Immune Tolerance II

How the immune system
distinguishes self from non-self
TregsTregsTregs

Lernziele

- Sie können die Entstehung von regulatorischen T /Treg) Zellen im Thymus beschreiben
- Sie kennen die wichtigsten Merkmale und transkriptionsfaktoren in Treg Zellen
- Sie können Beispiele nennen, wie Treg Zellen Immunantworten supprimieren
- Sie darlegen, wie eine Erkrankung wie die Multiple Skelrose entstehen kann.

Tolerance Mechanisms

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)

Regulatory T cells (Tregs)

Prüfung

Wichtig

Wichtig

Wichtig

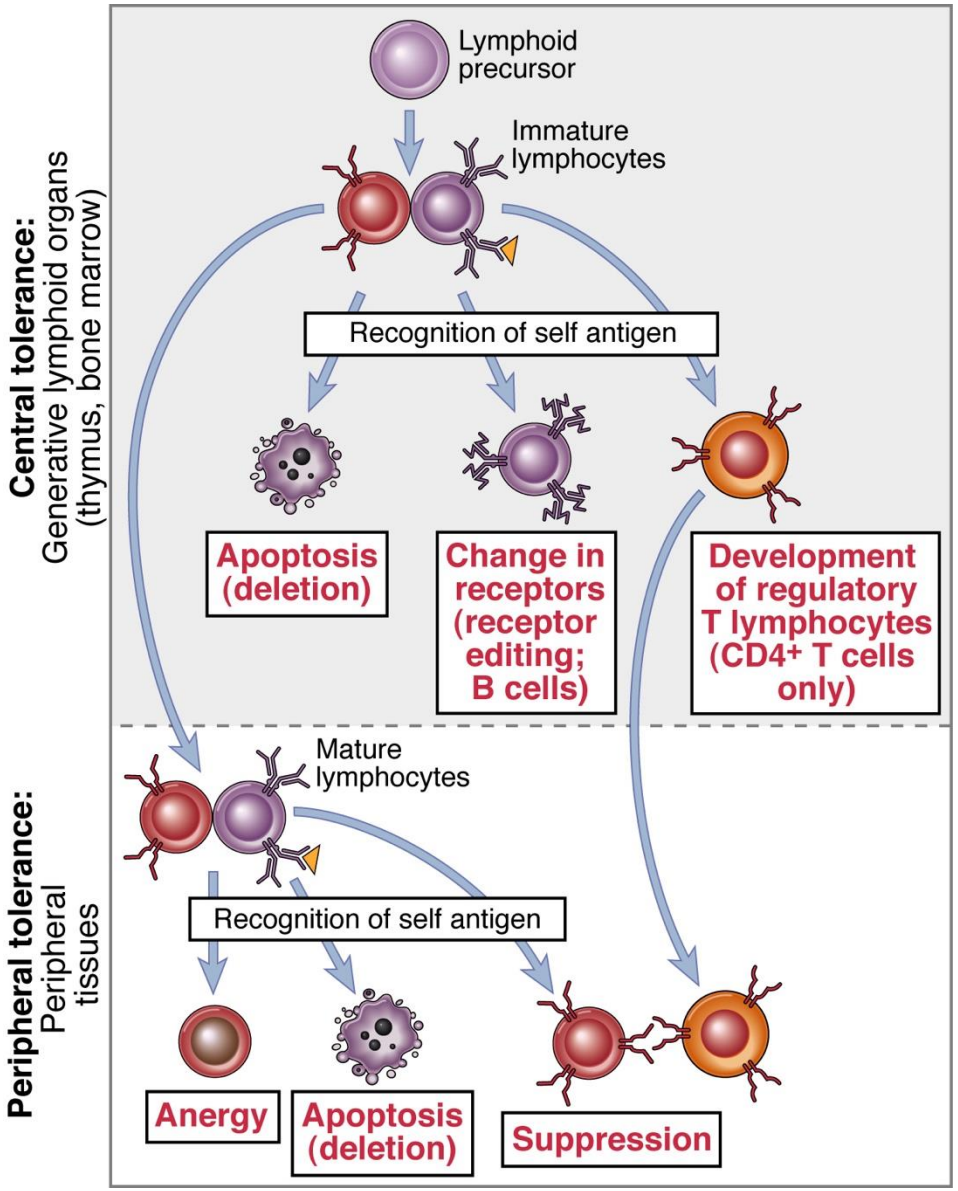
The main mechanism of peripheral tolerance: Tregs

Tregs suppress autoimmune responses

These (as well as all other T cells) arise in the thymus

So, again in the thymus (sorry!)

Central and Peripheral Tolerance

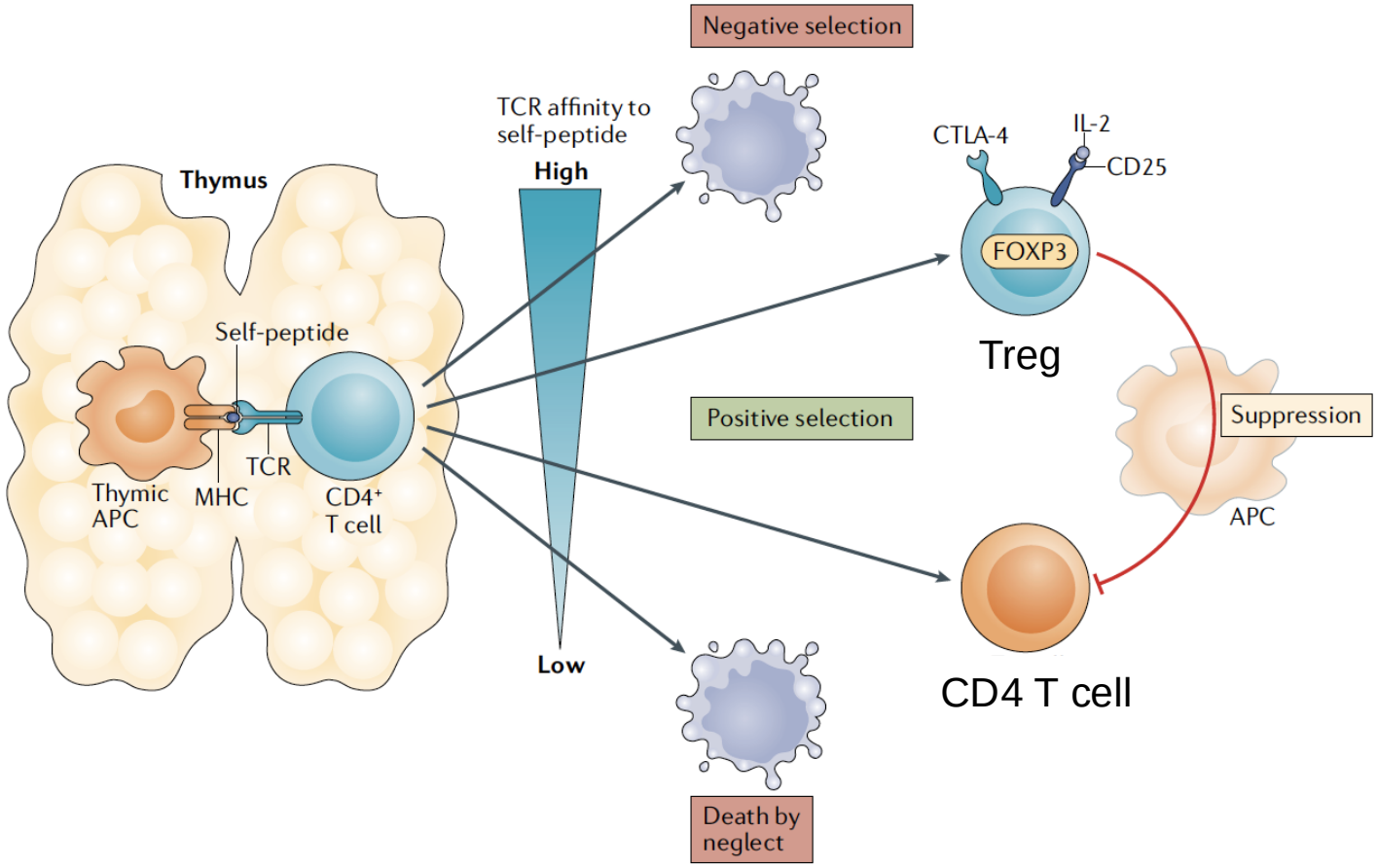


Abbas, Cellular and molecular Immunology

The principal fate of T cells that recognize self antigens is death (deletion), BUT:

