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# IMMUNITY – A BALANCE BETWEEN ATTACK AND DEFENSE

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Everything has its price – especially health, of course. At the Max Planck Institute for Evolutionary Biology in Ploen, Tobias Lenz and his team are researching what the evolutionary costs of perfect immunity might be and why we are not immune to all pathogens.

We've rarely been so keen to discuss pathogens and immunity as we are right now. The corona pandemic has highlighted the importance of having a robust immune system. But why do viruses, bacteria, and other microbes overcome our body's defenses time and time again? Isn't all-inclusive protection possible, and how much would it cost? Tobias Lenz and his team are analyzing the battle between defenders and attackers. They use computer-based approaches to investigate how the immune system reacts to pathogens, such as leprosy bacteria and HI viruses. Their research focus is on "MHC" genes.

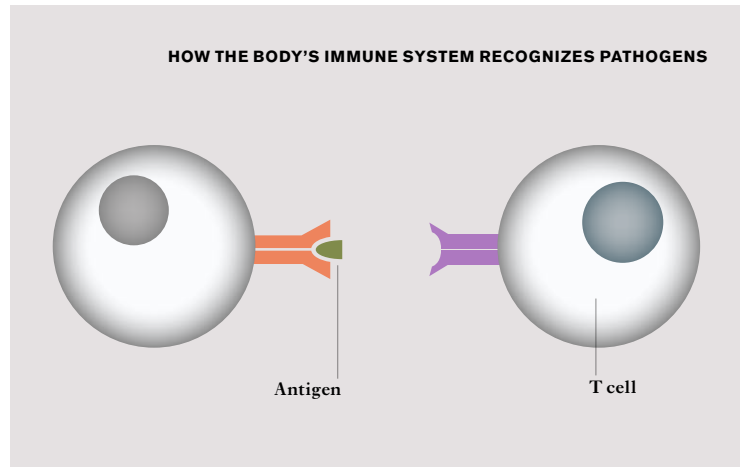
MHC stands for "major histocompatibility complex" and refers to a group of genes possessed by all vertebrates. Humans possess six such genes, here named "human leukocyte antigen" (HLA). They encode proteins that are responsible for the immune system's ability to recognize invaders. These proteins bind molecular fragments that are left behind by pathogens that have penetrated cells and that are displayed, like in a shop window, on the cell surface. Patrolling immune cells recognize them as foreign molecules and put the immune system on alert.

**"It might well be that we possess too many HLA genes for the modern day life we live today."**

TOBIAS LENZ

However, given the sheer immeasurable multitude of viruses, bacteria, fungi, and other parasites, how do such a small number of genes succeed in ensuring that barely any invaders avoid detection? The key lies in these genes' extremely high variability. They are the most variable genes in the entire genome. "The HLA-B gene, one of the human MHC genes, for instance, has more than 4000 known variants," says Tobias Lenz.

The MHC genes encode the information for the production of proteins on the surface (orange) of an immune cell. These can bind to molecular fragments from a virus, referred to as antigens, from the interior of a cell and present them to a T cell of the immune system (right). The T-cell can then trigger a defensive response.



The great variability in MHC genes ensures that a matching MHC protein exists for almost every intruder. Hence, if a specific pathogen is circulating in a population, those individuals with the matching MHC variant will be at an evolutionary advantage. Their carriers will become only mildly ill or perhaps not at all. And consequently, the frequency of this variant will increase within the population. To remain successful in the future, the pathogen needs to mutate and evolve in such a way that MHC variants cannot continue to provide protection. The mutated pathogen then needs to be matched by another MHC gene variant, and the evolutionary race enters the next round. The process can always result in evolution taking a different direction. Advantages can be rendered useless from one day to the next. However, not only do attackers quickly mutate from one generation to the next, they occasionally only appear in certain places and times. "In the long term, this means that no single variant will dominate the population, but that instead different ones will coexist," explains Tobias Lenz. This is what evolutionary biologists refer to as a "balanced polymorphism."

Lenz and his colleagues simulate the interplay between MHC genes and pathogens on the computer. With the help of specialized programs, they can observe the co-evolution of the adversaries in time-lapse. The researchers can also compare present-day genetic information with that of the past and, thus, learn how the MHC variants have changed over time. For example from skeletons from a medieval graveyard in Denmark. Here, the dead were from a leper colony. Such colonies were frequent in the past and up to the modern era, in order to prevent the spread of this often fatal disease. Thanks to antibiotics, most cases of leprosy are now curable.

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Tobias Lenz in his Institute's aquaria room. In addition to his work on human MHC genes, Lenz also investigates those of sticklebacks, whose immune system is similar to that of humans. The great diversity of MHC variants in the fish also plays an important role in their defense against parasites.

