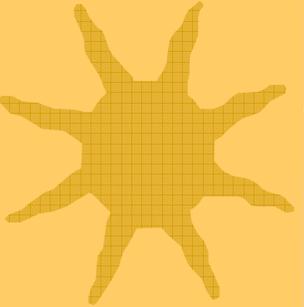


Autoimmunity

Department of Immunology
2nd Medical Faculty
Charles University,
University Hospital Motol

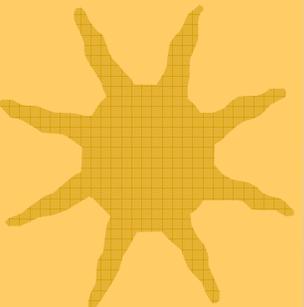


Autoimmunity - definition



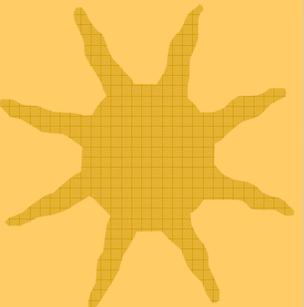
The reaction of immune system with self-antigen

discrimination between useful/damaging



➔ Autoimmunity physiology

➔ Autoimmunity pathology - autoimmune diseases





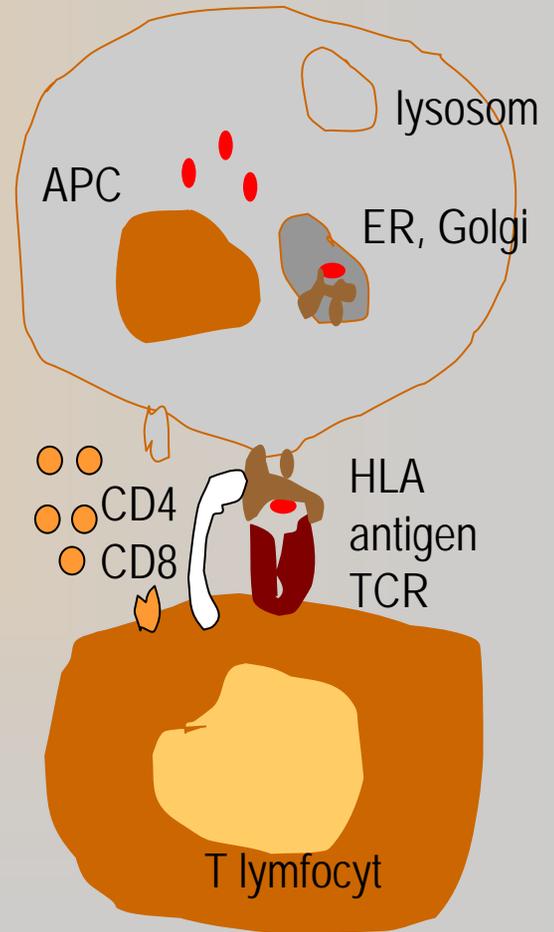
Central tolerance

★ positive selection

- preservation of T lymphocytes binding HLA/peptid (autoantigen) with medium affinity, elimination of T lymphocytes with weak affinity to HLA/peptid

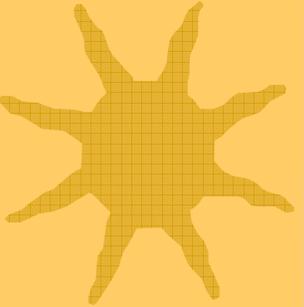
★ negative selection

- elimination of T lymphocytes binding HLA/peptid with strong affinity

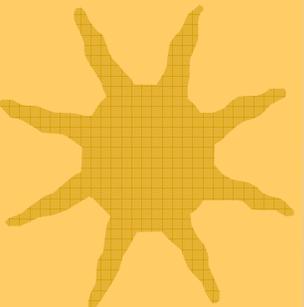




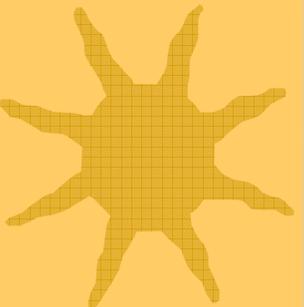
APS 1 – failure of negative selection in the thymus



autoimmune polyglandular syndrome type 1 (APS1)



APECED - autoimmune polyendocrinopathy – candidiasis -
ectodermal dystrophy



autoimmune regulator – AIRE gene

chromosom 21
q22.3

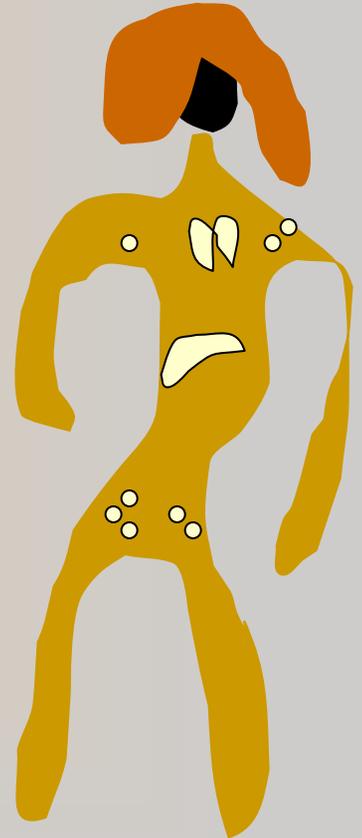




AIRE

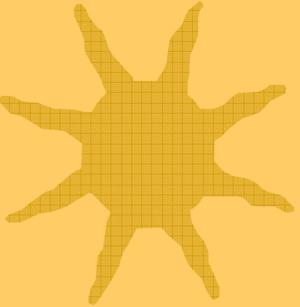
AIRE protein -transcription factor

- ★ role in the immune tolerance
- ★ expressed in lymphoid organs
- ★ controls expression of important self-antigens on thymic medullary epithelial cells



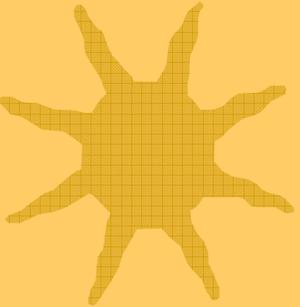


Peripheral tolerance

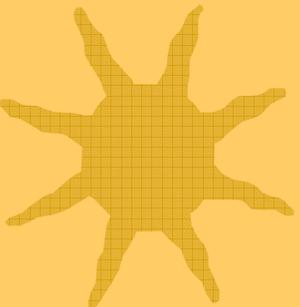


★ **clonal deletion** - elimination of autoreactive clones

★ **clonal anergy** - functional depression (insufficient costimulation)



★ **clonal ignorance** - inability of recognition of autoantigen



★ **suppression** – suppression of autoreactive T lymphocytes by other immunocompetent cells

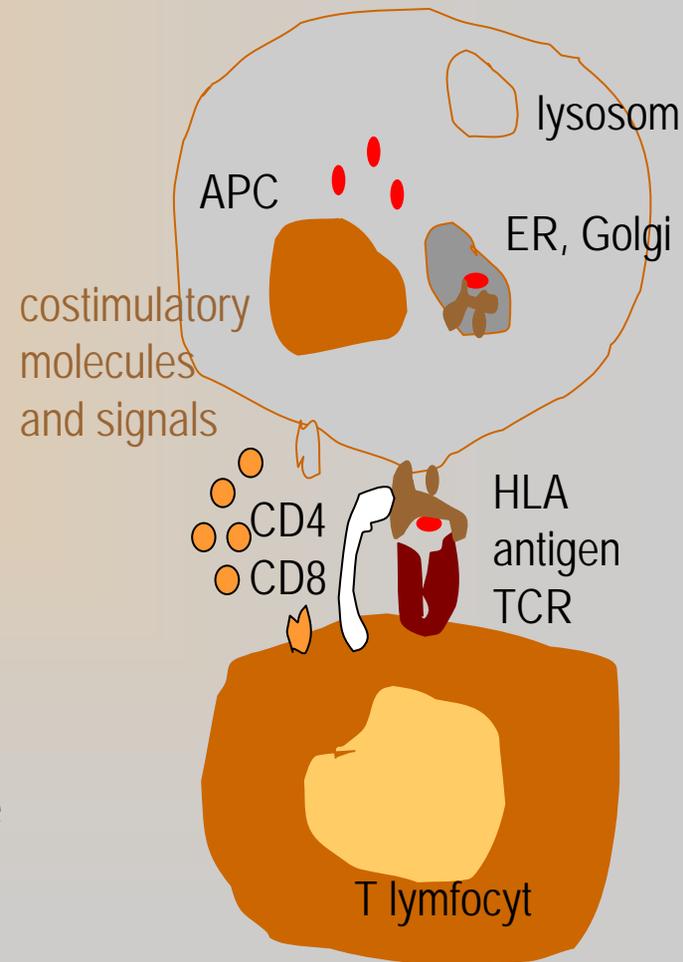
Autoimmunity and allergy X linked IPEX – deficiency of Tregs

break down of tolerance

ID, polyendocrinopathy
(diabetes, thyreopathy), diarrhea,
eczema, allergy

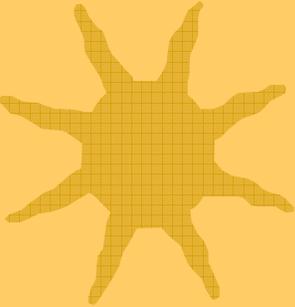
Scurfy gene - protein scurfin -
transcription factor

