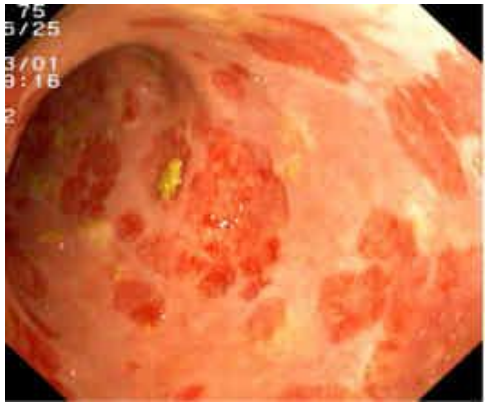
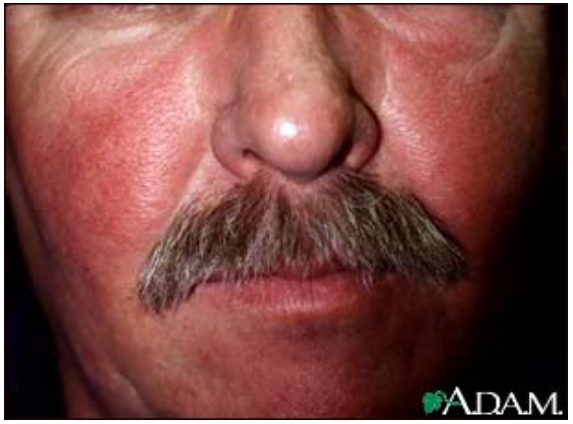
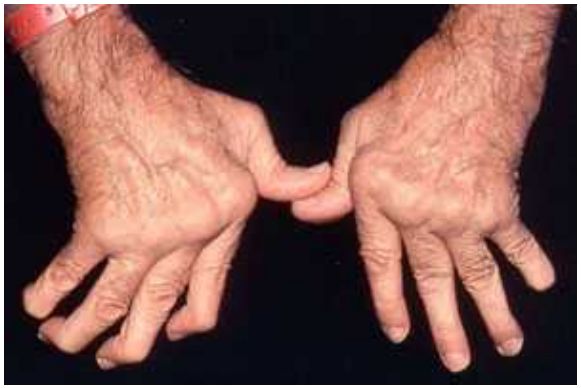


Autoimmunität





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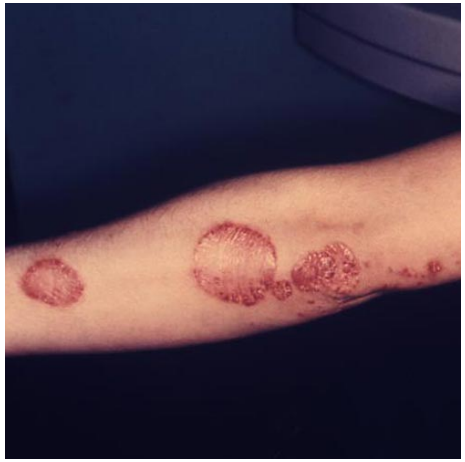

- *„Horror autotoxicus“* ⟺ ...a minefield of self-reactive cells.....
- Immunologisch privilegierte Orte und Autoimmunität
- Primäre Immundefizienzen und Autoimmunität
- Die häufigsten autoimmunologischen Erkrankungen
- Immunpathogenetische Mechanismen
- Genetische Faktoren: Assoziation mit HLA
- Infektionen und Autoimmunität

Der „*Horror autotoxicus*“ als teleologisches Diktum (Wende 19./20. Jhd.)

Immunantwort gegen körpereigenes Gewebe grundsätzlich nicht möglich, da mit dem Leben unvereinbar.

„ Acceptance of a fact in science may depend less upon Its truth than upon the willingness of the leaders In the field (Denkkollektiv) to acknowledge it“.
Ludwik Fleck (1896-1961)

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Endgültiges Umdenken: Experimentelle autoimmune Thyroiditis (1956)

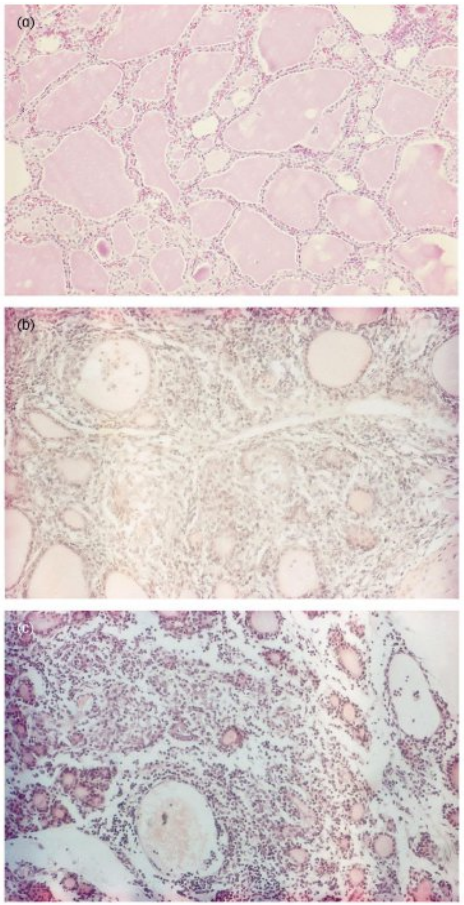

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Figure M18.1.1. Experimental autoimmune thyroiditis.

(a) The follicular architecture of the normal thyroid. (b) Thyroiditis produced by immunization with rat thyroid extract in complete Freund's adjuvant; the invading chronic inflammatory cells have destroyed the follicular structure. (Based on the experiments of Rose N.R. & Witebsky E. (1956) *Journal of Immunology* **76**, 417–427.) (c) Similarity of lesions in spontaneous human autoimmune disease to those induced in the experimental model.

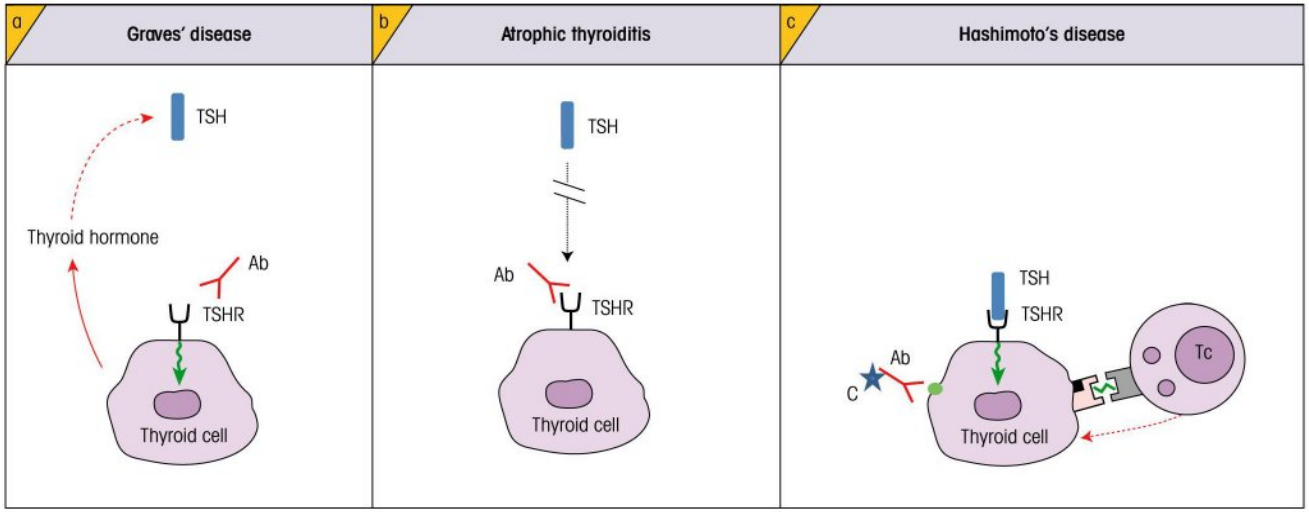

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Figure 18.16. Thyroid autoimmune dieases.

