الحمد لله
بسم الله الرحمن الرحيم
صلوات الله على نبينا محمد
Vasculitides: The Immunopathogenesis

Dr. Mohammadi Mohammad
LMD, PhD, MPH
(MMMohamadi@razi.tums.ac.ir)

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A small spoonful of **Terminology**

- **path·o·gen·e·sis, n.** — (پیماریژایی in Farsi)  
  - the production and development of disease (events and reactions and other pathologic mechanisms). Also, **pathog·e·ny**

- **path·o·ge·nic·i·ty, n.** — (پیماریژایی in Farsi)!?!  
  - the disease-producing capacity of a pathogen. [PATHOGENIC + -ITY]

- **vir·u·lence, n.**  
  - the relative ability of a microorganism to cause disease; degree of pathogenicity.

- **Vasculitis, n.** (vasculitides, plural)  
  - a general term for vessel wall **inflammation**, systemic or localized, immune-mediated or directly invaded by microbes.
    - Infections may indirectly generate vasculitis, e.g. through IC formation or by X_reaction. Note that immunosuppressive therapy is only appropriate for --?-- type!

- **WHAT R the IMMUNE MECHANISMS in VASCULITIS?**
<table>
<thead>
<tr>
<th>Defence</th>
<th>Surveillance</th>
<th>Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunodeficiency (&amp; Infection)</td>
<td>Autoimmunity (&amp; Malignancy)</td>
<td>Hypersensitivity Immunopathology</td>
</tr>
</tbody>
</table>

Homostasis ?!
Some Inter-related Concepts

Immunological Vasculitis
Hypersensitivity
Autoimmunity
Tolerance

EDUCATION?
Tolerance
in different classic Txtbks of Immunology
(Abbas, Benjamini, Janeway, Kuby, Roitt, Stites …)

• Tolerance (by C&M Immunology):
  – Unresponsiveness of the adaptive immune system to antigens, as a result of inactivation or death of antigen-specific lymphocytes, induced by exposure to the antigens.
  – (Active) Unresponsiveness of the (HEALTHY) adaptive immune system to (selected) antigens, as a result of (i.e. MECHANISMS:) inactivation or death of antigen-specific lymphocytes, induced by exposure to those antigens.

• Tolerance to self antigens is a normal feature of the adaptive immune system, but tolerance to foreign antigens may be induced under certain conditions of antigen exposure.
Tolerance Induction
Non-responsiveness

- **Immunocompromised State**
- **Sequestration**
- **Tolerance**
  - Central (by N&P selection / edition)
  - Peripheral, through
    - **Deletion** (AICD)
    - **Anergy** (Functional)
    - **Suppression**
Autoimmunity: an imbalance

Activating signals:
- MHC-II peptide
- Cytokines (IFN-g)
- CD40/CD40L
- CD28/CD80,86

Downregulating signals:
- Cytokines (IL-10, TGFβ)
- CD80,86/CTLA-4 (CD152)
Deletion

Negative Selection
Central Tolerance
Unresponsiveness

Anergy

Inhibitory Cytokines
Autoimmune responses resemble hypersensitivity reactions

• Type I: IgE mediated

• Type II: Antibodies against cell surfaces / extracellular matrix

• Type III: Immune complexes

• Type IV: Effector T cells

• Type V: Cell stimulating Antibodies

• Type VI: Cell Inhibitory Antibodies
Coombs and Gell’s Classification of Hypersensitivity

