Autoimmune Diseases: Goodpasture’s Syndrome and more

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Autoimmune diseases are a group of disorders that are characterized by abnormal reactions of the immune system against one’s own body. These usually manifest during the middle years and are, most of the time, chronic. Approximately 3.2% of the global population is composed of people who are afflicted with these, being generally more common among women.

Introduction to Autoimmune Diseases

Etiology of Autoimmune Diseases
A lot of factors are implicated in the development of autoimmune diseases. For example, environmental factors such as diet and lifestyle have been found to be associated with their development. Physiologic and emotional stress have also been known to influence the gravity of the diseases.

Overall it is more frequent in females (e.g.♀ : ♂ Systemic lupus erythematosus 10 : 1). Although it can be more common in males (e.g.♀ : ♂ Ankylosing spondylitis 0.5 : 1).

**Immune Tolerance and Autoimmune Regulator**

In a healthy human being, the immune system is known to possess a characteristic that keeps autoimmune diseases at bay: its non-reactivity to self-antigens. This physiologic indifference is called **tolerance**. This property is achieved through various mechanisms.

**Central immunological tolerance to self-antigens**

During lymphoid development, several numbers of lymphocytes are produced. However, this production is far from perfect and some potentially self-reacting immature lymphocytes can be produced along with viable ones. Fortunately, lymphoid organs such as the **thymus** (for T cells) and the **bone marrow** (for B cells) are made up of self-antigens. A significant amount is also brought in by the blood. These antigens are helpful in determining which among the immature lymphocytes are unreactive to healthy cells within the body and are good to go.

During the maturation process, developing lymphocytes are put to test by reacting with these self-antigens. Those which do react with the self-antigen are deleted by **apoptosis**.
This process is called **negative selection**.

The whole mechanism is only effective if self-antigens present in all of the parts of the body are present in the tissues involved in central tolerance. If the immature lymphocytes are only exposed to an insufficient amount of self-antigens, they would still attack the own body once deployed in the circulation.

**Peripheral immunological tolerance to self-antigens**

Although efforts are already employed in the generative lymphoid tissues in order to prevent the proliferation of self-reacting lymphocytes, some potentially autoimmune-disease causing cells do escape the system and enter the circulation.

The good thing is that the selection of functional lymphocytes fit for reacting only with harmful foreign pathogens does not end in the thymus and bone marrow. In peripheral tolerance, lymphocytes are continually screened for self-reactivity. This is made possible with the help of the peripheral tissues such as the lymph nodes, through **anergy**, **T cell suppression** or through **deletion**.

Anergy or functional unresponsiveness still involves the reaction of a self-reacting cell to a self-antigen but without the boost coming from the innate immunity. The self-reacting cell does not necessarily die but it becomes permanently unresponsive to the self-antigens from the rest of the body.

It is also established that helper T cells have the ability to block the self-reactivity of some mature T cells. This is possible because T cells contain inhibitory receptors in their surfaces that are responsible for binding to molecules unique to self-reacting T cells. The 2 receptors that are known to do this are **CTLA-4** and **PD-1**. The latter is connected with cellular death or apoptosis.

**The autoimmune regulator in the thymus**

As mentioned, the thymus contains antigens that are important in the development of a functional repertoire of **self-antigen-indifferent T cells**. These molecules are similar to the ones found in peripheral tissues and could sometimes actually come from the organ of origin delivered via the blood. In addition to this, the thymus could also produce antigens that mimic the ones found in the periphery. This is made possible by the **autoimmune regulator (AIRE) gene**. Production is mainly in the **medullary epithelial cells** of the thymus.
Genetic Susceptibility to Autoimmune Diseases and Mechanisms

Many studies have already proved that genetic polymorphisms are commonly involved in the development of autoimmune diseases. Afflicted individuals are found to have inherited multiple alleles necessary for them to confer susceptibility to a certain autoimmunity. This genetic component works with environmental factors in order to bring about manifestations of autoimmunity.
Examples of autoimmune disease susceptibility genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC CTLA4</td>
<td>Antigen presentation to T-cells</td>
<td>Nearly all polygenic autoimmune diseases</td>
</tr>
<tr>
<td></td>
<td>Immune regulation</td>
<td>Thyroid autoimmune diseases, type I diabetes,</td>
</tr>
<tr>
<td>PTPN22</td>
<td>Antigen receptor signaling</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>C1q, 2, 4</td>
<td>Complement</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>IL-2</td>
<td>Lymphocyte stimulation</td>
<td>Rheumatoid arthritis, type I diabetes, multiple sclerosis</td>
</tr>
<tr>
<td>IL-10</td>
<td>Inhibition</td>
<td>Systemic lupus erythematosus, rheumatoid arthritis</td>
</tr>
<tr>
<td>BLK</td>
<td>B-cell signaling</td>
<td>Systemic lupus erythematosus, rheumatoid arthritis</td>
</tr>
</tbody>
</table>

MHC alleles

**Major histocompatibility complexes** or **MHCs** are **surface proteins** found on lymphocytes that are important in determining whether a substance is foreign or not. It is encoded by the **human leukocyte antigen** or **HLA gene**.

