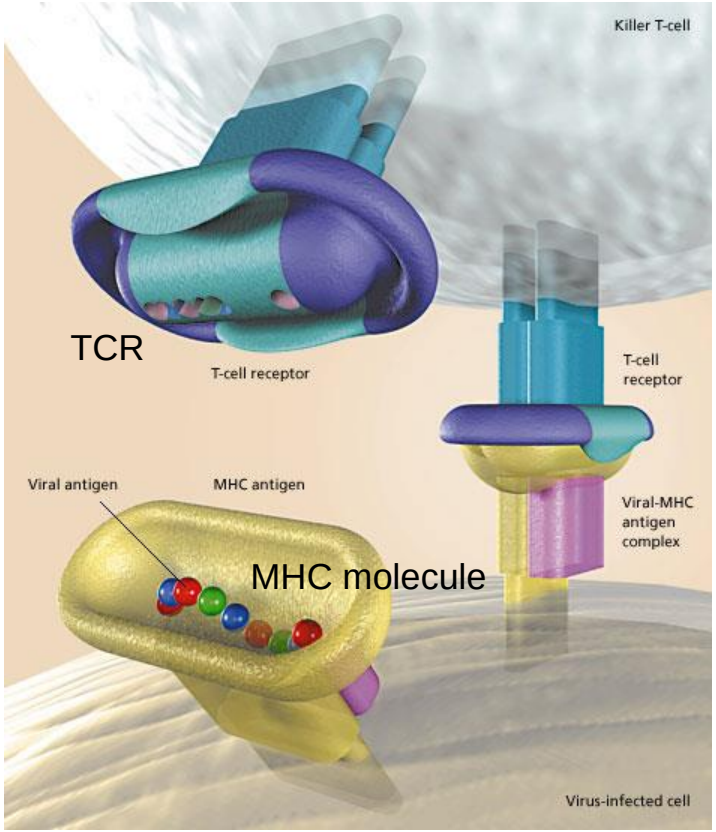
To avoid auto-reactivity, self-reactive clones must be eliminated (central tolerance) or suppressed (peripheral tolerance).

Das Leben einer B Zelle



Today we will not discuss antibody-mediated autoimmunity, because T cell-mediated tolerance is much more fun.

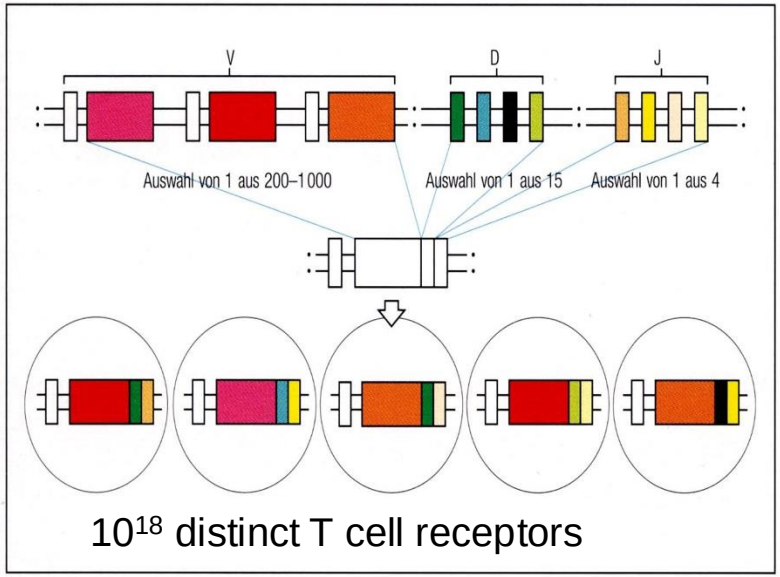
How do T cells recognize their antigen?