Some CD4 T cells may differentiate into regulatory (suppressive) T lymphocytes

Development of Regulatory T cells



Togashi, NatRev Clinoc 2019

Wichtig

Foxp3 – The Transcription Factor for Tregs

Wichtig

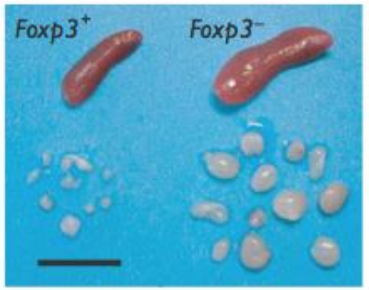
Wichtig

Definition of regulatory T cells:

$CD4^+CD25^+$**$Foxp3^+$**

Ultra Pazifist des Immunsystems

Foxp3$^{-/-}$ mice: loss of Tregs

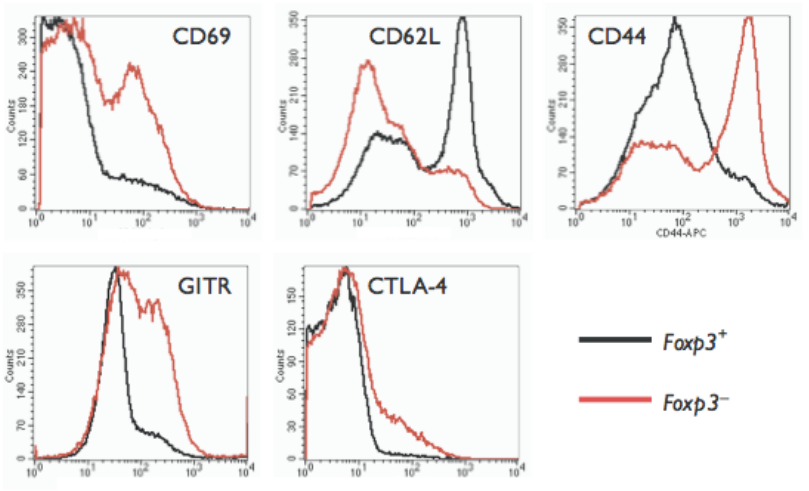


Splenomegaly
Lymphadenopathy

Severe inflammation

Fontenot, Rudensky, 2003

FACS analysis of $CD4^+$ T cells

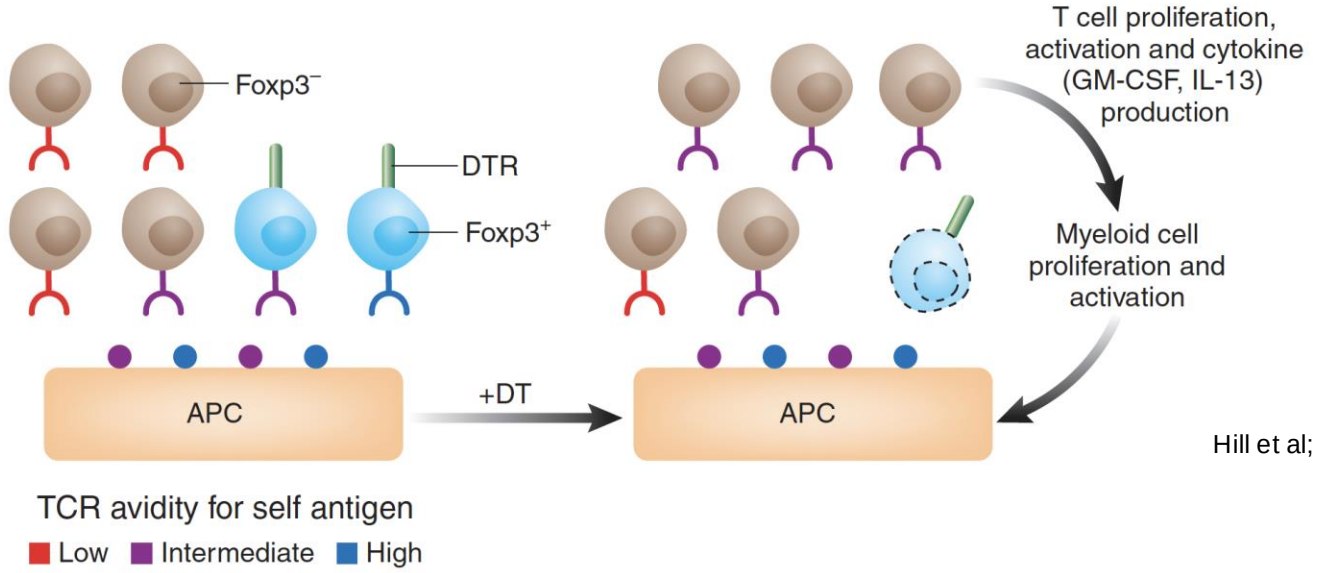


$CD4^+$ T cells display an activated phenotype in *Foxp3*$^{-/-}$ mice compared to WT control mice

Lethal lymphoproliferative autoimmune disease

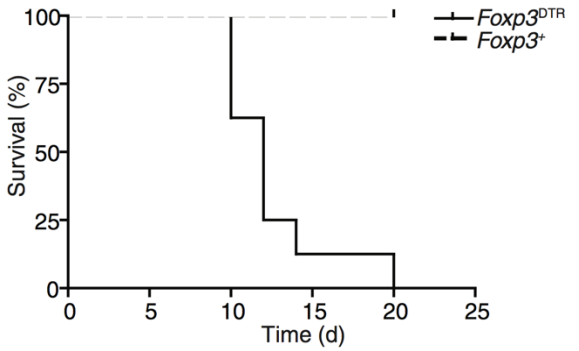
In humans: Mutations in *FOXP3* lead to Treg deficiency and multiorgan lymphocyte infiltrates, IPEX syndrome

Regulatory T cells maintain Self-Tolerance throughout Life



Hill et al; NatImm, 2007

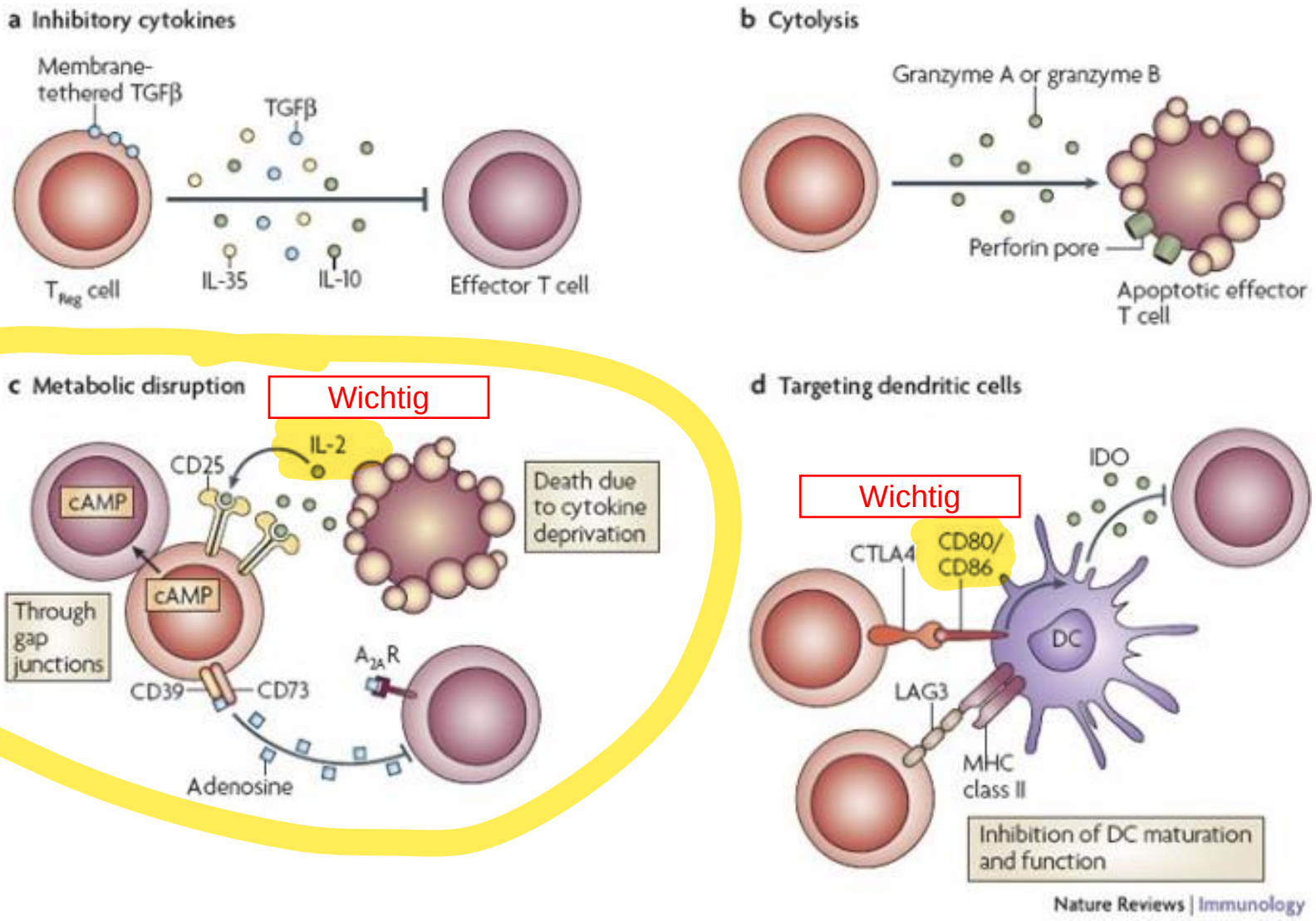
- Injection of DT results in depletion of Tregs in Foxp3^{DTR} mice.
- This leads to the activation of CD4^{+} T cells and severe systemic autoimmunity.