★ Due to deficiency of FoxP3 gene





Autoimmunune lymphoproliferative syndrome *- ALPS, Canale-Smith syndrome*

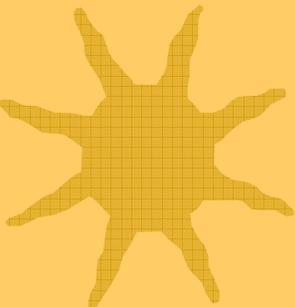


lymphoproliferation

splenomegaly

double negative TCR α/β , CD4 CD8 lymphocytes

associated clinical picture

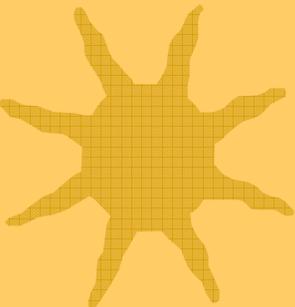


★ deficient apoptosis

deficit Fas (CD95/Apo1)

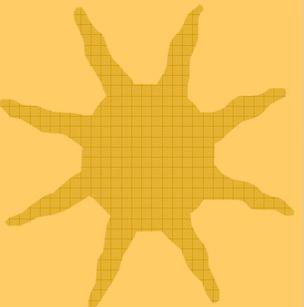
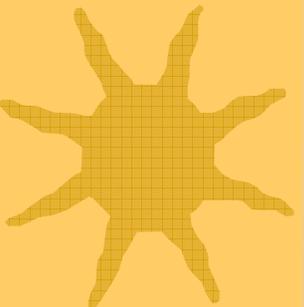
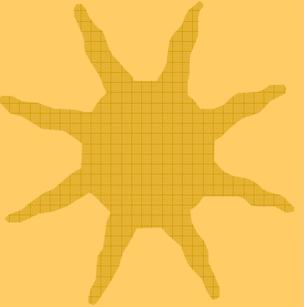
deficit Fas L

deficit in other apoptotic pathways





Pathogenesis



CD4⁺ T cells

- ★ A number of animal models of autoimmune disease are inhibited by treatment with anti-CD4 mAbs (collagen induced arthritis [CIA], EAE, Type I diabetes in NOD mice, nephritis in MRL lupus prone mice)
- ★ CD4⁺ T cells isolated from autoimmune donors can adoptively transfer disease to normal recipients
- ★ Activation of Th1 cells, γ -TNF, IFN- γ , IL-12, activation of macrophages (CIA, EAE, IBD in SCID mice, diabetes in NOD mice)



Animal models

Insulin dependent diabetes mellitus

Spontaneous: NOD mouse, BB rat

Induced: Rat insulin promoter transgenics, thymectomy and sublethal irradiation in rats

Arthritis

Induced: Collagen induced arthritis in rats and mice, adjuvant arthritis in mice

Systemic lupus erythematosus (glomerular nephritis)

Spontaneous: NZBxNAW F1, NZBxSWR F1, MRL1pr

Induced: Mercuric chloride in BN rats

Autoimmune thyroiditis

Spontaneous: Obese strain chickens

Induced: Experimental autoimmune thyroiditis in mice

Alkylosing spondylitis

Induced: HLA-B27 transgenic rats

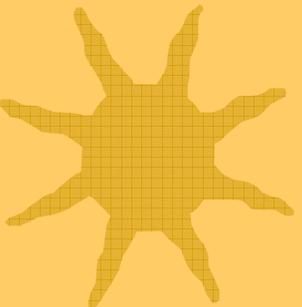
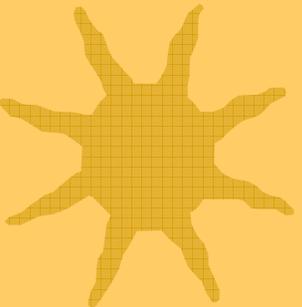
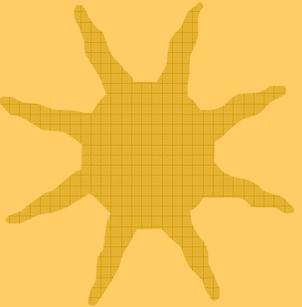
Inflammatory bowel disease

Spontaneous: IL-2, IL-10, TCR- α chain knock-out mice, SCID mice restored with CD4⁺ Tcell subsets

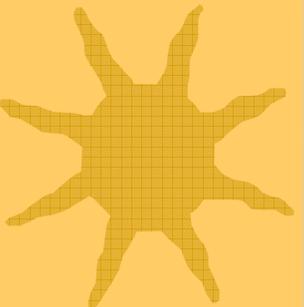
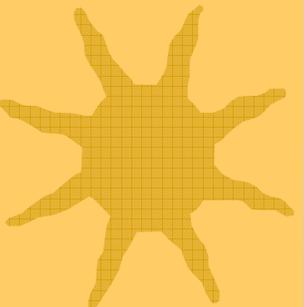
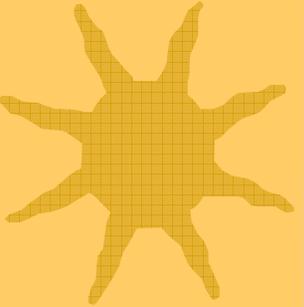
Induced: Haptenated colonic proteins in mice, proteoglycans in Lewis rats

Multiple sclerosis

Induced: experimental allergic encephalomyelitis in a variety of laboratory animals



Pathogenesis 2



- type II. by Coombs and Gel: cytotoxic immune reaction
 1. damage of tissue
 2. functional impact (stimulation, inhibition, neutralization)
- type III. by Coombs and Gel: immune complex
- type IV. by Coombs and Gel

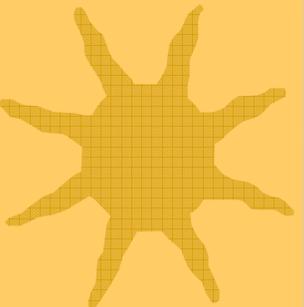
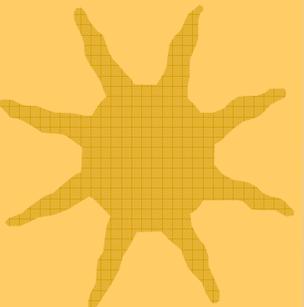
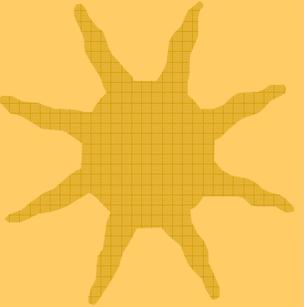
Autoimmune diseases classified by mechanism of tissue damage

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
Type III immune-complex disease		
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, rash
Rheumatoid arthritis	Rheumatoid factor IgG complexes	Arthritis
Type IV T cell-mediated disease		
Insulin-dependent diabetes mellitus	Pancreatic β -cell antigen	β -cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis	Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein	Brain invasion by CD4 T cells, weakness

Figure 13-27 Immunobiology, 6/e. (© Garland Science 2005)



Incidence of autoimmune diseases



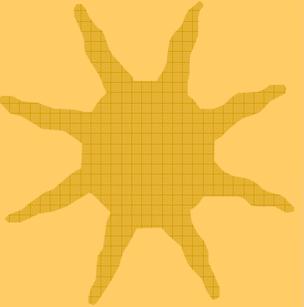
- ★ RA 1-3%
- ★ Sjögren's sy 1/20 000
- ★ Vasculitis 1/100 000

- ★ Prevalence of autoimmune diseases

5-7% of population

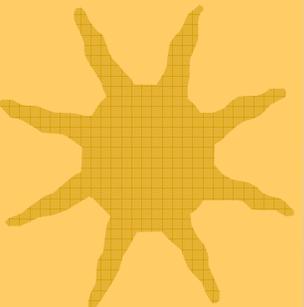


Factors influencing autoimmune disease



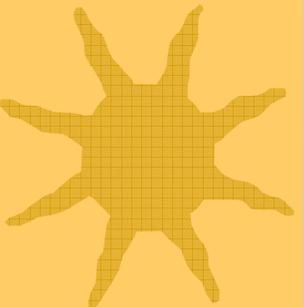
Internal triggering factors

- ★ genotype / HLA
- ★ cytokines
- ★ apoptosis genes
- ★ ID (IgA, CID, CVID, WA, C1,2,4),
- ★ hormones