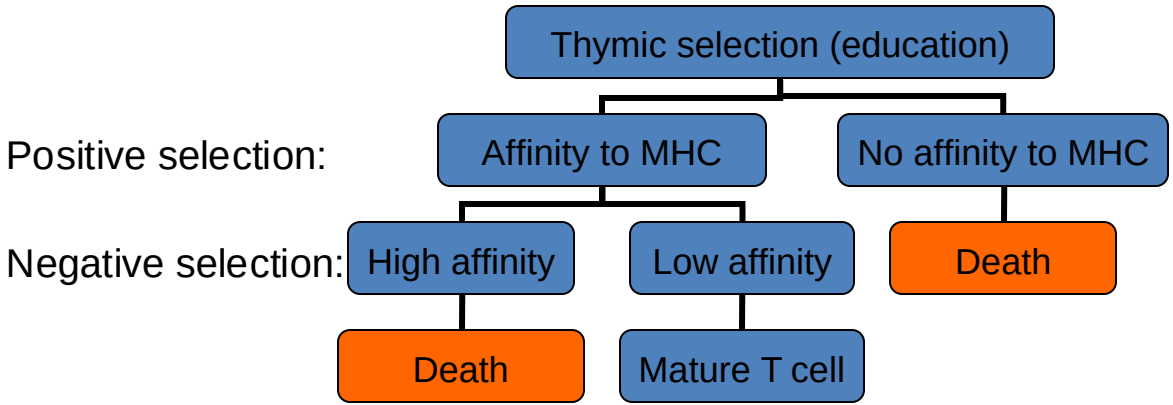
The smartest way to avoid autoimmunity is to educate T cells to only recognize foreign antigens and not self-antigens.

Central Tolerance

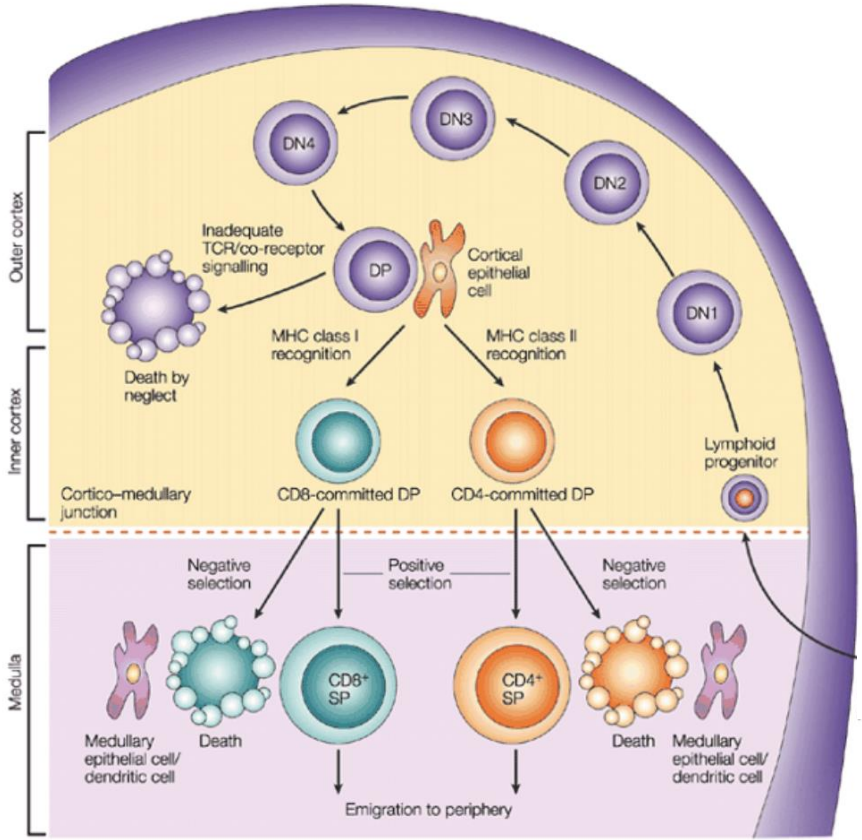
Thymus: T Cell Education



10^{18} distinct T cell receptors


Thymic selection (education)
Positive selection:
Affinity to MHC
No affinity to MHC
Negative selection:
High affinity
Low affinity
Death
Death
Mature T cell

Positive and Negative Selection in the Thymus



Positive selection

mediated by peptide-MHC recognition by cTECs

Negative selection

deletion of T cells specific for self antigens expressed by mTECs

Nature Reviews | Immunology

Where do self-peptides in the thymus come from?

