Casual Friday Presents

Autoimmune Mechanisms Pt 1 (key players)

A BIOGENETIX CLINICAL PRESENTATION

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The Increasing Prevalence of Autoimmunity and Autoimmune Diseases: An Urgent Call to Action for Improved Understanding, Diagnosis, Treatment and Prevention

Frederick W Miller [1]

Autoimmunity is characterized by self-reactive immune components and autoimmune disease by autoimmunity plus pathology. Both autoimmunity and autoimmune diseases are dramatically increasing in many parts of the world, likely as a result of changes in our exposures to environmental factors. Current evidence implicates the momentous alterations in our foods, xenobiotics, air pollution, infections, personal lifestyles, stress, and climate change as causes for these increases. Autoimmune diseases have a major impact on the individuals and families they affect, as well as on our society and health care costs, and current projections suggest they may soon take their place among the predominant medical disorders. This necessitates that we increase the scope and scale of our efforts, and coordinate our resources and studies, to understand autoimmune disease risk factors and pathogeneses and improve our diagnostic, therapeutic, and preventive approaches, as the costs of inaction will be profound and far greater without such investments.

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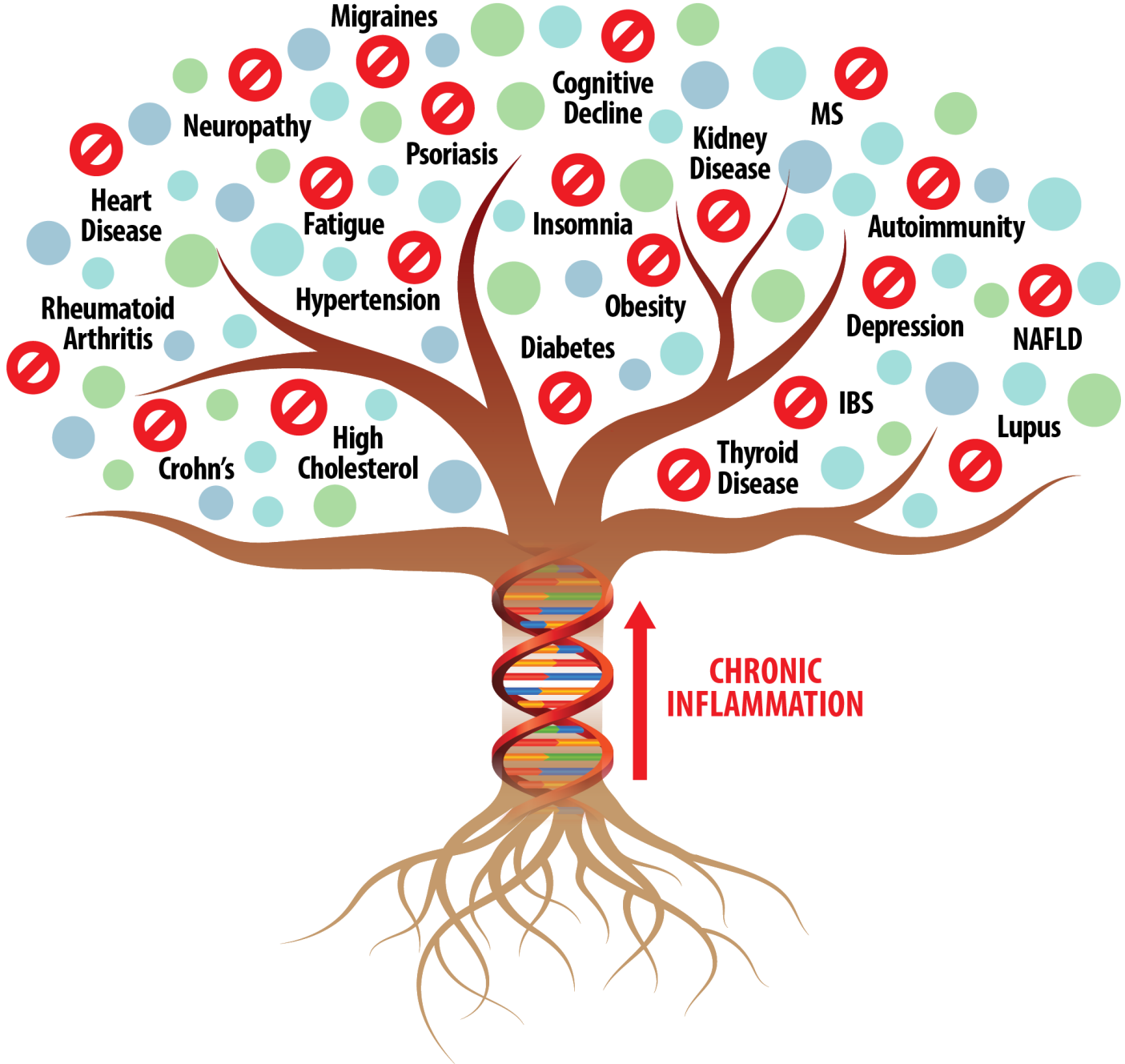
The precise mechanisms for the development of autoimmunity and autoimmune diseases remain unclear, however, a growing consensus has developed that they evolve from still-to-be-defined gene-environment interactions [5,6]. As a result of technological advances made possible by the human genome project and related investigations, many genetic risk factors for autoimmune diseases have been identified [7], but there has been relatively little progress in deciphering the even more profound impact of environmental influences [8,9]. This is not surprising given the difficult tasks of assessing the doses, durations, and effects of the myriad combined environmental exposures we experience over a lifetime [10] and the complex impacts they have on the maturation and function of the immune system [11].