These two have been the **most established genetic risk factor** when it comes to autoimmune diseases. It has been found out that susceptible individuals actually have an increased amount of polymorphisms in the HLA allele. This fact hastens the screening and diagnosis of some autoimmune disease with the help of **serologic testing techniques**.

Although many studies have already established the link between HLA gene polymorphisms and autoimmune diseases, it is noteworthy that even healthy individuals may have these. This goes to prove that HLA polymorphisms have to go along with environmental factors to manifest autoimmunity.

**MHC associations in autoimmune disease**

<table>
<thead>
<tr>
<th>Disease</th>
<th>MHC association</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC class I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>HLA-B8</td>
<td>3</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>HLA-B27</td>
<td>87</td>
</tr>
<tr>
<td>MHC class II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hashimoto’s disease</td>
<td>HLA-DR5</td>
<td>3</td>
</tr>
<tr>
<td>Type I disease</td>
<td>HLA-DQ8</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>HLA-DQ8 and HLA-DQ2</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>HLA-DQ6 (protective)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Polymorphisms in non-HLA genes**

In the same way, not all people afflicted with an autoimmune disease have higher counts of HLA polymorphisms when compared to healthy individuals. This is where variants in the genes coding for phenotypes that might work along with other risk factors come in. These alleles are usually involved in the regulation of **lymphocyte production**, **differentiation**, and **maturation**.
Inherited single-gene (Mendelian) abnormalities

Although somewhat rare compared to polymorphisms, single-gene abnormalities can be very pervasive and can readily manifest in individuals carrying the mutations. Most of the time, these mutations affect the mechanisms involved in **tolerance** and **lymphocyte regulation**. In specific, these Mendelian abnormalities can cause alterations in central tolerance, **production of regulatory T helper lymphocytes**, **anergy** and in **peripheral deletion of autoimmune B and T lymphocytes**.

Types of Autoimmune Diseases

Autoimmunity can take on **various forms in various locations** in the body. It has been known to manifest itself on the **blood components** (red blood cells and platelets); the **kidney** and **lungs**, **endocrine glands**, **muscles**, **connective tissues**, **nervous system**, and the **gastrointestinal tract**, among others.

There had been numerous cases of various autoimmune diseases that are already documented in the world today. They may come as a **single complication** or as a **syndrome**. Examples of which are listed below:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Major consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ disease</td>
<td>Autoantibodies: Stimulatory anti-TSH receptor Results in <strong>Hyperthyroidism</strong></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Inflamed joints</td>
</tr>
</tbody>
</table>

- **TSH receptor**

  - Thyroid epithelial cell
<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Autoantibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto´s disease</td>
<td>Thyroid peroxidase, thyroglobulin Lymphocytic infiltration of the thyroid</td>
<td>Thyroid peroxidase, thyroglobulin Lymphocytic infiltration of the thyroid</td>
</tr>
<tr>
<td></td>
<td>Destruction of thyroid tissue ⇒ Hypothyroidism</td>
<td>Destruction of thyroid tissue ⇒ Hypothyroidism</td>
</tr>
<tr>
<td>Sjögren´s syndrome</td>
<td>Reduced secretory gland function</td>
<td>Reduced secretory gland function</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Vitamin B12-deficient anemia</td>
<td>Vitamin B12-deficient anemia</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Demyelination</td>
<td>Demyelination</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Inflammation of spine and sacroiliac joints</td>
<td>Inflammation of spine and sacroiliac joints</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>Autoantibodies: insulin, glutamic acid decarboxylase, insulinoma antigen-2 (IA-2), zinc transporter 8</td>
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</tr>
<tr>
<td></td>
<td>Lymphocytic infiltration of the pancreas</td>
<td>Lymphocytic infiltration of the pancreas</td>
</tr>
<tr>
<td></td>
<td>Destruction of β-cells in islets of Langerhans ⇒ Hyperglycemia</td>
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</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Skin, heart, joints, lungs, kidney, brain</td>
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</tr>
</tbody>
</table>

**Goodpasture’s Syndrome**

A rare autoimmune disease, Goodpasture’s syndrome, involves both the **lungs** and the **kidneys**. This disease is essentially characterized by the **destruction of the type IV collagen** found in the basement membrane of the renal glomeruli and pulmonary alveoli which rapidly causes **inflammation** to these structures. It manifests as **rapidly progressive glomerulonephritis** and **necrotizing hemorrhagic interstitial pneumonitis**. Unlike most autoimmune diseases, it occurs among the younger population (teens or 20s) and is more common in men. It is known as AntiGBM disease.
Pathogenesis of Goodpasture’s syndrome

In Goodpasture’s syndrome, autoantibodies that target the basement membrane of glomeruli cause damages in the glomeruli. These antibodies specifically have a high preponderance to the noncollagenous domain of the α3 chain of the type IV collagen. It is known as Goodpasture’s antigen. This particular collagen is required for the maintenance of the structure of the glomeruli.