Peripheral Antigen Expression in the Thymus
”Autoimmune Regulator” AIRE

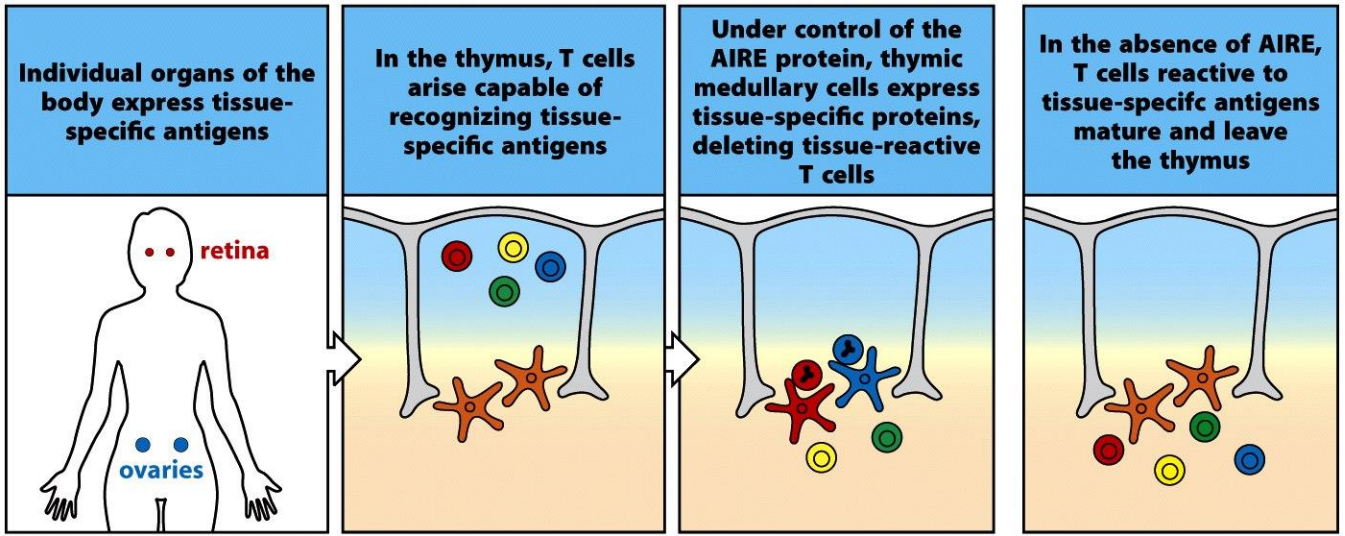
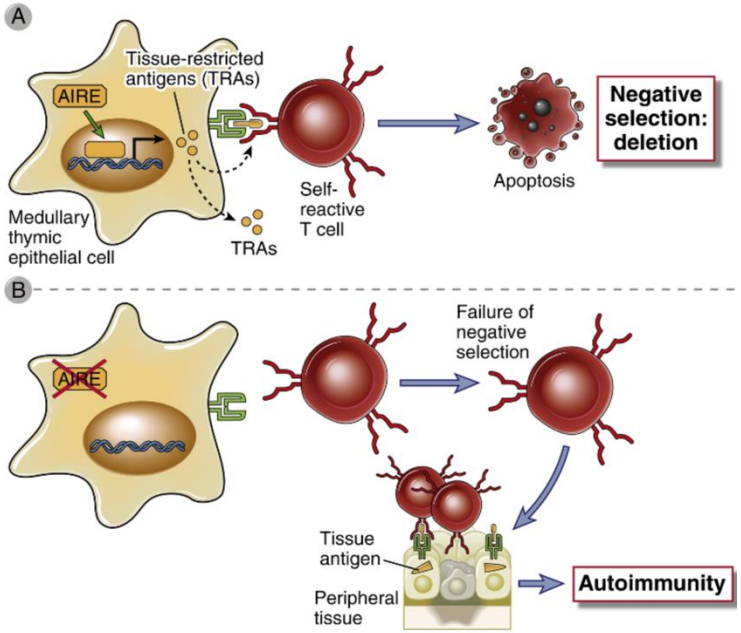


Figure 14-4 Immunobiology, 7ed. (© Garland Science 2008)

Prüfung

Negative Selection

How can thymocytes ‘see’ autoantigens in the thymus?