Studies have found increased frequencies of autoimmunity and autoimmune diseases over recent decades [12,13]. Yet, there are many challenges in accurately assessing changes in the incidence and prevalence of autoimmunity and autoimmune diseases over time. First, as noted above, there is a lack of universal consensus on definitions of cases and disease criteria [3]. Secondly, many autoimmune disorders individually are rare and heterogeneous conditions that are likely underdiagnosed, with evidence of varying ethnic, racial, and geographic distributions, making current estimates of their actual numbers problematic [14–16]. Third, there are inadequate centralized and standardized national and international databases on which to base these estimates, and there are referral biases to tertiary care centers from which much of our current information arises. Methodologies for autoantibody and other immune assays are constantly evolving, and each varies in accuracy, sensitivity, and specificity [17]. Finally, with increased understanding, classification and diagnostic criteria for some autoimmune diseases have evolved over time [18].


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Crohn's
High Cholesterol
Lupus
Thyroid Disease
CHRONIC INFLAMMATION

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Familial clusterings and recent molecular genomic advances clearly show the importance of genetic factors in the development of autoimmune diseases [7]. Nonetheless, most genes are neither good nor bad, but only their environments make them so. Moreover, our genetic architecture, which has evolved over millennia to allow us to thrive in prior environments, may in many ways be ill-suited to our rapidly changing modern environmental challenges. The contemporary consensus is that in autoimmune disorders, multiple genetic and environmental risk factors interact in complex ways over long time spans to induce disease evolution from the genetic risk factor stage, to subclinical immune activation and autoimmunity, to early clinical signs and symptoms, and to finally result in a phenotype meeting classification or diagnostic criteria [5,29–31].

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The innate immune system: Fast and general effectiveness

Go to:

The innate immune system is the body's first line of defense against intruders. It responds in the same way to all germs and foreign substances, which is why it is sometimes referred to as the "non-specific" immune system. It acts very quickly – for instance, it makes sure that bacteria that have entered the skin through a small wound are detected and destroyed on the spot within a few hours. But the innate immune system can't always stop germs from spreading.

The innate immune system provides

- protection offered by the skin and mucous membranes
- protection offered by immune system cells and proteins

Protection offered by the skin and mucous membranes

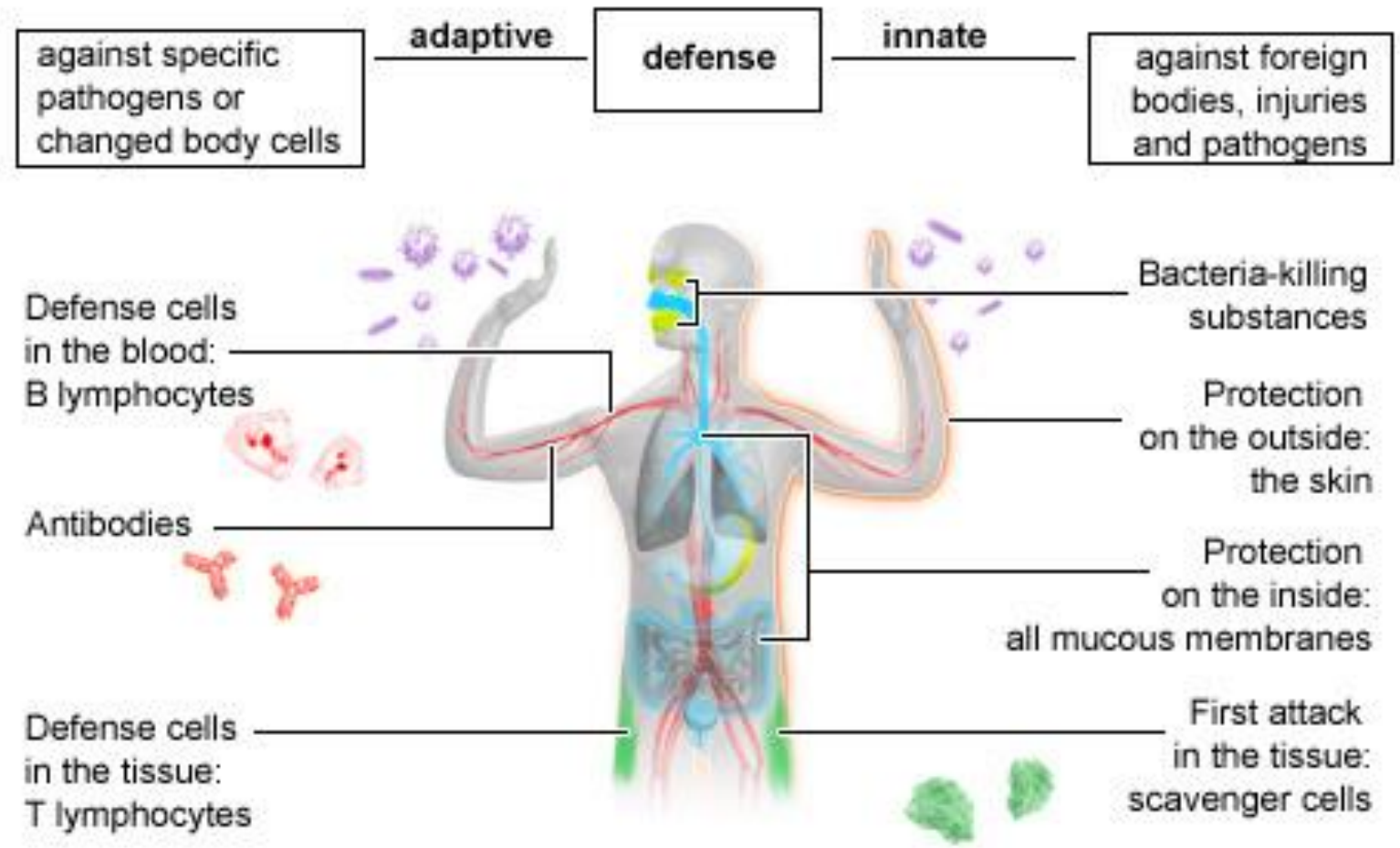
Go to:

All outer and inner surfaces of the human body are a key part of the innate immune system. The closed surface of the skin and mucous membranes already forms a physical barrier that stops germs from entering. On top of that, substances like acid, enzymes and mucus prevent bacteria and viruses from growing. Certain movements in the body also stop germs from settling – for example, movements of hair-like structures (cilia) in the lungs or movements of the bowel muscles. Some fluids in the body have a similar effect – including tear fluid, sweat and urine (which flushes the organs of the urinary system).

Protection offered by immune system cells and proteins

Go to:

If germs get past the skin or mucous membranes and enter the body, the innate immune system fights them using special immune system cells and proteins.



https://www.ncbi.nlm.nih.gov/books/NBK279396/

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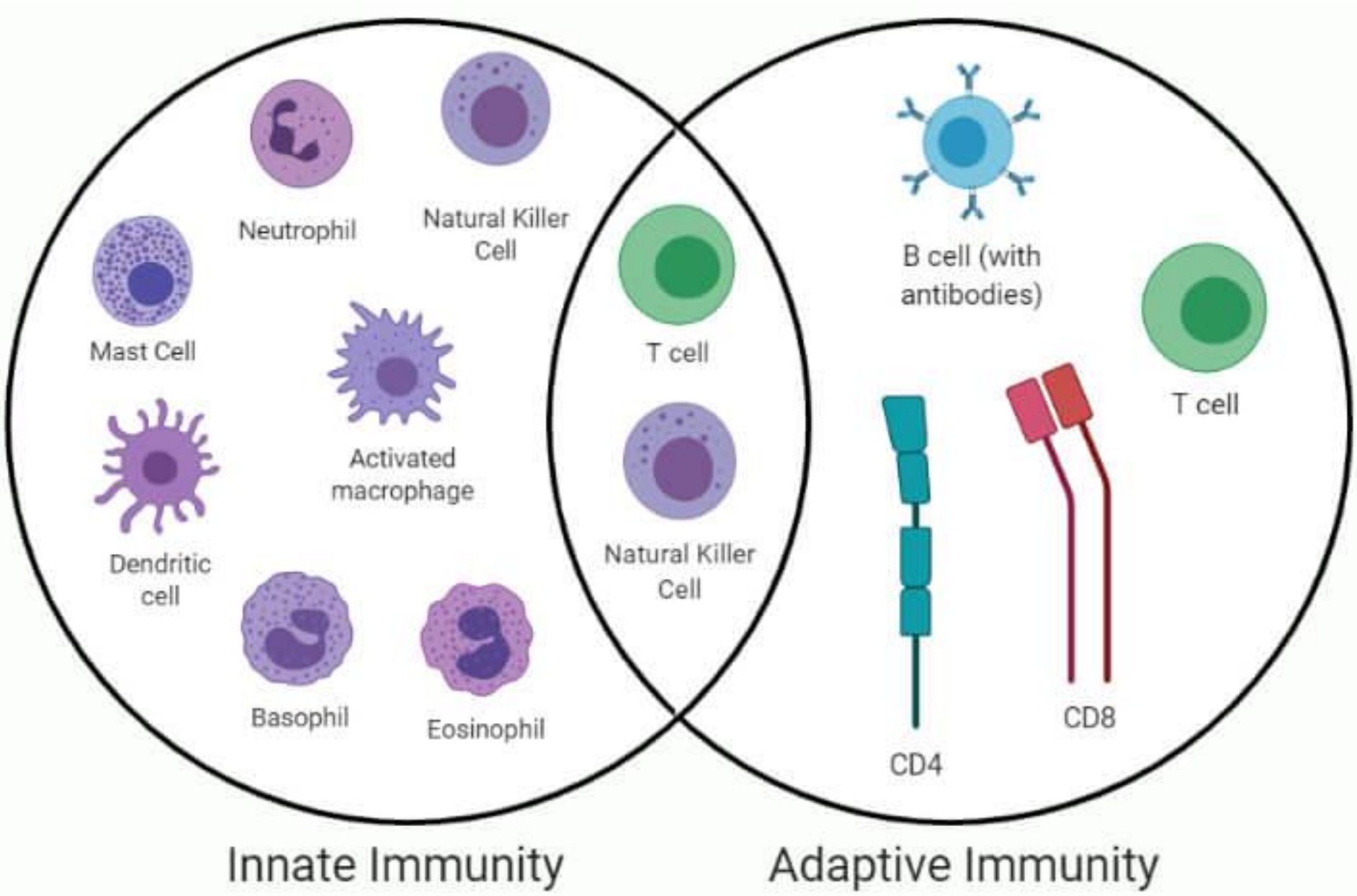
Several proteins (enzymes) help the cells of the innate immune system. A total of nine different enzymes activate each other in a kind of chain reaction: One enzyme in the first stage alerts several enzymes in a second stage, each of which activates several enzymes in a third stage, and so on. This allows the immune response to grow stronger very quickly.