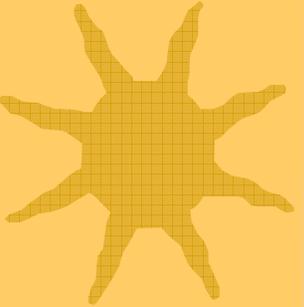
External triggering factors

- ★ infections
- ★ UV
- ★ drugs
- ★ chemicals (including food)
- ★ stress

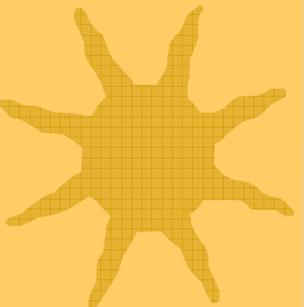




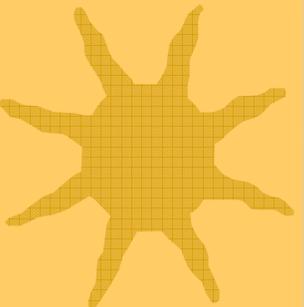
Genes associated with autoimmunity



★ HLA



★ non-HLA genes



★ cytokines genes polymorphism (CTLA 4)

★ APECED

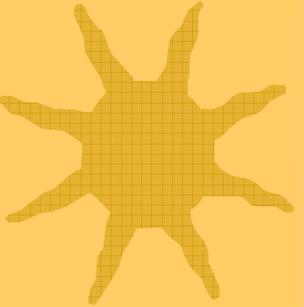
Many autoimmune diseases are associated with certain HLA types and with gender

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 I 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 13-20 Immunobiology, 6/e. (© Garland Science 2005)

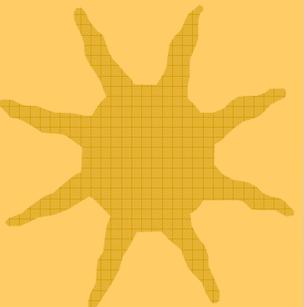


Autoimmune disease - genetic factors



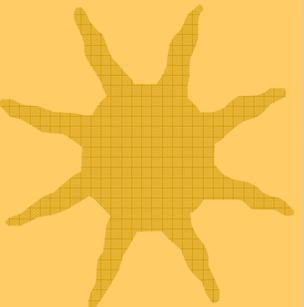
Increased sibling risk in:

		MHC, susceptibility allele
Rheumatoid arthritis	8	DR1 DR4
Type 1 diabetes	15	DR3 DR4
Alkylosing spondylitis	54	B-27
Mutliple sclerosis	20	
Ulcerative colitis	12	
SLE	20	
Crohn's disease	20	



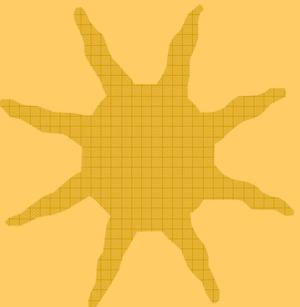
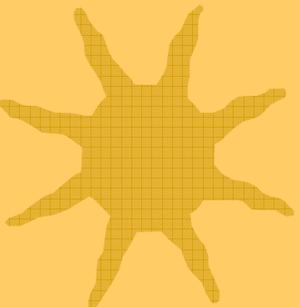
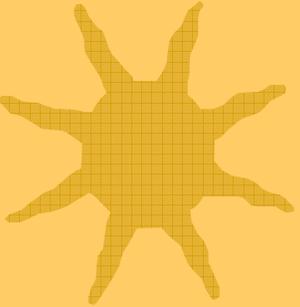
Major genetic loci in a number of autoimmune diseases are the MHC genes

Class I and Class II	Antigen presentation (RA, diabetes)
Complement	SLE
TNF	IBD





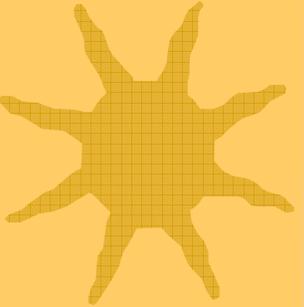
Genetic factors



- ★ Non MHC loci
 - 13 mapped genes-NOD mouse
 - 18 mapped genes in human Type 1 diabetes (genome wide scan)
- ★ IDDM-2 Allelic variation of a minisatellite tandem repeat in the regulatory region of the insulin gene <expression of insulin in the thymus of susceptible individuals
- ★ Idd-3 Maps to IL-2, allelic variation in coding region of IL-2
- ★ MRL 1pr/pr: Mutation in the Fas gene leading to impaired apoptosis
- ★ The same loci have been mapped in a number of different autoimmune diseases probably reflecting key immune regulatory genes



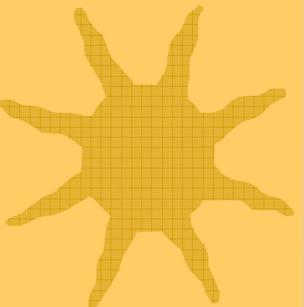
Autoimmune disease ***- escape from immunological tolerance***



1. Infection

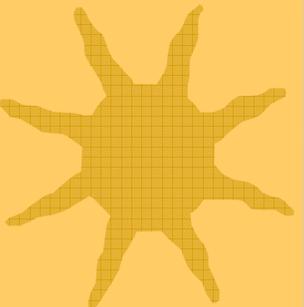
Evidence that infection may be involved in development of autoimmunity:

- Disease occurrence in clusters
- Discordance in identical twins



Immune pathology associated with many infectious diseases looks like autoimmune disease

Lyme disease *Borrelia burgdorferi*



Late phase is accompanied by skin lesions like scleroderma and inflammation in the joints like arthritis



How could infection work?

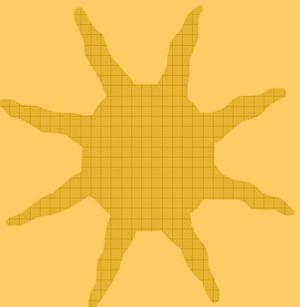
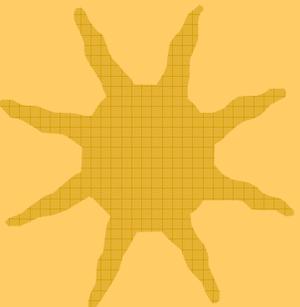
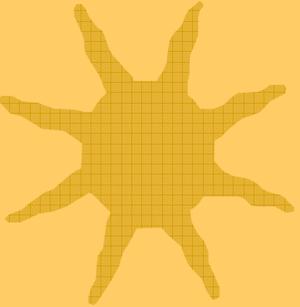
Mechanism	Disruption of cell or tissue barrier	Infection of antigen-presenting cell	Mechanism	Binding of pathogen to self protein	Molecular mimicry	Superantigen
Effect	Release of sequestered self antigen; activation of nontolerized cells	Induction of co-stimulatory activity on antigen-presenting cells	Effect	Pathogen acts as carrier to allow anti-self response	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
Example	Sympathetic ophthalmia	Effect of adjuvants in induction of EAE	Example	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis

Fig 13.42 part 1 of 2 © 2001 Garland Science

Fig 13.42 part 2 of 2 © 2001 Garland Science



How could infection work?



