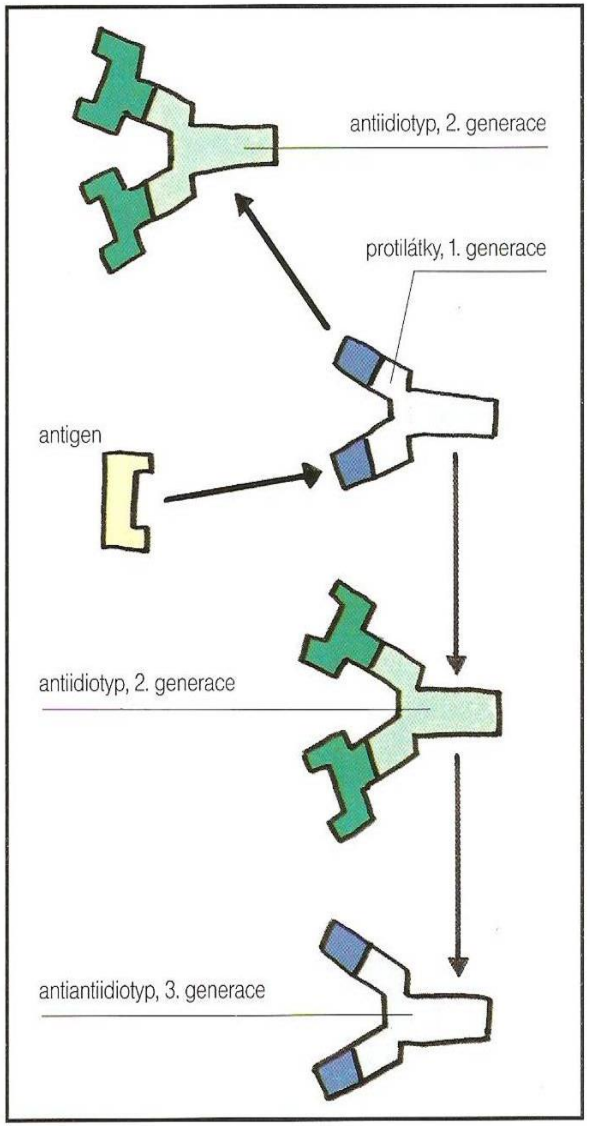
Autoimmunity

- All of us have many autoantibodies
- Difference is in quantiy and consequences
- Mechanisms how normal immunity change to autoimmunity are multiple
- Disease from autoimmunity arises when autoimmunity changes normal reactions

Idiotypes and autoimmunity



Obr. 8: Vznik antiidiotypických protilátek indukovaný antigenně působícím konečným dílem variabilní oblasti protilátky.

Autoimmunita

Immunology 12

Autoimmunity

Self vs. not self

- Innate IS – based on very rought nonspecific receptors to detect self/non self
- Specific IS – must recognise many tiny details – based on BCR resp.TCR, generated
- **BCR / TCR** – some can recognise self others non self molecules
- SYSTEM to discriminate and control cells with receptors to detect self molecules

Autoimmunity is a complex

- RA, DM, MS, SLE,
- psoriaza, Crohn disease, autismus .....

Conditionned – by different mechanisms

Risks – different influences (genetic, metabolic, environmental ....)

COMMON FOR ALL – disruption of tolerance of self

- disease of IS to recognise and discriminate self and non self and inhibit the selfdisrupting processes

Tolerancem of self

- TOLERANCE – not able to answer to epitope with agresive reaction
- based on innactivation or killing the cells with receptors (BCR/TCR against self molecules) – not by production of new ones
- produced during the development – Central tolerance

or

- when LY - in circulation – Periferal tolerance
- HOW ??

Central tolerance

- during differenciation of T and B in primary organs (thymus, bone marrow)
- apoptosis of autoreactive cells.
- **negative selection**

In Bone marrow B lymfocyte with IgM (BCR) against self – apoptosis

In Thymusv Tlymfocyte (CD4+ alebo CD8+) meet pMHC I or pMHC II on the TCR – apoptosis

Problems – not every self antigen enter in contact with lymphocytes in primary organs during lymphogenesis

THAT´S WHY....

