Medical Immunology for M.D. Students

Hypersensitivity Reactions (3)

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Delayed type HSR (Type IV)

- An exaggerated interaction between Ag and the normal T cell mediated immune responses.
- It is characterized by T cell response driving an inflammatory reaction involving macrophages.
- The immune response might be directed against microorganisms (*Mycobacterium tuberculosis*, *Leishmania* spp.) or against contact Ags (nickel salts, poison ivy).
- The effector T cell response in type IV HSR is an adaptive response that is considered an essential line of defence against intracellular pathogens, however, if the response is excessive it can cause tissue damage.
- Typically, T cells are sensitized through the dendritic cell presentation during infection or contact with the triggering chemical.

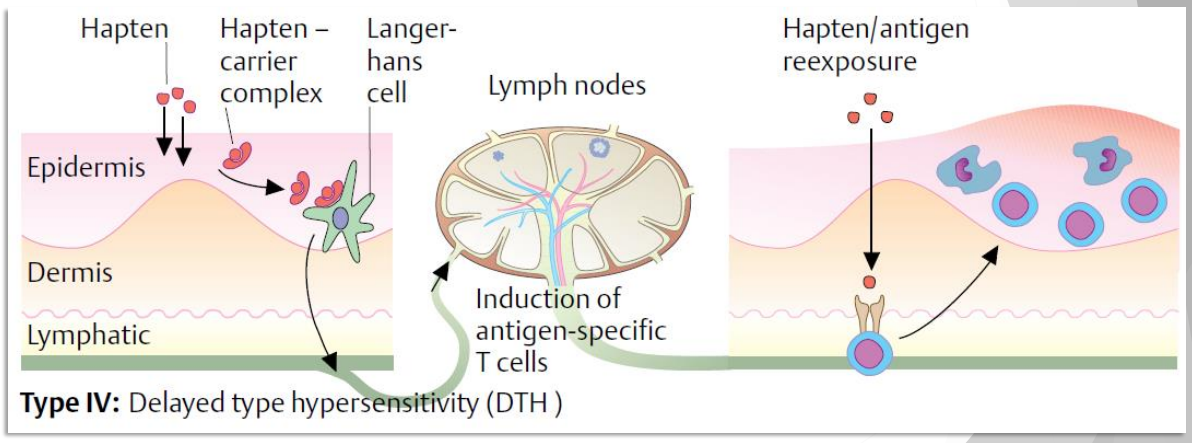
Delayed type HSR (Type IV)

- Subsequent exposure to the same Ag will result in recruitment of Ag-specific T cells to the site with the development of an immune response within 48-72 hours.
- Granulomas are formed by aggregation of macrophages and lymphocytes.
- Contact HSR is often seen following contact with immunologically active components (haptens) of sensitizing agents such as nickel or pentadecacatechol (the sensitizing agent in poison ivy).
- Haptens are too small to be antigenic by themselves hence they conjugate to proteins to form neo-Ags
- Langerhans cells (the skin APC) play a key role in contact HSR IV, by uptaking the hapten-modified proteins followed by migration to regional LNs and presentation of Ags to T cells.

Delayed type HSR (Type IV)

- Type IV HSR can be induced by soluble Ags from variety of microorganisms.
- Reaction to these Ags demonstrates a past infection with the pathogen (tuberculin skin test).
- The same test can be used as a measure of cell-mediated immunity.
- Granulomatous HSR usually stems from persistence of intracellular organisms or particles within macrophages.
- This leads to chronic stimulation of T cells which ends up in the formation of granulomas that contain epithelioid cells, lymphocytes and macrophages.
- IFN-γ is essential for granuloma formation.
- Chronic diseases that manifest in type IV granulomatous HSR include: leprosy, TB, schistosomiasis and sarcoidosis.

Delayed type HSR (Type IV)



Autoimmune disease (AID)

- Autoimmunity can be defined as adaptive immune responses directed against self Ags. It underlies many diseases, some of which are organ-specific and others are systemic in nature. AIDs arise as a result of loss of self-tolerance.
- The autoimmune responses can involve Abs (auto-Abs) or self reactive T cells, which can cause tissue damage through HSRs II to IV.
- Auto-Abs can be found in some healthy individuals, however, their very low levels and low affinities for self Ags hinder the occurrence of subsequent AID.
- Genetic factors play a role in the development of AID including factors such as HLA type, CTLA-4 SNP.
- The auto-Ags are almost impossible to be eradicated from self, hence, AIDs tend to be active for a long time (chronicity).
- Women are more susceptible than men to autoimmunity (overall more than 75%).

HLA association with AID

Some HLA associated autoimmune diseases

Disease	HLA	Pts[a]	Ctrls[a]	RR[b]
Ankylosing spondylitis	B27	> 95	9	> 150
Subacute thyroiditis	B35	70	14	14
Psoriasis vulgaris	Cw6	87	33	7
Graves disease	DR3	65	27	4
Myasthenia gravis	DR3	50	27	2
Addisons disease	DR3	69	27	5
Rheumatoid arthritis	DR4(some)	81	33	9
Juvenile idiopathic arthiritis	DR8	38	7	8
Celiac disease	DQ2 (+DQ8)	92	28	30
Narcolepsy	DQ6(02)	> 95	33	> 40
Multiple sclerosis	DQ6(02)	86	33	12
Type 1 diabetes	DQ8(+)	81	23	14
Type 1 diabetes	DQ6(02)	< 0.01	33	0.02

[a] The figures show antigen frequencies in a Norwegian population.