A. Disruption of tolerance

- Smoking can trigger Goodpasture's syndrome

Alveolar basement membrane normally not exposed to immune system

Smoking damages alveoli, exposes collagen

Anti-collagen Ag damages lung and kidney

- Anti-sperm Ab produced in some men after vasectomy
- Injection of myelin basic protein (MBP) produces MS-like EAE in mice
- May be triggered by injury or infection



B. Immune stimulation

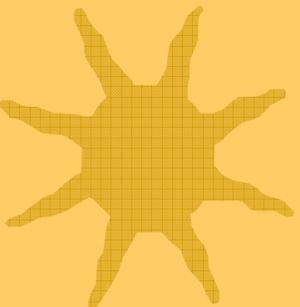
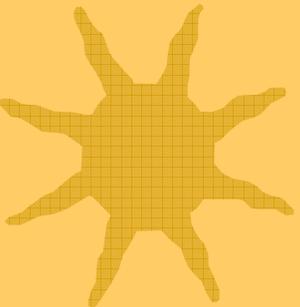
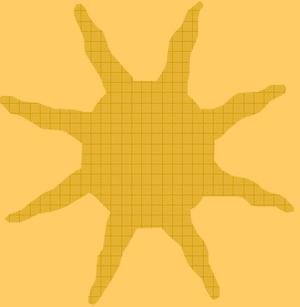
- ❖ Inappropriate MHC II expression
- ❖ High level of APCs with “second signal” breaks anergy
- ❖ Activation of T and B responses to self Ag

C. Superantigen

- ★ Several infectious agents (ie. Mouse mammary tumour virus) contain antigens with the ability to polyclonally activate a subset of CD4⁺ T cells bearing particular V β TCR families
 - Hypothesis is that this may activate autoreactive cells
 - If this were true, we would expect to see > of certain V β in autoimmune lesions
 - Isolated reports in rheumatoid arthritis and diabetes
 - No strong evidence

D. Cross reaction

- ★ Cross reaction of peptide present in micro-organism with self peptide present in the host
 - Coxsackie virus peptide contains homology to a T cell epitope in GAD which is recognised by a subset of patients with type I diabetes

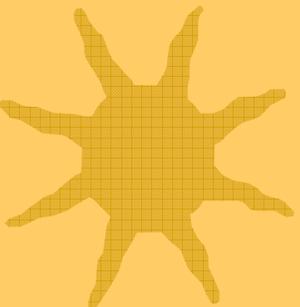
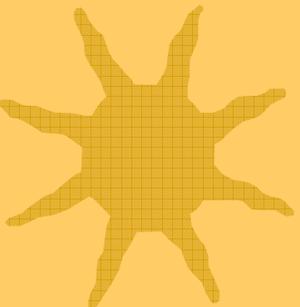
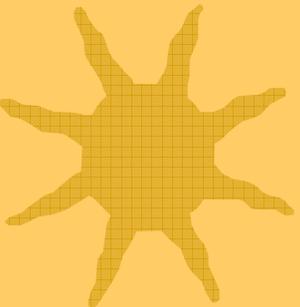




UV radiation

- ★ (Modification of autoantigens)
- ★ failure of control of suppression of autoreactive T lymphocytes

TLI (high doses 42,5 Gy a frakcionované 17x2,5) - induction of organ-specific autoimmune diseases in mice – prevention by adoptive transfer of CD4+ lymphocytes



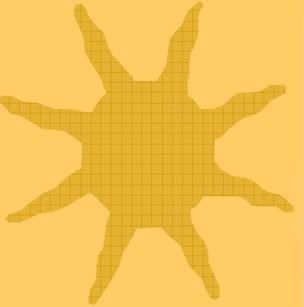


Drugs and foods

- ★ **gluten – celiac disease**
- ★ cow milk - diabetes type I.?
- ★ L-tryptofan, oil - eosinofil fasciitis
- ★ L-canavanin - SLE
- ★ aromatic amines (hydrazines) - SLE
- ★ saturated fats – diferent AI diseases (radicals of oxygen)
- ★ **beta-blocators, hydantoins**
- ★ **Prokainamid** (inhibition of DNA metyl-transferase)
- ★ **D- penicilamin, hydralazin, oral contraceptives, isonizaid** (acetylation)
induction of autoantibodies (ds- DNA, histony, cardiolipin)
- ★ N-nitroso-compound (diabetes type I.)
- ★ SiO₂ (silicosis, vasculitis, SLE, sclerodermia, RA, D-PM, glomerulonefritis)
- ★ silicone´s polymers (sclerodermia, SLE, RA)

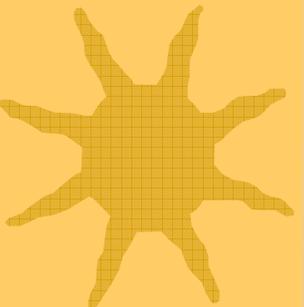


Diagnosis



clinical picture

laboratory

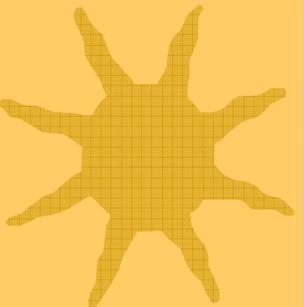


autoantibodies

autoreactive lymphocytes

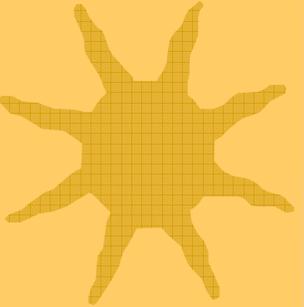
autoantigens

related genes

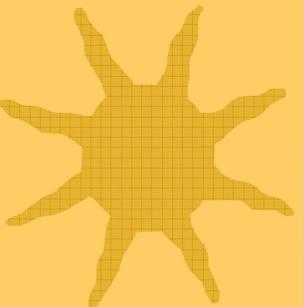




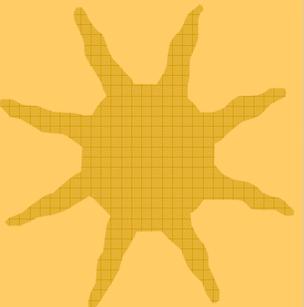
Mozaic of autoimmunity



★ break down of autotolerance

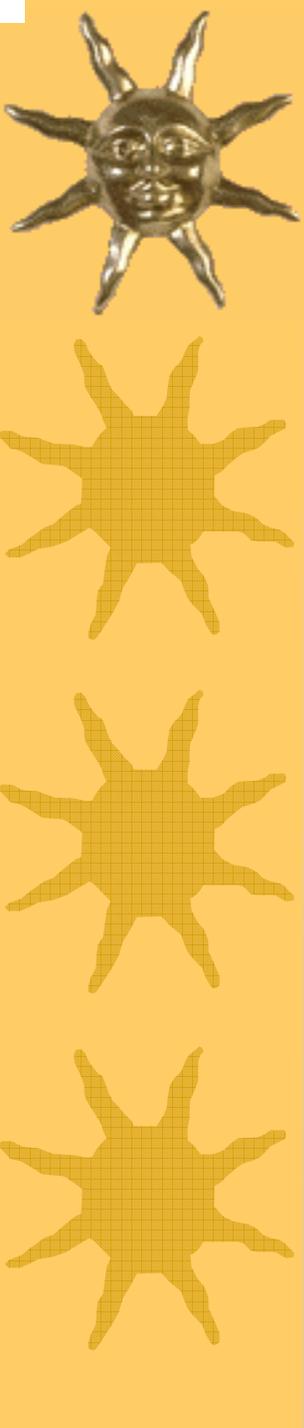


★ „normal“ immune reaction against autoantigens



★ redundancy of mechanisms involved in tolerance

★ combination of influencing factors

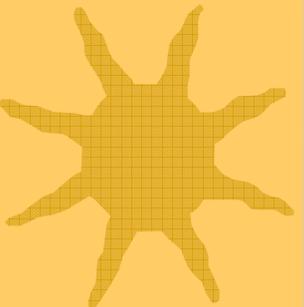
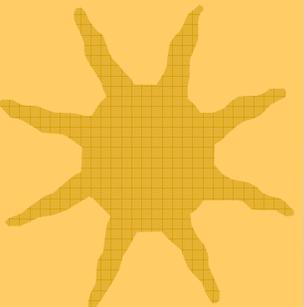
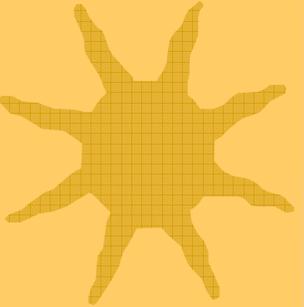


Systemic autoimmune diseases

- SLE
- Dermatomyositis
- Sklerodermia
- Sjögren´s syndrome
- Vasculitis
- Rheumatoid arthritis
- MCTD – mixed connective tissue disease
- Antiphospholipide syndrom
- Sarcoidosis



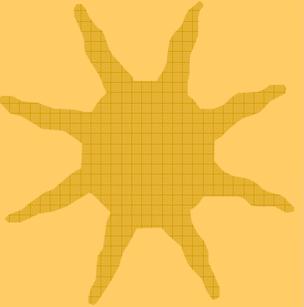
SLE



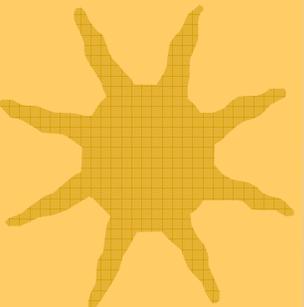
-
- ★ “ A multisystem disease characterised by autoantibodies directed against nuclear components”
 - ★ Incidence 1:4000
 - ★ Complex multifactorial etiology
 - ★ Relapsing and remitting
 - ★ Clinical and serological diversity



