IMMUNOLOGY LECTURE - week 11

AUTOIMUNITY (Lippincott´s Immunology - chapter 16)

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

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

The innate immune system relies upon a set of "hard-wired" genetically encoded receptors that have evolved to distinguish self from nonself. The adaptive immune system faces a much greater challenge in making such distinctions. The B cell receptors (BCRs) and T cell receptors (TCRs) of the adaptive immune system are randomly generated within each individual,

without "preknowledge" of the epitopes that may be encountered. As a result, some BCRs and TCRs recognize nonself and others recognize self. Several mechanisms are utilized to identify and control or eliminate cells that are potentially selfreactive. The failure of these mechanisms to inactivate or eliminate self-reactive cells leads to **autoimmunity**.

Rheumatoid arthritis, some forms of diabetes, multiple sclerosis, psoriasis, and systemic lupus erythematosus, to name only a few, are autoimmune diseases. Autoimmunity is complex. It may arise by different mechanisms, and its risk is affected by a variety of environmental and genetic factors, many of which are as yet unidentified. Together, however, these various

influences contribute to a breakdown in self tolerance, that is, the ability of the immune system to effectively distinguish self from nonself and to refrain from attacking self.

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 ??

Tolerance is the failure of the immune system to respond to an epitope in an aggressive way. Most **self-tolerance** results from the deliberate inactivation or destruction of lymphocytes bearing BCRs or TCRs that recognize and binds self epitopes. Inactivation or destruction may occur during early development (central tolerance) or may be imposed on lymphocytes in the

periphery (peripheral tolerance). An understanding of how the immune system naturally imposes self-tolerance can provide critical clues for the development of therapeutic strategies for autoimmune diseases caused by the loss of self-tolerance.

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

Central tolerance occurs during the early differentiation of B cells in the bone marrow and T cells in the thymus. Normally, both B and T cells that bind self-epitopes at distinct early stages of development meet an apoptotic death, thus eliminating large numbers of potentially self-reactive cells before they enter the circulation B cells express surface IgM as their BCRs. Epitope recognition by BCRs of developing B cells within the bone marrow triggers their apoptotic death, a process known as **negative selection**. Likewise, the binding of peptide-MHC complex (pMHC I or pMHC II) by TCRs of single positive (CD4+CD8– or CD4–CD8+) thymocytes causes them to undergo apoptotic death. This process removes many potentially autoreactive B and T cells before they enter the periphery. A major caveat imposed on central tolerance is that not all self-epitopes are to be found in the primary lymphoid organs, especially those selfepitopes that arise after lymphogenesis, such as those that arise during puberty. Other means are needed to prevent the Several additional mechanisms, collectively called **peripheral tolerance**, control or eliminate autoreactive B and T cells after they exit the bone marrow or thymus.

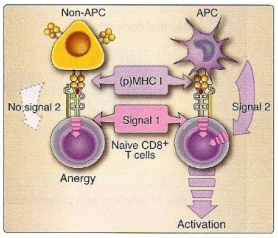
Anergy

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

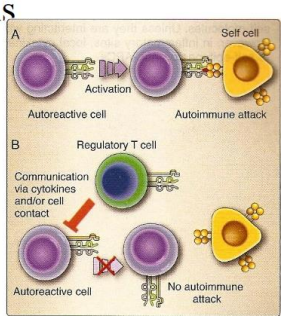
Balance in Th1 and Th2 – influences

if the disease arises or not

an antigen:

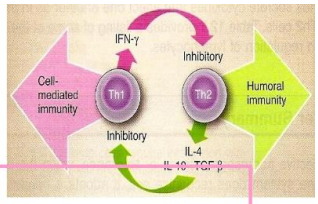
dominance of Th1 = 0 inflamation,

dominance of TH2 = CM inflamation



One such mechanism is the induction of **anergy**, a state of nonresponsiveness in lymphocytes after their receptors bind antigen (B cell) or pMHC (T cell) provides a whimsical view of anergy). Another mechanism is **suppression**, whereby regulatory cells inhibit the activity of other cells.

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

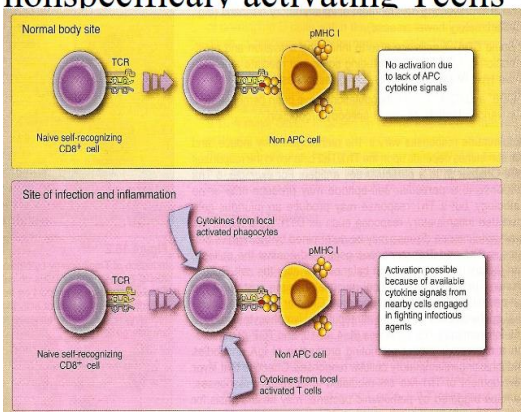
Loss of Self-Tolerance

Despite the various mechanisms that are in place to prevent responses to self epitopes, autoimmunity still occurs occasionally. How does this happen? What types of situations provide opportunities for self-reactive immune cells to escape the traps set for them and become free to attack the body's cells and tissues? There are, in fact, several different situations that make this possible.