Kim et al; NatImm, 2007

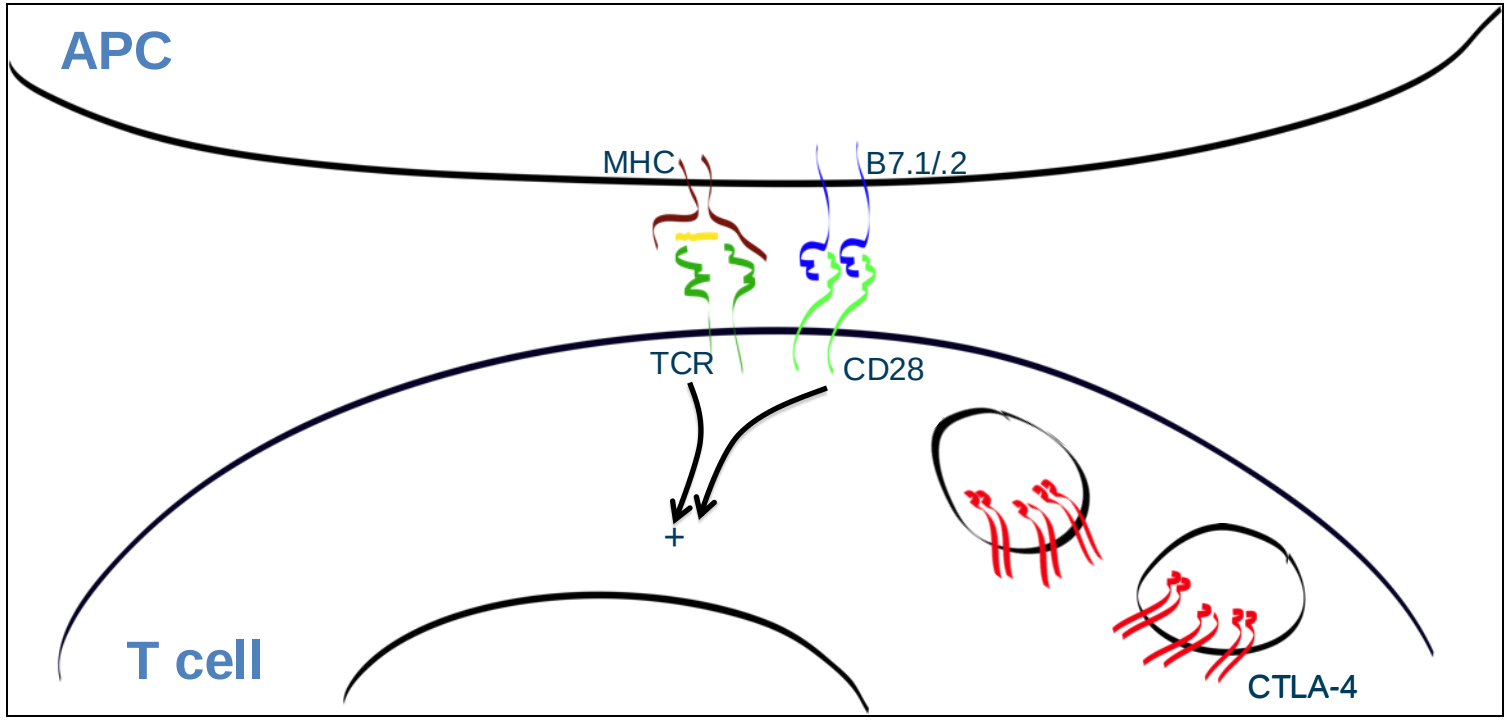
Wirkmechanismen regulatorischer T Zellen

Immunsupprimierende Wirkung



Vignali et al., Nat Rev Immunol 2008

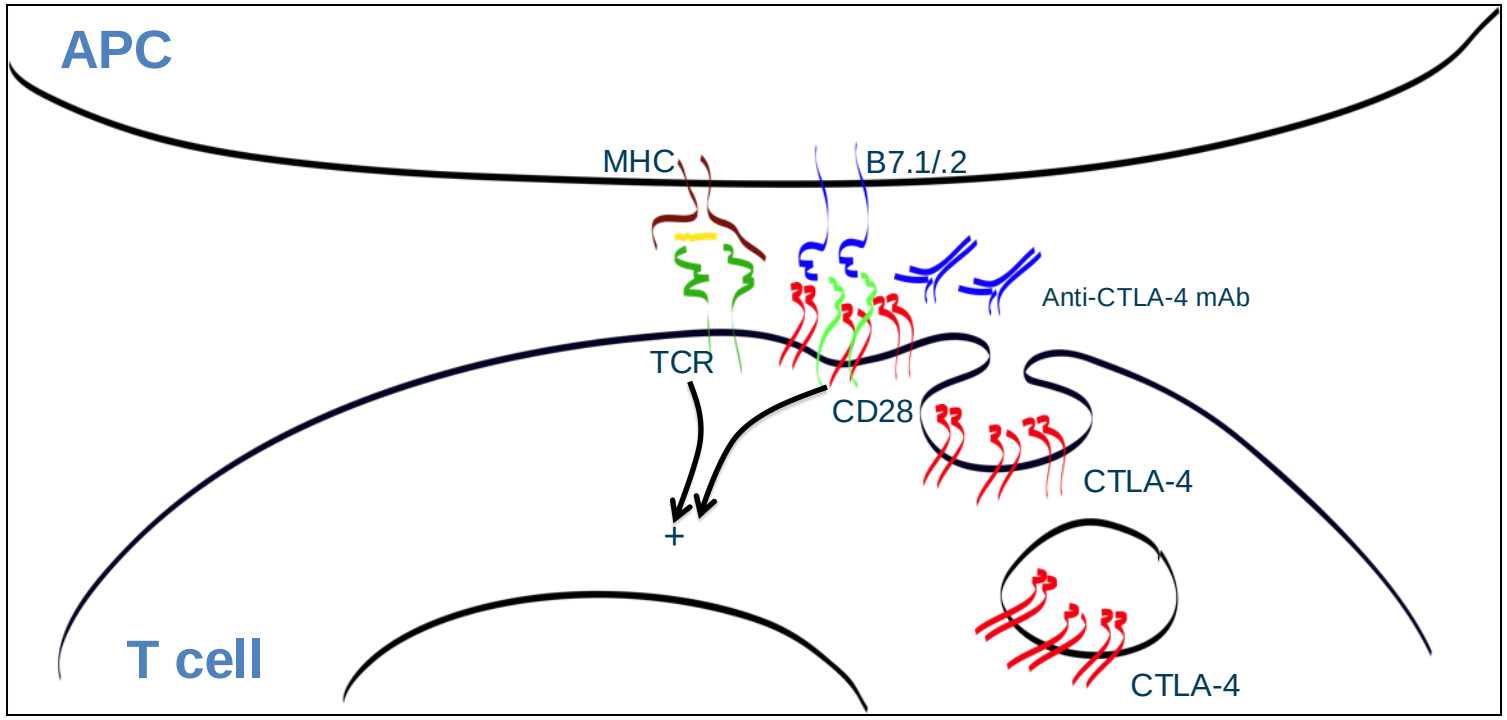
Restricting Immunity Through CTLA-4[1]



MHC, major histocompatibility complex; TCR, T-cell receptor.