SLE



American College of Rheumatology criteria (4/11)



Arthralgia

Neurological abn

Oral ulcers

Haematological abn

Serositis

Renal disease

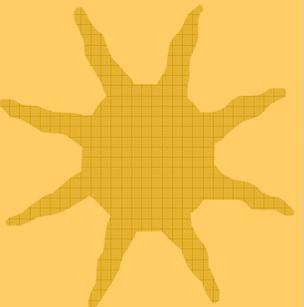
Malar rash

Anti-nuclear factor

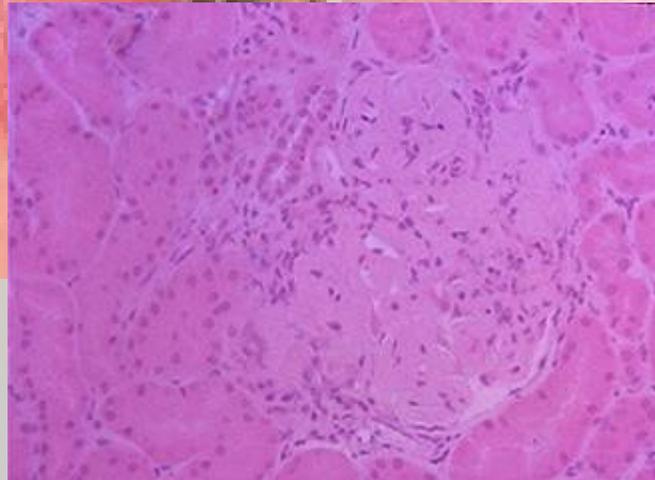
Discoid rash

Immunological abn

Photosensitivity



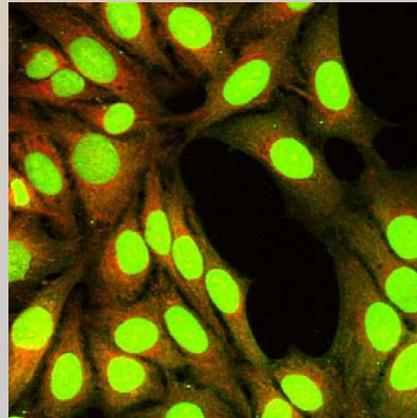
Clinical features of SLE





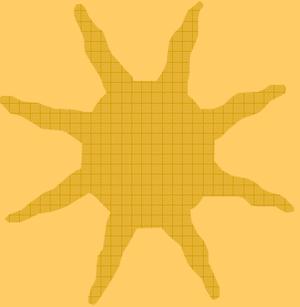
Autoantibodies in SLE

- ★ ANA (prevalence ~ 100%)
- ★ anti – dsDNA (prevalence 40-90%, levels fluctuate with disease activity)
- ★ ENA (anti – Sm)
- ★ autoantibodies against blood cells



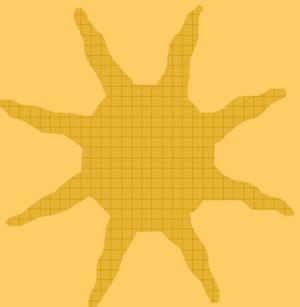


Sjögren's syndrom

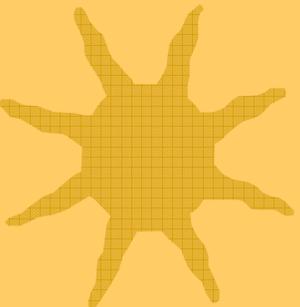


★ Sicca syndrom – dryness of eyes, nose, mouth, airways, vagina, skin

★ polyarthralgia



• autoantibodies: ENA - SS-A
- SS-B



risk of AV block in newborns



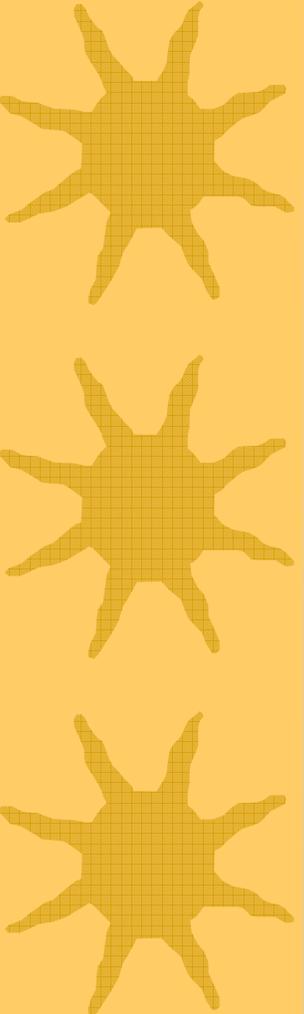
Dermatomyositis

- proximal muscle weakness
- arthralgia, arthritis, dyspnea, dysphagia, arrhythmia, and dysphonia
- paraneoplastic manifestation: breast ca, ca GIT, lung ca
- autoantibodies: ENA – Jo1, PM/Slc





Systemic sclerosis



- ★ Systemic connective tissue disease
- ★ Essential vasomotor disturbances; fibrosis; subsequent atrophy of the skin, subcutaneous tissue, muscles, and internal organs
- ★ Raynaud's phenomenon
- ★ Major features include centrally located skin sclerosis that affects the arms, face, and/or neck.
- ★ Minor features include sclerodactyly, erosions, atrophy of the fingertips, and bilateral lung fibrosis.
- ★ SSc is diagnosed when a patient has 1 major and 2 minor criteria.

Systemic sclerosis

- autoantibodies: ANA
ENA (anti-topoisomerase I - Scl-70)
anti-centromerese (ACA)





Antiphospholipid syndrome

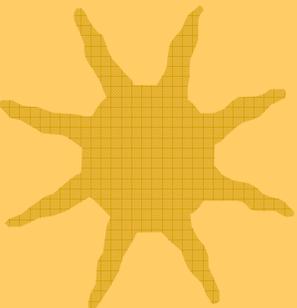
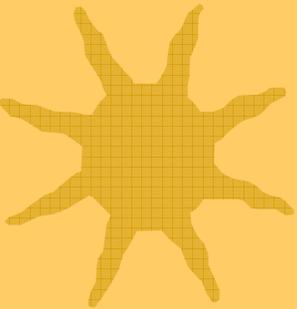
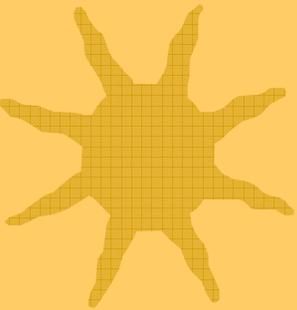
- ★ excessive clotting of blood and/or certain complications of pregnancy

trombosis



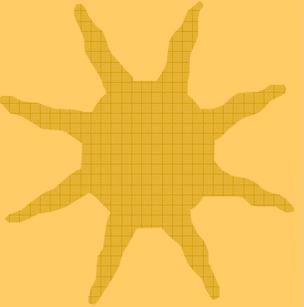
abortus

- ★ presence of antiphospholipid antibodies (cardiolipin - ACLA or lupus anticoagulant antibodies)
- ★ prolonged APTT
- ★ in over half of patients with SLE



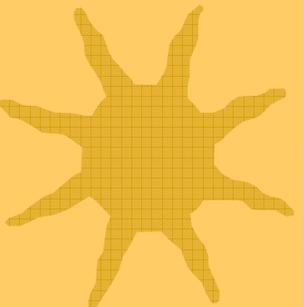


Vasculitis



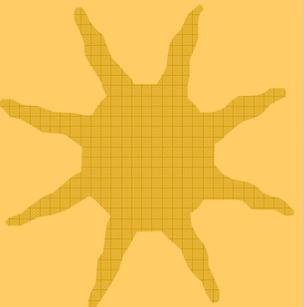
★ **Large vessel**

- Takayasu
- Giant cell (temporal) arteriitis



★ **Medium and small vessel**

- Polyarteritis nodosa
- Churg-Strauss arteritis



★ **Small vessel**

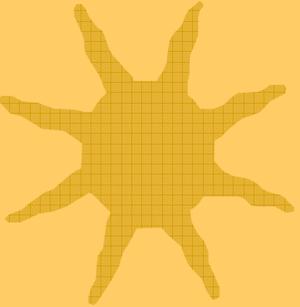
- Kawasaki disease
- Henoch-Schönlein purpura
- Wegener's granulomatosis