Periferal tolerance

Other mechanisms to control and eliminate autoreactive lymphocytes after they lefr bome marrow

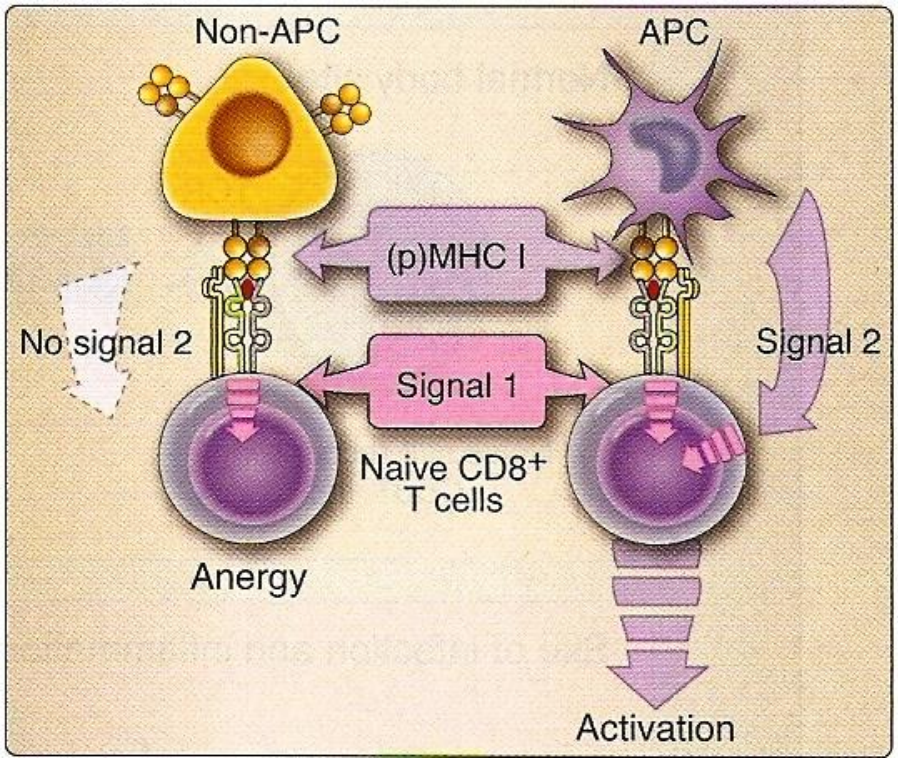
- **ANNERGY** – nonresponsivness after specific antigen is bound
- **SUPRESSION** – regulative cells inhibit activity of other cells