The three major types of thyroid autoimmune disease are illustrated. (a) In Graves' disease autoantibodies bind to the thyroid-stimulating hormone receptor (TSHR) on thyroid epithelial cells. These antibodies act as agonists and mimic the effect of TSH. The autoantibodies are continuously produced from plasma cells and therefore their production is not directly affected by the levels of thyroid hormone, unlike the levels of TSH that are subject to a negative feedback loop and therefore decrease when adequate levels of thyroid hormone are produced. Constant activation of the thyroid cells by the stimulatory autoantibody results in hyperthyroidism. (b) In atrophic thyroiditis (primary myxedema) autoantibodies are also produced to the TSH receptor but bind to different epitopes to those found in Graves' disease and act as antagonists rather the agonists. Their ability to block access of TSH to the TSHR results in hypothyroidism. (c) The autoantibodies in Hashimoto's disease are predominantly directed against thyroid peroxidase and thyroglobulin. The thyroid cells can be attacked by cytotoxic T-cells recognizing peptides derived from these autoantigens and/or by complement-fixing antibodies directed to intact autoantigen. Alhough TSH is able to bind to the TSH receptor and stimulate the thyroid cells the destruction of the thyroid by the autoimmune attack results in hypothyroidism. These diseases most likely form a spectrum of autoimmune thyroid conditions with some Hashimoto's disease patients also possesing either stimulatory or inhibitory anti-TSHR.

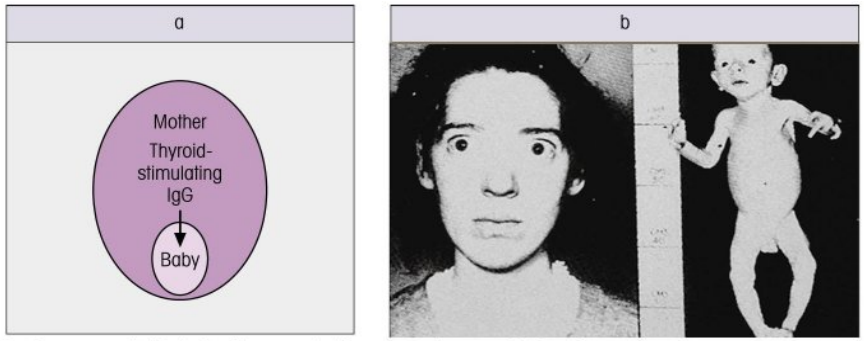

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Figure 18.17. Neonatal thyrotoxicosis.

(a) The autoantibodies that stimulate the thyroid through the TSH receptors are IgG and cross the placenta. (b) The thyrotoxic mother therefore gives birth to a baby with thyroid hyperactivity that spontaneously resolves as the mother's IgG is catabolized. (Photograph courtesy of A. MacGregor.)

Ivan Roitt

...we are all sitting on a minefield of self-reactive cells, with potential access to their respective autoantigens.

However as autoimmune disease only occurs in a minority of the population the body must possess homeostatic mechanisms to prevent such self-reactive cells being triggered under normal circumstances.

...the key to the system is control of the autoreactive T-helper cell as the evidence heavily favors the T-dependence of virtually all autoimmune responses.

Immunologisch privilegierte Orte: Gehirn, Auge, Testes, Uterus (Fetus)

☞ Dortige Antigene sind oft Ziel autoimmunologischer Attacken

Besonderheiten:

1. Kein Lymphabfluß durch konventionelles lymphat. Gewebe
2. Umgeben von Gewebebarrieren, die naive Lymphocyten ausschließen
3. Produktion immunsuppressiver Faktoren (TGF-β)
   (Antigen + TGF-β ➔Treg; Antigen + TGF-β + IL-6 ➔ Th17)
4. Expression von CD95L (FasL) (➔ Apoptose von T-Effektorzellen)

Beispiele:

Ophthalmia sympathica; meist schwere Entzündung der Uvea des ursprüngl. gesunden Auges nach schwerer Traumatisierung des anderen Auges. Urs.: Autoimmunisierung gegen bei der Verletzung freigewordene Uveabestandteile. Ther.: Enukleation des traumat. Auges, Kortikoide, Immunsuppressiva

Multiple Sklerose (EAE: experimentelle autoimmune Enzephalomyelitis)
Chronisch-entzündliche Demyelinisierung des ZNS.
Mausmodell EAE: Tiere erkranken nach Immunisierung mit Myelinbestandteilen und Adjuvans

