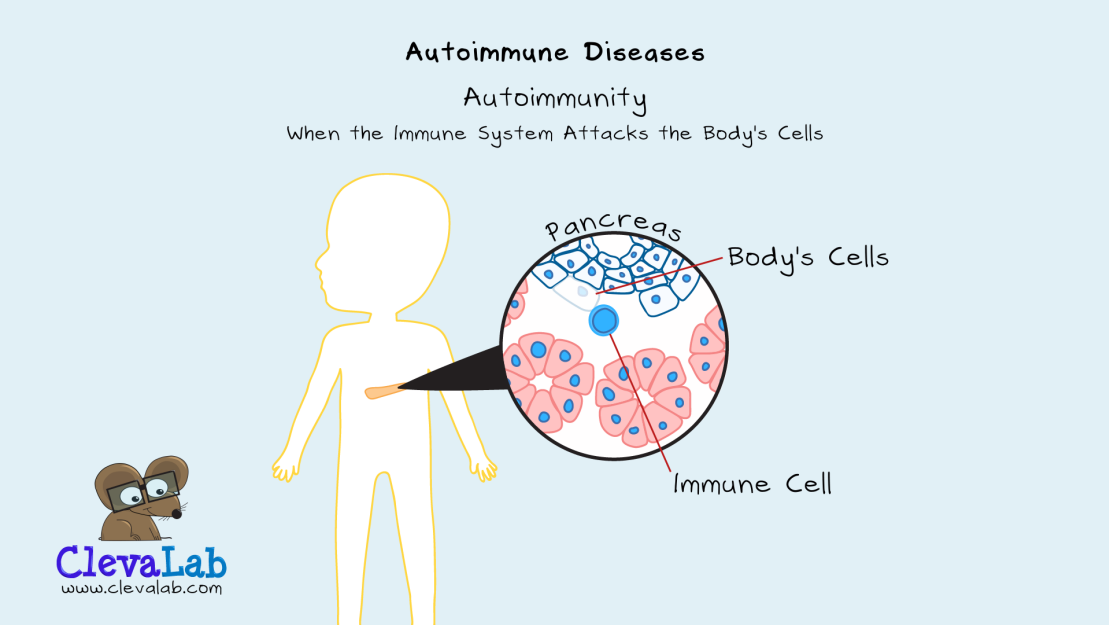
ClevaLab
Explaining the Why of Biology

What Is Autoimmune Disease & How Does it Develop?

More than 100 autoimmune diseases affect 5-10% of people worldwide, yet most people don't know what's actually happening inside their body when the immune system turns on itself. This post explains what autoimmune disease is, how autoreactive B and T-cells develop and escape immune tolerance, and why mechanisms like molecular mimicry and epitope spreading can trigger disease. Watch the YouTube video or read on below to find out more.

What is Autoimmune Disease?

In autoimmune diseases, the body's immune system attacks the body's cells. This attack on the self by the immune system is called autoimmunity. There are more than a hundred autoimmune diseases. Some include Type 1 diabetes, Multiple Sclerosis, Lupus and Rheumatoid Arthritis. They can affect one organ, such as the pancreas in Type I Diabetes or the whole body, as in Lupus. 80% of all people diagnosed with autoimmune diseases are women. But it is unknown if this is due to hormones or genetic differences between men and women.