Anergy

Binding of Ag on TCR T CD48+ via MHC I

Antigen was not processed by APC

no secondary signal

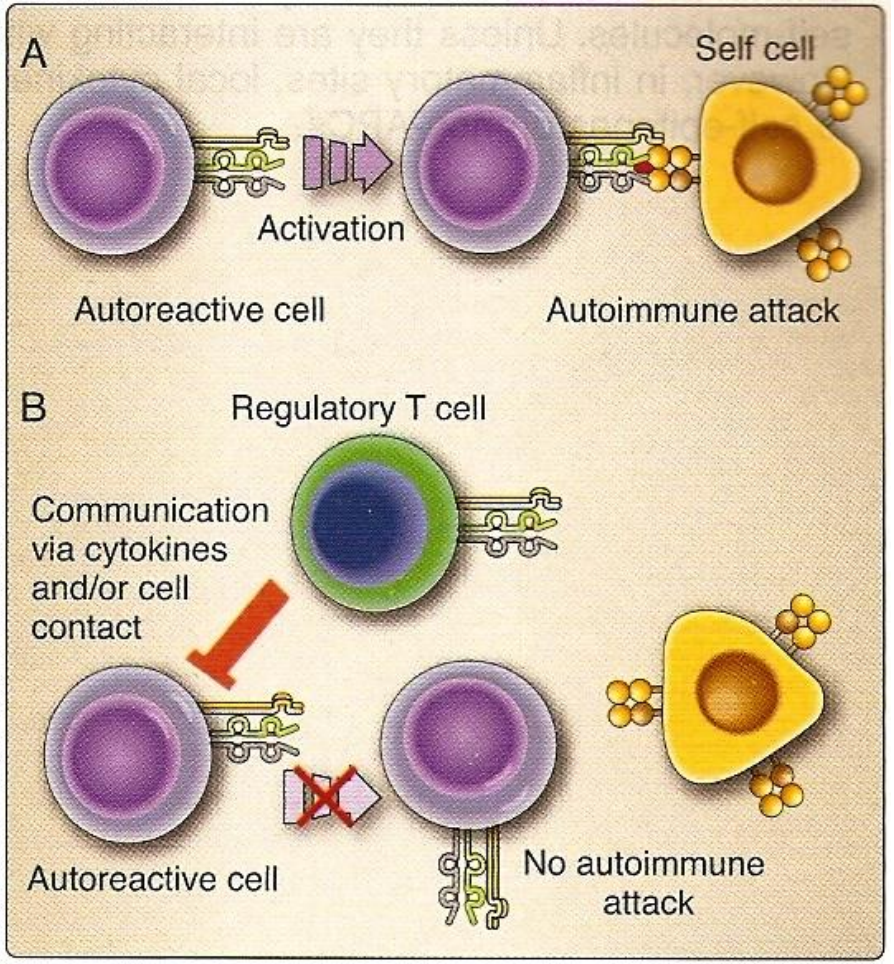


1st signál without 2nd leads to ANNERGISATION of T cell

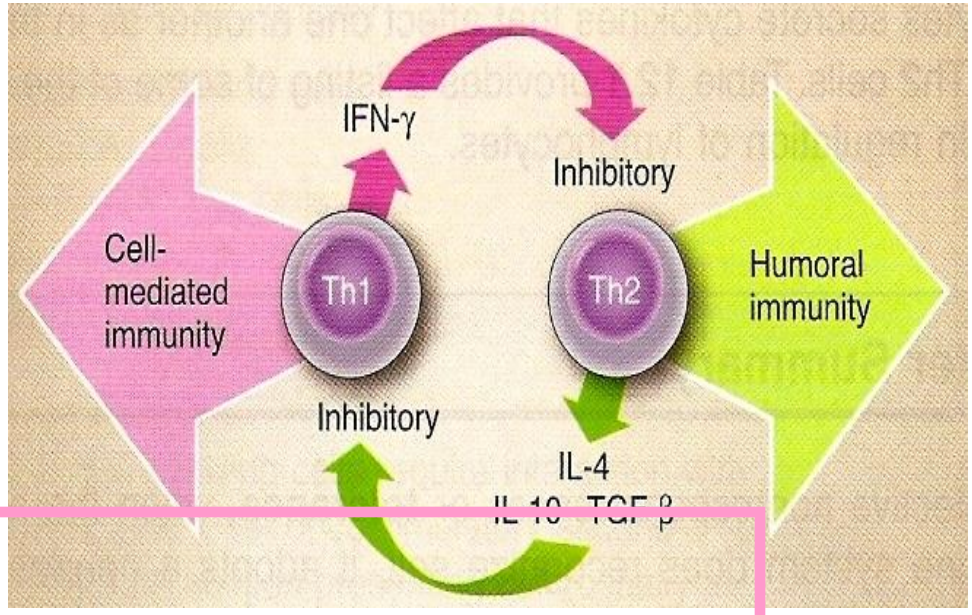
Anergised T cells cannot be activated even not after the additional 2nd signal – PROBLEMS = disease

Supression- inhibition of regulatory cells

- Regulatory cells = T cells
- CD4+CD25+ prevencia IBD
- CD8+ inhibition of CD4+ in DTH
- CD8+ a CD4+ subpopulations – inhibition of Ab production
- Balance in Th1 and Th2 – influences if the disease arises or not
- an antigen:
- dominance of Th1 = 0 inflamation,
- dominance of TH2 = CM inflamation



Th1/Th2
theory of hygiene



Th2

IL4, IL10,TGFβ

- production of Ab, class switch, decreases activity of Th1

Th1

IFγ – activity of macrophages, stimulation of IgG1, IgG3(primary opsonisating Ab, phagocytosis), inhibition of Th2