☞ Autoreaktive T-Zellen sind stets präsent und aktivierbar

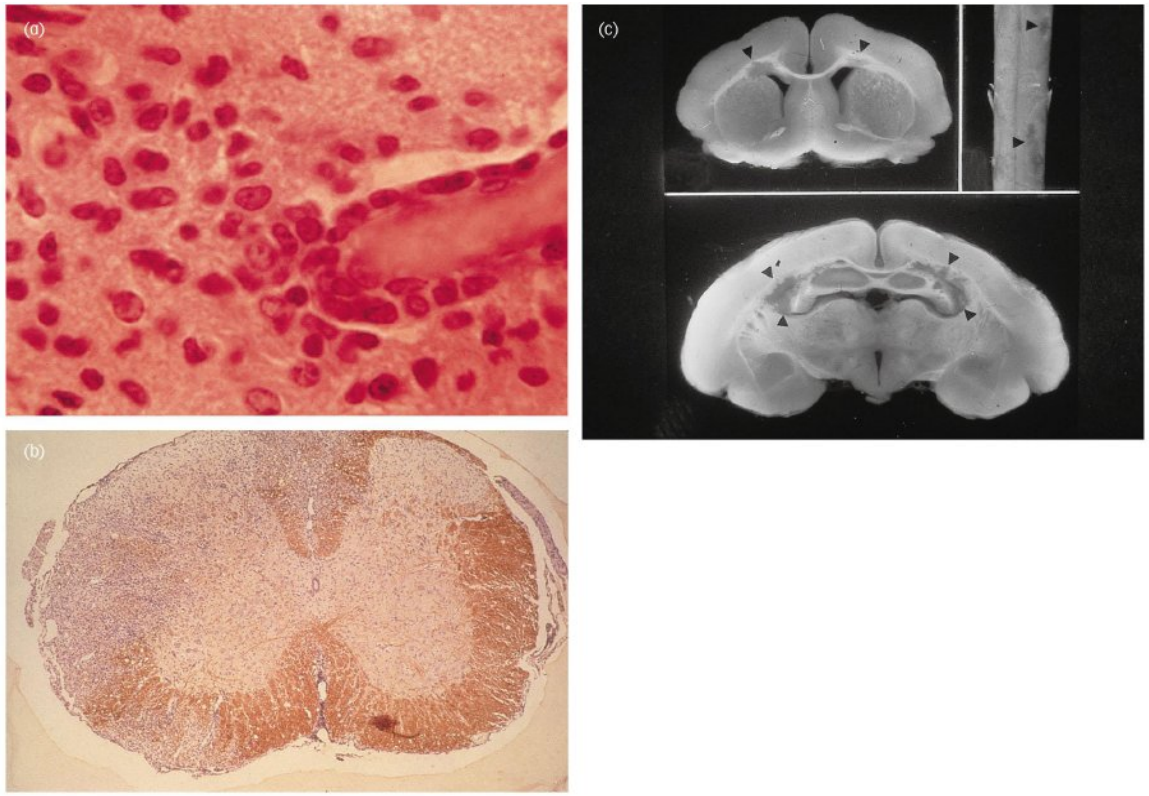

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Figure 18.24. Experimental autoimmune encephalomyelitis (EAE), a demyelinating model for multiple sclerosis induced by immunization with brain antigens in complete Freund's adjuvant (CFA).

(a) Early lesion of EAE in the rat at 9 days after immunization with rat spinal cord homogenate in CFA. The lesion in brain white matter, which is probably a few hours old, shows perivenous infiltration of lymphocytes and monocytes (a pure mononuclear inflammation) with cells invading the nervous parenchyma. Myelin is not stained. (b) Lumbar spinal cord of rat with chronic EAE after immunization with myelin proteolipid protein. Large demyelinating lesions in dorsal columns, in both left (large) and right (small) columns, as well as on lower left. Also gray matter involved with ongoing inflammation, in particular affecting left dorsal horn. Normal myelin is stained brown. (c) Chronic relapsing EAE in guinea-pig. Large demyelinated plaques in brain white matter (arrows) closely similar to plaques of multiple sclerosis. (Legend and slides provided by B. Waksman; (b) originally from Trotter and (c) from Lassmann and Wisniewski.)

Paradoxon: Einige primäre Immundefizienzen verursachen Autoimmunität

FoxP3-Defekte: **IPEX**
(Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked)
Ausgeprägte Darmentzündungen (Durchfall, Wasting), Diabetes, Hypo/Hyperthyreoidismus, Nahrungsmittelallergien, Hepatitis, Nephritis, Anämie. Auch auto-Antikörper-vermittelt.

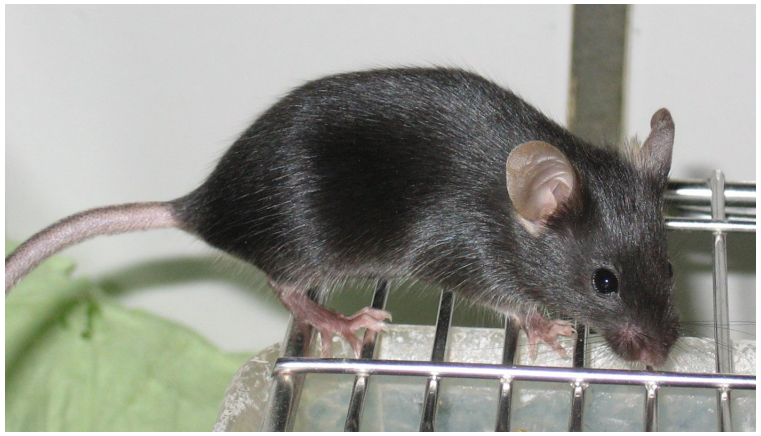
Defekte von CD95 (Fas), CD95L (Fas-Ligand), CD152 (CTLA-4): **ALPS**
(Autoimmunes lymphoproliferatives Syndrom)
Splenomegalie, Lymphadenopathie, erhöhte B- u. T-Zell-Zahlen, Autoantikörper

AIRE-Defekte: **APS-1**
(autoimmun-bedingtes pluriglanduläres Syndrom Typ I)
Antikörper gegen viele verschiedene Autoantigene (Schilddrüse, Pankreas, Haut, Leber, Blutzellen etc.)
Anfällig gegen Infektionen mit *Candida albicans* (wegen Autoantikörpern gegen IL-17, IL-22, IFN-α !)
Fehlbildungen der Nägel, Zähne
(Synonym: APECED; Autoimmun-Polyendokrinopathie-Candidiasis-Ektodermaldystrophie-Syndrom Typ I)
Finnen 1:25.000; Sarden 1:14.000; irakische Juden 1:9.000

FoxP3 ("scurfin"): exclusively expressed by Tregs

- Transcription factor (repressor) of the forkhead family
- Loss of function mutation gives rise to the scurfy phenotype:

  X-linked recessive lymphoproliferative disease
  Hyperresponsive $CD4^+$ T cells
  over-expression of various cytokines (IL-2, IL-4, etc.)
  Autoimmune pathologies (diabetes, thyroiditis etc.)
  Severe infections



- Human equivalent: IPEX
  (Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked)

  Diabetes, Dermatitis, hemolytic Anemia
  (usually lethal within the first year of life in affected males)

Paradoxon: Einige primäre Immundefizienzen verursachen Autoimmunität

FoxP3-Defekte: **IPEX**
(Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked)
Ausgeprägte Darmentzündungen (Durchfall, Wasting), Diabetes, Hypo/Hyperthyreoidismus, Nahrungsmittelallergien, Hepatitis, Nephritis, Anämie. Auch auto-Antikörper-vermittelt.

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Finnen 1:25.000; Sarden 1:14.000; irakische Juden 1:9.000

Autoreaktive T-Zellen werden in der Peripherie deletiert.

Activation-induced cell death.

Fas – FasL- induzierter Zelltod.