To this day, leprosy still occurs sporadically in Southeast Asia. Some people there have an HLA variant that increases their susceptibility to the disease. Is it possible that most of the people in Europe who contracted leprosy possessed this variant? “In collaboration with researchers from the University of Kiel, we have indeed discovered that the HLA variant that makes people more susceptible to leprosy is found at a higher frequency in these bones from the Middle Ages,” says Lenz.

## A variant with advantages and disadvantages

But why has this gene variant persisted over the centuries and not been eliminated by natural selection? “We now know that this variant isn’t solely disadvantageous. Yes, it provides poor protection against leprosy, but it also helps protect those who carry it from hereditary type 1 diabetes,” explains Tobias Lenz. Hence, the negative selective pressure due to leprosy is counterbalanced by the positive selective pressure of better protection against diabetes. That might explain why this HLA variant still exists in the population.

44 HIV is another example for a balanced polymorphism: some HLA variants in the immune system are better at keeping HIV in check than others. “We’ve demon-

strated that some variants are able to present a particularly large number of different HIV antigens. This makes HIV more visible for the immune system, so it can be fought more efficiently.” In contrast, the less effective variants may confer resistance to another pathogen. HLA variants may also be involved in the fact that SARS-CoV-2 causes severe symptoms in only a small percentage of those infected. As coronaviruses have circulated among humans for many years, most of us possess gene variants that can recognize the viruses. “We’re susceptible to SARS-CoV-2, because it’s relatively new, but thanks to thousands of years of natural selection, most people’s immune systems can limit its effects,” says Tobias Lenz. Along with colleagues from around the world, he is currently investigating the extent to which HLA genes may be involved. Although thousands of different HLA variants exist in humans, each one of us has only a handful of them. High variability, it turns out, also has a drawback: autoimmunity.

MHC proteins are adapted to bind molecules from bacteria, viruses, and other parasites and present them on the cell surface. There, these foreign molecules are recognized by a particular type of immune cell known as T cells. A selection process for T cells occurs in the embryo: those that recognize foreign molecules are retained, while those that recognize the body’s own molecules are removed. However, this process isn’t perfect, and so T cells that recognize the body’s own molecules keep emerging. The more HLA variants a person

Degenerated pigment cells from the skin. An immune system with a large variety of HLA types is better able to recognize and fight such cancer cells. As a consequence, immunotherapy is more effective in skin cancer patients with a high variability of these genes, but in such patients, treatment can also frequently trigger inflammatory reactions.

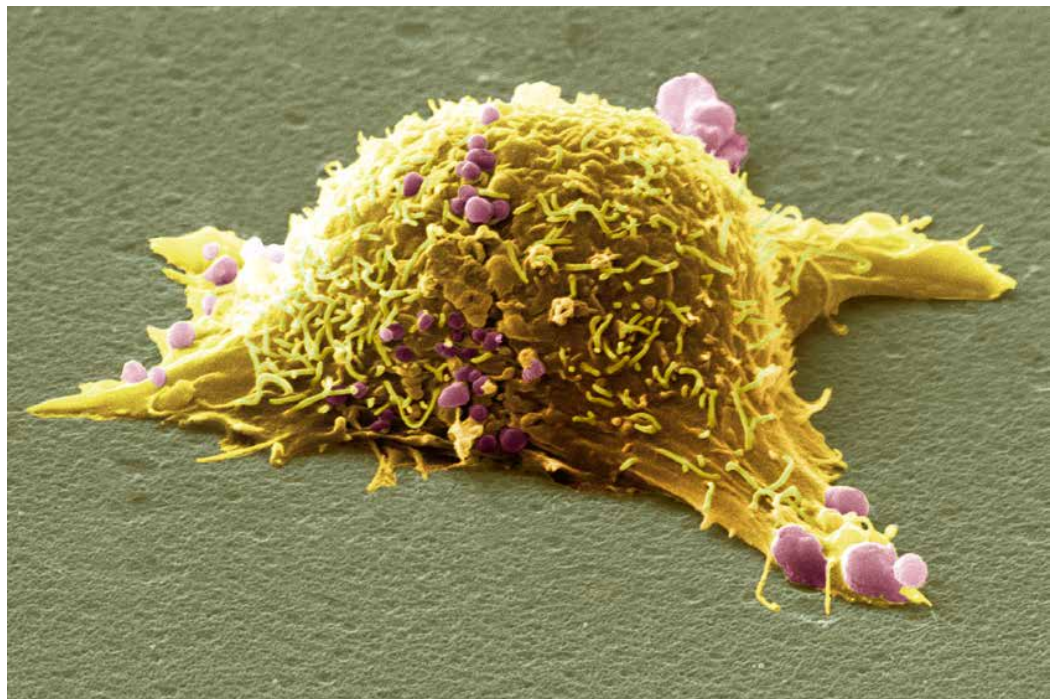
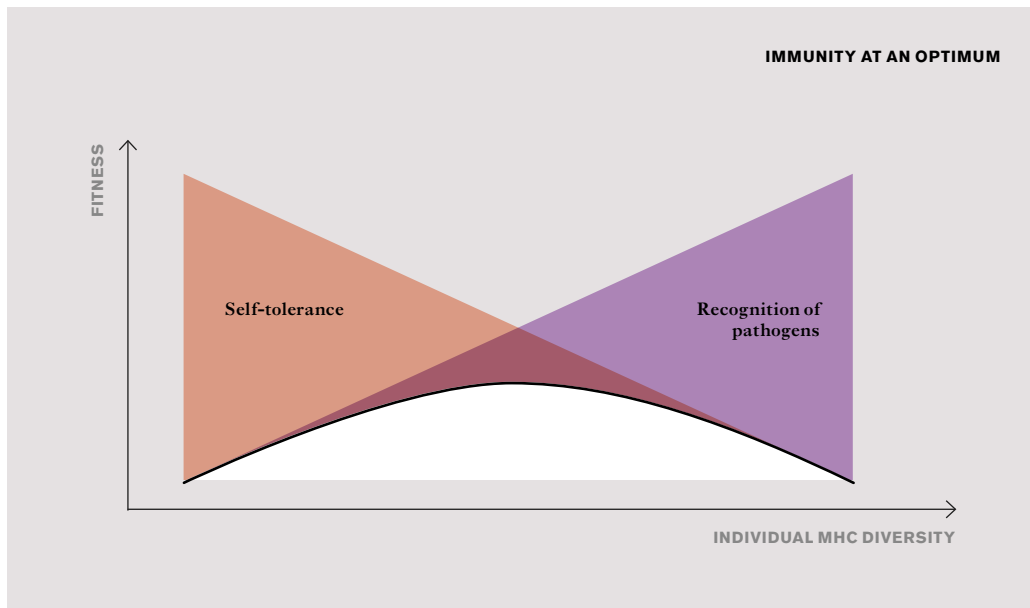


