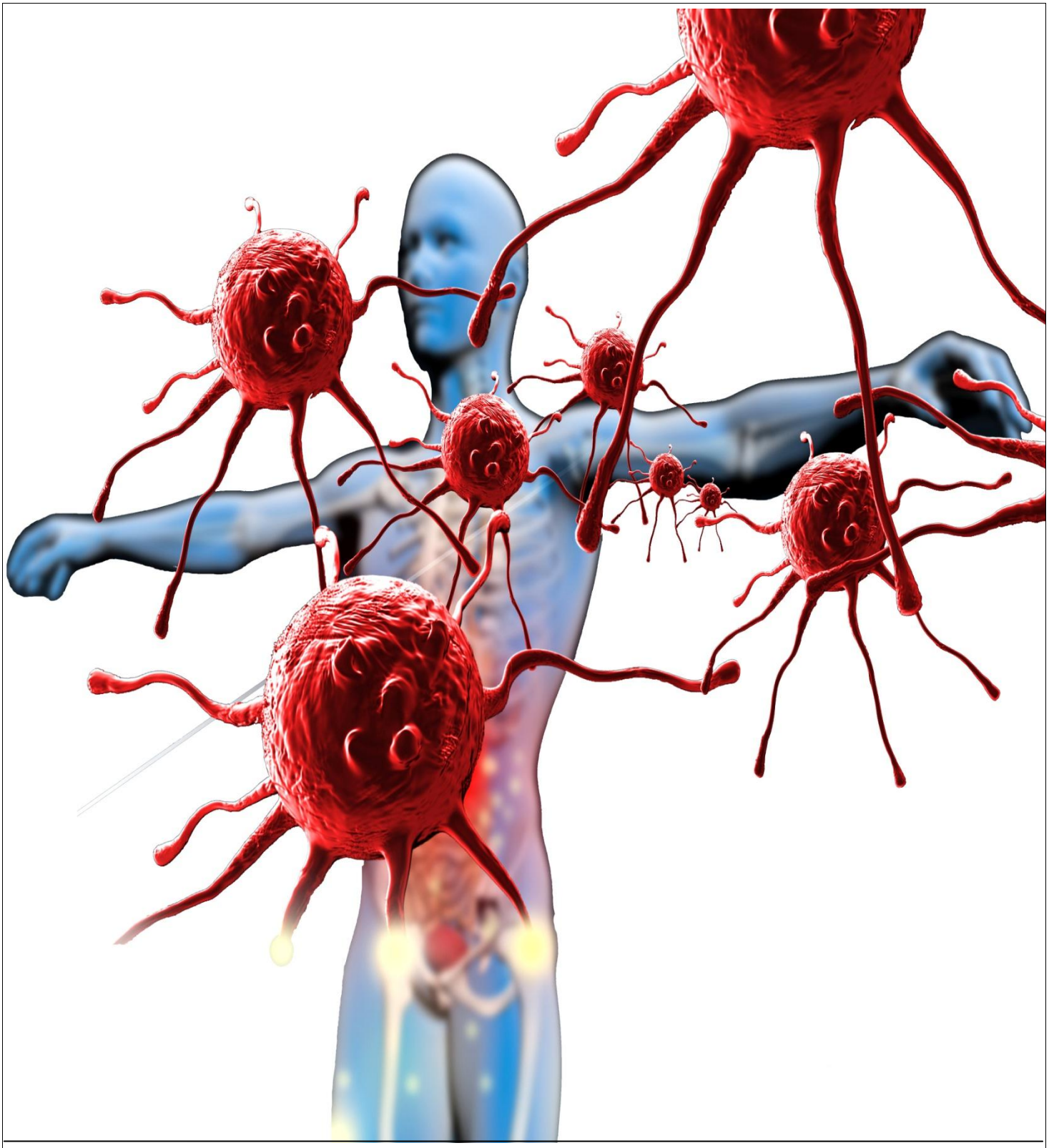

IMMUNOLOGY

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#20

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Immunodeficiency Syndromes

Continued

In the previous lecture, in the discussion of immunodeficiency, we found that:

- It is either **acquired** (and this form is **more common**, the main cause in many countries is **malnutrition**, in addition to HIV, and other infections) or **inherited** (and this one is actually **rare**).
- The hereditary syndromes may include:
  I – Complement deficiency;
  II – Phagocytic immunity deficiency;
  III – B-Cell-associated or immunoglobulin-associated deficiencies;
  IV – T-cell-associated deficiencies;
  V – Severe Combined Immunodeficiency Diseases (SCID) involving both B and T cells.