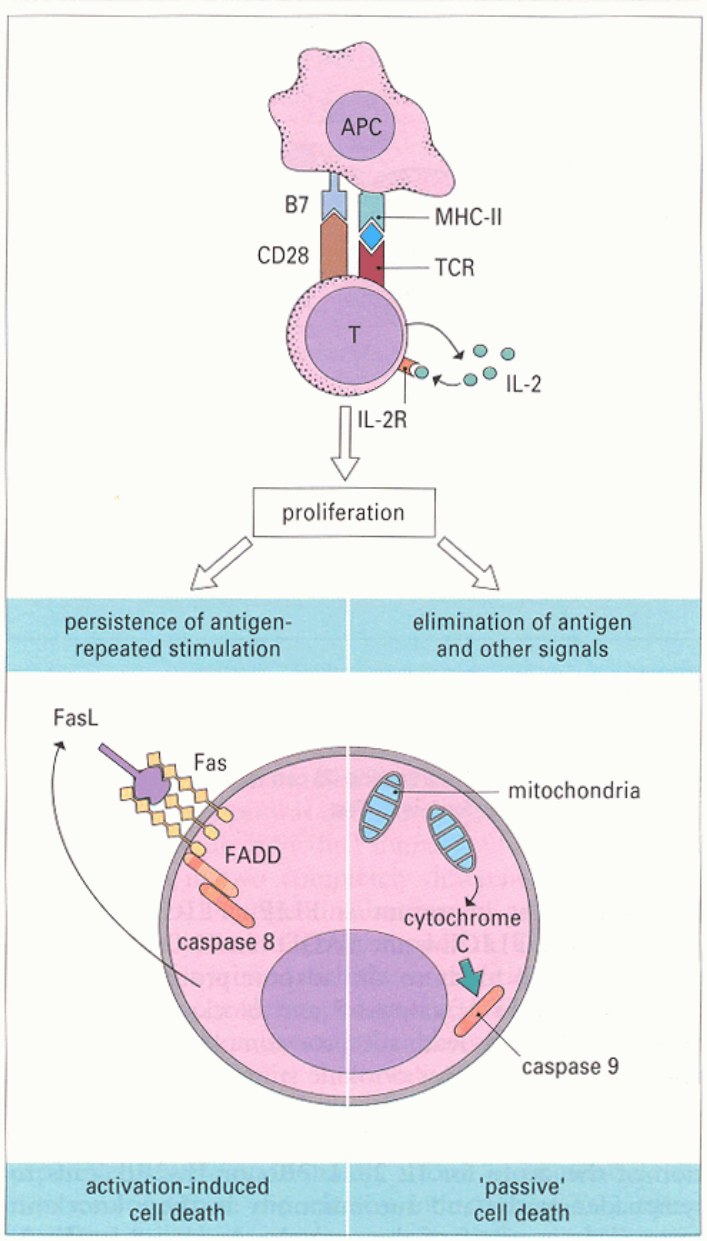

Fig. 12.13

Paradoxon: Einige primäre Immundefizienzen verursachen Autoimmunität

☞ FoxP3-Defekte: **IPEX**
(Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked)
Ausgeprägte Darmentzündungen (Durchfall, Wasting), Diabetes, Hypo/Hyperthyreoidismus, Nahrungsmittelallergien, Hepatitis, Nephritis, Anämie. Auch auto-Antikörper-vermittelt.

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(Synonym: APECED; Autoimmun-Polyendokrinopathie-Candidiasis-Ektodermaldystrophie-Syndrom Typ I)
Finnen 1:25.000; Sarden 1:14.000; irakische Juden 1:9.000

Der Transkriptionsfaktor AIRE

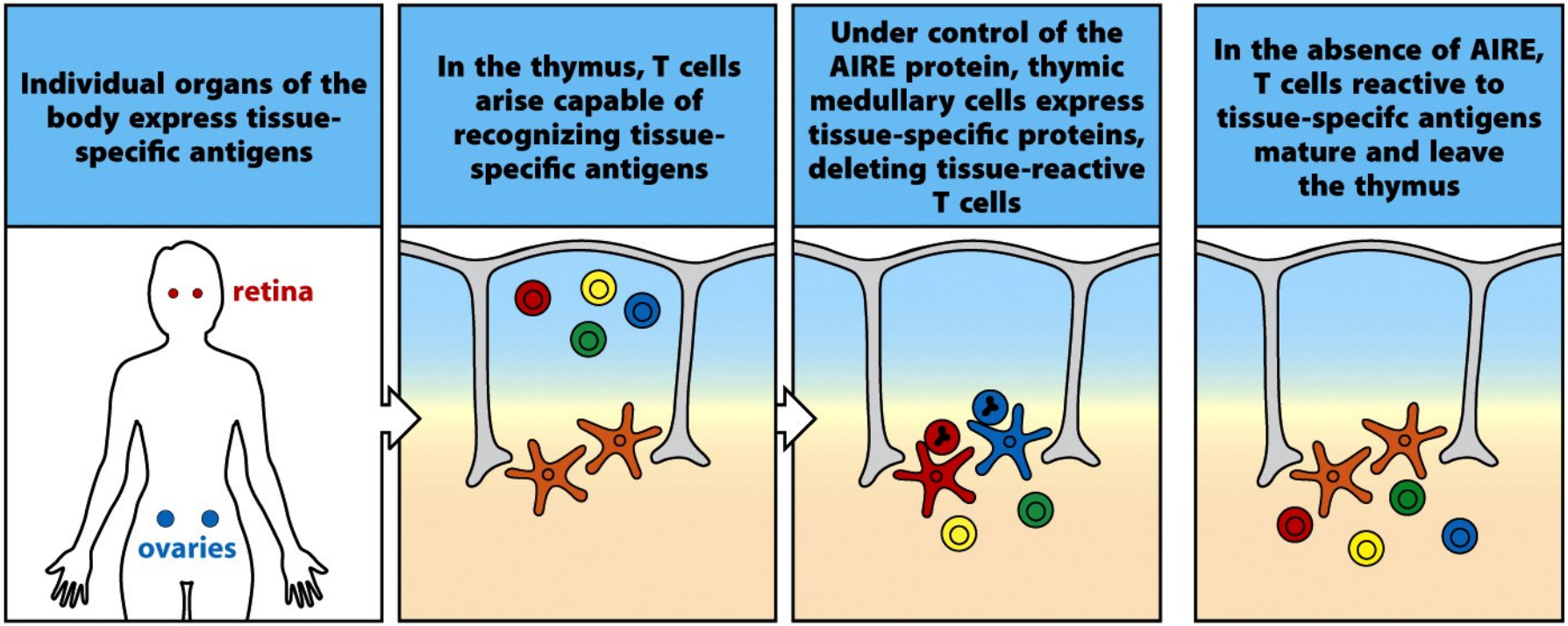
AIRE: Autoimmune regulator.

- Transkriptionsfaktor
- Wird stark von medullären Thymusepithelzellen exprimiert
- Autosomal rezessive Mutation führt zum

autoimmun-bedingten pluriglandulären Syndrome, Typ1 (APS-1)

APECED - autoimmune polyendocrinopathie – candidiasis -ectodermal dystrophie

Als **autoimmun-bedingtes pluriglanduläres Syndrom** werden seltene, aber statistisch überzufällig beobachtete Assoziationen mehrerer **autoimmun bedingter Erkrankungen** des Endokriniums, aber auch nicht endokriner Organsysteme, bezeichnet.