- The same antigen can increase Th1 and Th2 reaction

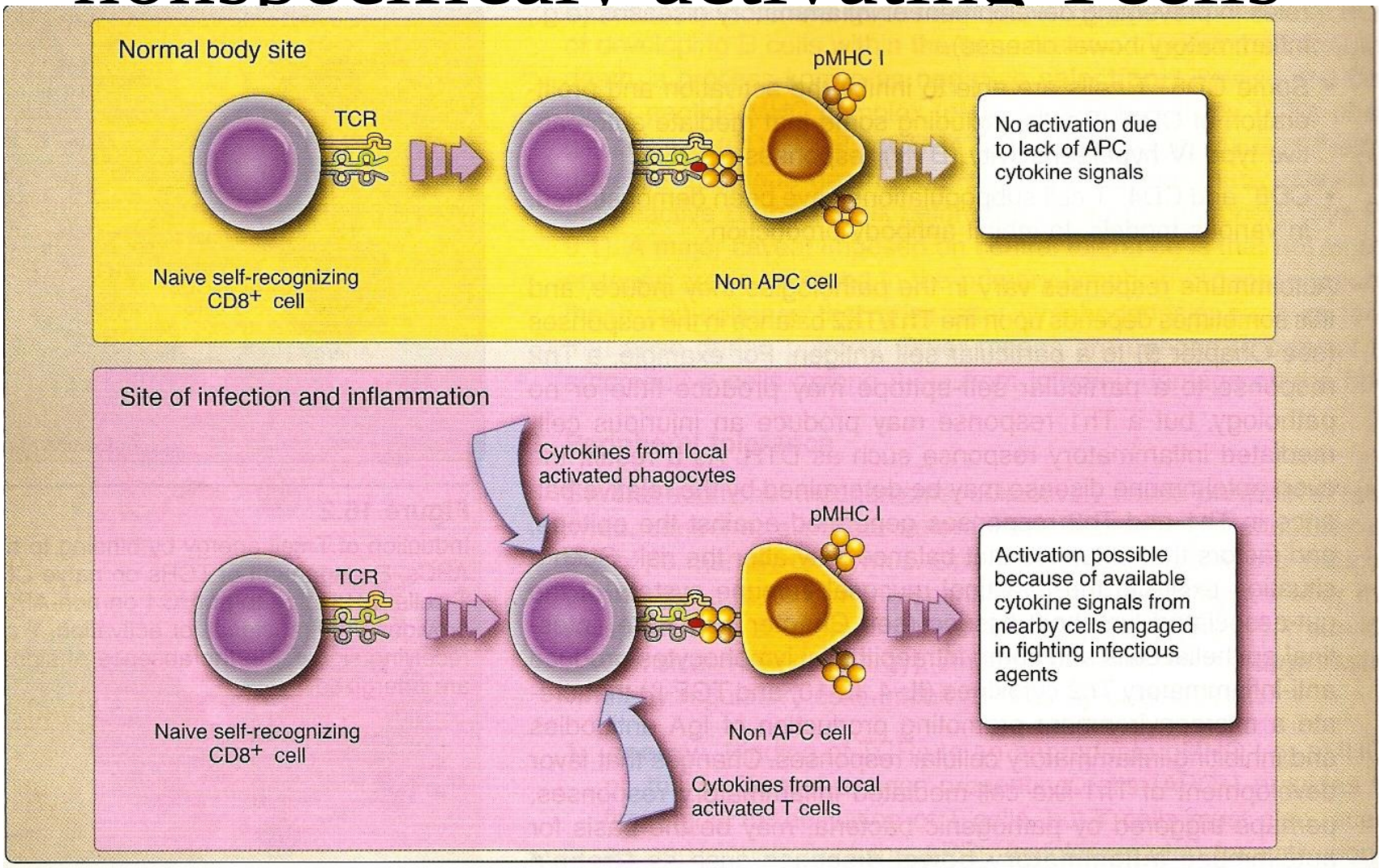
Loss of tolerance of self

- Molecular mimicry
- Spread of epitopes
- Loss of supression
- Sequestred antigens
- Neoantigen

Inflamation and autoimmunity

- Infection – commonly to start autoimmunity.
- Big ammount of endogennous cytokines activate T cells, without APC and even annergised cells
- Inflamation in the place of infection = proinflamatory cytokines
- TCR recognise self molecules – big amount of nonspecific signals to activate without the 2nd signal from APC