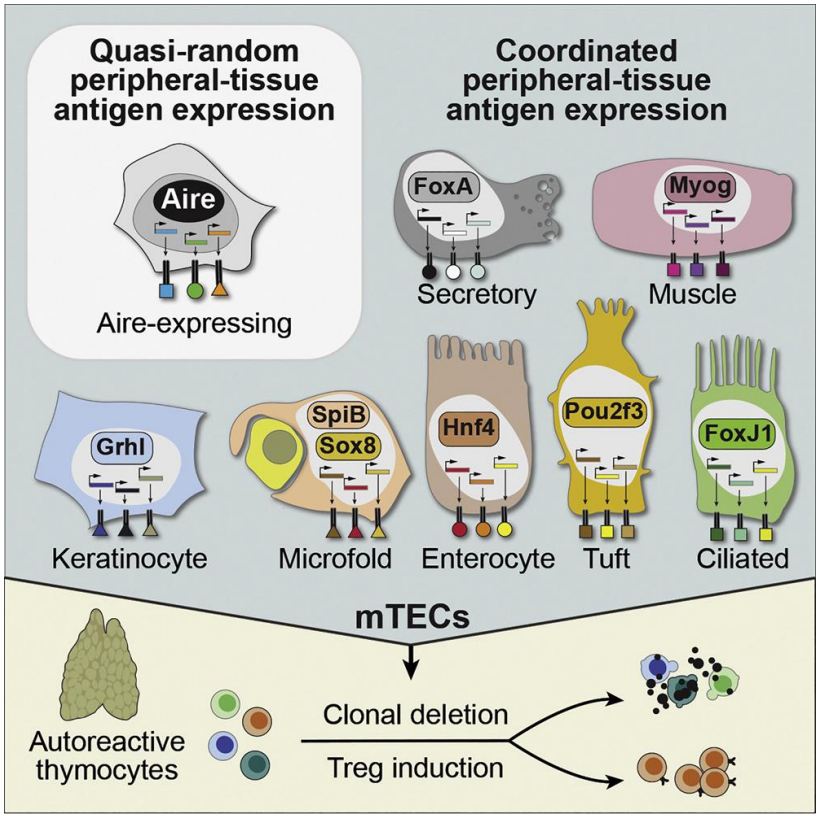
Autoimmune regulator (**Aire**) expressed by mTECs mediates gene expression of tissue restricted antigens (TRAs)

mTECs present TRAs to immature T cells
leading to the deletion of self-reactive T cells

Mutations in the gene encoding Aire cause severe autoimmunity

→ autoimmune polyendocrinopathy-candidiases-ectodermal dystrophy (APECED) → human monogenic disorder

Mit der Pubertät schrumpft der Thymus ”altersbedingt”



Peripheral Tolerance

To understand peripheral tolerance
we need to look at the function of dendritic cells