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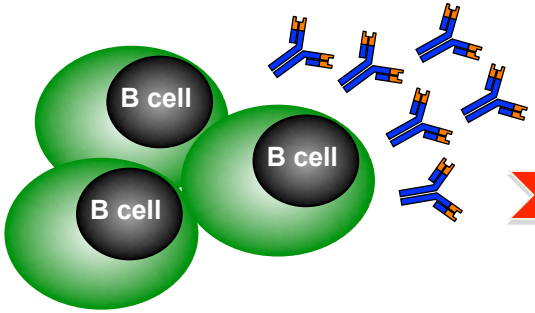
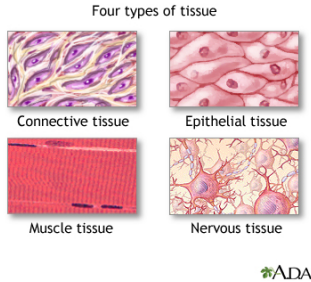
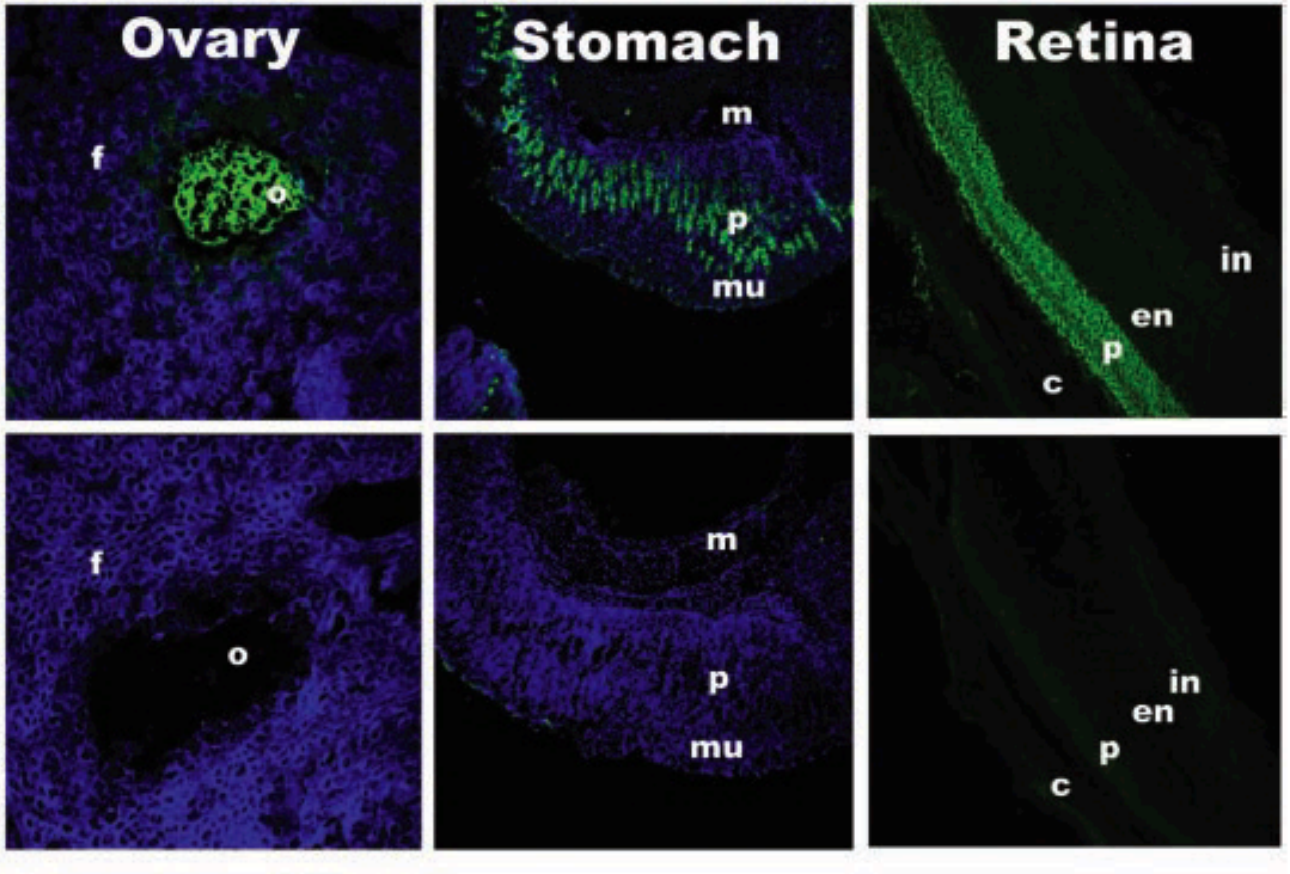
Serum



Histologie





$Aire^{-/-}$

$Aire^{+/+}$

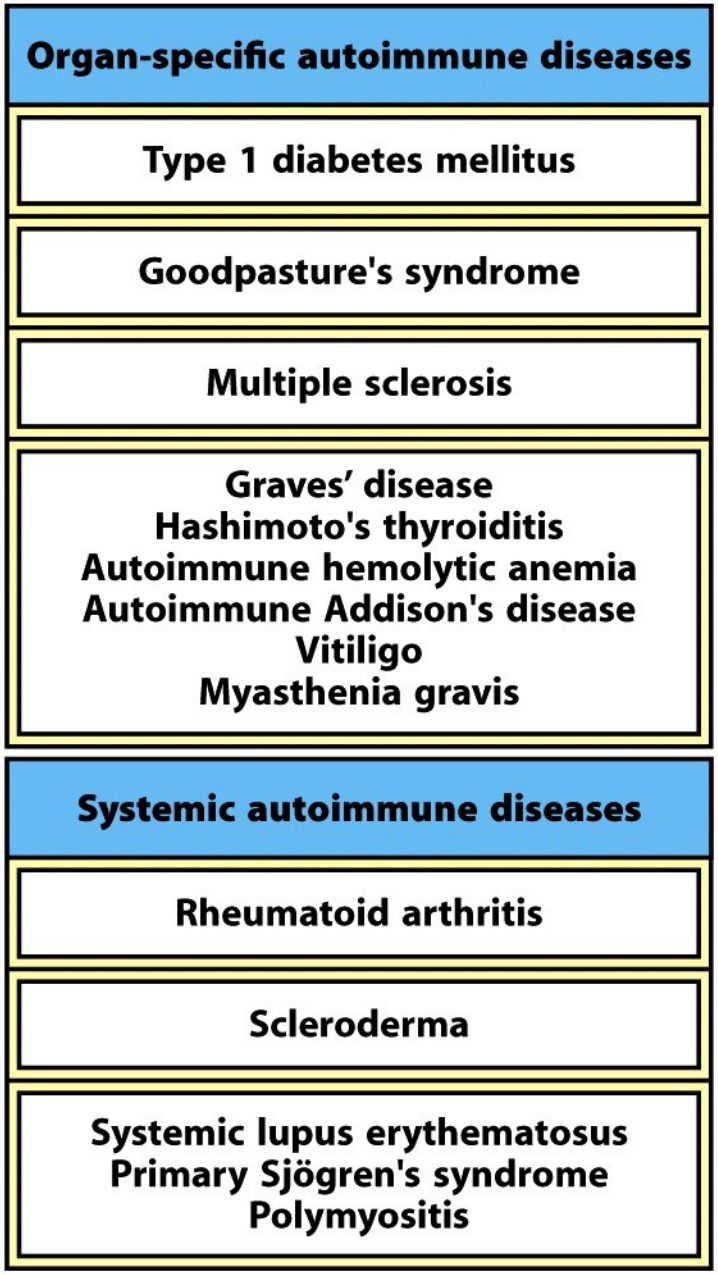


Figure 14-11 Immunobiology, 7ed. (© Garland Science 2008)