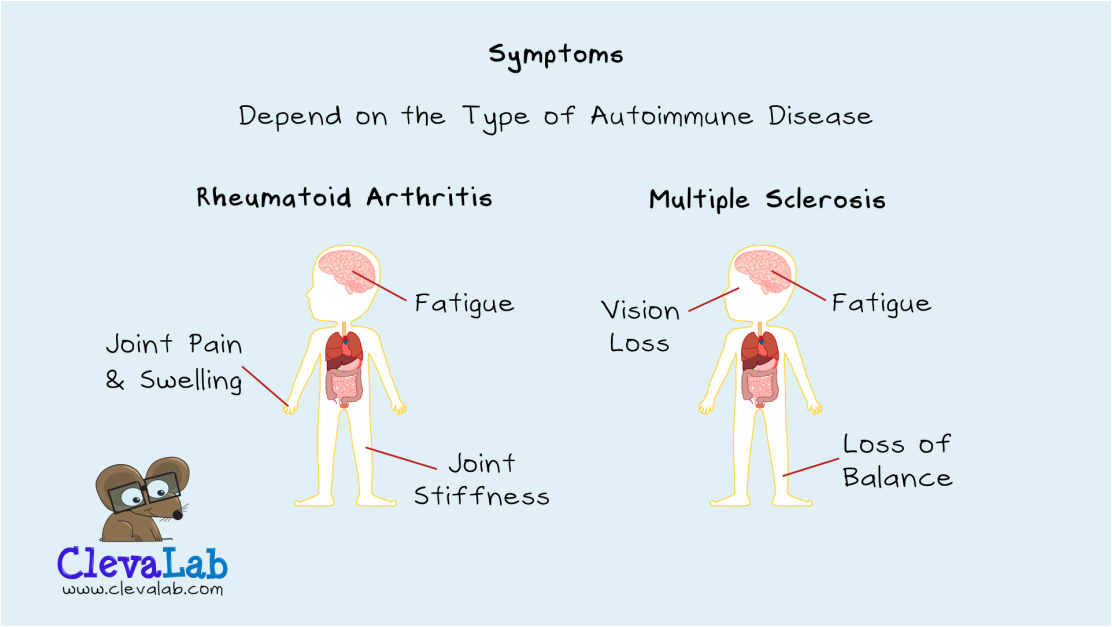


What Is the Risk of Getting an Autoimmune Disease?

The risk of getting an autoimmune disease depends on genetics and environmental exposures. Environmental exposures include viruses, bacteria, diet and drugs. These exposures may be driving the increase in autoimmune diseases each year. Currently, autoimmune diseases affect 5 to 10% of people worldwide.

Symptoms of Autoimmune Diseases:

Symptoms experienced will depend on the type of autoimmune disease. For example, in rheumatoid arthritis, there is fatigue, joint stiffness, pain and swelling. In Multiple Sclerosis, there is fatigue, vision loss, and loss of balance.



How Are Autoimmune Diseases Diagnosed?

Diagnosis of autoimmune diseases involves looking at many factors. Some include symptoms, a full blood count, inflammatory markers, autoantibodies and MHC testing.

Autoantibodies are detectable in the blood years before the onset of symptoms. Yet, not all people with autoantibodies develop an autoimmune disease. For example, 10-45% of people have antinuclear antibodies, but not all go on to develop an autoimmune disease. Unfortunately, the genetic and environmental components that create an autoimmune disease remain unknown.

Autoimmunity - How Does It Happen?

Autoimmunity can result from both autoimmune antibodies and autoimmune T-cells. But a healthy person's immune system doesn't attack its tissues. This non-reactivity to self-tissues is immune tolerance. There are many checkpoints to remove self-antibodies and T-cells. But if these checkpoints fail, autoimmunity or loss of tolerance can occur.

So, where do things go wrong? First, let's look at how antibodies and T-cells get made. And also how autoantibodies and self-T-cells could emerge. Antibodies bind and neutralise pathogens or mark them for removal by the immune system. B-cells are the source of antibodies in the body. New B-cells arise from stem cells in the bone marrow. And it's in the bone marrow that the antibody the B-cell will make gets set. But, before leaving the bone marrow, B-cells get tested for autoreactivity. If they react to self-antigens, they die. If not, they move to the spleen. In the spleen, immature B-cells get exposed to self-antigens and

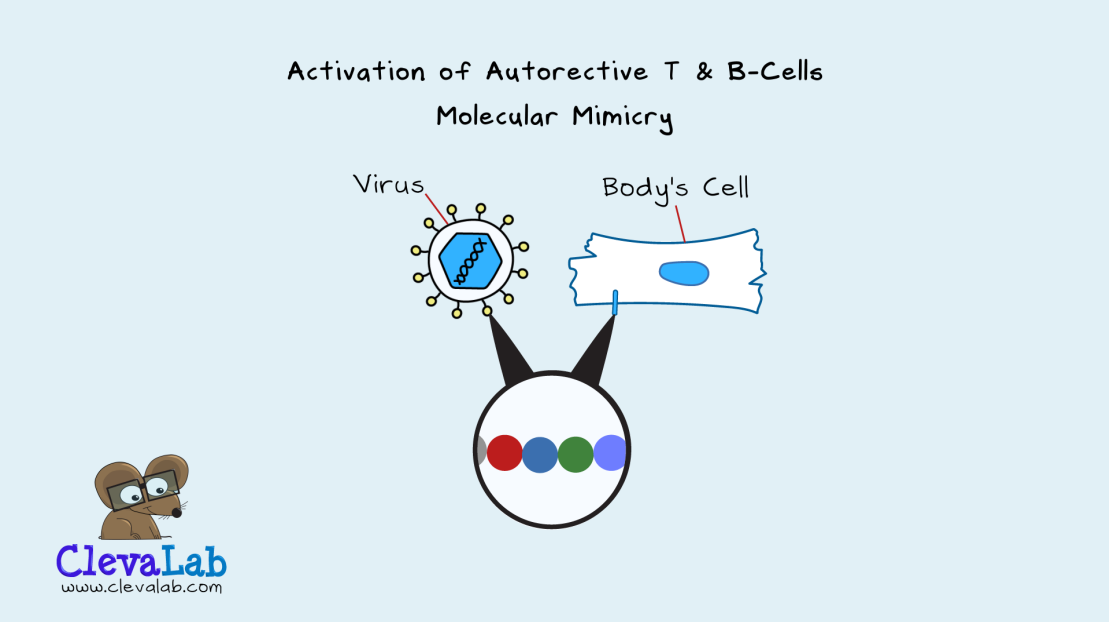
die if they react. They then get released and move to the lymph nodes to await an infection. Autoreactive B-cells arise if there's an error at these self-antigen checkpoints.