<table>
<thead>
<tr>
<th>Type</th>
<th>Immune Reactant</th>
<th>Antigen</th>
<th>Effector Mechanism</th>
<th>Example of Hypersensitivity Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE antibody, $T_{h2}$ cells</td>
<td>Soluble antigen</td>
<td>Mast-cell activation</td>
<td>Allergic rhinitis, asthma, systemic anaphylaxis</td>
</tr>
<tr>
<td>II</td>
<td>IgG antibody</td>
<td>Cell- or matrix-associated antigen</td>
<td>Complement, FcR$^+$ cells (phagocytes, NK cells)</td>
<td>Some drug allergies (eg penicillin)</td>
</tr>
<tr>
<td>III</td>
<td>IgG antibody</td>
<td>Soluble antigen</td>
<td>Complement Phagocytes</td>
<td>Serum sickness, Arthus reaction</td>
</tr>
<tr>
<td>IV</td>
<td>T cells</td>
<td>Cell-associated antigen</td>
<td>Macrophage activation</td>
<td>Contact dermatitis, tuberculin reaction</td>
</tr>
</tbody>
</table>

Allergic reactions or **hypersensitivity** cause tissue damage. Janeway, ed8, 2012

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune reactant</strong></td>
<td>IgE</td>
<td>IgG</td>
<td>IgG</td>
<td>TH1 cells</td>
</tr>
<tr>
<td><strong>Antigen</strong></td>
<td>Soluble antigen</td>
<td>Cell- or matrix-associated antigen</td>
<td>Cell-surface receptor</td>
<td>Soluble antigen</td>
</tr>
<tr>
<td><strong>Effector mechanism</strong></td>
<td>Mast-cell activation</td>
<td>Complement, FcR+ cells (phagocytes, NK cells)</td>
<td>Antibody alters signaling</td>
<td>Complement, phagocytes</td>
</tr>
<tr>
<td><strong>Example of hypersensitivity reaction</strong></td>
<td>Allergic rhinitis, allergic asthma, atopic eczema, systemic anaphylaxis, some drug allergies</td>
<td>Some drug allergies (e.g. penicillin)</td>
<td>Chronic urticaria (antibody against FcεRI alpha chain)</td>
<td>Serum sickness, Arthus reaction</td>
</tr>
<tr>
<td><strong>Type IV</strong></td>
<td>CTL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytotoxicity</strong></td>
<td></td>
<td></td>
<td>Macrophage activation</td>
<td>IgE production, eosinophil activation, mastocytosis</td>
</tr>
</tbody>
</table>

[Diagram showing immune reactant, antigen, effector mechanism, and example of hypersensitivity reaction for each type.]
Vascular Damage by Type-II Hypersensitivity

IgG reacts with epitopes on the host cell membrane. Phagocytes then bind to the Fc portion of the IgG and discharge their lysosomes.
IgG or IgM reacts with epitopes on, in, near to the host cell membrane and activates the classical complement pathway, aggravating the inflammation. Membrane attack complex (MAC) then causes lysis of the cell.
Autoimmune responses resemble hypersensitivity reactions

- **Type II**: Antibodies (Abs) against cell surfaces/extracellular matrix
- **Type III**: Insoluble immune complexes deposited in tissues
- **Type IV**: Effector T cells
Type II Hypersensitivity
Autoimmunity

Injury caused by antitissue antibody

**Mechanism of antibody deposition**
- Antibody deposition
- Antigen in extracellular matrix

**Effecter mechanisms of tissue injury**
- Complement- and Fc receptor-mediated recruitment and activation of inflammatory cells
- Neutrophils and macrophages
- Enzymes, reactive oxygen intermediates

**Tissue injury**
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Autoantigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Rh blood group antigens, I antigen</td>
<td>Destruction of red blood cells by complement and FcR⁺ phagocytes, anemia</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenic purpura</td>
<td>Platelet integrin GpIIb:IIIa</td>
<td>Abnormal bleeding</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>Noncollagenous domain of basement membrane collagen type IV</td>
<td>Glomerulonephritis, pulmonary hemorrhage</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Epidermal cadherin</td>
<td>Blistering of skin</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Streptococcal cell-wall antigens. Antibodies cross-react with cardiac muscle</td>
<td>Arthritis, myocarditis, late scarring of heart valves</td>
</tr>
</tbody>
</table>
Type III Hypersensitivity