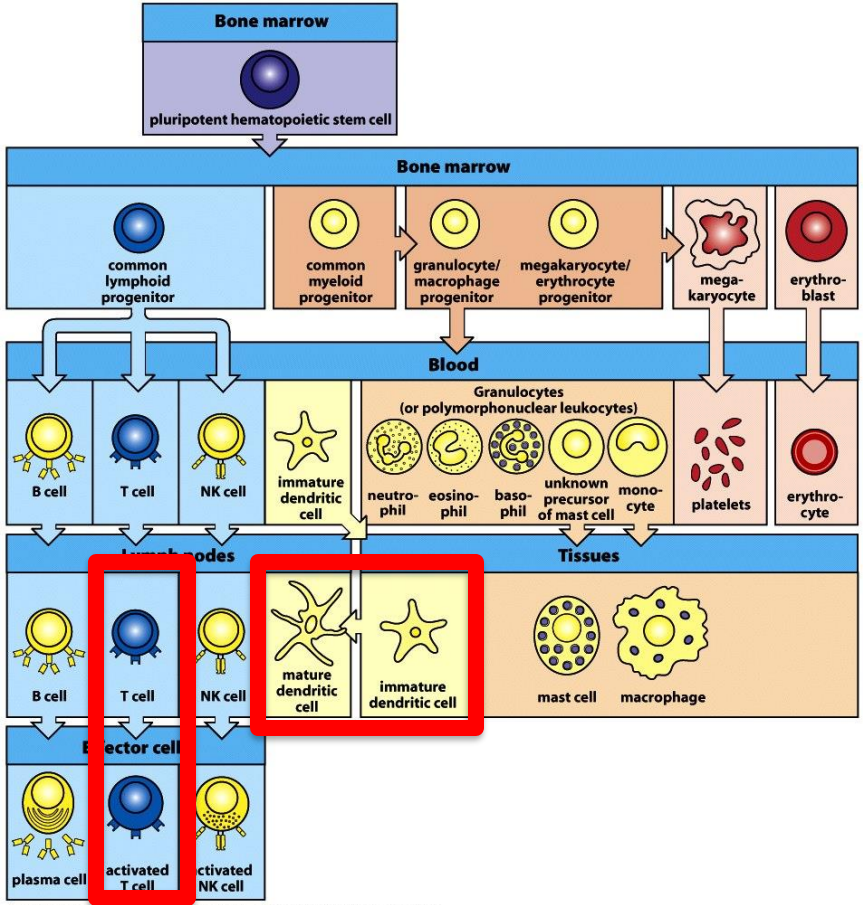
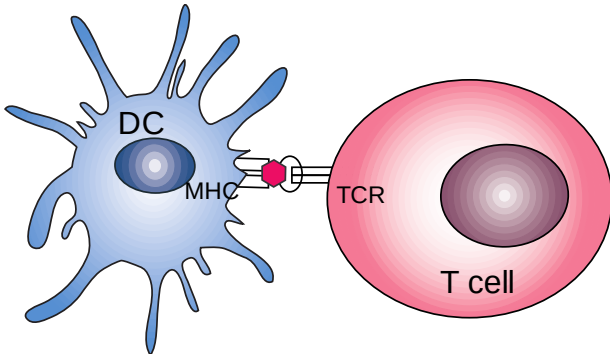


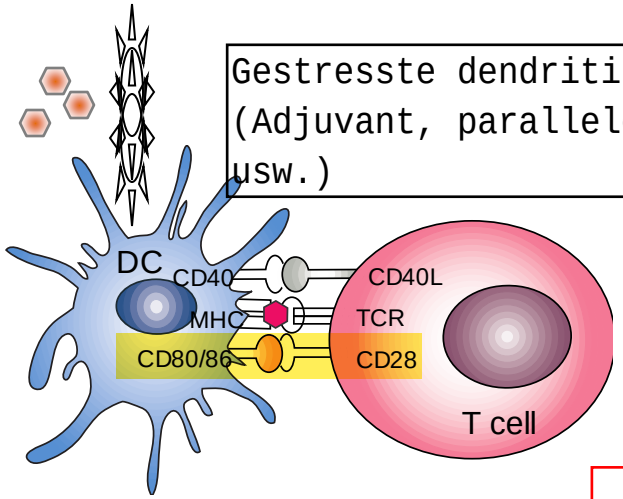
Figure 1-3 Immunobiology, 7ed. (© Garland Science 2008)

Cooperation between innate and adaptive immunity: Antigen Presentation and ‘Stranger/Danger’ Signals

Ruhende dendritische Zelle



Gestresste dendritische Zelle (Adjuvant, parallele Infektion usw.)