1. Quezada SA, et al. *Br J Cancer.* 2013;108:1560-1565.

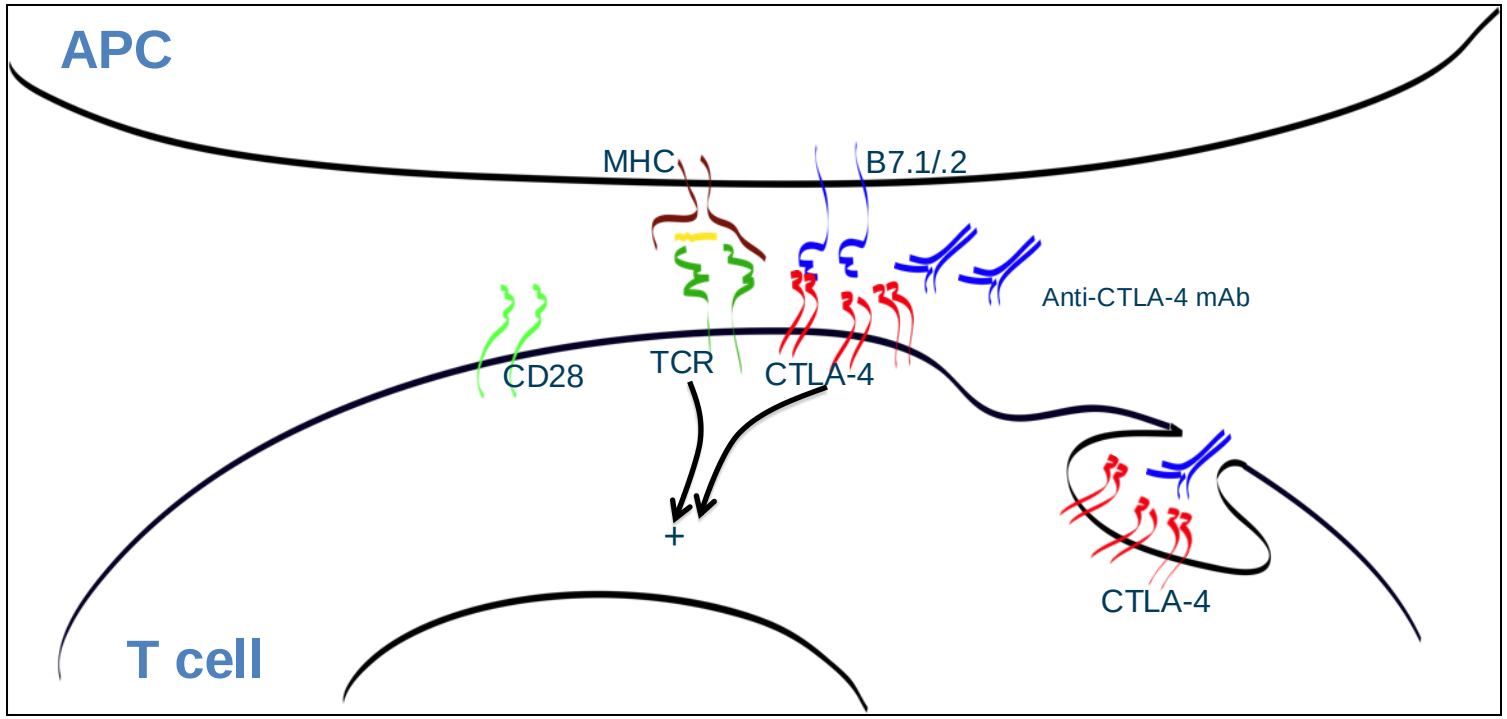
Restricting Immunity Through CTLA-4[1]



mAB, monoclonal antibody.

1. Quezada SA, et al. *Br J Cancer.* 2013;108:1560-1565

Restricting Immunity Through CTLA-4[1]



mAB, monoclonal antibody.

1. Quezada SA, et al. *Br J Cancer.* 2013;108:1560-1565

So what now?

Why does immune tolerance fail
in some people?
→ AUTOIMMUNITY

1900: Horror autotoxicus

Julius Morgenroth (1871-1924) *Paul Ehrlich (1854-1915)*

1908 Nobel Prize in Medicine

Autoimmunerkrankungen

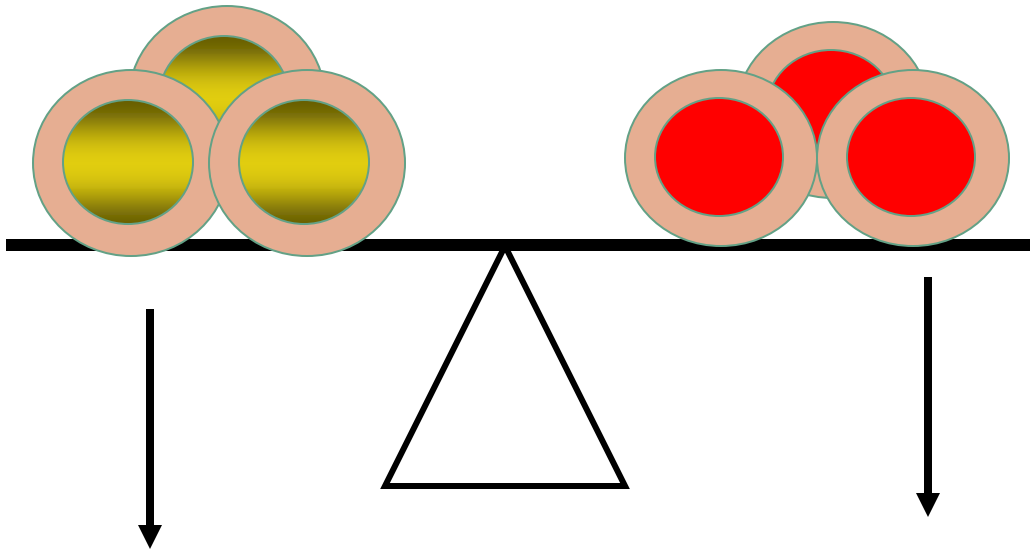
Disease	Disease mechanism	Consequence
Graves' disease	Autoantibodies against the thyroid-stimulating-hormone receptor	Hyperthyroidism: overproduction of thyroid hormones
Rheumatoid arthritis	Autoreactive T cells against antigens of joint synovium	Joint inflammation and destruction causing arthritis
Hashimoto's thyroiditis	Autoantibodies and autoreactive T cells against thyroid antigens	Destruction of thyroid tissue leading to hypothyroidism: underproduction of thyroid hormones
Type 1 diabetes (insulin-dependent diabetes mellitus, IDDM)	Autoreactive T cells against pancreatic islet cell antigens	Destruction of pancreatic islet β cells leading to non-production of insulin
Multiple sclerosis	Autoreactive T cells against brain antigens	Formation of sclerotic plaques in brain with destruction of myelin sheaths surrounding nerve cell axons, leading to muscle weakness, ataxia, and other symptoms
Systemic lupus erythematosus	Autoantibodies and autoreactive T cells against DNA, chromatin proteins, and ubiquitous ribonucleoprotein antigens	Glomerulonephritis, vasculitis, rash
Sjögren's syndrome	Autoantibodies and autoreactive T cells against ribonucleoprotein antigens	Lymphocyte infiltration of exocrine glands, leading to dry eyes and/or dry mouth; other organs may be involved, leading to systemic disease

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

Balancing lymphocyte activation and control

Activation
Effector T cells

Tolerance
Regulatory T cells



Chronische Entzündungen
und Autoimmunität

Krebs entsteht und es kann
keine Immunreaktionen
vonstatten gehen

Reactions against pathogens

Inflammatory disease
(reactions against self)