Autoimmunität betrifft ca. 5% der westl. Bevölkerung

Erkrankung	Ursache	Folge	Prävalenz
Psoriasis	Autoreaktive T-Zellen gegen Haut-assoziierte Antigene	Hautentzündungen mit schuppigen Stellen	1 in 50
Rheumatoide Arthritis	Autoreaktive T-Zellen und Antikörper gegen Antigene der Gelenksynovialis	Gelenkentzündung und Zerstörung	1 in 100
Morbus Basedow (Graves` disease)	Antikörper gegen TSH-Rezeptor	Hyperthyreose; Überproduktion der Schilddrüsenhormone	1 in 100
Hashimoto Thyreoiditis	Autoantikörper und autoreaktive T-Zellen gegen Schilddrüsenantigene	Hypothyreose; Zerstörung der Schilddrüse und Hormonmangel	1 in 200
Systemischer Lupus erythematodes	Autoreaktive T-Zellen und Antikörper gegen DNA, Chromatin, Ribonukleoproteine	Glomerulonephritis, Vasculitis, Ausschlag	1 in 200
Sjögren-Syndrom	Autoreaktive T-Zellen und Antikörper gegen Ribonukleoproteine	Lymphocyteninfiltration in exokrinen Drüsen führt zu trockenem Mund/Augen. Andere Organe können betroffen sein	1 in 300
Morbus Crohn	Autoreaktive T-Zellen gegen Antigene der intestinalen Flora	Intestinale Entzündung und Vernarbung	1 in 500
Multiple Sklerose	Autoreaktive T-Zellen gegen Antigene in Gehirn und Rückenmark	Zerstörung der Myelinscheiden führt zu Muskelschwäche, Ataxie etc.	1 in 700
Diabetes mellitus	Autoreaktive T-Zellen gegen Antigene der Pankreaszellen (Insulin !)	Zerstörung der β-Zellen	1 in 800

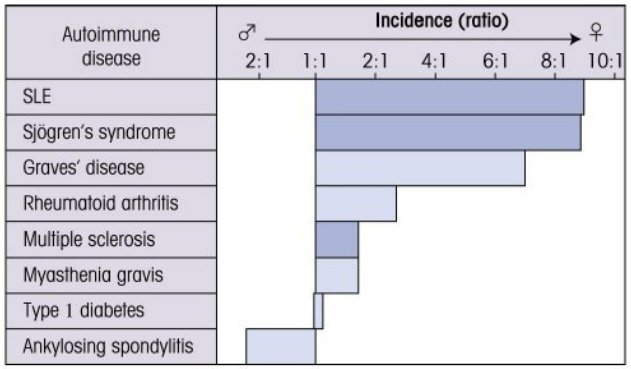


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Figure 18.4. Increased incidence of autoimmune disease in females.

Ankylosing spondylitis is one of very few autoimmune diseases that bucks the trend and is more common in males than females.

Autoimmunreaktionen umfassen T-, B-Zellen und das angeborene Immunsystem

Autoimmune diseases involve all aspects of the immune response			
Disease	**T cells**	**B cells**	**Antibody**
Systemic lupus erythematosus	Pathogenic Help for antibody	Present antigen to T cells	Pathogenic
Type 1 diabetes	Pathogenic	Present antigen to T cells	Present, but role unclear
Myasthenia gravis	Help for antibody	Antibody secretion	Pathogenic
Multiple sclerosis	Pathogenic	Present antigen to T cells	Present, but role unclear

Figure 14-16 Immunobiology, 7ed. (© Garland Science 2008)

Some common autoimmune diseases classified by immunopathogenic mechanism

Syndrome	Autoantigen	Consequence
Type II antibody against cell-surface or matrix antigens		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and FcR^+ phagocytes, anemia
Autoimmune thrombocytopenic purpura	Platelet integrin GpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Noncollagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell-wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves

Figure 14-19 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Some common autoimmune diseases classified by immunopathogenic mechanism

Syndrome	Autoantigen	Consequence
Type III immune-complex disease		
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Rheumatoid arthritis	Rheumatoid factor IgG complexes	Arthritis
Type IV T-cell-mediated disease		
Type 1 diabetes	Pancreatic β-cell antigen	β-cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Multiple sclerosis	Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein	Brain invasion by CD4 T cells, muscle weakness, and other neurological symptoms

Figure 14-19 part 2 of 2 Immunobiology, 7ed. (© Garland Science 2008)

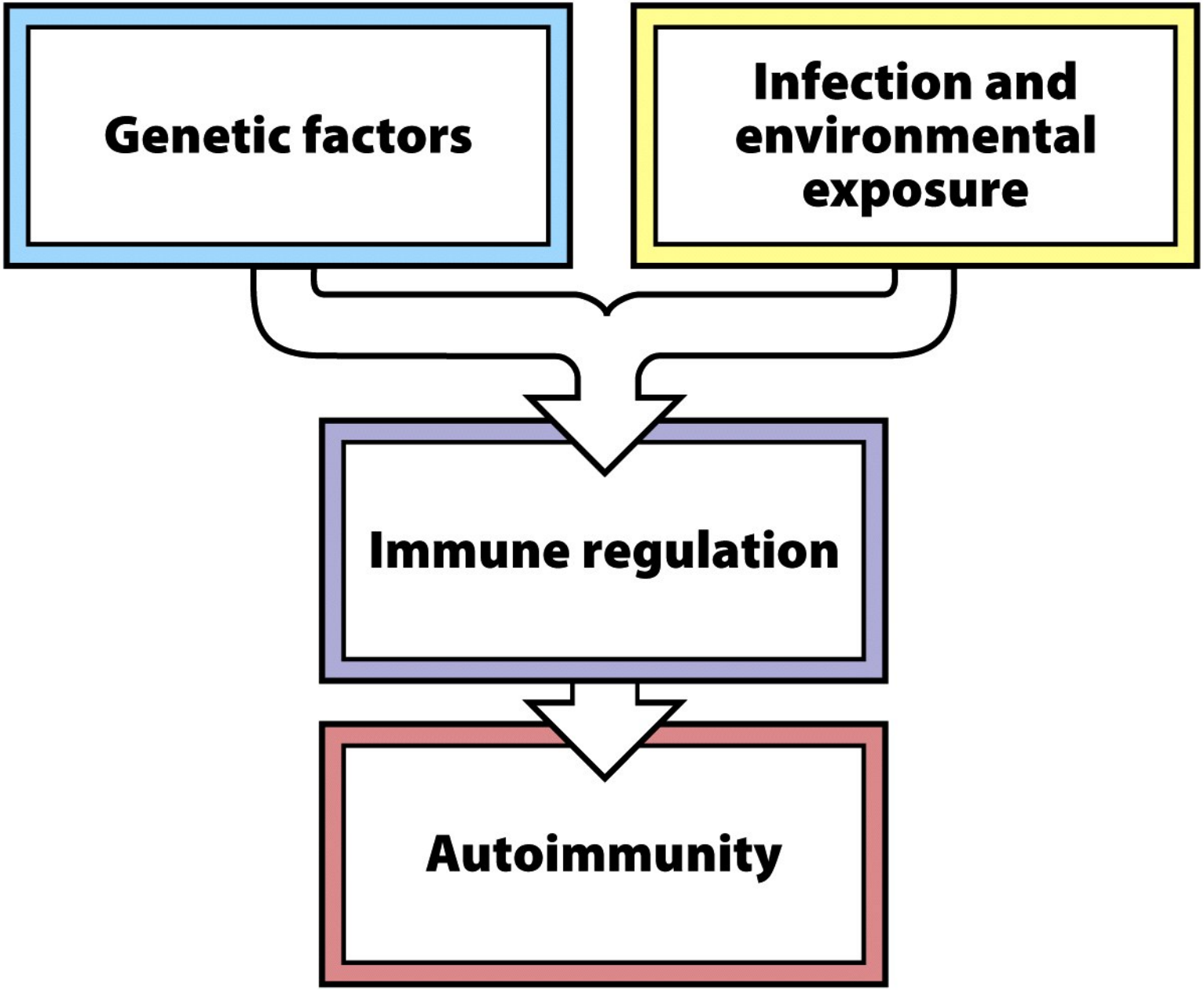

Figure 14-3 Immunobiology, 7ed. (© Garland Science 2008)