The antibodies that have destroyed the glomeruli can cross-react with the basement membranes of other organs in the body. This is where pneumonitis in Goodpasture’s come into the picture. Since the structure of the alveoli is destroyed by the same antibodies, inflammatory processes ensue in this area.

The genetic component of this disease is associated with some polymorphisms, in particular, HLA subtypes. It is also speculated that this disease has to be manifested after exposure to physiologic stress such as viral infections, hydrocarbon solvent inhalation, and smoking. This is to make the antigens that trigger the basement membrane-damaging antibodies more available to the antibodies.

Clinical manifestations of Goodpasture’s syndrome

Goodpasture’s syndrome can be exhibited through pulmonary and renal signs and symptoms. During the disease’s process, patients suffering from the disease could show the following manifestations:

- Hemoptysis
- Focal pulmonary consolidations in the chest x-ray
- Hematuria
- Foam formation in the urine
- Edema
- Uremia

Therapy of Autoimmune Diseases

The approach to the treatment of autoimmune diseases is very diverse. Since problems in the immunity take on a lot of forms and can affect various parts of the body, drugs and other treatment modalities have been developed in order to come up with a selection of highly specific treatment choices that can be customized per patient.
These treatment modalities have also greatly improved the prognosis of the once fatal diseases. An example of which is **plasmapheresis** in Goodpasture's syndrome. This technology involves the **removal of circulating antibodies and other mediators in the plasma**, thereby keeping the exaggerated immune component of the blood from destroying both the lungs and the kidneys. **Immunosuppressive medications** that are given **in conjunction to plasmapheresis** could also greatly halt the development of complications caused by Goodpasture's syndrome. This combination can also be used in other autoimmune disorders.

Deciding which treatment modality among the hundreds of ways to tackle autoimmunity to include in the treatment regimen would mean that a deeper understanding of the disease progression of the autoimmune disorder should be observed. This is to ensure a safe and efficient curative and rehabilitative period.

Other forms of therapeutic approach to autoimmune diseases are listed below:

- Replacement of missing component such as thyroxine (Hashimoto's disease), insulin (type 1 diabetes mellitus), and vitamin B₁₂ (pernicious anemia)
- Inhibition of hormone production through surgery or chemical suppression
- Thymectomy
- Pharmacologic agents such as anticholinesterase drugs, cytokine agonists and inhibitors, adhesion molecule inhibition, disease-modifying antirheumatic drugs, non-steroidal anti-inflammatory drugs, steroids, anti-B cells, anti-mitotic drugs
- Pooled normal immunoglobulin (such as in Guillain-Barre syndrome and myasthenia gravis).

**Review Questions**

The correct answers can be found below the references.

1. **Which of the following statements correctly describes negative selection in central tolerance?**

   A. Mature lymphocytes that react with self-antigens are sent back to the thymus and blood marrow for destruction and disposal from the circulation.
   
   B. After exposure to self-antigens in the thymus, reactive T lymphocytes are inactivated or set off for apoptosis.
   
   C. Autoantibodies in the organs involved in central tolerance (thymus and bone marrow) are specific to antigens coming from the same organs.
   
   D. None of the above

2. **Which of the following is correct about the genetic component of the pathogenesis of autoimmune disorders?**

   A. Mendelian single-gene mutations are very common among patients suffering from autoimmune disorders.
   
   B. The presence of multiple allele polymorphisms in the HLA gene is a cause of immediate concern due to possible overt autoimmune manifestations.
   
   C. The development of autoimmunity is a cross between genetic abnormalities and environmental factors.
   
   D. Non-HLA polymorphisms are responsible for abnormalities in the encoding of MHCs needed for antigen identification of lymphocytes.

3. Goodpasture's syndrome is characterized by a simultaneous immunologic
attack on the renal glomeruli and pulmonary alveoli. Which of the following describes the pathogenesis of this disorder?

A. Autoantibodies destroy the type IV collagen that maintains the structure of glomeruli and alveoli.
B. Immune complexes deposit on the glomeruli and alveoli, resulting in localized inflammatory reactions.
C. Helper T cells identify the cells lining the glomeruli and alveoli as non-self and trigger a cascade of inflammatory reactions.
D. None of the above

References


Correct answers: 1B, 2C, 3A

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