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

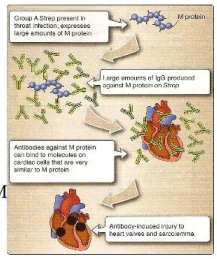


Infection is frequently associated with development of autoimmunity. Experimental evidence in vitro has shown that under certain circumstances, the addition of high levels of exogenous cytokines can cause the activation of naïve T cells in the absence of interactions with APCs, and in some cases, even anergized T cells can be activated. Inflammation at sites of infection, originating with activated phagocytes responding to the presence of infectious agents, can generate elevated levels of pro-inflammatory cytokines that may mimic the effects seen in vitro.

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



Molecular mimicry is a process in which infection by particular microbes is associated with the subsequent development of specific autoimmune diseases. The antigenic molecules on some infectious agents are similar enough to some host self molecules that B and T cell responses generated against the microbial antigens can result in damage to host cells bearing similar molecules . The best-understood example of this process is the cardiac damage resulting from rheumatic fever after infection by *Streptococcus pyogenes* ("strep," the causative agent of strep throat) . Group A β-hemolytic strains of *S. pyogenes* express high levels of an antigen known as the M protein, a molecule that shares some structural similarities with molecules found on the valves and membranes of the heart. If the levels of IgM and IgG generated against the M protein during infection reach sufficient levels, there may be sufficient binding to host cells to induce damage and reduced cardiac function. In addition to cardiac sites, antibodies against the M protein can also cross-react to some degree with molecules on host cells in the joints and kidneys. The accumulated damage to cardiac and other tissues may be fatal. It is therefore important that patients who present with sore throats be tested to determine whether strep is present and, if so, to begin antibiotic therapy to clear the infection before vigorous antibody responses against strep antigens can develop.

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

Epitope spreading

Another phenomenon that may contribute to the influence of infectious organisms on autoimmunity is **epitope spreading**. The epitope that initiates a response leading to autoimmunity might not be the epitope that is targeted by immune responses that develop later during the pathogenesis of the disease. For example, initial responses against an infectious agent may result in damage that exposes self-epitopes in ways that subsequently trigger true autoimmune responses. In some animal models of human multiple sclerosis, responses to particular viral epitopes regularly precede the development of responses to specific

epitopes associated with the myelin sheath that protects neuronal axons. Epitope spreading is suspected to play a role in several autoimmune diseases, including systemic lupus erythematosus, inflammatory bowel disease (Crohn's disease and ulcerative colitis), multiple sclerosis, pemphigus vulgaris, and some forms of diabetes.

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

Sequestred antigens

- Structures outside IS

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

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

Some self-molecules are “sequestered” and are normally never exposed to the immune system for various reasons. As a result, if they do become exposed, as a result of injury for example, the immune system may view them as foreign and attack them. Among the best-understood examples of sequestered antigens are those associated with spermatogonia and developing sperm within the lumen of testicular tubules. The tubules are sealed off early in embryonic development, prior to development of the immune system, by enclosure within a sheath of tightly joined Sertoli cells. Immune cells do not penetrate the barrier presented by the Sertoli cells and therefore are never exposed to self-molecules that are unique to the testicular tubule lumen. If these are exposed by injury (or by procedures such as surgery or vasectomy), immune responses may occur against the self (but seemingly foreign) molecules. It is believed that some cases of male sterility are caused by this mechanism. Collectively, sites in the body that are associated with some degree of isolation from the immune system are called **immunologically privileged sites**. In addition to the lumen of the testicular tubule, these sites include the cornea and the anterior chamber of the eye, the brain, and the uterine environment during pregnancy.