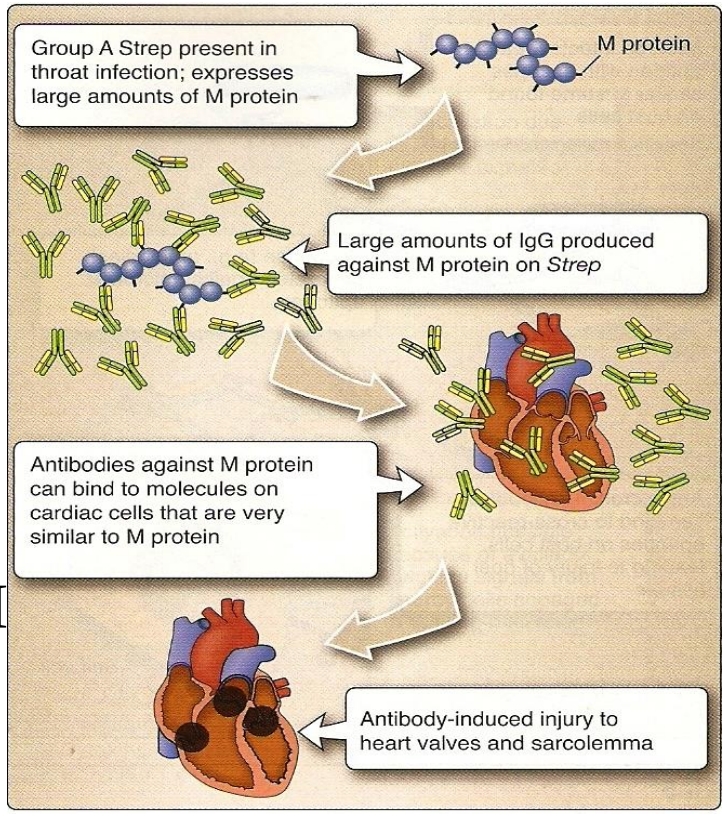
Inflamatory cytokines nonspecificaly activating Tcells



Molecular mimicry

- Infection caused by microbe starts specific autoimmune disease because of similarity of microbe antigen with human structures

- *Str.pyogenes* – M protein joins, kidney, heart – RA
- Coxackie virus, CMV – glutamat decarboxylase – DM 1
- CMV, VHC, morbilli virus fosfatase IA-2 – enzyme of β cells of pancreas - DM



Spread of epitope

- Epitope starting autoimmunity does not necessery need to be similar to self
- Viral infection disrupts self structure of the body, and discloses antigens against that autoimmunity will be directed
- (viral infection start reaction against epitopes of myelin sheath., SM)

- Disease has period of calm and relaps. During relaps – reaction is against the same antigen or also other new antigens

Sequestred antigens – exclusion (outside reach of IS)

- Some structures are not reachable by IS

Immunologically privileged places

organs – cornea, anterior chmber of eye, brain, intrauterine surface in gravidity

molecules – c**ryptoantigens** – not reachable by immunocompetent cells becuase hidden

after the shape of molecule is changed – denaturation, processing, binding – disclosure of hidden antigens – production of antibodies

Reumotoid factor: RF

- reumatoid = reumatism-like
- IgG molecule against Str.pyogenes (and also heart structure....) binds => changes in 3 dimensional conformation of Fc fragment => disclosure of antigens
  => production of IgM against Fc fragment of IgG = RF
- Binding of IgM on IgG produces immunocomplexes. RF present in several autoimmune diseases

Sequestred antigens

- Structures outside IS

Exposed after injuries, inflamations – when border seaprationg them from IS are broken:

- spermia in testes, thyroid glad.....

.