No response to self

Controlled response to
pathogens

Factors that break down immune tolerance

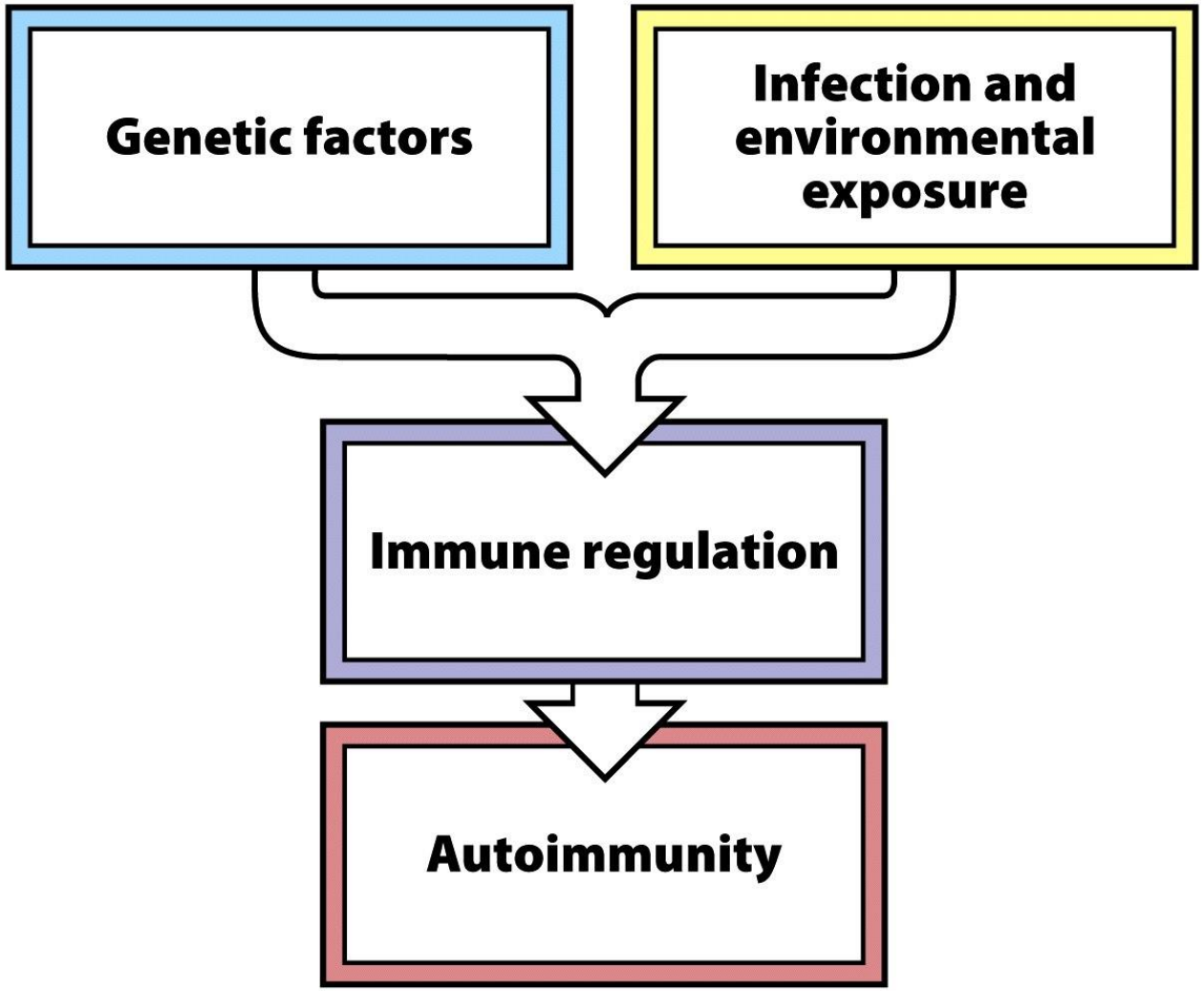


Figure 14-3 Immunobiology, 7ed. (© Garland Science 2008)

Genetics of Autoimmunity

- Human autoimmune diseases are complex polygenic traits
  - Identified by genome-wide association mapping
  - Single gene mutations are useful for pathway analysis
- Some polymorphisms are associated with multiple diseases
  - May control general mechanisms of tolerance and immune regulation
- Other genetic associations are disease-specific
  - May influence end-organ damage

Genetics of Autoimmunity: Recent Successes of Genomics

Wichtig

Polymorphisms associated to autoimmune disease

Wichtig

- *NOD2*: polymorphism associated with ~25% of Crohn's disease
  - Microbial sensor
- *PTPN22*: most common autoimmunity-associated gene; polymorphism in RA, SLE, others
  - Phosphatase
- *CD25 (IL-2Rα):* associated with MS, others; genome-wide association mapping
  - Role in Tregs and T cell activation

Single Gene Mutations That Cause Autoimmunity

Wichtig

Wichtig

- *AIRE*: Failure of central tolerance
  APECED, also called APS1 (Autoimmune polyendocrine syndrome)
- *CTLA4*: Polymorphisms associated with several autoimmune diseases
- *FOXP3*: Multiorgan lymphocytic infiltrates, Treg deficiency,
  IPEX Syndrome

Infections and Autoimmunity

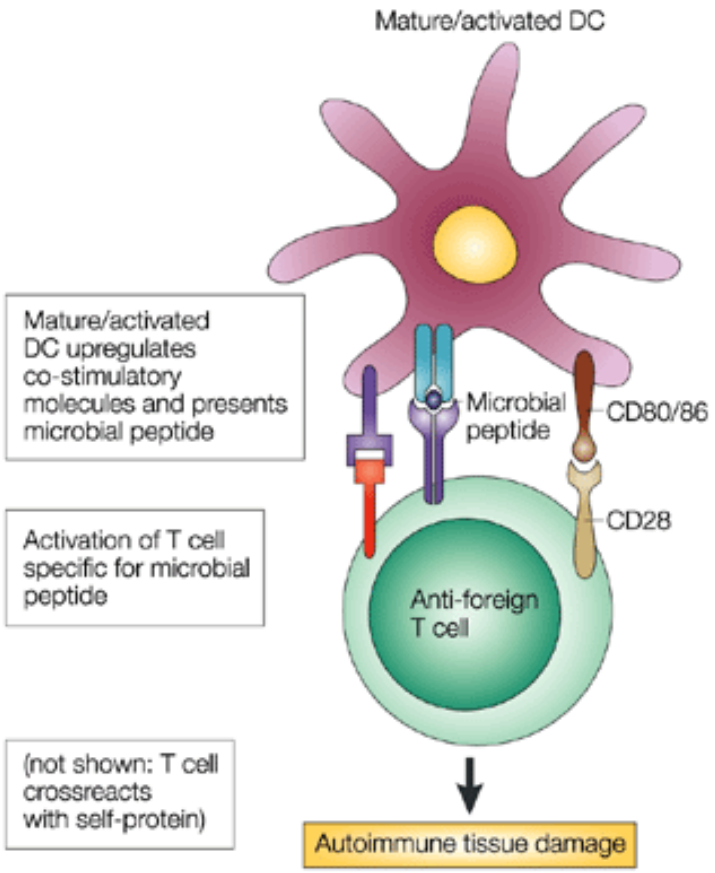
Infections can trigger autoimmune reactions

- Clinical prodromes, animal models
- Autoimmunity develops after infection is eradicated (i.e. the autoimmune disease is precipitated by infection but is not directly caused by the infection)

How can infections lead to autoimmunity?