Suszeptibilität für Autoimmunität ist häufig assoziiert mit HLA Genotyp

Associations of HLA serotype with susceptibility to autoimmune disease			
Disease	**HLA allele**	**Relative risk**	**Sex ratio (♀: ♂)**
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Type 1 (insulin-dependent) diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4–5

Figure 14-33 Immunobiology, 7ed. (© Garland Science 2008)

Häufige Assoziation mit MHC Klasse II – Allelen legt Beteiligung von $CD4^+$ T-Zellen in der Ätiologie der Erkrankungen nahe

Suszeptibilität für Typ 1 Diabetes ist assoziiert mit MHC I und MHC II Allelen

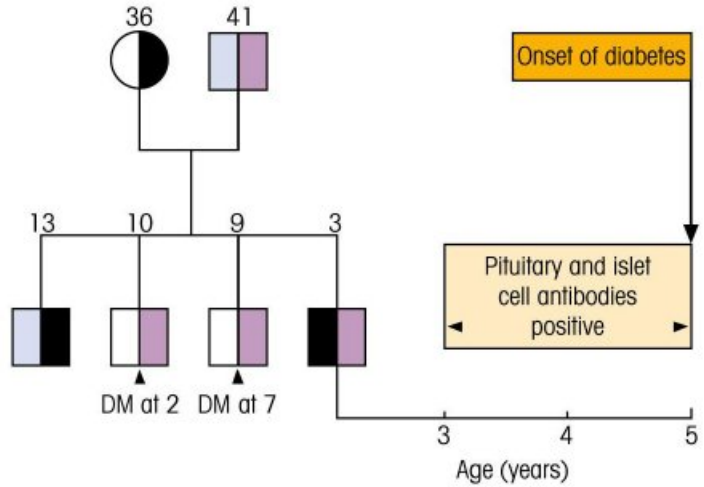

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Figure 18.2. HLA haplotype linkage and onset of type 1 diabetes (DM).

Haplotypes: □ A3, B14, DR6; ■ A3, B7, DR4; ▢ A28, B51, DR4; and ▩ A2, B62, C3, DR4. Disease is linked to possession of the A2, B62, C3, DR4 haplotype. The 3-year-old brother had antibodies to the islet cell surface for 2 years before developing frank diabetes indicative of the lengthy pathological process preceding disease. (Data provided by G.F. Bottazzo.)

Suszeptibilität für Typ 1 Diabetes ist assoziiert mit HLA Genotyp

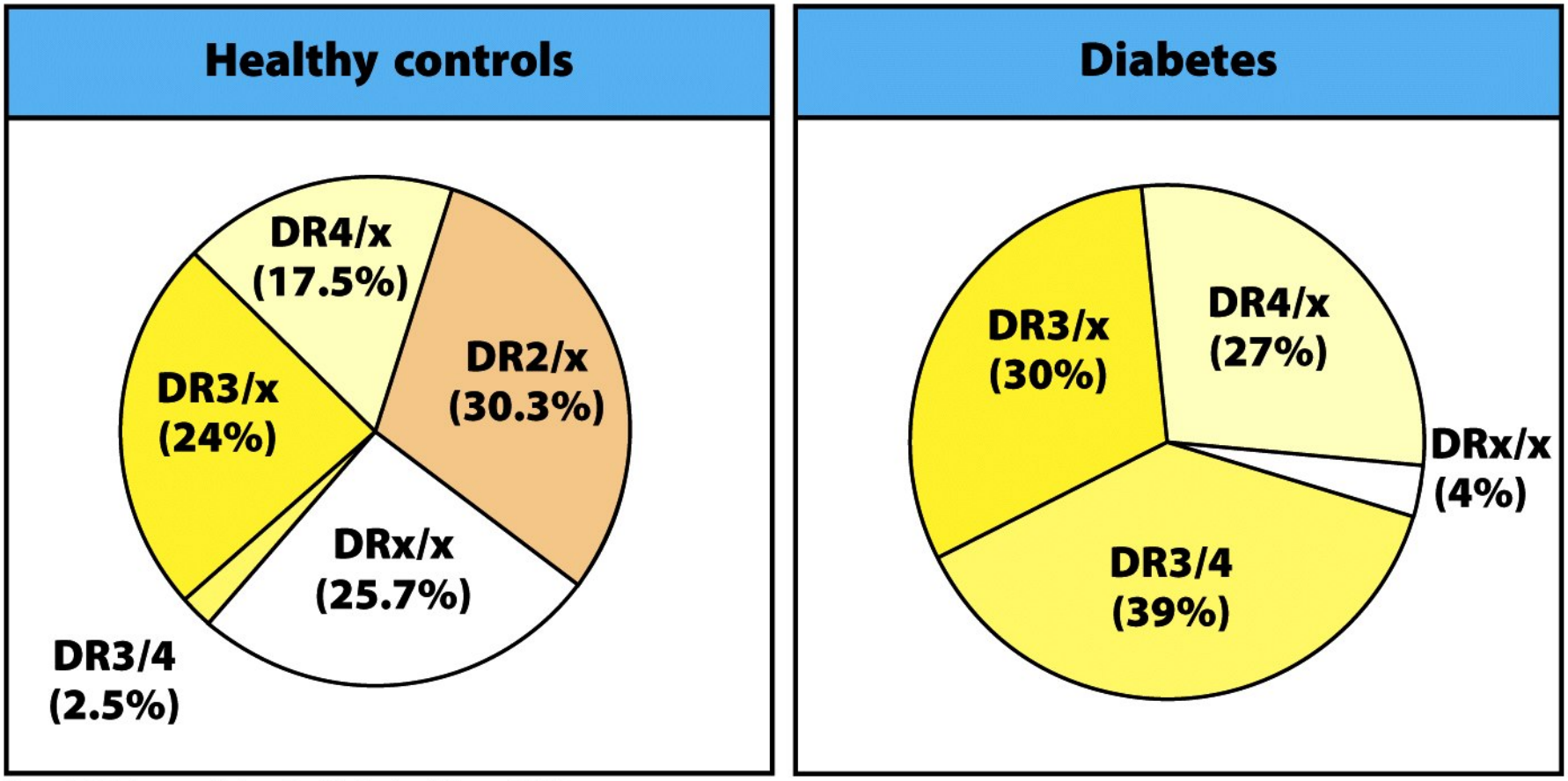

Figure 14-34 Immunobiology, 7ed. (© Garland Science 2008)