This process of tolerance also happens for T-cells. A killer T-cell's job is to recognise foreign peptides on cell surfaces and kill the cells. A helper T-cell's job is to identify foreign peptides and help B-cells make antibodies. With the help of killer and helper T-cells, the body can fight infections both inside and outside of cells. T-cells originate from stem cells in the bone marrow. Then, they migrate to the thymus, where they mature. Here they get exposed to self-antigen, and any self-reactive T-cells will die. Some self-reactive T-cells can leave the thymus. But, a T-cell that recognises self-antigen without tissue inflammation will die.

How Are Autoreactive Cells Switched On?

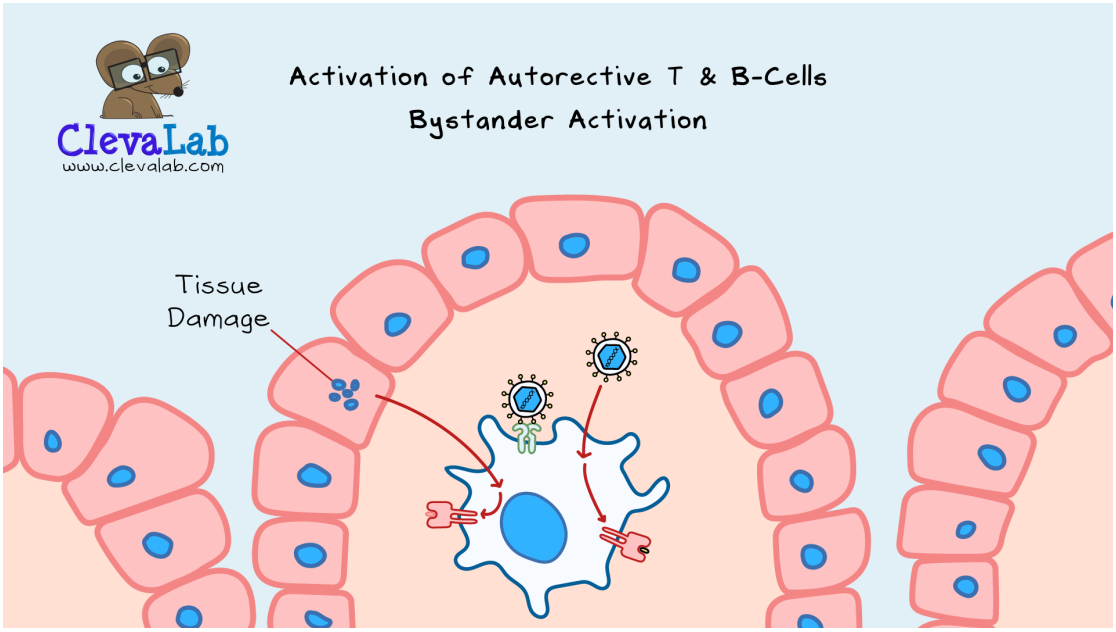
Once autoreactive B and T-cells are present in the body, they can become activated in several ways. Some include molecular mimicry, bystander activation and epitope spreading.

Molecular mimicry is when a viral or bacterial peptide is like a self-peptide. A peptide is a short part of a protein. Shared peptides between viral and human proteins are high. So these shared peptides can activate self-B and T-cells to attack both virus and normal cells.