Wichtig

Molecular Mimicry



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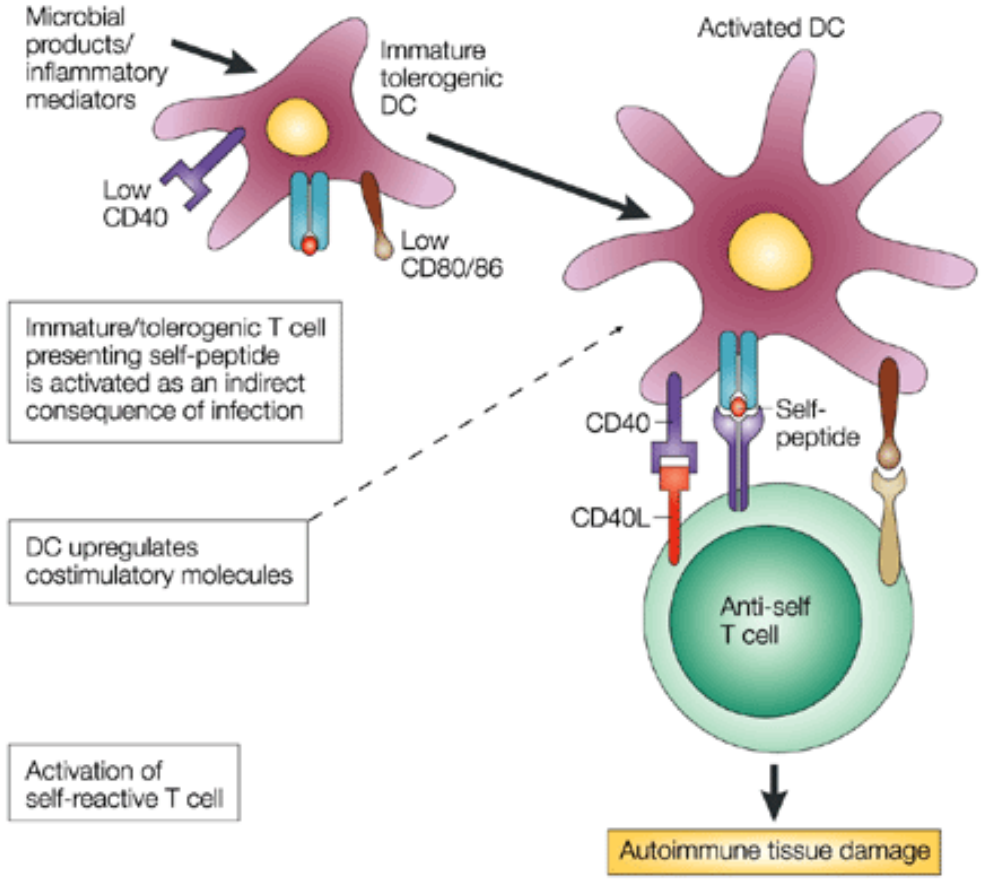
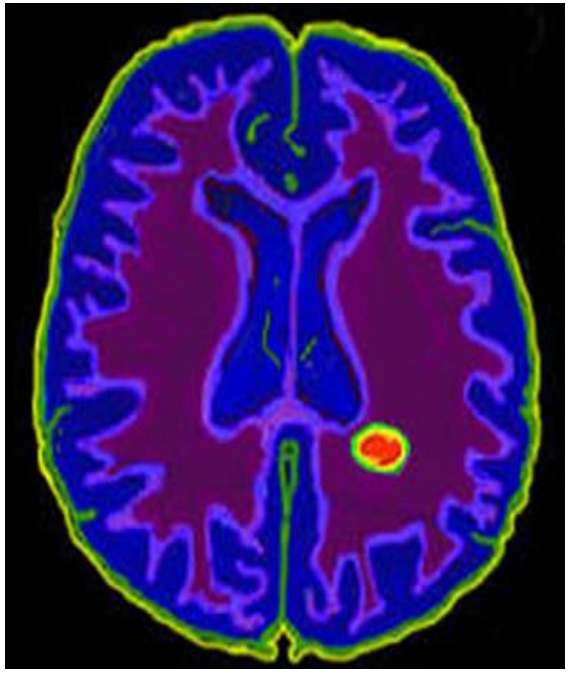
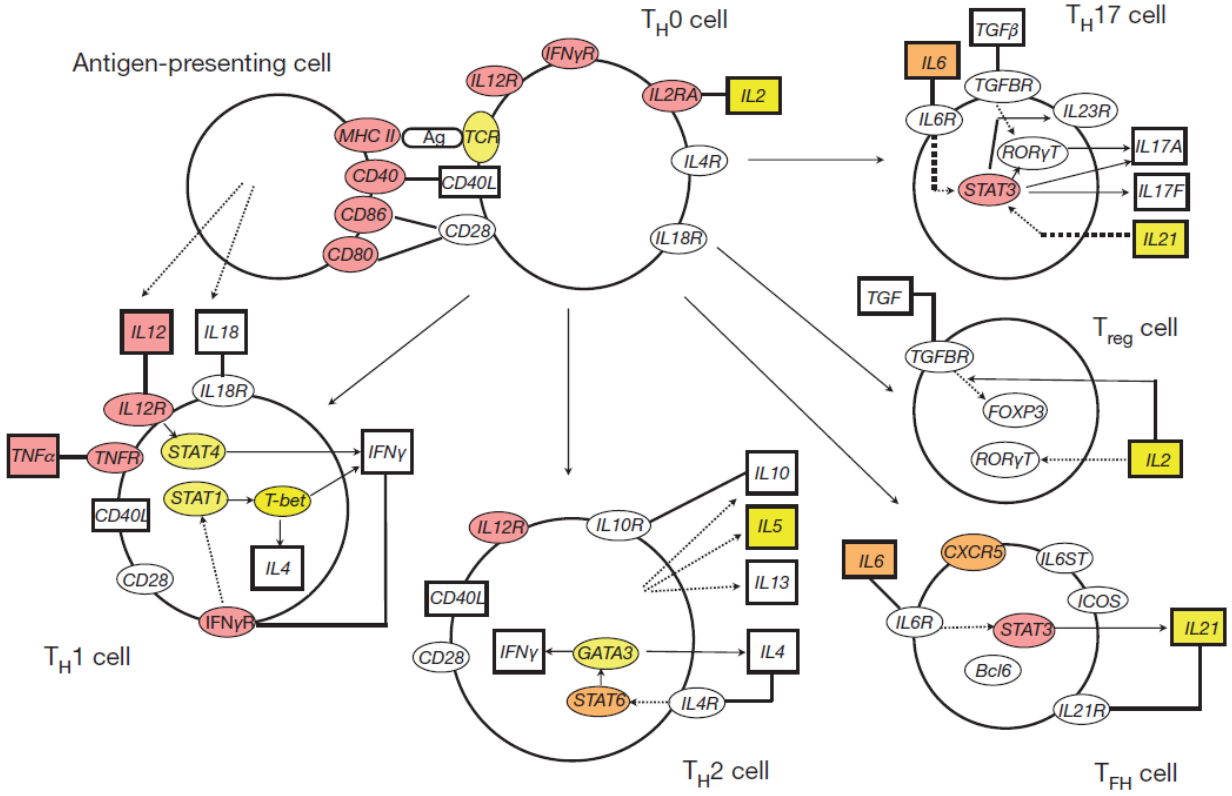
Bystander Activation



MS – Attacke des Immunsystems auf das Zentrale Nervensystem



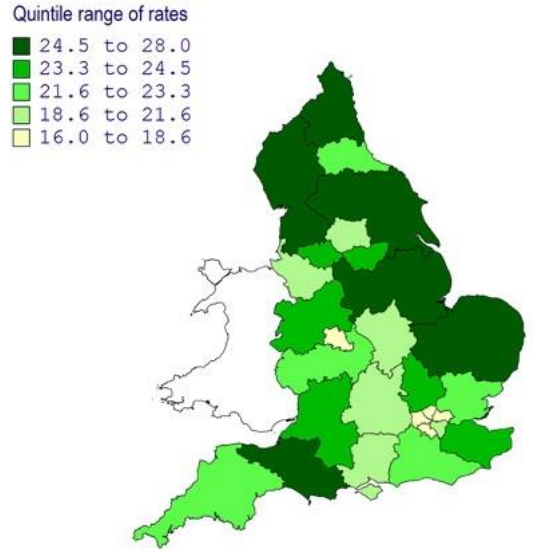
Mehr als 230 Stellen des Genoms entscheiden über MS Risiko

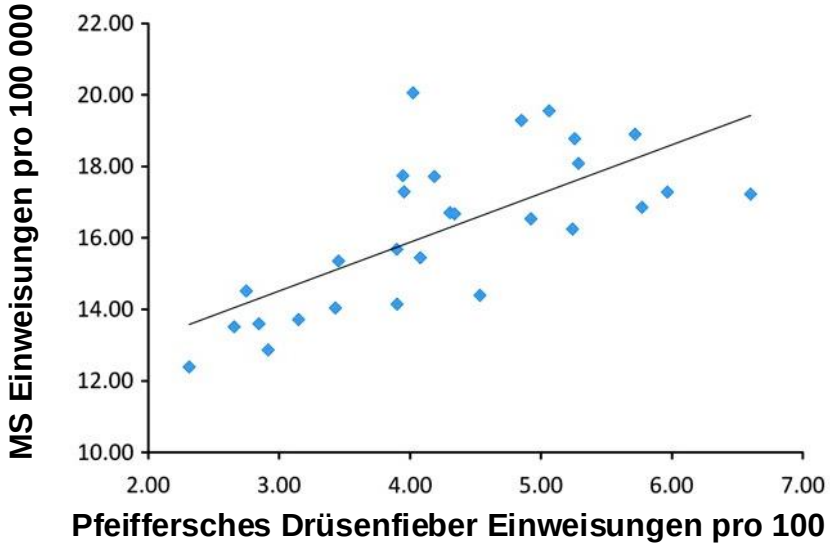


Sawcer et al., Nature 2011, Cotsapas et al., Cell 2018

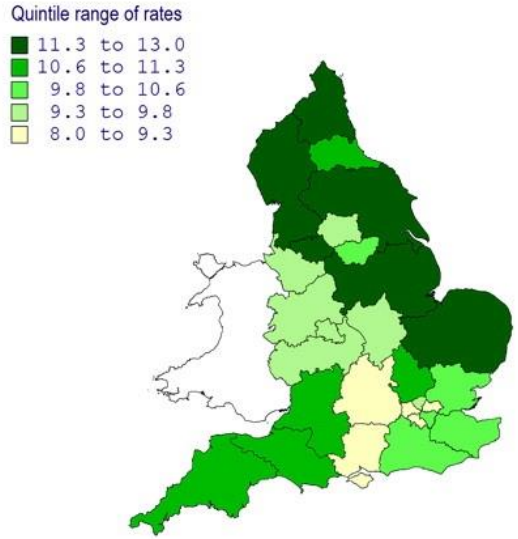
In Gebieten mit hoher MS Frequenz tritt Pfeiffersches Drüsenfieber auch gehäuft auf