Autoimmunity

Immune complex–mediated tissue injury

Mechanism of antibody deposition

Circulating immune complexes

Effecter mechanisms of tissue injury

Complement- and Fc receptor–mediated recruitment and activation of inflammatory cells

Blood vessel

Neutrophils

Site of deposition of immune complexes

Neutrophil granule enzymes, reactive oxygen intermediates

Vasculitis
Some common autoimmune diseases classified by immunopathogenic mechanism

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Autoantigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type III immune-complex disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed essential cryoglobulinemia</td>
<td>Rheumatoid factor IgG complexes (with or without hepatitis C antigens)</td>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DNA, histones, ribosomes, snRNP, scRNP</td>
<td>Glomerulonephritis, vasculitis, rash</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid factor IgG complexes</td>
<td>Arthritis</td>
</tr>
</tbody>
</table>
Type IV Hypersensitivity

**Delayed-type hypersensitivity**
- APC or tissue antigen
- CD4+ T cell
- CD8+ T cell
- Cytokines
- Inflammation
- Normal cellular tissue
- Tissue injury

**T cell-mediated cytolysis**
- CD8+ CTLs
- Cell lysis and tissue injury
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Autoantigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>Pancreatic β-cell antigen</td>
<td>β-cell destruction</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Unknown synovial joint antigen</td>
<td>Joint inflammation and destruction</td>
</tr>
<tr>
<td>Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis</td>
<td>Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein</td>
<td>Brain invasion by CD4 T cells, weakness</td>
</tr>
</tbody>
</table>
# Failure of vitamin $B_{12}$ absorption in pernicious anaemia

<table>
<thead>
<tr>
<th>normal</th>
<th>pernicious anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>diet</td>
<td>diet</td>
</tr>
<tr>
<td>stomach</td>
<td>parietal cell secretion</td>
</tr>
<tr>
<td></td>
<td>plasma cell secretion</td>
</tr>
</tbody>
</table>

**B$_{12}$ absorbed from gut**

**B$_{12}$ not absorbed**
<table>
<thead>
<tr>
<th>Disease</th>
<th>T cells</th>
<th>B cells</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Pathogenic Help for antibody</td>
<td>Present antigen to T cells</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Pathogenic</td>
<td>Present antigen to T cells</td>
<td>–</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Help for antibody</td>
<td>Antibody secretion</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Pathogenic</td>
<td>Present antigen to T cells</td>
<td>Present, but role unclear</td>
</tr>
</tbody>
</table>
Grandmother's Gift

Rh+

Rh-

Rh+
• *Vasculitis* is a clinicopathologic process characterized by inflammation of and damage to blood vessels.

• The vessel lumen is usually compromised, and this is associated with ischemia of the tissues supplied by the involved vessel.

• A broad and heterogeneous group of syndromes may result from this process, since any type, size, and location of blood vessel may be involved.
Potential Mechanisms of Vessel Damage in Vasculitis Syndromes

Pathogenic immune complex formation and/or deposition
- Henoch-Schönlein purpura
- Vasculitis associated with collagen vascular diseases
- Serum sickness and cutaneous vasculitis syndromes
- Hepatitis C–associated essential mixed cryoglobulinemia
- Hepatitis B–associated polyarteritis nodosa

Production of antineutrophilic cytoplasmic antibodies
- Wegener's granulomatosis
- Churg-Strauss syndrome
- Microscopic polyangiitis

Pathogenic T lymphocyte responses and granuloma formation
- Giant cell arteritis
- Takayasu's arteritis
- Wegener's granulomatosis
- Churg-Strauss syndrome
Pathophysiology and Pathogenesis

• Generally, most of the vasculitic syndromes are assumed to be mediated at least in part by immunopathogenic mechanisms that occur in response to certain antigenic stimuli.

• However, evidence supporting this hypothesis is for the most part indirect and may reflect epiphenomena as opposed to true causality.