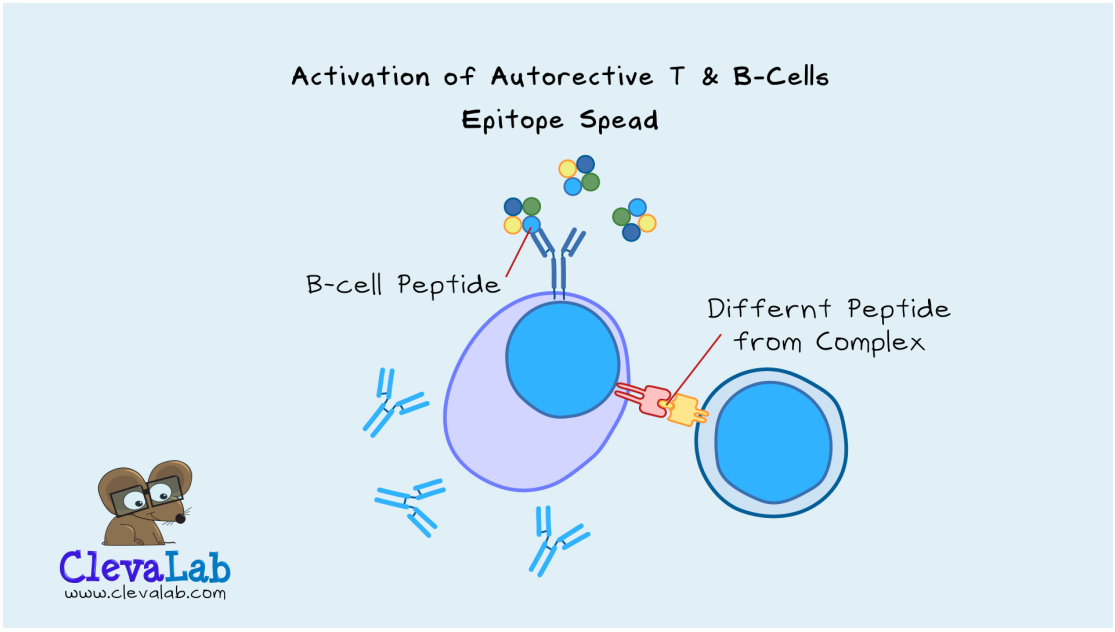


But there must also be inflammation before B and T-cells can get activated. Dendritic cells, the sensing cells of the immune system, detect infections. Pathogens activate dendritic cells via their pattern recognition receptors. It is only activated dendritic cells that can trigger B and T-cells. But, tissue damage means that dendritic cells can also take up self-antigens. If the pattern recognition receptors also activate this dendritic cell. It can then activate autoimmune and viral B and T-cells. This activation of autoimmune cells is bystander activation.

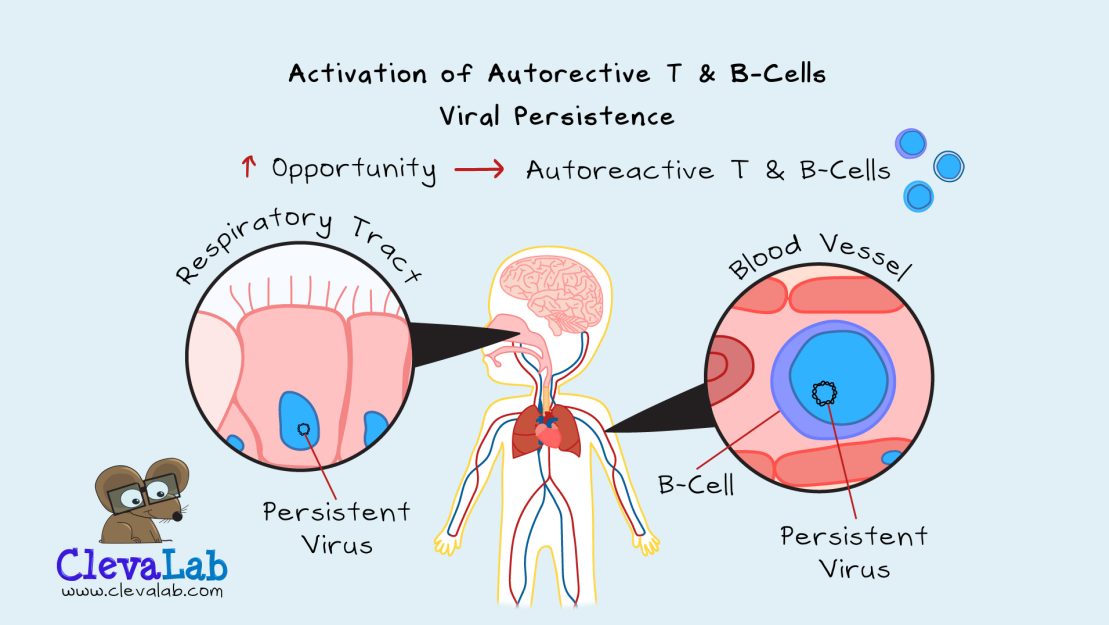
The B-cell receptor is capable of binding and processing protein complexes. So it can internalise groups of proteins and show these to T-cells. The T-cell activating the B-cell doesn't need to match the same peptide as the B-cell. So a T-cell activated due to molecular mimicry can then activate B-cells producing