The tasks of these enzymes include:

- marking germs as targets for phagocytes,
- attracting other immune system cells from the bloodstream,
- destroying bacteria cell walls to kill the bacteria, and
- fighting viruses by destroying the viral envelope (the outermost layer of a virus) or cells that have been infected with viruses.

The natural killer cells are the third major part of the innate immune system. Their main job is to identify cells that have been infected by a virus, as well as abnormal cells that may turn into (or have turned into) tumor cells. To do this, they search for cells with an abnormal surface, and then destroy the cell surface using substances called cytotoxins.


Neutrophil
Natural Killer Cell
Mast Cell
Activated macrophage
Dendritic cell
Basophil
Eosinophil
T cell
Natural Killer Cell
B cell (with antibodies)
T cell
CD4
CD8
Innate Immunity
Adaptive Immunity

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The adaptive immune system: Fighting the germs directly

Go to:

If the innate (general) immune system fails to destroy the germs, the adaptive (specialized) immune system takes over. The adaptive immune system specifically targets the type of germ that is causing the infection. But to do that, it first needs to recognize the germ as such. This means that it's slower to respond than the innate immune system, but it's more accurate when it does respond. It also has the advantage of being able to "remember" germs. So the next time the adaptive immune system faces a germ it has already met, it can start fighting the germ faster.

This memory is also the reason why there are some illnesses you can only get once in your life, because afterwards your body becomes "immune" to them. It may take a few days for the adaptive immune system to respond the first time it comes into contact with the germ, but the next time the body can react immediately. The second infection then usually goes unnoticed, or is at least milder.

The adaptive immune system is made up of:

- T cells in the tissue between the body's cells
- B cells (also in the tissue between the body's cells)
- Antibodies in the blood and other bodily fluids

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T cells

Go to:

T cells (also called T lymphocytes) are made in bone marrow. They travel in the bloodstream to the thymus, where they mature. The "T" in their name comes from "thymus."

T cells have three main jobs:

- They use chemical messengers to activate other cells of the immune system, starting the adaptive immune system response (T helper cells).
- They detect tumor cells or cells that have been infected by viruses and destroy them (cytotoxic T cells).
- Some T helper cells become memory T cells after the infection has cleared up. They "remember" the germ that was fought off, and are then ready to activate the adaptive immune system quickly if the body is infected by the same germ again.

T cells have specific features (receptors) on their surfaces that germs can attach to – like a lock that one particular key will fit. The immune system can make a matching T cell type for each germ within a few days of infection.

Then if a germ attaches to a matching T cell, the T cell starts to multiply – making more T cells that can specifically fight that germ. Because only the cells that match the germ multiply, the immune response is “tailor-made.”

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B cells

Go to:

B cells (B lymphocytes) are made in the bone marrow, where they mature into specialized immune system cells. They take their name from the "B" in "bone marrow." Like the T cells, there are many different types of B cells that match particular germs.

B cells are activated by T helper cells: T helper cells send signals to B cells that match the same germs as they do. This stimulates the B cells to make copies of themselves and turn into plasma cells. The plasma cells quickly make very large amounts of antibodies and release them into the blood. Because the T helper cells only activate the B cells that match the attacking germs, the body only makes the exact antibodies that are needed.

Some of the activated B cells turn into memory cells and become part of the "memory" of the adaptive immune system.