Wichtig

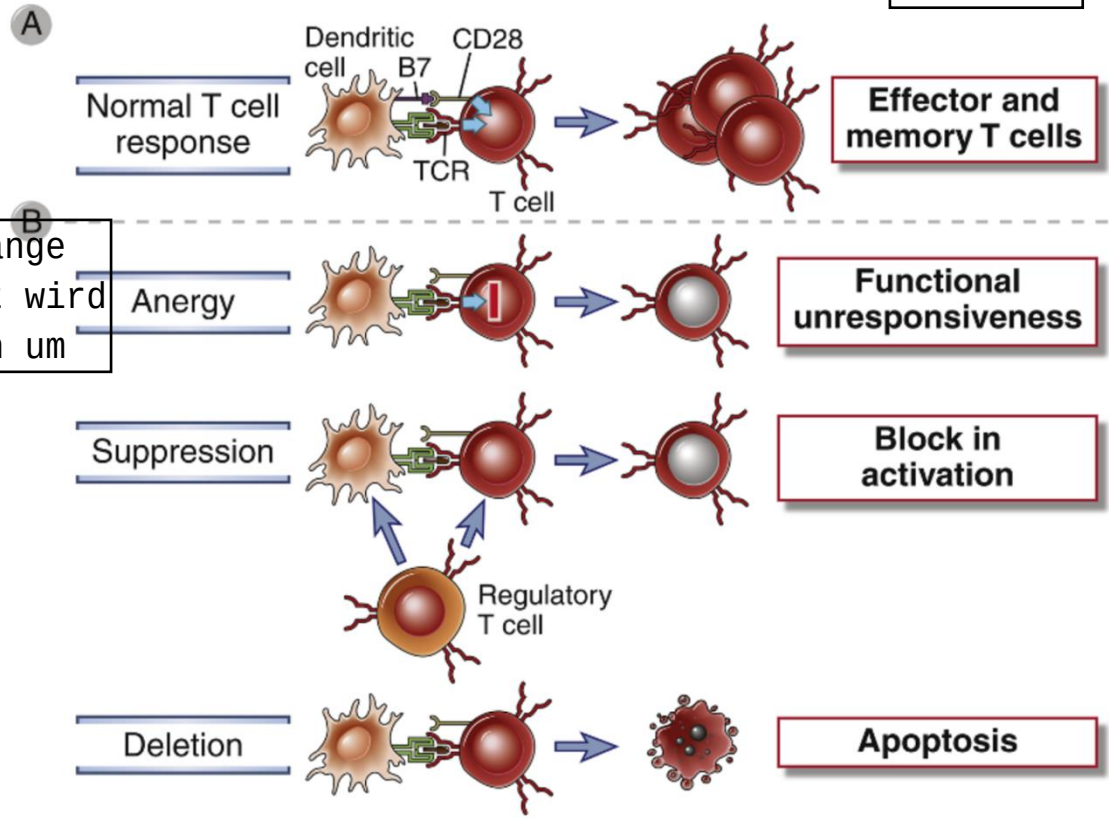
In the absence of danger, antigen presentation (for example self-antigen) causes **tolerance**

DAMPs/PAMPs:
(e.g.: microbes, bacterial DNA, vaccine adjuvant)
Activation of dendritic cells
Costimulatory molecules
Immunity

Peripheral Tolerance via Antigen Presenting cells

B7 = CD80

CD28 Merken



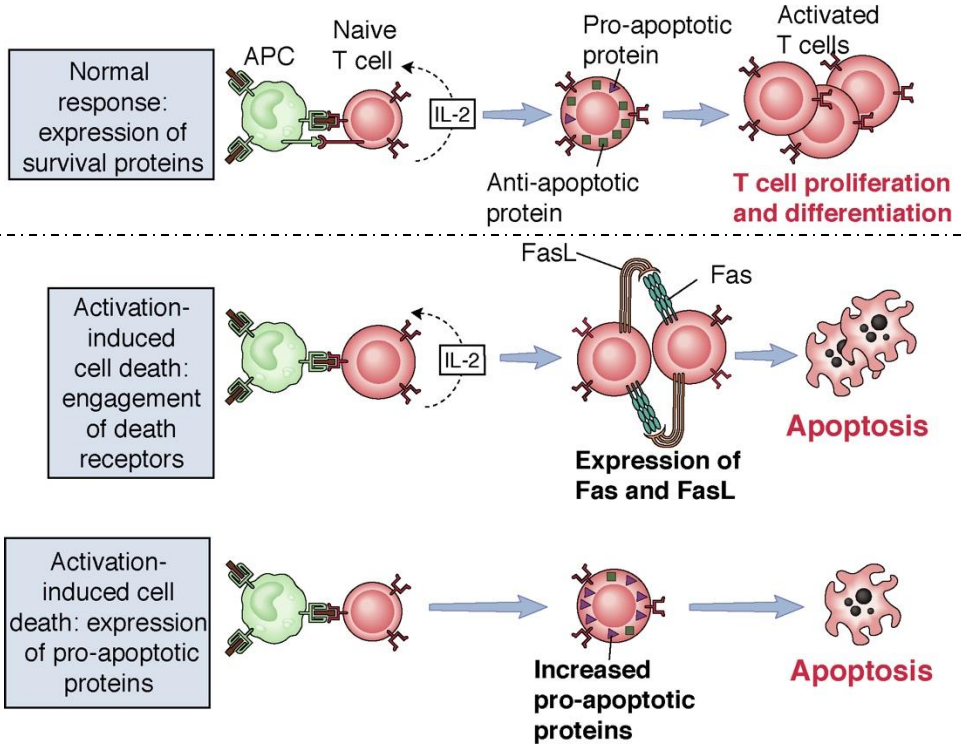
Wenn T-Zelle lange nicht aktiviert wird bringt sie sich um