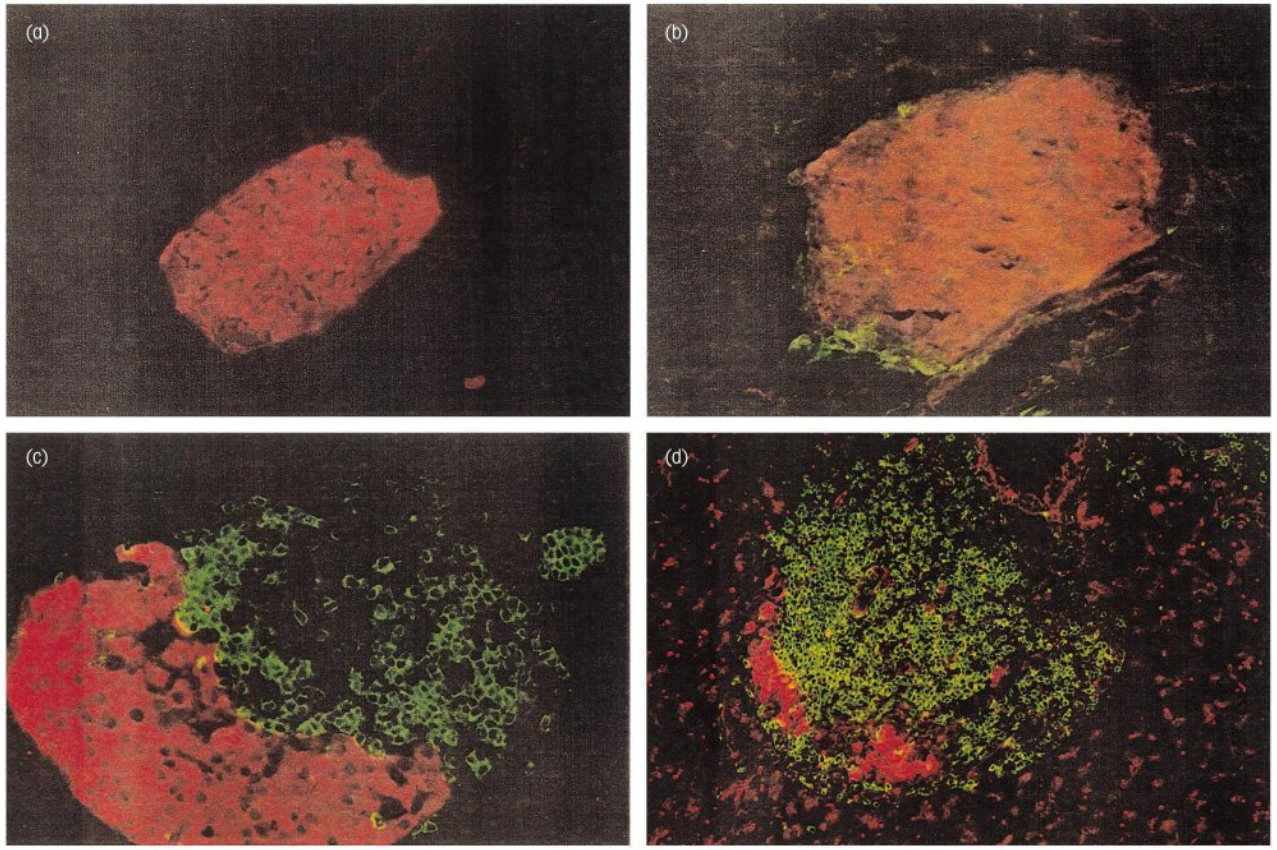

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Figure 18.23. Destruction of pancreatic islet β-cells by infiltrating T-cells in the nonobese diabetic (NOD) mouse.

(a) Normal intact islet. (b) Early peri-islet infiltration. (c) Penetration of the islet by infiltrating T-cells. (d) Almost complete destruction of insulin-producing cells with replacement by invading T-cells. Insulin stained by rhodamine-conjugated antibodies and T-cells by fluoresceinated anti-CD3. (Data reproduced from Quartey-Papafio R. *et al.* (1995) *Journal of Immunology* **154**, 5567–5575; photographs kindly provided by J. Phillips.)

Infektionen können Autoimmunreaktionen auslösen

Beispiel	Mechanismus	Effekt
Ophthalmia sympathika	Zerstörung der Zell/ Gewebsbarrieren	Freisetzung von Autoantigenen; Aktivierung von T-Zellen
Rheumatisches Fieber Lyme Arthritis	Molekulare Mimikry	Aktivierung kreuz-reaktiver B- u. T-Zellen

Kreuzreaktivität zwischen fremden und körpereigenen Molekülen: Molekulare Mimikry

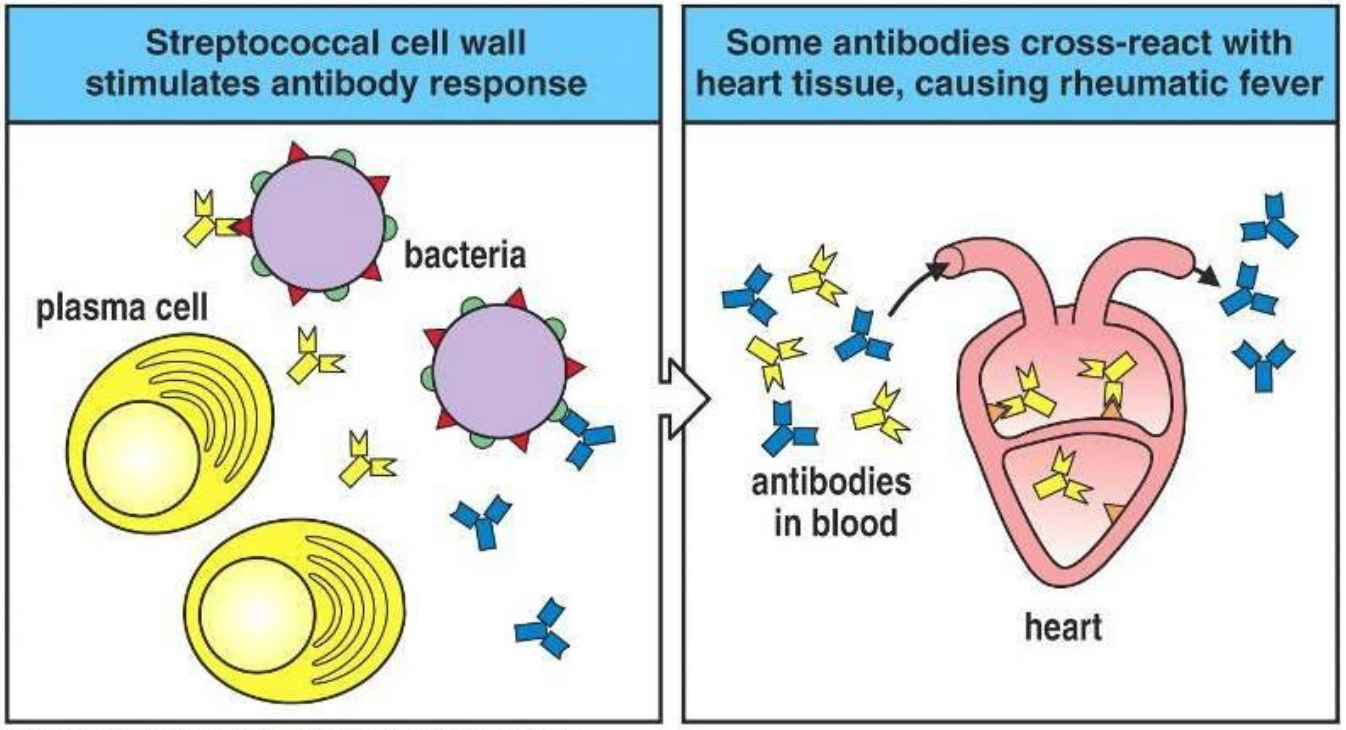

Figure 11-29 The Immune System, 2/e (© Garland Science 2005)