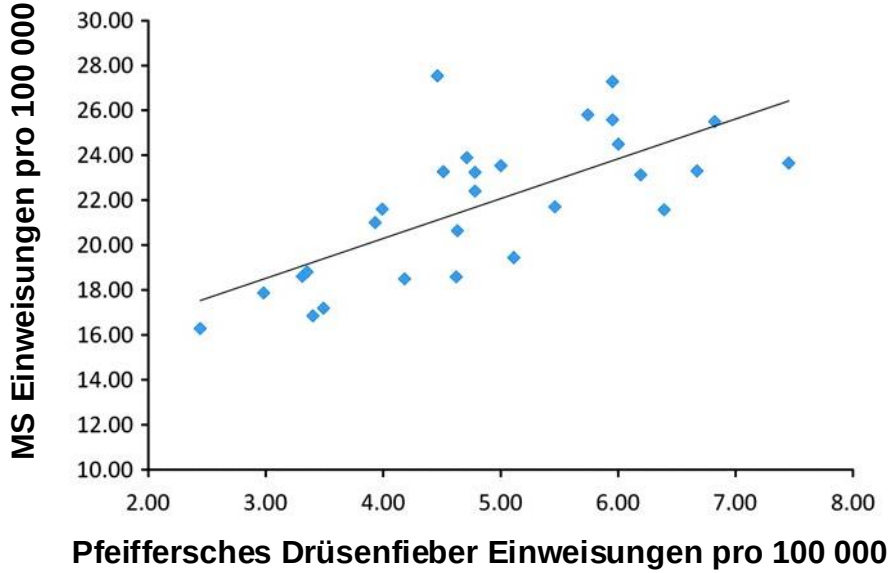
Männer





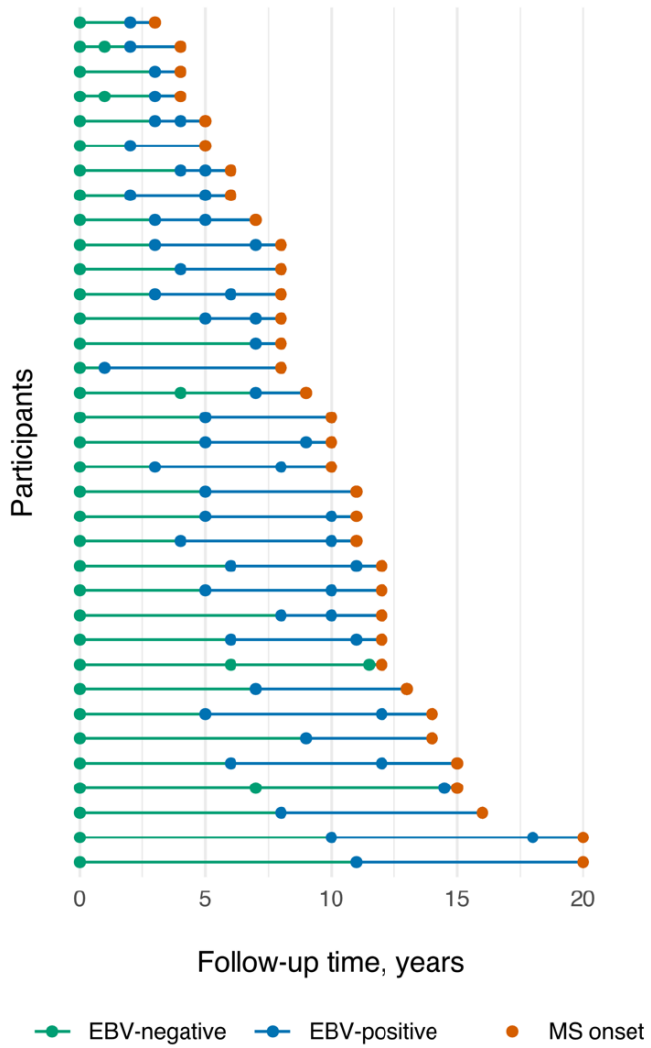
Frauen

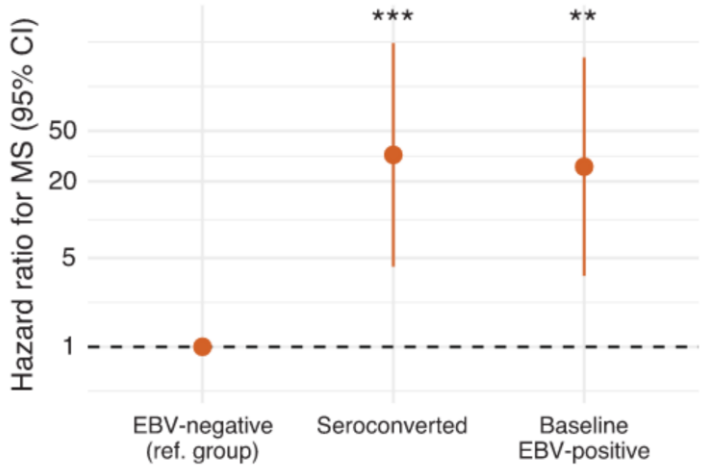


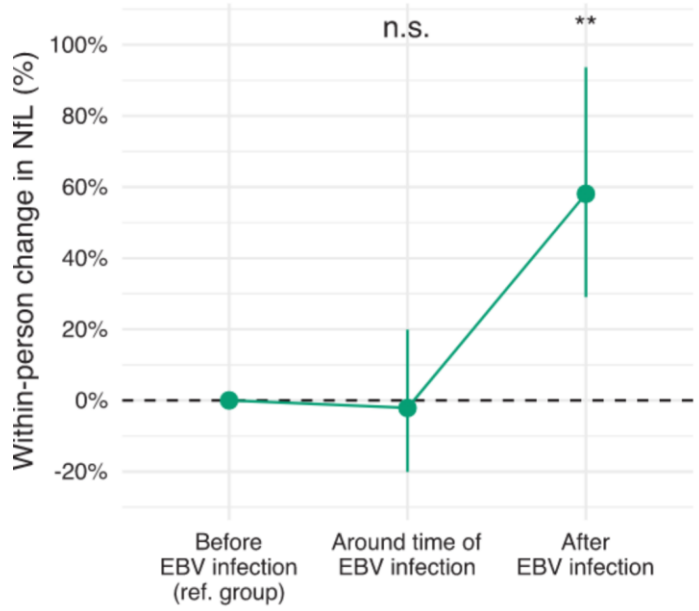


Ramagopalan et al., J Neurol Neurosurg Psychiatry 2011

EBV Infektion erhöht das MS Risiko 32fach







Bjornevik et al., Science 2022

Der Epstein Barr Virus (EBV) hat sich zum Umwelthauptrisikofaktor bei der MS entwickelt

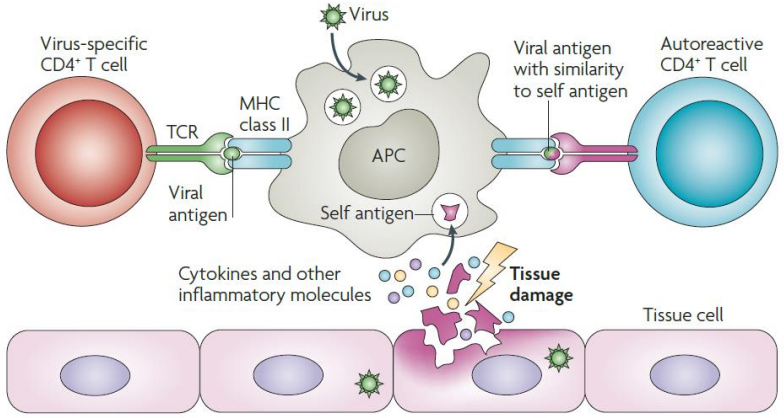
Table 1 | **Established and possible lifestyle and environmental risk factors for MS**

Factor	OR	HLA gene interaction	Combined OR (nongenetic factor + HLA allele)	Effect during adolescence	Immune system implied	Level of evidence
Smoking	~1.6	Yes	14	No	Yes	+++
EBV infection (seropositivity)	~3.6	Yes	~15	Yes	Yes	+++
Vitamin D level <50 nM	~1.4	No	NA	Probably	Yes	+++
Adolescent obesity (BMI >27 at age 20 years)	~2	Yes	~15	Yes	Yes	+++
CMV infection (seropositivity)	0.7	No	NA	Unknown	Yes	++
Night work	~1.7	No	NA	Yes	Yes	++
Low sun exposure	~2	No	NA	Probably	Yes	++
Infectious mononucleosis	~2	Yes	7	Yes	Yes	++
Passive smoking	~1.3	Yes	6	No	Yes	+
Organic solvent exposure	~1.5	Unknown	Unknown	Unknown	Unknown	+
Oral tobacco/nicotine	0.5	No	NA	Unknown	Yes	+
Alcohol	~0.6	No	NA	Unknown	Yes	+
Coffee	~0.7	No	NA	Unknown	Yes	+