The different cells of the adaptive immune system communicate either directly or through soluble chemical messengers such as cytokines (usually proteins). These chemical messengers are made by various cells in the body.

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Antibodies

Go to:

Antibodies (proteins with sugar groups attached to them) travel around the body in the bloodstream. They are made by the immune system to fight germs and foreign substances. Antibodies can quickly recognize germs and other potentially harmful substances, and then attach to them. This makes the "intruders" harmless and attracts other immune system cells to help. Antibodies are made by B cells. Germs and substances that can trigger the production of antibodies are called "antigens."

An antibody only attaches to an antigen if it matches exactly, like a key in the lock of the antibody. In this way, antibodies recognize matching germs and trigger the fast response of the adaptive immune system.

Antibodies have three main functions:

- They make germs harmless – for example, by directly attaching to the cell surface of viruses or bacteria, or by binding harmful substances made by these germs. This prevents the germs from latching onto normal body cells and infecting them.
- They activate other immune system cells by attaching to their surface. Also, it's much easier for phagocytes to fight off germs that have a lot of antibodies attached to them.
- They activate proteins that help in the immune system response.

So the antibodies of the adaptive immune system also help the innate immune system to do its job.

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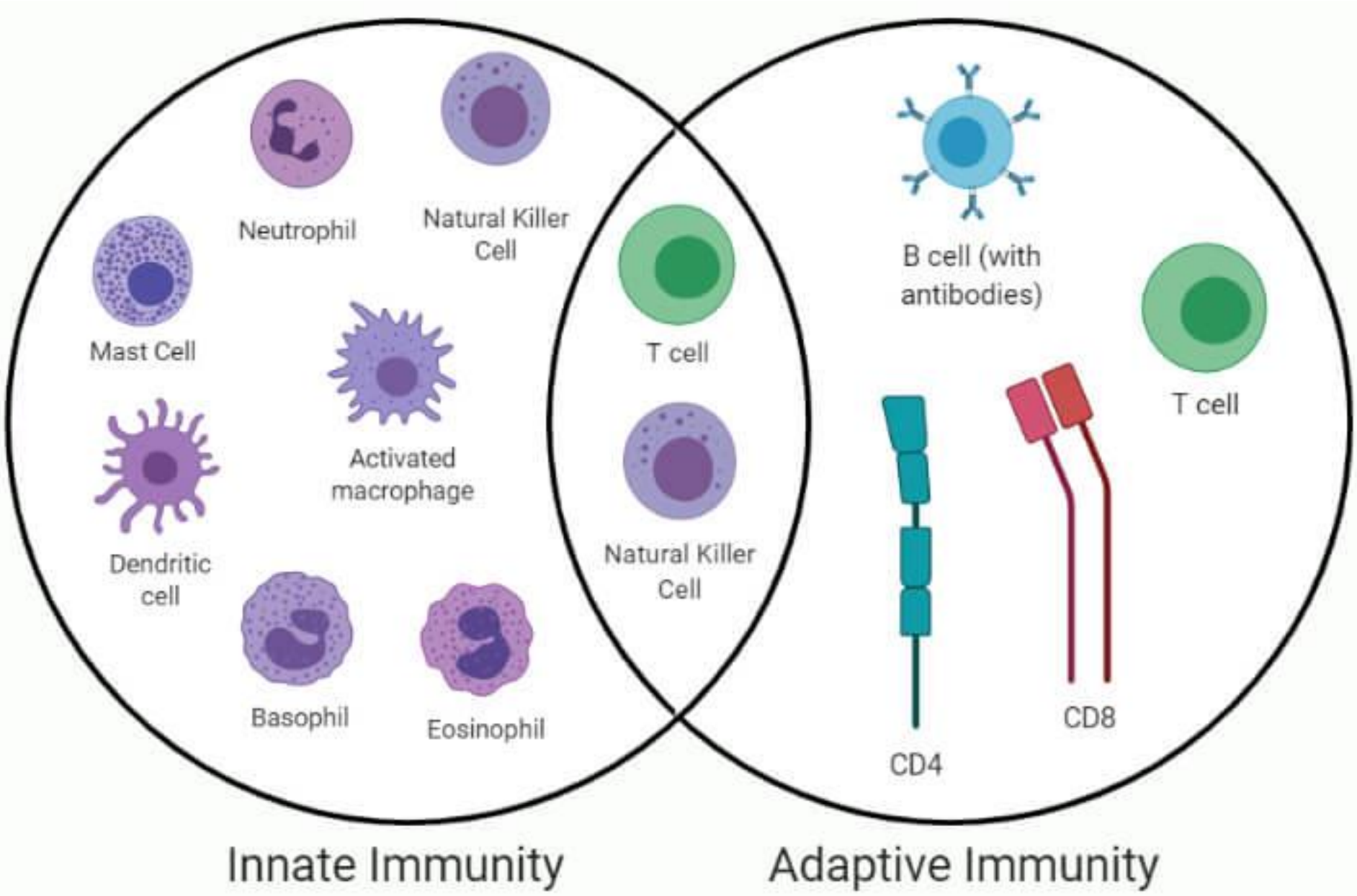
Neutrophil
Natural Killer Cell
Mast Cell
Activated macrophage
Dendritic cell
Basophil
Eosinophil
T cell
Natural Killer Cell
B cell (with antibodies)
T cell
CD4
CD8
Innate Immunity
Adaptive Immunity