★ IK deposits

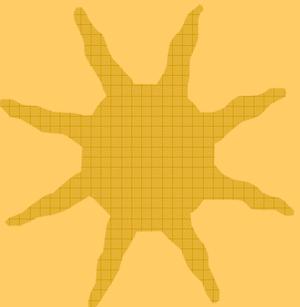
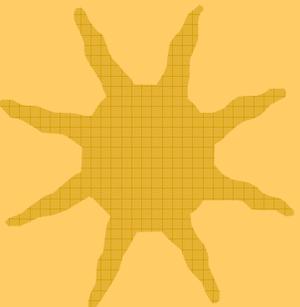
★ autoantibodies: ANCA



Autoimmune systemic diseases *- characteristic autoantibodies*

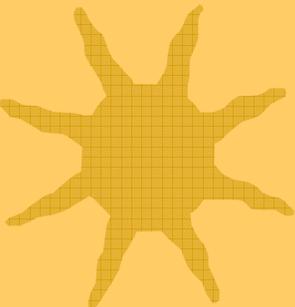
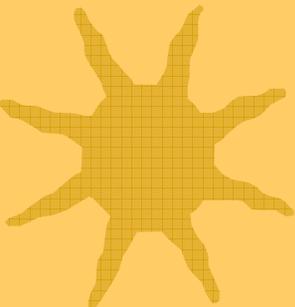
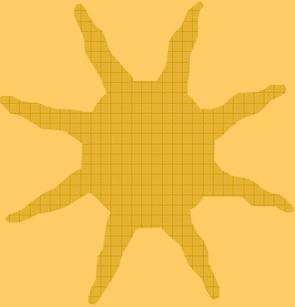


- | | |
|----------------------------|---------------------|
| ★ SLE | ANA, dsDNA |
| ★ Rheumatoid arthritis | RF |
| ★ Dermato/polymyositis | ENA Jo-1 |
| ★ Sjögren´s syndrome | ENA SS-A, SS-B |
| ★ Sklerodermia | ENA Scl 70 |
| ★ MCTD | ENA RNP |
| ★ Antiphospholip. syndrome | anti-phospholipides |
| ★ Vasculitides | ANCA |





Organ-specific autoimmune diseases



Endocrine system

- Autoimmune (Hashimoto's) thyroiditis
- Hyperthyroidism (Graves' disease; thyrotoxicosis)
- Type I diabetes mellitus (insulin-dependent or juvenile diabetes)
- Insulin-resistant diabetes
- Autoimmune adrenal insufficiency (Addison's disease)
- Autoimmune oophoritis

Hematopoietic system

- Autoimmune haemolytic anemia
- Paroxysmal cold hemoglobinuria
- Autoimmune thrombocytopenia
- Autoimmune neutropenia
- Pernicious anemia
- Pure red cell anemia

Neuromuscular system

- Myasthenia gravis
- Autoimmune polyneuritis
- Multiple sclerosis
- Experimental allergic encephalomyelitis

Skin

- Pemphigus and other bullous diseases

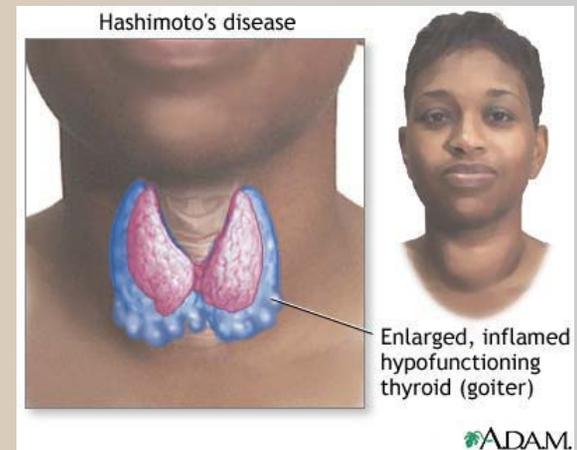
Cardiopulmonary System

- Rheumatic carditis
- Goodpasture's syndrome
- Postcardiotomy syndrome (Dressler's syndrome)

Autoimmune diseases of thyreoid

1. Hashimoto's thyreoiditis

- hypofunction of thyreoid
- autoantibodies against thyreoglobulin and microsomes of thyreocytes



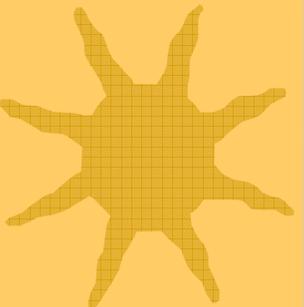
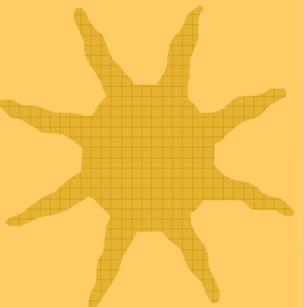
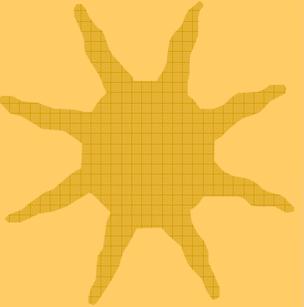
2. Graves-Basedow's disease

- hyperfunction of thyreoid, thyreotoxicosis
- autoantibodies against TSH receptor

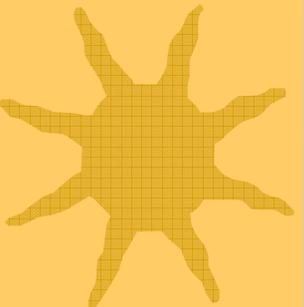
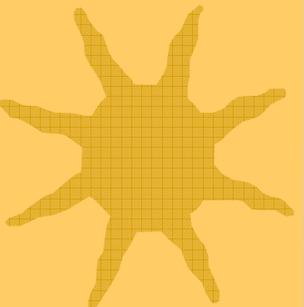
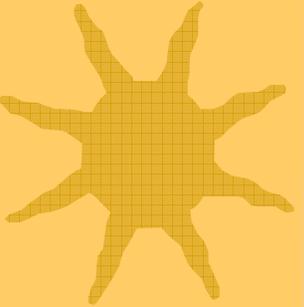




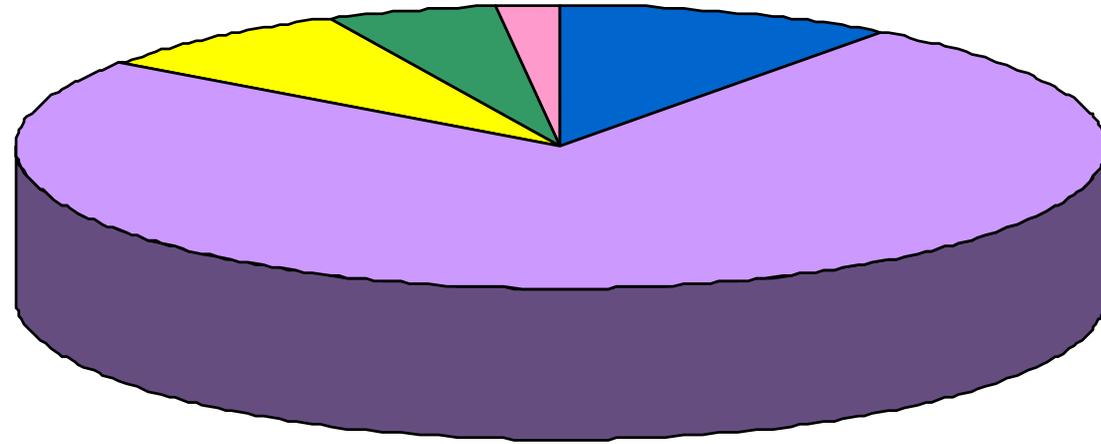
Diabetes



- ❖ Hyperglycaemia
- ❖ Different mechanisms cause different forms
- ❖ Genetic and environmental component to all forms
- ❖ Diabetes gives rise to complications;
 - microvascular- nephropathy, neuropathy, retinopathy
 - macrovascular - cardiovascular disease
- ❖ Two major forms of diabetes:
 - Type 1 diabetes (autoimmune)
 - Type 2 diabetes (metabolic)



Diabetes subgroups



■ Type 1 ■ Type 2 ■ LADA ■ MODY ■ MIDD

LADA = Latent Autoimmune Diabetes in Adults

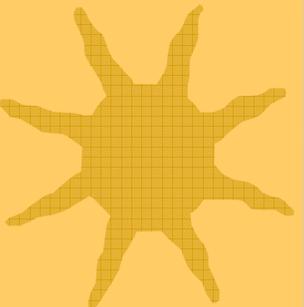
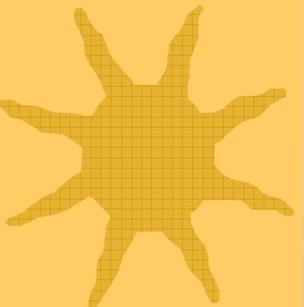
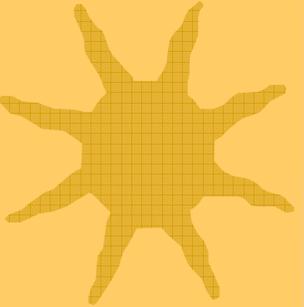
MODY = Maturity Onset Diabetes in the Young