Lack of costimulation

Abbas, Cellular and molecular Immunology

Deletion

‚Activation-induced cell death': death of mature self-reactive T cells



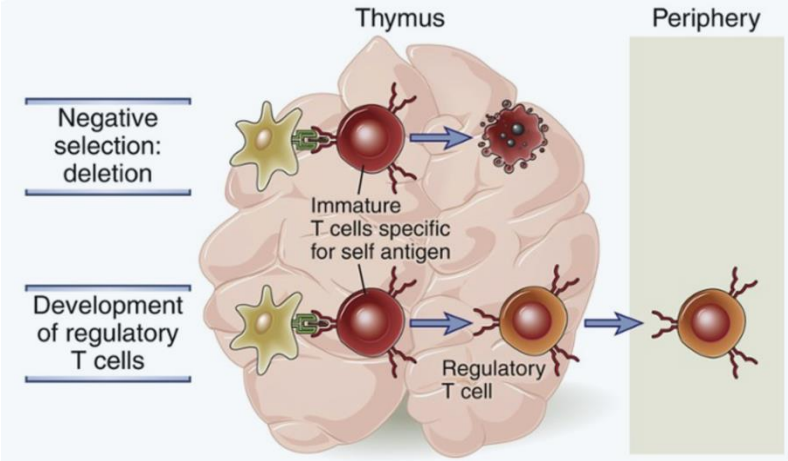
From Abbas and Lichtman. Basic Immunology 2nd ed, 2006

Both pathways cooperate to prevent reactions against self

Zentrale Toleranz ist die Eliminierung von auto-reactiven B Zellen im Knochenmark
Und die Eliminierung von autoreaktiven T Zellen im Thymus
https://www.youtube.com/watch?v=cMhE5BfmFkM
Aber was hat der Thymus mit peripherer Toleranz zu tun?

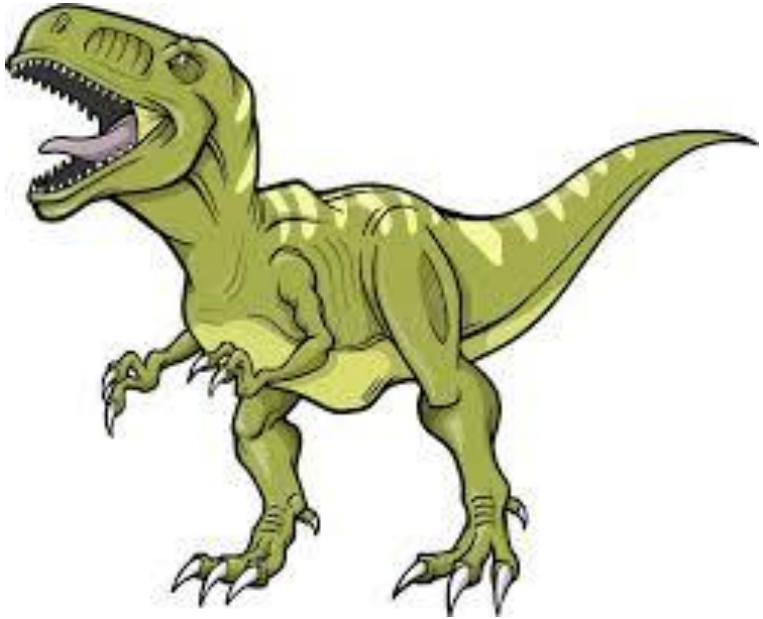
Prüfung

Wichtig | Wichtig



Negative selection is not 100% effective, some autoreactive T cells escape thymic censorship and are released into the circulation

Recognition of self antigens can also lead to the development of regulatory T cells (next lesson)



- Regulatory T cells
- (Tregs)
- Next week

- Für die die’s noch nicht ganz verstanden haben: https://youtu.be/cMhE5BfmFkM