[b] RR: relative risk; i.e. how many times more frequent the disease is in those having the corresponding HLA molecule compared to those lacking it.

Mechanisms of loss of self-tolerance

- **Molecular mimicry:**
- The process in which a microbial infection will result in subsequent development of AID as a result of enough similarity between some self Ags and microbial Ags.

❖ ***Examples:***

- **Rheumatic fever:** Abs against the M protein of *Streptococcus pyogenes* cross reacts with the cardiac myosin
- **Ankylsoing spondylitis:** possible association with *Klebsiella* sp.
- **Reactive arthritis:** Possible association with *Chlamydia trachomatis*.

Mechanisms of loss of self-tolerance

- **Epitope spreading:** Microbial antigens can initiate an immune response with tissue damage that exposes self epitopes triggering an AID.
- Examples (suspected):
  - Systemic lupus erythematosus
  - Inflammatory bowel disease
  - Multiple sclerosis
  - Pemphigus vulgaris
  - Insulin dependent DM

Mechanisms of loss of self-tolerance

- **Sequestered antigens:** The presence of self molecules that are normally isolated and never exposed to the immune system. The sites of these self molecules are called immunologically privileged sites. (e.g. Lumen of the testicular tubules, the cornea, anterior chamber of the eye).
- Other form of sequestered antigens is due to the 3D protein structure which might shelter epitopes in the interior of the molecule (cryptic antigens). If the molecule is denatured or cleaved, these epitopes become exposed and recognized by self reactive immune response. (e.g. rheumatoid factor).
- **Failure of T_{reg} cells inhibition:** Potential role in SLE.

Classical systemic autoimmune diseases

- SLE.
- Rheumatoid arthritis:
- Systemic chronic inflammatory disease that is manifested in destructive polyarthritis with extra-articular manifestations.
- Diagnosis depends on the clinical features with serologic testing for rheumatoid factor (neither highly sensitive nor specific) and for antibodies against cyclic citrullinated peptides (anti-CCP).
- Other conditions include systemic sclerosis, Sjögren syndrome and mixed connective tissue disease (MCTD).

Endocrine autoimmune diseases

- Graves disease: discussed earlier
- Hashimoto's thyroiditis: Abs are formed to a number of thyroid proteins, including thyroglobulin and thyroid peroxidase, both of which are involved in the uptake of iodine. Binding of the auto-Abs to these proteins interferes with iodine uptake, leading to decreased thyroid function and hypothyroidism. The resulting type IV HSR is characterized by an intense infiltration of the thyroid gland by lymphocytes and macrophages.
- Insulin dependent DM: Caused by an autoimmune attack against insulin-producing β-cells of the pancreas. The immune attack is considered type IV HSR.

Gastrointestinal autoimmune diseases

- Inflammatory Bowel Diseases (IBDs): a group of inflammatory disorders affecting the GI tract. The major types are Crohn's disease and ulcerative colitis, both of which are debilitating conditions.
- Celiac disease (gluten sensitive enteropathy): a chronic condition that is characterized by the presence of circulating auto-Abs in addition to an enteropathy, triggered by exposure to the gliadin fraction of gluten, a family of proteins found in wheat, barley, and rye.
- Exposure to gliadin, causes recognition by specific T cells in the setting of specific HLA allelles. Once the enzyme tissue transglutaminase modifies the glutamine into glutamic acid, the gliadin molecule can tightly adhere with the HLA of lymphocytes.
- The gliadin peptides, bound to dentritic cells, activate a proinflammatory response in which CD4+ cells participate in upregulation of IFN-γ, TNF-α, and IL-21. The end results are the observed villus blunting and atrophy.

Neurologic autoimmune diseases

- Multiple sclerosis
- It is characterized by lesions termed "plaques" in the white matter of the brain and spinal cord, resulting in the progressive destruction of the myelin sheath of axons (with several myelin proteins as the auto-Ags).
- Autoreactive T cells and activated macrophages is thought to be stimulated by a preceding viral infection.
- Intrathecal oligoclonal bands (bands of IgG in the CSF) are present in the majority of patients.

Neurologic autoimmune diseases

- Guillain-Barré Syndrome:
- The disease follows a variety of infections including upper respiratory tract infections, EBV, CMV mononucleosis, and Campylobacter jejuni gastroenteritis.
- Auto-Abs against myelin proteins are produced resulting in demyelinating polyneuropathy.
- The main symptom of the disease is rapidly progressive ascending paralysis.

Nephrologic autoimmune diseases

- IgA nephropathy:
- One of the most common types of glomerulonephritis globally.
- It is an immune complex-mediated disease defined by the presence of diffuse mesangial IgA deposits in the kidenys.
- Clinically, it is characterized by hematuria, but proteinuria can occur with progression to end-stage renal disease.

Hematologic autoimmune diseases

- Various forms of the hematologic autoimmune diseases (autoimmune haemolytic anemia, thrombocytopenia, granulocytopenia) can be attributed to auto-Abs attaching to blood cells with subsequent cellular destruction.
- Several drugs can get attached to the platelet cell membrane forming a neoantigen that induces the production of antibodies resulting in platelet destruction (e.g. some β-lactams, tetracyclins, INH).
- Pernicious anemia is caused by auto-Abs to intrinsic factor, a membrane protein on gastric parietal cells. Intrinsic factor facilitates uptake of vitamin B12 from the small intestine. Binding of the auto-antibody to intrinsic factor blocks absorption of vitamin B12, which is necessary for hematopoiesis, thus, the number of functional mature erythrocytes decreases below normal causing megaloblastic anemia.

Thanks for listening