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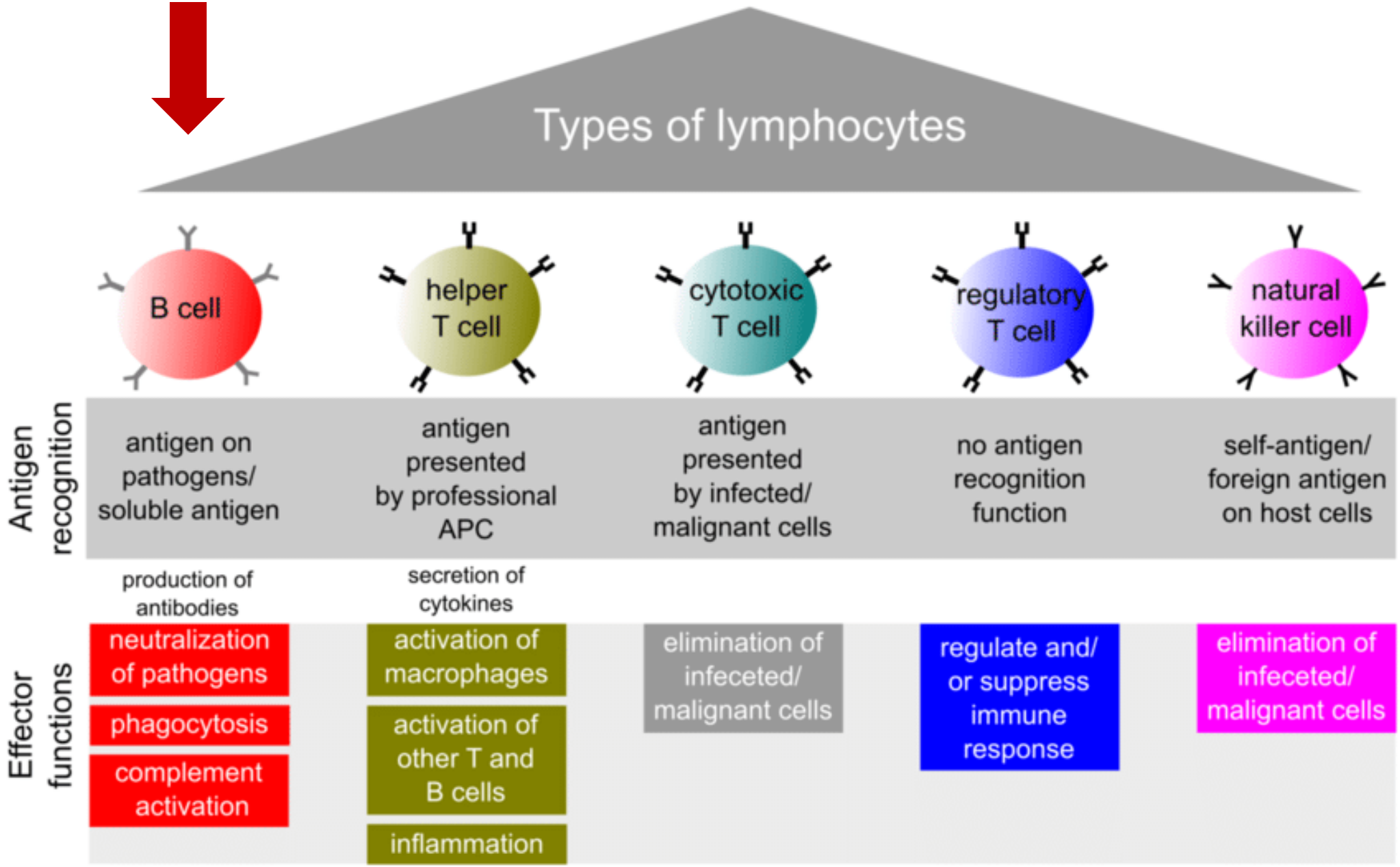

https://www.researchgate.net/publication/280663544/figure/fig2/AS:792466320019456@1565950102293/Types-of-lymphocytes-and-their-effector-functions-The-lymphocyte-family-includes-five.png