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The relationship between MHC diversity and an individual's fitness (black curve). The greater the diversity of MHC variants, the better the body is protected against pathogens and parasites. At the same time, however, the immune system's tolerance towards the body itself decreases. The body's optimal MHC diversity is located at the apex of the curve.

## SUMMARY

MHC genes produce an abundance of differing proteins that help the immune system to recognize intruders.

Some MHC variants provide protection against specific pathogens but can also trigger autoimmune diseases.

The more of these variants a person possesses, the better they are equipped to fight pathogens. The price, however, is a higher risk of developing autoimmune diseases.

possesses, the more foreign molecules they can present – in the case of pathogens that can mutate as rapidly as HIV, that's a huge advantage! Unfortunately, however, this will also lead to more of the body's own molecules being presented. This can cause the immune system to turn against itself, resulting in autoimmune diseases. Multiple sclerosis, type 1 diabetes, celiac disease, psoriasis, ankylosing spondylitis, and many more – all are associated with certain HLA variants. Throughout evolution, the diversity of HLA genes seems to have settled at an optimal level. "This means we're well protected against pathogens, while at the same time the risk of autoimmune diseases is minimized," says

Tobias Lenz. But is this still the case in our hygiene-oriented society? Autoimmune diseases are on the rise in many countries. Does this suggest that the balance between infection defense and autoimmune disease has shifted in favor of the latter? "It's possible that we possess too many HLA genes for the age we live in." Hence, the diversity of immune genes influences our susceptibility to both infectious and autoimmune diseases. The immune system and the HLA genes may also play a role in cancer, as immune cells can recognize and eliminate cells that are dividing uncontrollably. This helps to destroy some tumors at an early stage. Also, a tumor, even one at an advanced stage, can occasionally shrink in a seeming miracle.

This can occur when one of the mutations frequently manifesting in tumors causes the immune system to suddenly recognize the tumor cells as foreign and attack them.

## More effective treatment

Together with oncologists from the Memorial Sloan Kettering Cancer Center in New York, Tobias Lenz and his team have investigated the influence a cancer patient's own contingent of HLA genes has on the success of immunotherapy. Such a treatment with "checkpoint inhibitors" aims to induce immune cells to act against the body's own cells that are multiplying uncontrollably. "Our results have shown that immunotherapy is more effective in patients with metastatic skin cancer if they possess a broad diversity of HLA variants," says Lenz. However, HLA genes are also associated with common side effects of immunotherapy, such as skin rashes or liver and intestinal inflammation. In cancer as well, the immune system has to maintain a balance between combating tumor cells on the one hand and avoiding autoimmune diseases on the other. The price for possessing a perfect defense against pathogens would be that such a system could turn against one's own body – too high a cost to bear. Thus, the legions of pathogens will keep discovering ways to outsmart our immune system.

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