• It is unknown why some individuals might develop vasculitis in response to certain antigenic stimuli, whereas others do not. It is likely that a number of factors are involved in the ultimate expression of a vasculitic syndrome. These include the genetic predisposition, environmental exposures, and the regulatory mechanisms associated with immune response to certain antigens.
Pathogenic Immune-Complex Formation

- Vasculitis is generally considered within the broader category of *immune-complex diseases* that include serum sickness and certain of the connective tissue diseases, of which systemic lupus erythematosus (Chap. 313) is the prototype.
Production of antineutrophilic cytoplasmic antibodies

- ANCA are antibodies directed against certain proteins in the cytoplasmic granules of neutrophils and monocytes. These autoantibodies are present in a high percentage of patients with certain systemic vasculitis syndromes, particularly Wegener's granulomatosis and microscopic polyangiitis, and in patients with necrotizing and crescentic glomerulonephritis. There are two major categories of ANCA based on different targets for the antibodies.
Production of antineutrophilic cytoplasmic antibodies

- Proteinase-3 and myeloperoxidase reside in the azurophilic granules and lysosomes of resting neutrophils and monocytes, where they are apparently inaccessible to serum antibodies. However, when neutrophils or monocytes are primed by tumor necrosis factor (TNF) or interleukin (IL) 1, proteinase-3 and myeloperoxidase translocate to the cell membrane where they can interact with extracellular ANCA. The neutrophils then degranulate and produce reactive oxygen species that can cause tissue damage. Furthermore, ANCA-activated neutrophils can adhere to and kill endothelial cells in vitro. Activation of neutrophils and monocytes by ANCA also induces the release of proinflammatory cytokines such as IL-1 and IL-8.
delayed hypersensitivity and cell-mediated immune injury
Pathogenesis of Granulomatous Inflammation (in Wegener Granulomatosis)

In Wegener granulomatosis, an inciting antigen (perhaps proteinase 3 [PR3]) activates dendritic cells. Antigen-loaded activated dendritic cells travel from the lungs to peripheral lymph nodes and present antigen to naive CD4+ T cells, which differentiate into activated antigen-specific T cells. Interleukin 12 (IL-12) produced by activated dendritic cells skew the T cells to a type 1 helper (T_H1) phenotype.
Proliferating activated T1 cells return to the lungs where antigen persists. Interferon-γ (IFN-γ) and tumor necrosis factor α (TNF-α) secreted by T1 cells (predominantly CD4+ CD8−) induce macrophage migration and maturation and eventual granuloma formation and tissue destruction.

Chronic T cell activation may promote affinity maturation of autoreactive B cells that results in secretion of PR3-antineutrophil cytoplasmic antibodies (ANCAs) in the granulomas.
• Other mechanisms such as:
  • direct cellular cytotoxicity,
  • antibody directed against vessel components,
  • antibody-dependent cellular cytotoxicity have been suggested in certain types of vessel damage.
از توجه شما متشکرم
Trauma to one eye results in the release of sequestered intraocular protein antigens

Released intraocular antigen is carried to lymph nodes and activates T cells

Effector T cells return via bloodstream and encounter antigen in both eyes

Figure 13-13 Immunobiology, 6/e. (© Garland Science 2005)
These Sites Sequester Self Antigens, But Few Autoimmune Diseases Are Due to Release Of Hidden Self Antigens.
پارامترهای چند مفهوم:

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Hapten</th>
<th>Immunogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
<td>+</td>
<td>محور سیستم ایمنی</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>واکنش‌گرها محصولات آن</td>
</tr>
</tbody>
</table>

Antigen: بیولوژیکا لازم به توجه، که با واکنش‌گرها به آن واکنشی می‌گیرد.
Hapten: نیازمند واکنش یکنواخت با واکنش‌گرها.
Immunogen: واکنش‌گرها برای واکنش با آن واکنش می‌کنند.
THANKYOU FOR YOUR ATTENTION