Here we continue the discussion of the last three types:

III) B-Cell-Associated or Immunoglobulin-associated Deficiencies

These include:

1- Bruton's Agammaglobulinemia (discussed)
2- Transient Hypogammaglobulinemia of Infancy (discussed)

3- Selective IgA Deficiency

- Is relatively quite **common**, with an incidence of 1:700 of people suffering from the disease. While other hereditary deficiencies are very rare (having incidences of 1 in a million or 1 in 20 thousands).

Remember that: IgA is the second major Immunoglobulin in the serum, it is also found as a dimer in secretions to prevent infections through several mucosal surfaces. And is delivered to the infant in milk.

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- A problem in the conversion of B cells into plasma cells that produce IgA
- The patients can be completely **normal**. But some may suffer with recurrent **upper respiratory tract infections**.
- They have a tendency to develop **allergies and autoimmune diseases**.
- They are **not given blood transfusions**, instead, they are **only given packed red blood cells** that have been washed. Whole blood contains IgA, and these people may have **allergic reactions** to this IgA and anaphylactic reactions (their immunity has never seen IgA before).

4- Selective IgG Deficiency

- It involves a **certain subclass**, the most common being the ones affecting **IgG_2 and IgG_3**. IgG_4 may happen, and IgG_1 is very rare. However if IgG4 deficiency happens, it is not actually a problem and has **no symptoms of immunodeficiency**, while those of 2 and 3 can cause immunodeficiency symptoms.

Remember that: IgG is the major Ig in the serum. It is found in 4 subclasses, numbered according to occurrence. IgG2 doesn't cross the placenta and IgG4 doesn't activate complement. IgG is also important in opsonization and ADCC.

5- X-Linked Hyper-IgM Syndrome

- Absence of **CD40L** of T cells, and thus, no isotype switching by B cells.
- Consequently, levels of **IgM are high**. IgM is normally produced upon exposure to polysaccharide antigens (T-independent), however in this case, the absence of class switching to other classes in other antigens (T-dependent) also makes the levels of **IgG and IgA (and IgE) very low**.
- **X-linked**, so only men are affected.

Remember that: CD40L is found on the surface of T cells, and is bound to its receptor (CD40) on the surface of APCs. It is involved in the activation of APCs (increase respiratory burst in macrophages and activation, affinity maturation and class switching in B cells.)

6- Common Variable Immunodeficiency

- Is relatively more **common**.
- Is **variable in onset**. You know that, generally, inherited diseases have early onset in life. However in this disease, the onset of symptoms occurs between the **ages of 15 and 30** years (late).
- Unknown cause. B cells are normally found in the blood but they are unable to produce antibodies.
- May have predilection to **autoimmune** diseases and some **allergies**.

7- Good Syndrome

- A Hypogammaglobulinemia associated with **thymoma**. The mechanism is not fully understood.
- It occurs in adults around the **40s and 50s**.

> **Remember that**: Tumors usually increase with old age.

8- Selective IgM Deficiency

- These people **do not have IgM**, yet they still have the other Igs normally. This is contradictory, since we know that all B cells initially express IgM then may switch to another class of Igs. The reason behind this is unknown. (Yes, immunology is rich with mysteries).

IV) T-Cell-Associated Deficiencies

1- DiGeorge Syndrome

- A congenitally inherited condition, due to abnormal development of the **3rd and 4th pharyngeal pouches** (these are supposed to give rise to the thymus gland, parathyroids, part of the heart, and part of the face).
- So, absence of the thymus causes the **absence of T cells** and thus the immunodeficiency. Some of them **might fully recover** if left untreated in the 3rd, 4th or 5th years of life. This might be due to some bits of thymus that become active, or that the function of the absent thymus is taken over by an ectopic tissue. Otherwise, they might be treated with **thymus transplant**.

- Additional problems include: absence of the parathyroids causing **hypocalcaemia**. Face malformation, in the lower jaw, and these are described as **fish-faces**. **Cardiac abnormalities**.

2- Chronic Mucocutaneous Candidiasis

- Is a deficiency in a certain, **small, population of T cells** that are involved in immunity against the fungus ***Candida albicans***. Other T cells that deal with other microorganisms are normal. **Antibodies as well are all normal**, including those against *Candida albicans*. So there is an impaired **cell-mediated immunity** against candida albicans.
- It is thought that it might be a kind of an **autoimmune** disease, since it is sometimes associated with some **endocrinopathies**, and if you consider the thymus as an endocrine organ, you may explain the disease as an autoimmune disease involving endocrine glands including the thymus and causing a deficiency in certain T-cell populations.

V) Severe Combined Immunodeficiency Diseases (SCID)

- Combined since they affect **both T and B cells**. They include a variety of syndromes.

1- X-Linked SCID:

- Are **50%** of all SCID.
- Associated with the absence of the **γ-chain of the interleukin-2 receptor** (interleukin receptor has 3 chains; α (CD25 of T regulatory cells), β and γ). Knowing that this chain is found in many interleukin receptors and not only that of IL-2.
- T cells will not function properly, and this will consequently affect the function of B cells (Production of Abs) and NK cells.