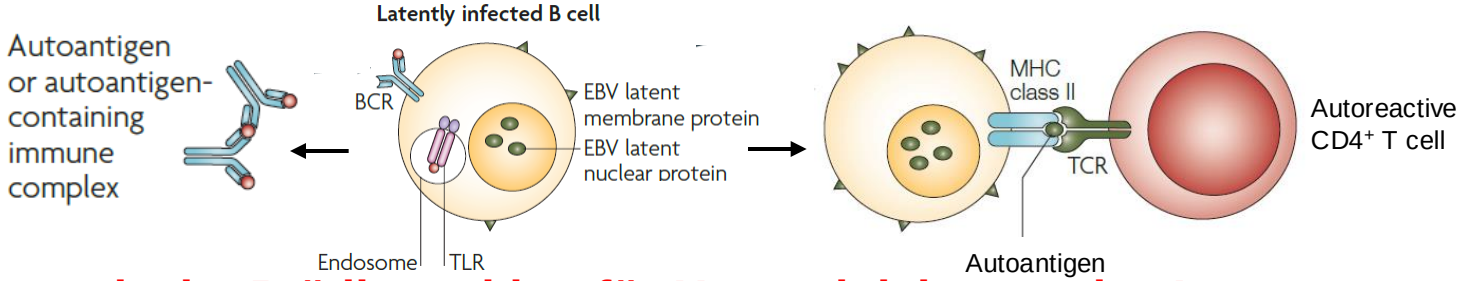
Olsson et al., Nat Rev Neurol 2017

Mögliche Mechanismen der EBV Assoziation mit MS

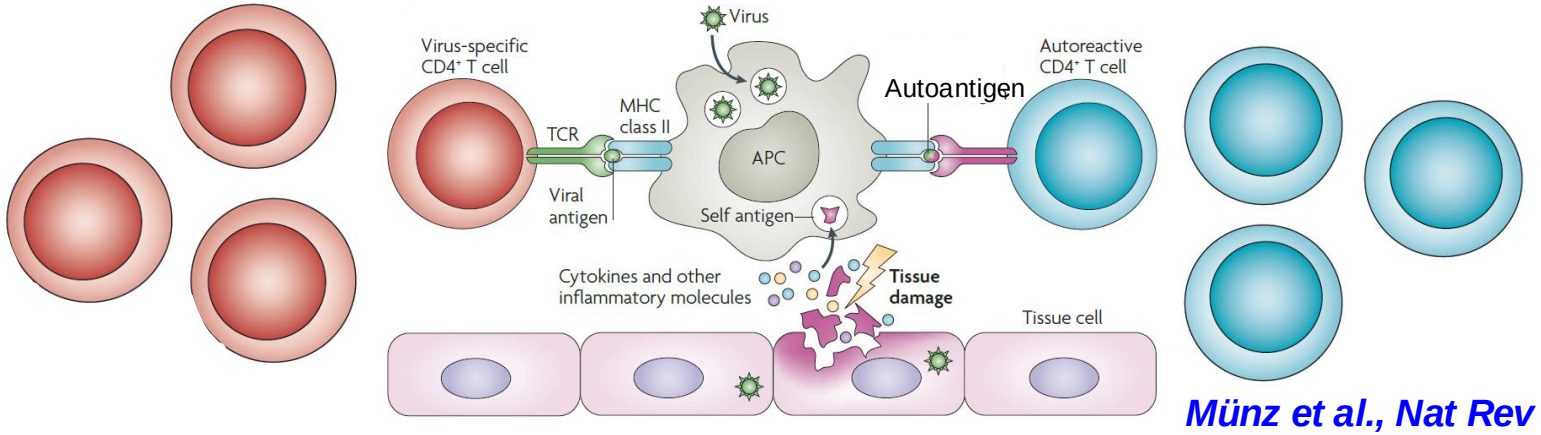
1. Molekulares Mimikry



2. EBV infizierte B Zellen als antigenpräsentierende Zellen im ZNS



3. Ähnliche genetische Prädisposition für Hyperaktivierung des Immunsystems während der Erstinfektion mit EBV und ZNS Autoimmunität

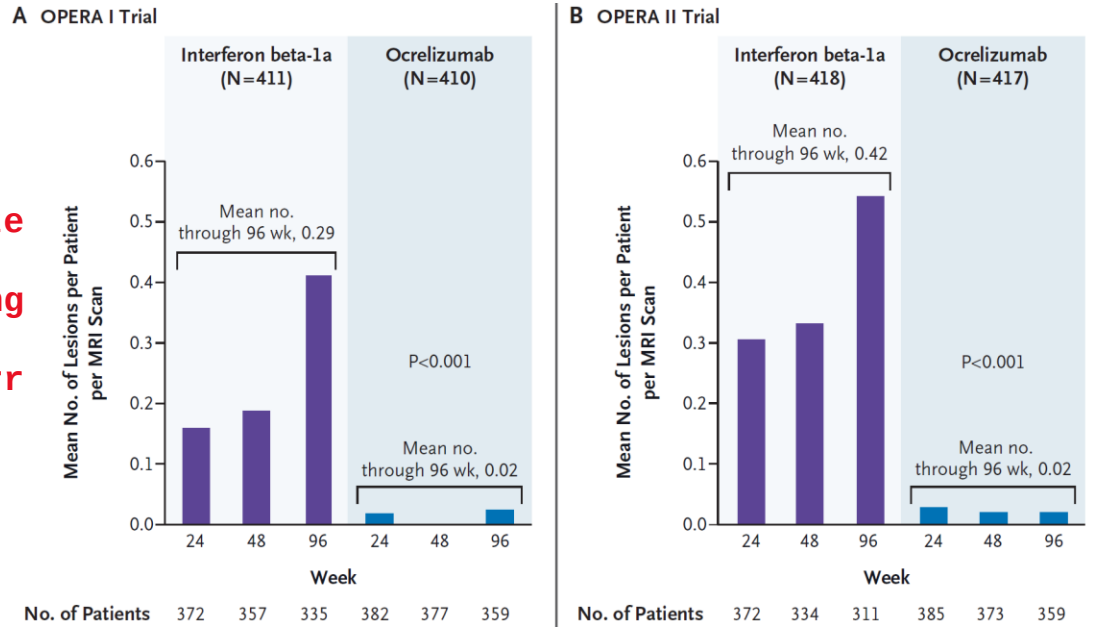


Münz et al., Nat Rev Immunol 2009

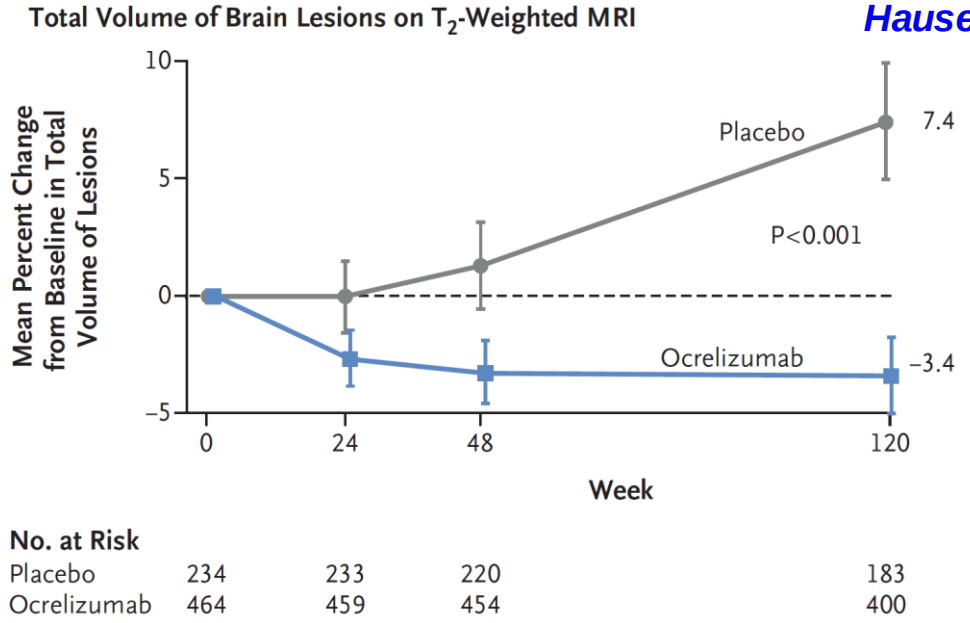
B Zell-depletierende Therapien in MS

Obwohl MS eine t-Zell vermittelte Immunerkrankung ist, stoppt die Krankheit bei B-Zell-Depletierung

<-- Vielleicht, weil Epstein-Barr Virus B-Zellen angreift



Hauser et al., N Engl J Med 2017



Montalban et al., N Engl J Med 2017

Autoimmunity is primarily understood as:

- Loss of immune tolerance and
- Activation of autoaggressive T & B cell clones

Loss of tolerance due to

- Genetic predisposition and
- Infection ~~(mimicry)~~

Next lecture:
Autoimmunity or Cytokinopathy