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

Molecules may also sometimes possess a type of immunologically privileged site. The three-dimensional configurations of some molecules may shelter epitopes in the interior from contact with the immune system. If the molecule is altered by denaturation or cleavage, however, the

“hidden” internal epitopes may become exposed and available for recognition and binding by antibodies . These are termed **cryptic epitopes**. The presence of rheumatoid factor, associated with inflammatory rheumatoid diseases, provides an example of this phenomenon. The binding of IgG molecules trigger conformational changes in their Fc regions that expose “hidden” sites, some of which facilitate the binding of complement or Fc receptors and some of which expose cryptic carbohydrate structures that can be recognized and bound by IgM antibodies. IgM antibodies directed at the cryptic carbohydrate structures on antigen-bound IgG molecules are called **rheumatoid factors**. The binding of IgM to IgG augments the formation of immune complexes and the activation of complement. The presence of rheumatoid factor is associated with several inflammatory autoimmune diseases.

- 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

Suppressor cells of various types serve to maintain peripheral tolerance. Evidence suggests that the numbers of these suppressor cells decline with age, increasing the risk that previously suppressed autoreactive lymphocytes can become active. A pattern of increasing risk with increasing age is indeed seen in some autoimmune diseases, such as **systemic lupus erythematosus** (**SLE**). However, it can be difficult to differentiate between an increase in risk due to changes that result from aging and the simple fact that increased age provides more opportunity for a disease to occur.

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

Autoimmune diseases involve numerous different molecules, cells, and tissues that are targeted by the autoimmune responses. Some autoimmune diseases are systemic or diffuse, because of the distribution of the target antigens. For example, SLE and rheumatoid arthritis affect a variety of joints and other body tissues. Other diseases affect specific organs and tissues.

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

Some autoimmune diseases result from the binding of self-reactive antibodies, leading to Type II and Type III hypersensitivity responses. The antibodies responsible for initiating the diseases are usually of the IgG isotype, although IgM antibodies can contribute as well. The activation of complement and the opsonization of injured cells promote inflammatory responses that increase the damage inflicted on the targeted cells and tissues. Autoreactive T cells are typically present as well, but their role is primarily the activation of the autoreactive B cells rather than directly attacking host cells. Examples of these autoimmune diseases include:

-Autoimmune hemolytic anemia: type II hypersensitivity
-Goodpasture's syndrome: type II hypersensitivity
-Hashimoto's thyroiditis: type II hypersensitivity
-Rheumatic fever: type II hypersensitivity
-Rheumatoid arthritis: type III hypersensitivity
-Systemic lupus erythematosus: type II and type III hypersensitivity

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

Type IV hypersensitivity responses involve cell-mediated injury leading to autoimmune disease. These may include cytotoxic T cell responses or macrophages driven by DTH responses. The inflammation that is generated can eventually involve numerous simultaneously ongoing responses. In some diseases, particular antibodies may also be characteristically present, but they have not been demonstrated to contribute to the disease pathologies. The following are examples of autoimmune diseases involving type IV hypersensitivity responses. Rheumatoid arthritis provides an example of an autoimmune disease that involves both humoral and cell-mediated injury.

- Insulin-dependent diabetes mellitus (type 1)
- Multiple sclerosis

- Reactive arthritis
- Rheumatoid arthritis

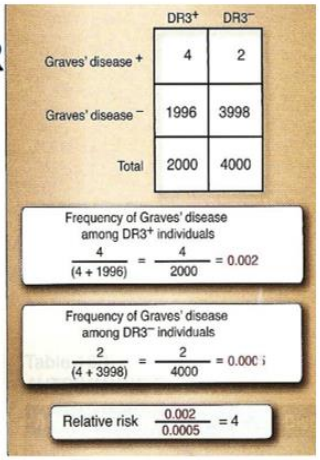
Affected Tissue	Disease	Target Antigen
Anterior parts of the eye	Uveitis (anterior)	Beta B1-crystalin, other proteins of the ciliary body epithelium
Connective tissue	Scleroderma	Scl-70, PM-Scl antigens
Erythrocytes	Autoimmune hemolytic anemia	Erythrocyte surface molecules
Heart valves and sarcolemmal 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

RELATIVE RISK -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

The risks for many autoimmune diseases appear to be associated with the presence of particular HLA genes . In some cases (e.g., HLA-B27 and HLA-DR3), a single HLA gene is associated with increased risk for multiple autoimmune diseases. The molecular mechanisms underlying these statistical associations are still uncertain but presumably involve some influence on

processing and presentation of self epitopes to self-reactive T cells. The strength of the statistical association between a particular HLA gene and a particular autoimmune disease is expressed as the **relative risk**. The relative risk compares the frequency of the particular disease among carriers of a particular HLA gene with the frequency among noncarriers. For example, the relative risk of 6 for the association of SLE with HLA-DR3 means that SLE occurs approximately three times more frequently among DR3+ individuals than among DR3– individuals. Relative risk calculations are made within defined populations, and results may vary among groups of different ethnic or geographic origin.

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