MIDD = Mitochondrial Diabetes and Deafness

- ❖ Autoimmune diabetes = Type 1 diabetes + LADA

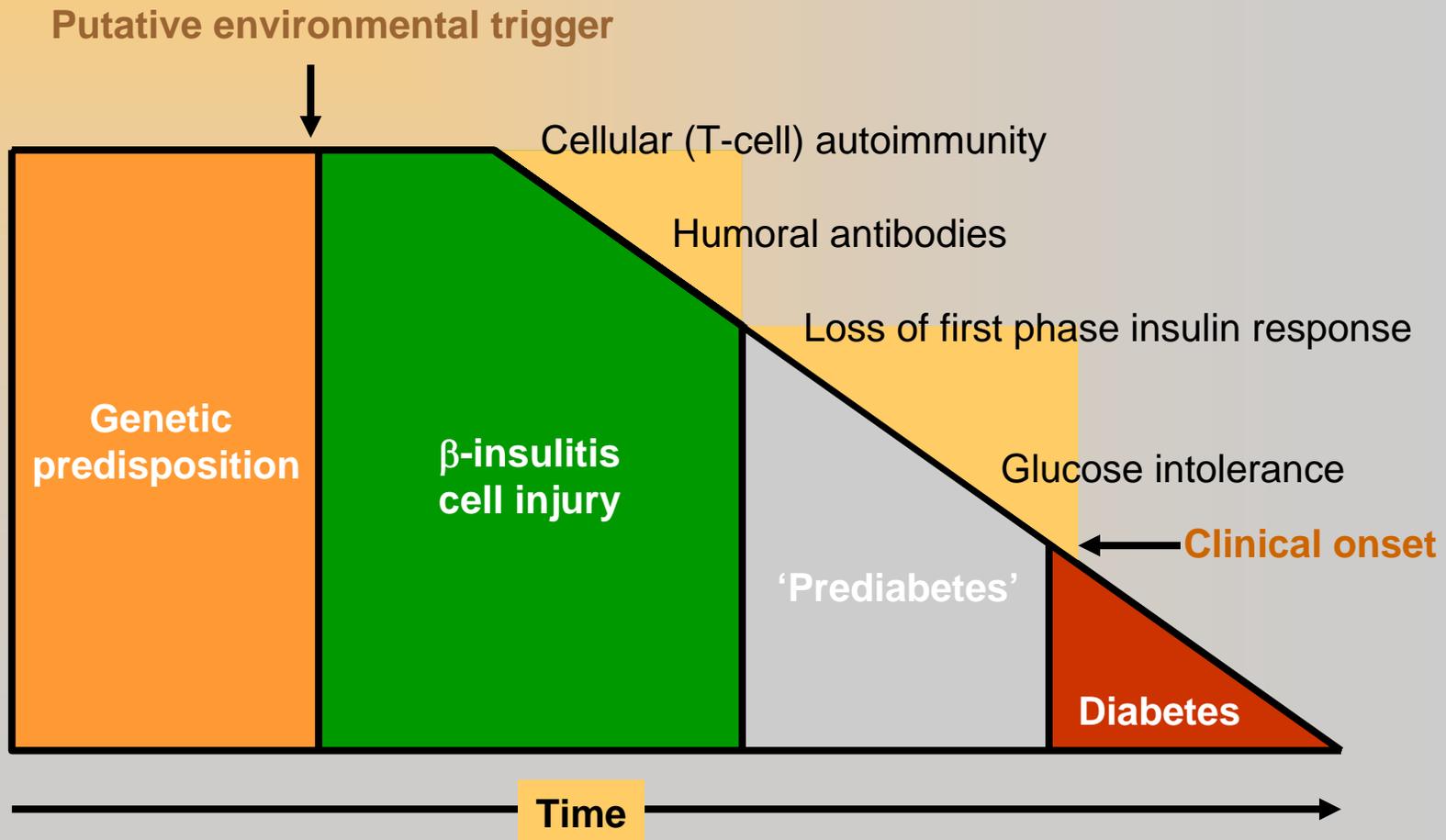


Type 1 diabetes (T1D)



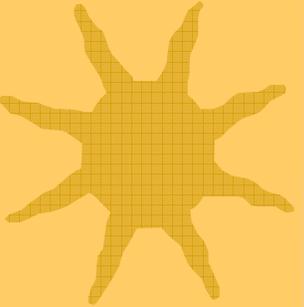
- ❖ Also known as
insulin-dependent diabetes mellitus (IDDM) or
juvenile-onset diabetes
- ❖ Organ-specific autoimmune disorder (pancreatic islets)
- ❖ Hyperglycaemia results from:
 - specific auto-destruction of insulin-secreting β -cells in the islets of Langerhans in the pancreas
 - autoantibodies against GAD65
- ❖ Etiology and pathogenesis of autoimmune diabetes largely unknown