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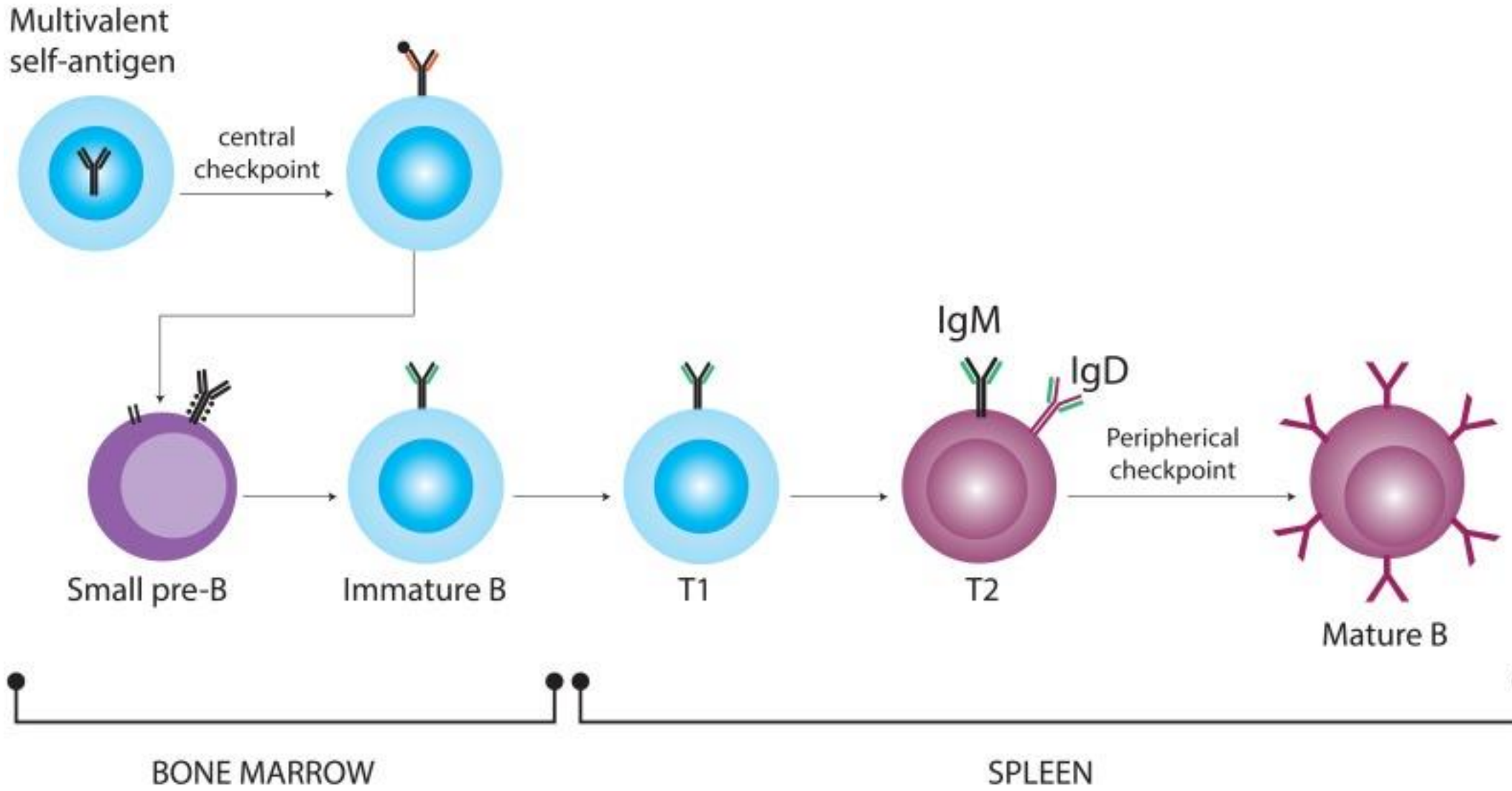
B lymphocytes are the effectors of humoral immunity, providing defense from pathogens through different functions including antibody production. B cells constitute approximately 15% of peripheral blood leukocytes and arise from hemopoietic stem cells in the bone marrow (BM). It is here that their antigen receptors (surface immunoglobulin) are assembled. In the context of autoimmune diseases defined by B and/or T cell auto-reactive that upon activation lead to chronic tissue inflammation and often irreversible structural and functional damage; B lymphocytes play an essential role by not only producing auto-antibodies but also functioning as Antigen-Presenting Cells (APC) and as a source of cytokines. In this chapter, we describe B lymphocyte functions in autoimmunity and autoimmune diseases from ontogenesis to targeted therapies in this group of pathologies.

This mechanism is essential for maintaining non-responsiveness to thymus-independent self-antigens such as lipids and polysaccharides. B cell tolerance is also important in preventing the development of antibody responses to protein antigens. Both central and peripheral mechanisms are implicated in B cell tolerance. In the central tolerance, the immature B lymphocytes that recognize self-antigens in the BM with high affinity are deleted or active mechanisms to change their specificity by receptor editing. This fate is defined by the strength of BCR signaling: a strong BCR signal by binding with high affinity to an autoantigen will lead to deletion or receptor editing while an intermediate binding affinity will permit B cells to survive and continue to the periphery (34).