- Loss of suppresion – decrease of supresors with the age., previously suprimed cells are activated – with the age some AI diseases become more frequent (. **SLE – systemic lupus erythematosus)**
- Neoantigens – self structure is changed by binding to a foreign (chemical) structure– what makes it nonself. Not real autoimmunity – finishes after exposition is over

Autoimmune diseases

- Systemic - diffuse vs. specific organ
- Different molecules, organs, tissues – tissue present in different organs (SLE)
- Crohn disease – ileum
- Goodpasture´s disease – kidney, lung
- Hashimoto thyreoiditis – thyroid gland
- IDDM type I – β cells of pancreas
- Sclerosis multiplex (white matter of
- Sjorgen sy – tear chanals

Disease is based on by cell mediated or humoral immunity

Humoral reaction

- Binding of autoreactive Ab (IgG or IgM => hypersensitivity II. or III. type

Mechanisms: activation of C´, opsonisation, inflamation, disruption of target cells and tissues. Autoreactive T cells stimulise autoreactive B cells

Examples: (II.) Hemolytical anemia, Goodpasture sy, Hashimoto thyreoiditis, Reumatic fever, (III.) Reumatic artritis, Systemic lupus – II+III

CMI- autoimmunity reactin – cell mediated immunity

- Hypersensitivity IV.
- cytotoxic T cells
- (Delayed Type Hypersensitivity – DTH) - macrophages based

Examples: IDDM – 1., MS, RA, reactive artritis,

Reumatoid artritis

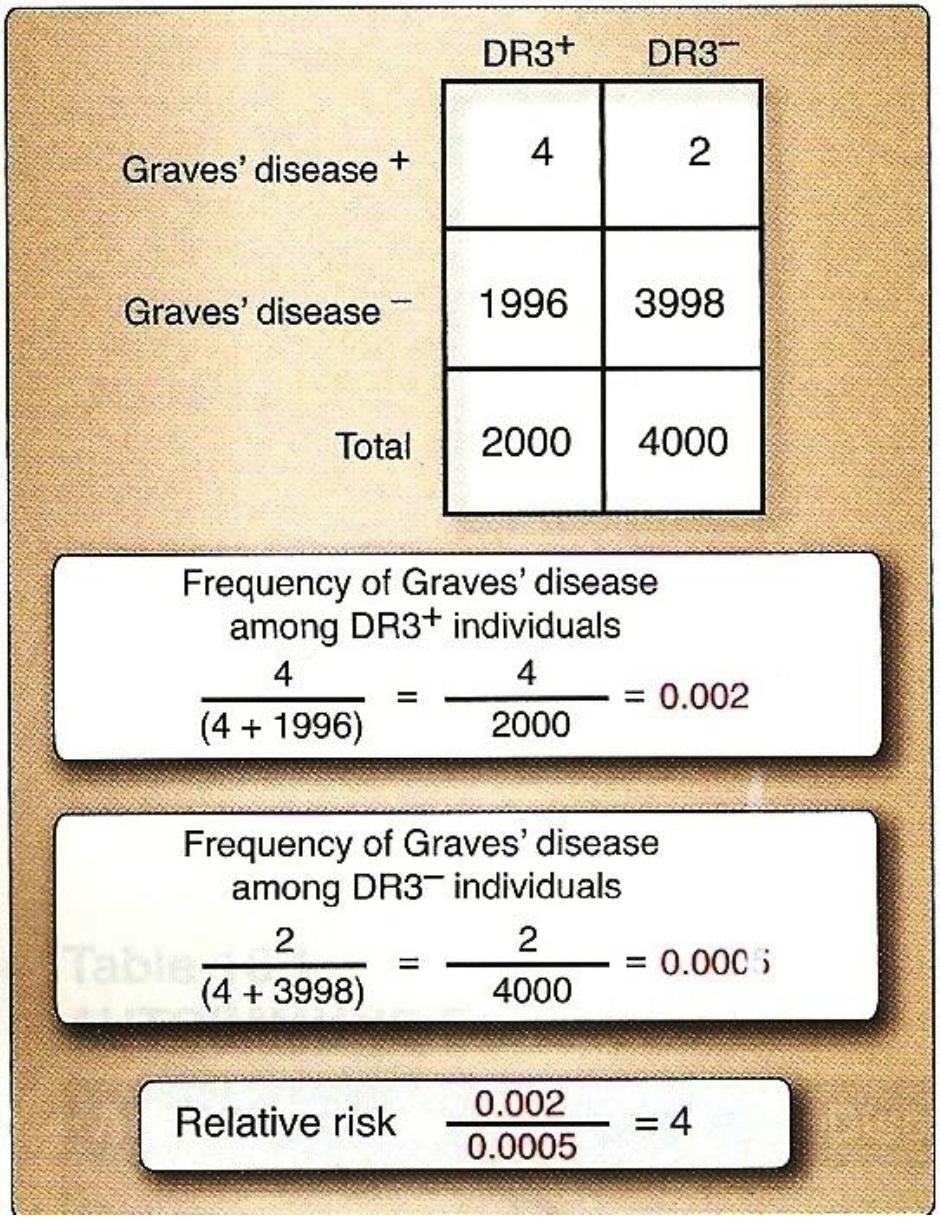
Affected Tissue	Disease	Target Antigen
Anterior parts of the eye	Uveitis (anterior)	Beta B1-crystalin, other proteins of the ciliary body epithelium
Connective tissue	Scleroderma	Scl-70, PM-Scl antigens
Erythrocytes	Autoimmune hemolytic anemia	Erythrocyte surface molecules
Heart valves and sarcolemmal membranes	Rheumatic fever	Streptococcal M protein, cardiac muscle antigens
Joints of lower extremities; sometimes eyes and genital, urinary, or GI systems	Reiter's disease (reactive arthritis)	Possible association with infectious agents
Kidneys, lungs	Goodpasture's syndrome	Type IV collagen of basement membranes
Large intestine	Ulcerative colitis	Unknown
Lower spine	Ankylosing spondylitis	Unknown
Myelin of the central nervous system	Multiple sclerosis	Myelin proteins (several)
Pancreatic islet β cells	Type I insulin-dependent diabetes mellitus (IDDM)	Glutamate decarboxylase, preproinsulin, other β cell products
Platelets	Thrombocytic purpura	Platelet integrin molecules
Skeletal muscle	Myasthenia gravis	Acetylcholine receptor
Skeletal muscle	Polymyositis	Jo-1, PM-Scl antigens
Skin	Pemphigus vulgaris	Desmoglein-3
Skin	Psoriasis	Unknown, but there is some association with streptococcal infections
Skin, vasculature, muscle, joints, kidney	Systemic lupus erythematosus (SLE)	Nucleic acids, chromosomal proteins
Small intestine	Crohn's disease	Unknown
Spermatogonia, sperm	Male sterility (??)	Unknown
Synovial membranes, joints	Rheumatoid arthritis	Unknown
Tear ducts	Sjögren's syndrome	Ro/SS-A antigens
Thyroid gland	Graves' disease	TSH receptor
Thyroid gland	Hashimoto's thyroiditis	Thyroglobulin