Summary: natural history of T1D

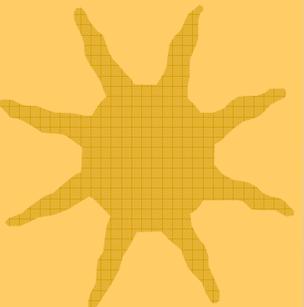




Localized autoimmune diseases with systemic autoantibodies



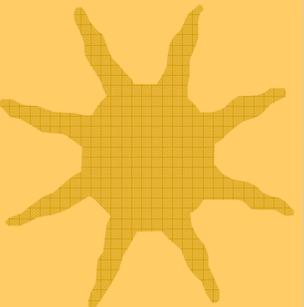
★ IBD: Crohn disease
ulcerative colitis



★ celiac disease

★ autoimmune hepatitis

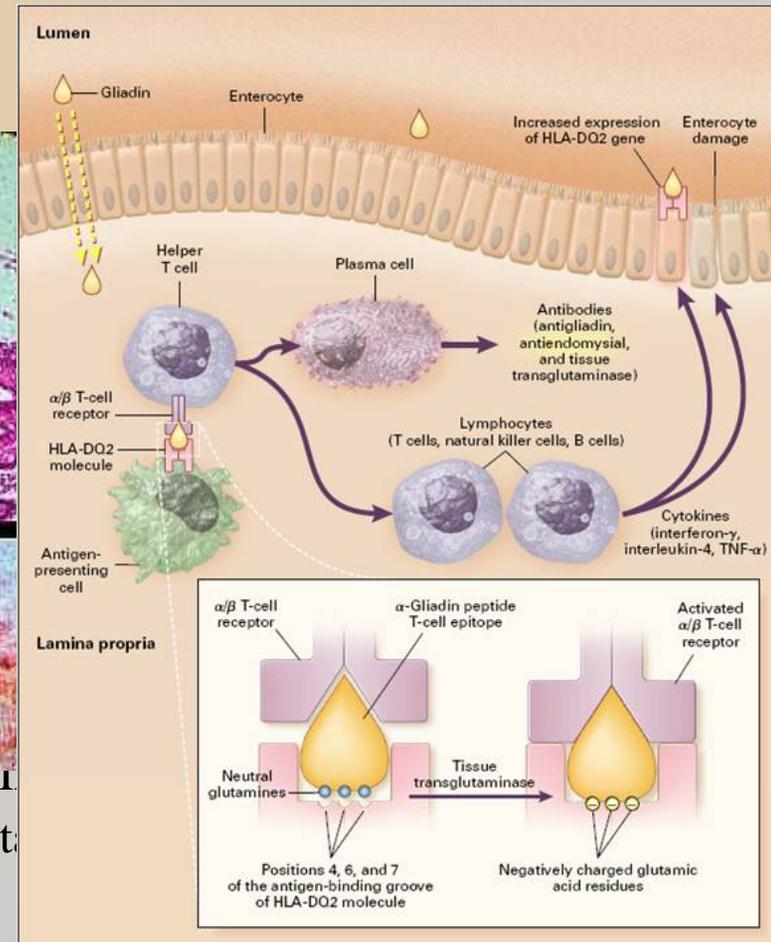
★ primary biliary cirrhosis





Localized autoimmune diseases with systemic autoantibodies

★ Celiac disease



★ autoant

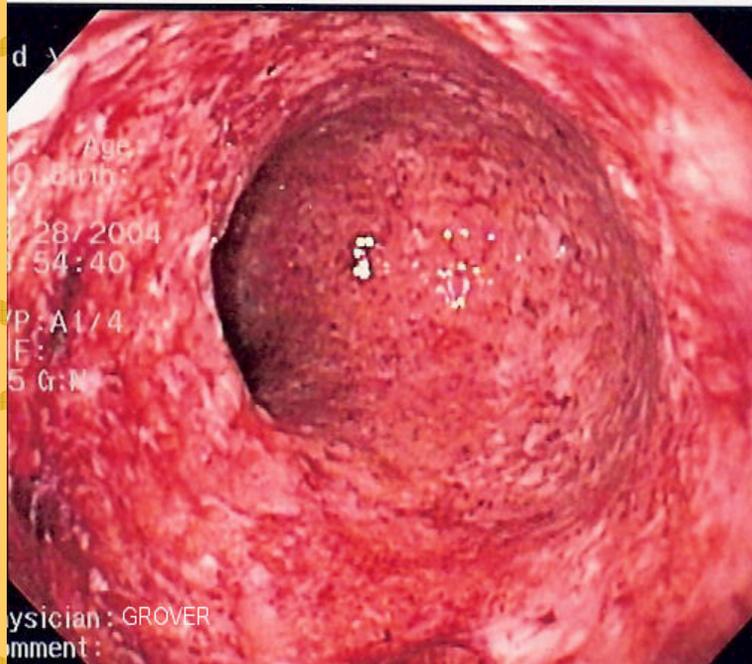
ai (EM
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IBD – inflammatory bowel diseases

CROHN'S DISEASE

ULCERATIVE COLITIS

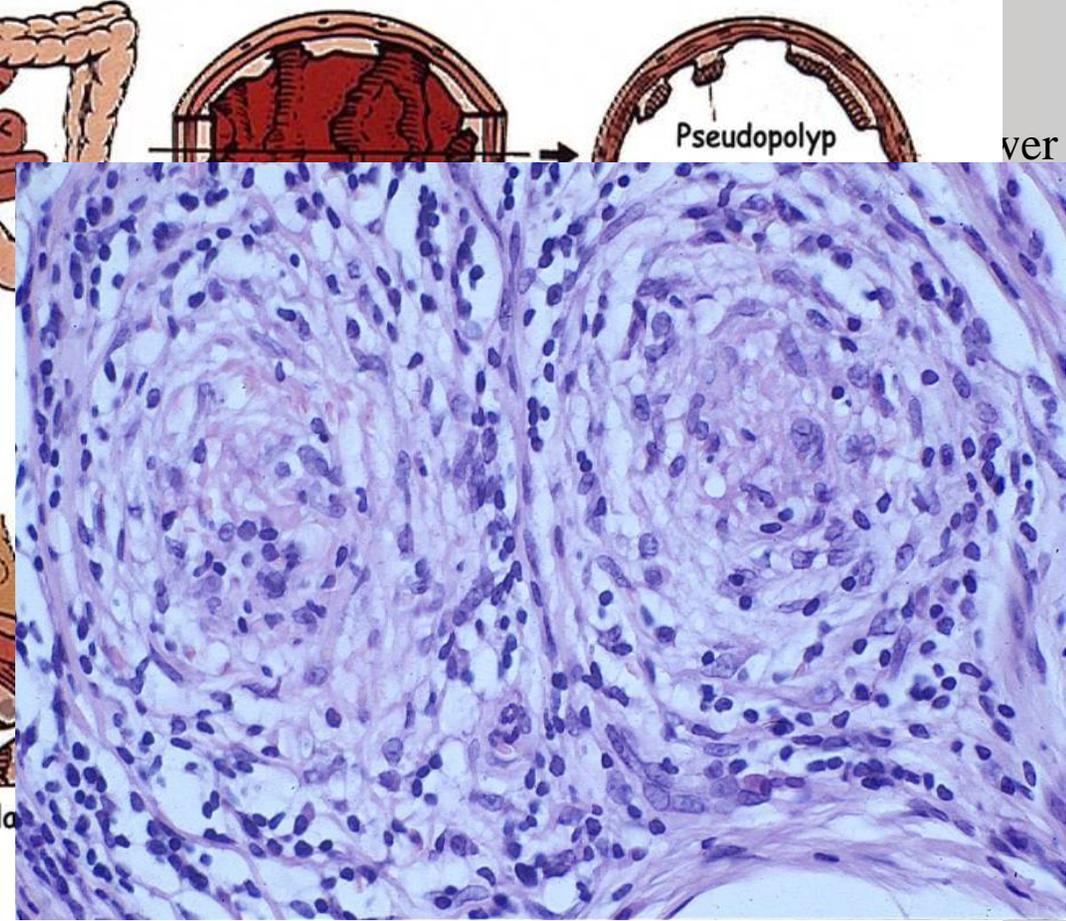


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Age:
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Small intestine

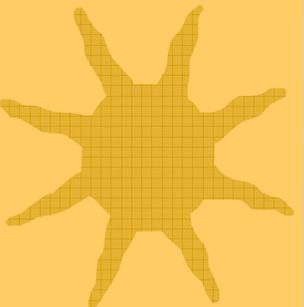
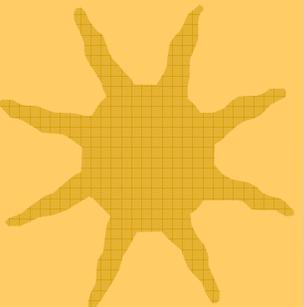
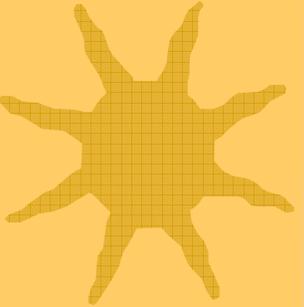
Transmural infla



ver



Therapy of autoimmune diseases



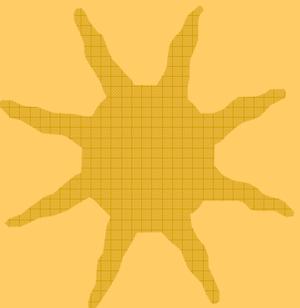
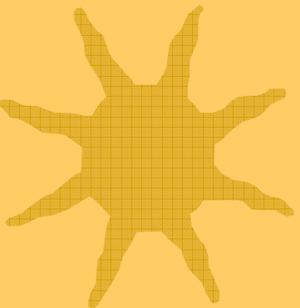
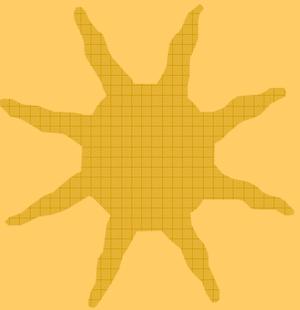
corticosteroids	complex.action, cytokin inhibition	Prednison metylprednisolon
antiproliferative	inhib .DNA synthesis	cyclofosfamid azathioprin methotrexate mykofenolate
inhibitors of immunophilins	inhib. of cytokines	CyA, tacrolimus, rapamycin
iv.Ig	immunoglobulins complex, antiidiotypes	IVIg
Ab against T ly.	inhib. depletion	ATG, anti CD3



Therapy

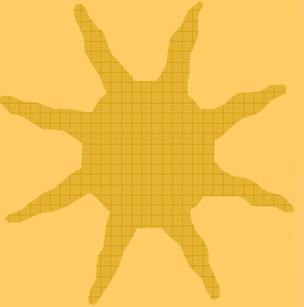
Antigen-specific

- systemic application of Ag
 - Copaxone
- Ag po.
 - γ/δ T lymphocytes
 - insuline
- experimental approaches
 - modified Ag
 - gene therapy



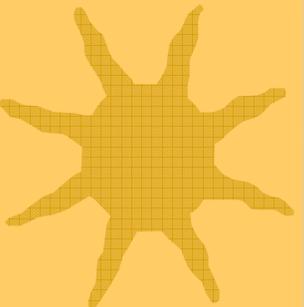
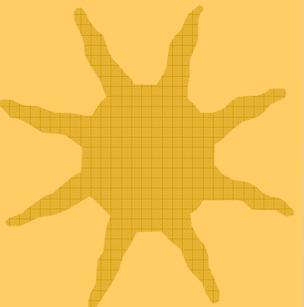


Antigen non specific treatment



Cytokine mediated treatment

- TNFalpha
 - infliximab, etanercept
- antiinflammatory cytokines
 - Il-10
 - IL-1
 - IFN beta
- others
 - blocade of adhesion molecules
 - blocade of costimulatory signals





Bone marrow transplantation

Stem cell transplantation

ALPS

rheumatoid arthritis, systemic scleroderma,
multiple sclerosis

allogenic (mortality risk) or autologous (risk of relaps)