Receptor editing is a major mechanism of central tolerance in B cells. Immature B cells in the BM that encounter multivalent self-antigens revert to pre-B stage, and continue to rearrange κ and, if necessary, λ light chain genes, and generate newly generated B cells that have a novel light chain that is no longer self-reactive. Immature B cells with novel light chains that are no longer part of a self-reactive BCR migrate to the periphery as BT1cells where they mature into newly generated IgM and IgD expressing recirculating BT2 cells and, then, into mature recirculating B cells.

If a mature B cell recognizes self antigens in peripheral tissues without specific helper T cell response, this cell may be functionally inactivated by anergy mechanisms or die by apoptosis. The AICDA is required for B cell tolerance in humans. This enzyme is required for CSR and somatic hypermutation. Patients with AICDA deficit develop primary immunodeficiencies and autoimmune complications. Single B cells from AICDA-deficient patients show an abnormal Ig repertoire and high frequencies of auto-reactive antibodies (35).



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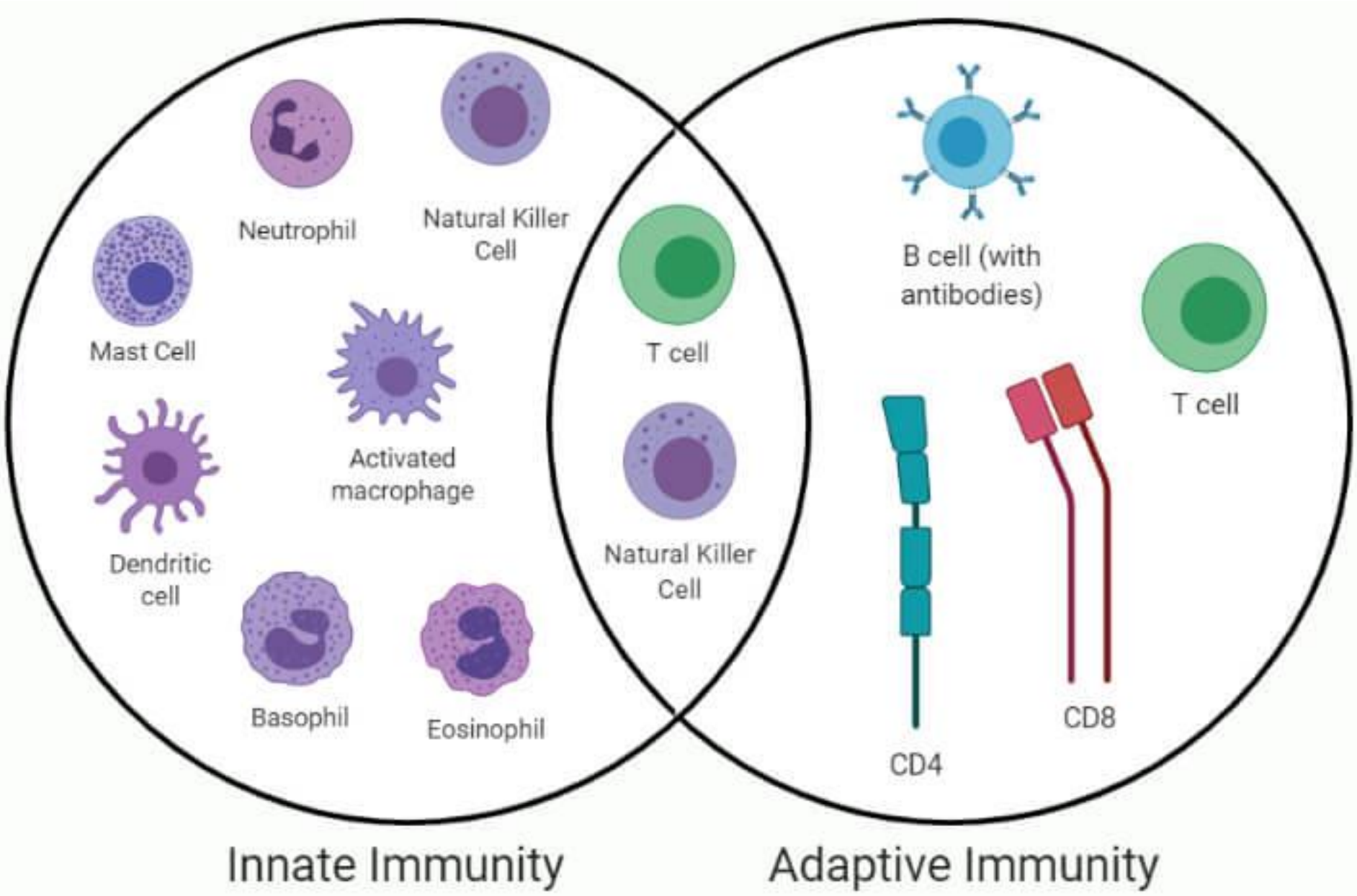
Neutrophil
Natural Killer Cell
Mast Cell
Activated macrophage
Dendritic cell
Basophil
Eosinophil
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Natural Killer Cell
B cell (with antibodies)
T cell
CD4
CD8
Innate Immunity
Adaptive Immunity

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