HLA – connection with autoimmune diseases

- Risk of autoimmune disease can be connected with HLA genes
- Sometimes one HLA gene is connected with several diseases
- Mechanisms are not clear, statistical connection influenced by processing and presentation of epitopes to T cells
- Strenghth of statistical connection = RR = relative risk

Relatívne riziko-RR

- compare frequency of of disease in carriers of gene to not carriers of the gene
- calculated for a certain group of people
- usually about (2-5) – other factors influence



- (HLA B 27:ankylosing spondylitis = 100

HLA connection to autoimmune diseases,RR

Disease	HLA Gene[a]	Relative Risk[b]
Acute uveitis	B27	10
Ankylosing spondylitis	B27	100
Goodpasture's syndrome	DR2	15
Graves' disease	DR3	4
Hashimoto's thyroiditis	DR5	3
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	20–25
Multiple sclerosis	DR2	5
	DR3	10
Myasthenia gravis	DR3	3
	B8	3
Pemphigus vulgaris	DR4	15
Psoriasis vulgaris	Cw6	5–13
Reiter's disease	B27	35
Rheumatoid arthritis	DR4	4
Systemic lupus erythematosus	DR3	6

Detection of autoantibodies

antibody against several structures:

anti nuclear antibodies ANA – homogenouse, specled, rought specled, centromer.....

- - extracted nuclear antibodies ENA
- - anti ds DNA antibodies dsDNA
- - anti ss DNA antibodies ssDNA
- - anti myeloperoxidase antibodies – anti MPO
- - .....

Principal of immunofluorescence detection of antibodies

cells of annimals + serum of patient + conjugate anti hu IgG labelled by fluorochrome IFA method