other antibodies. So long as the original peptide is present in the complex. This spreading of antibodies can also happen within parts of the same protein. For example, let's take a cell surface receptor. Let's assume that there's an autoantibody for the internal part of the receptor. A B-cell can take in the whole receptor during tissue damage and present these as peptides to T-cells. Autoreactive T-cells targeting the outer part of the receptor then get activated. In turn, they can activate B-cells reactive to many other sites on the receptor. These antibodies can bind to the receptor always present and exposed to the immune system. Antibodies that bind the exposed proteins could lead to more prolonged inflammation. Epitope spread is the name given to this process. Epitope spreading leads to more inflammation and disease progression in autoimmune diseases. Autoimmune diseases likely develop due to more than one of these mechanisms.

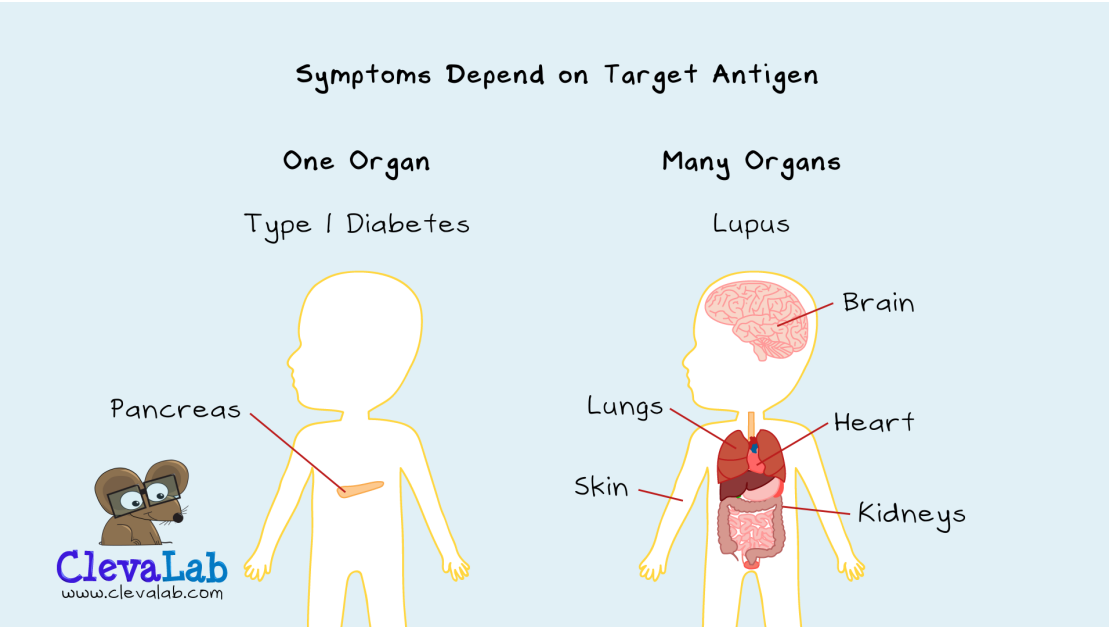


Another possible contributor to developing an autoimmune disease is viral persistence. In some people, some viruses persist within cells, and the immune system cannot remove them. This constant activation of the immune system allows for more opportunities over a person's lifetime to activate an autoreactive T or B-cell.



Autoimmune Disease Symptoms Depend on Their Target:

The symptoms caused by these autoreactive T-cells or autoantibodies depend on their target. A target present in only one organ, like in Type I Diabetes, will limit the damage to one organ, the pancreas. But if the target exists in many organs, as in Lupus, then autoantibodies can cause damage to many organs. In Lupus, the autoantibodies target proteins in the cell's nucleus. So Lupus can affect all cells of the body.



Unfortunately, there is no cure for autoimmune diseases. While we know that viruses, bacteria, and genetics play a role, we don't know the exact cause of disease. So treatments focus on reducing symptoms and inflammation. Examples include immunosuppressants, steroids and NSAIDs. We need more research into why people develop autoimmune diseases. The development of targeted therapies depends on more knowledge about the causes.

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