2- JAK3 Kinase deficiency

- Are **10%** of all SCID, and are autosomal recessive.
- **JAK3 kinase** (Just Another Kinase 3) is involved in signal transduction to many immune cells.

3- Omenn Syndrome

- Are **30%** of all SCID, and are autosomal recessive.
- **RAG1 and RAG2** enzymes are deficient, the enzymes responsible for gene rearrangement of B and T cells.

4 - Enzyme deficiencies:

- **Adenosine Deaminase** Deficiency & **Purine Nucleoside Phosphorylase** Deficiency.
- Cause accumulation of toxic metabolites in cells including B and T cells.

5 - Ataxia Telangiectasia:

- Ataxia means **loss of balance**, telangiectasia means development of **blood capillaries in abnormal sites**.
- Are autosomal recessive deficiency on **chromosome 11** causing an **impaired DNA repair**, thus affecting many cells, including neurons and causing several neuronal deficiencies that are mainly manifested as an infection in the cerebellum (hence the ataxia). Also blood vessels might be affected causing telangiectasia (abnormal growth of blood vessels) especially in the face and conjunctiva. Of course, there is immunodeficiency.

Remember that: Ataxia Telangiectasia is a disease caused by a mutation in the gene for a protein called ATM that detects DNA damage and induces the damage response mediated through p53. It is associated with high chances of neoplasia.

6 - Wiskott–Aldrich Syndrome:

- **X-linked**, and involves a **triad** of symptoms:
- 1) A deficiency of **WASP** (Wiskott-Aldrich Syndrome Protein), a protein involved in signal transduction in conjunction with a cell surface molecule (**CD43**) which is also absent, affecting activation of T cells, with consequent **SCID**.
- 2) Also, **platelets** are reduced in number and small in size, thus patients have bleeding disorders.
- 3) **Eczema** can also develop.

7 – Bare Lymphocyte Syndrome

- A deficiency of **MHC molecules**.
- If MHC class I are absent, this causes a deficiency in CD8 cells.
- If MHC class II are absent, this causes a deficiency in CD4 cells.
- **Or both** would be absent, with deficiency of both cells.

Remember that: by the end of negative selection in the thymus, double positive T cells become single positive keeping one CD (4 or 8) molecule according to the MHC molecule it interacted with (II or I).

We should be very careful with patients with SCIDs:

- Diagnosis should be made as early as possible, so that they are **not given any live vaccines** (in fact, any immunodeficient person should not be given a live vaccine, but SCIDs in particular are very vulnerable). For example, many viral vaccines are actually attenuated "live" viruses that may cause infections in SCIDs.
- **No blood transfusions** in SCID, since the blood might contain WBCs like T lymphocyte that can attack the body without being stopped by the immunity causing **GVHD** (**graft versus host disease**). However, they can be given **irradiated** blood that doesn't contain any WBCs.

This sheet in a nutshell:

B-cell problems (problems of antibodies, problems of humoral part of acquired immunity):

- Bruton's Agammaglobulinemia.
- Transient Hypogammaglobulinemia of Infancy.
- Selective IgA: common, might be normal, and might have URT infections, allergies (as in blood transfusion, so only packed RBCs) and autoimmune diseases.
- Selective IgG: IgG2 and 3 are most common and have symptoms, IgG4 and 1 are rare and not symptomatic.
- X-linked Hyper-IgM: no CD40L, no class switch, only IgM is produced largely, rest are very low.
- Common variable: common, variable (late in life), no Igs, can have autoimmune and allergy.
- Good syndrome: thymoma causing little Igs, happens late in life.
- Selective IgM: Only IgM is NOT produced (opposite of XL Hyper-IgM).

T-cell problems (problems of the cell-mediated part of acquired immunity)

- DiGeorge syndrome: 3rd and 4th pharyngeal pouches abnormal: no thymus (no T cell, but might recover later), no parathyroid (no calcium), lower jaw and heart problems.
- Chronic mucocutaneous candidiasis: no T cell immunity to *Candida albicans*, maybe autoimmune destruction of thymus.

SCID

- 50% are X-linked (no γ chain of IL receptor)
- 10% are JAK3 kinase (JAK3 kinase transmits signal from IL receptor)
- 30% Omenn syndrome (RAG1 and RAG2)
- Other enzymes (AD and PNP)
- Ataxia telangiectasia (impaired DNA repair)
- Wiskott-Aldrich syndrome (X-linked) Triad of (no WASP or CD43 causing SCID, bleeding, and eczema)
- Bare lymphocyte syndrome (no MHC)
- In SCID, all are AR except for two are X-linked, no live vaccine, no blood transfusion (only irradiated).
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The End

Live