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Healthcare industry BW

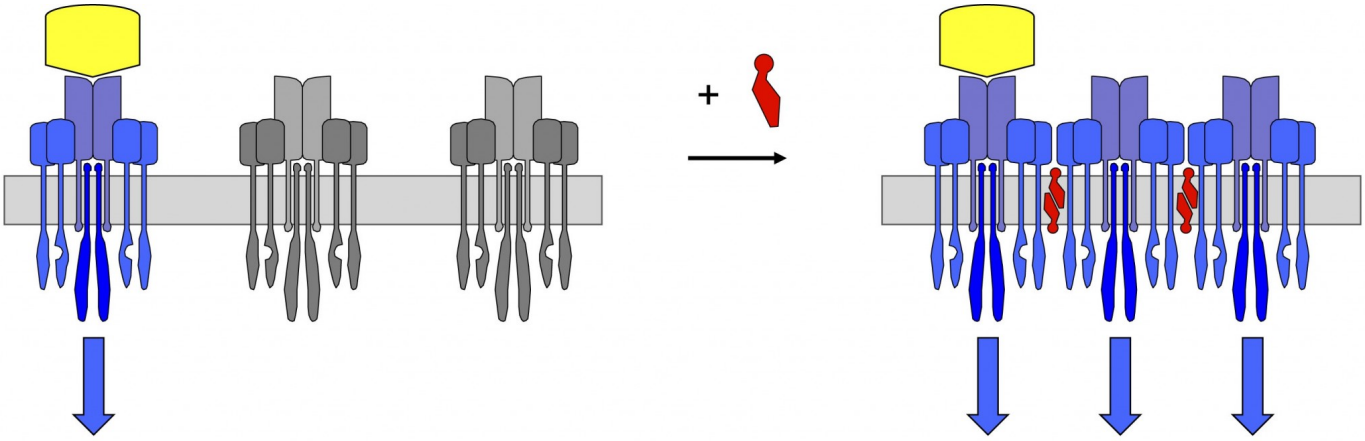
Cholesterol boosts the memory of the immune system

Cholesterol has been demonised for a long time, as high cholesterol levels are seen as major risk factors for atherosclerosis, myocardial infarction and gallstones. However, cholesterol is an essential component of mammalian cell membranes and is required for proper membrane function. It exists in huge quantities in the human body. In addition to being essential for cell survival, and hence all animal life in general, cholesterol also plays a crucial role in the production of specific immune responses, as Prof. Dr. Wolfgang Schamel from the Institute of Biology III and the Centre for Chronic Immunodeficiency (CCI) and Prof. Dr. Rolf Schubert from the Department of Pharmaceutical Technology at the University of Freiburg have shown.

When it is first infected with a pathogen, our immune system does not immediately eliminate the pathogen, which can then proliferate. It takes a relatively large number of pathogens to activate the immune system. The pathogen concentration usually reaches high enough levels to activate the immune system at a time when the infected organism shows signs of severe illness. However, the human body is obliged to go through this balancing act in order to get rid of the intruder. "A T cell needs to decide whether it attacks an intruder or not," said Prof. Dr. Wolfgang Schamel from the Centre for Chronic Immunodeficiency (CCI) at the Freiburg University Medical Centre, going on to add, "a lot of information needs to be acquired from other cells and a mistake must not be allowed to happen." If the immune system were to combat an intruder too quickly, it might erroneously destroy own body structures and trigger autoimmune diseases. The immune system therefore waits for a considerable period of time in order to ensure that the targeted substance is actually foreign to the body. If a pathogen (or antigen) is identified as dangerous, the immune system remembers this.

When our immune system comes across the same pathogen (antigen) a second time, it can react to the intruder swiftly and with high levels of sensitivity: the immune system's memory T cells have remembered the intruder and bind to and recognise it by way of the T cell receptors (TCRs). The organism is able to react more effectively to the intruder than during the first encounter; it does this in three ways: first, the memory T cells remember the site where the pathogen entered the body and migrate there in order to be present should the pathogen infect the body a second time; second, the number of T cells that are specific for a certain bacterium is dramatically increased. "Moreover, the T cells are much more sensitive to the pathogen than during the first encounter," said Schamel who is mainly interested in finding out the reasons why the sensitivity of T cells increases.

Memory T cells learn from aggregating T cell receptors



In a naïve cell (left), the receptors (blue) on the membrane are arranged individually. Pathogens (yellow) must bind to many receptors in order to activate the immune defense. In a memory cell (right), the receptors are joined together by cholesterol (red). When a pathogen binds to one receptor of a cluster, all of the receptors within the cluster are activated.

Naïve T cells are resting T cells that have not yet encountered a pathogen. The TCRs are arranged individually on the T cell membrane. The arrangement of the TCRs is very much like a meadow dotted with fruit trees. Around 25,000 TCRs are arranged individually on the T cell membrane, and each fends for itself. Schamel found that in so-called memory T cells, which remember the pathogen, the receptors are arranged in groups on the membrane, just like trees in a wood. An antigen that encounters a naïve T cell only leads to the activation of a single TCR, which is not enough for an efficient immune response to occur. Therefore, a large number of receptors need to be confronted with a large number of pathogens in order for the immune system to react. In so-called memory T cells, which remember the pathogen, the receptors cooperate amongst themselves by informing each other. When a pathogen binds to a receptor from a cluster, all of the receptors (twenty or more) within the cluster are activated at once. This makes the immune system more sensitive and enables it to react to even low concentrations of pathogens. An immune response occurs within minutes after the encounter with a pathogen, which then does not have the chance to multiply. The grouping of TCRs into nanoclusters therefore leads to an increase in sensitivity to pathogens.

Immunobiologist Schamel, who has focused on T cell receptors for many years, wanted to obtain insights into how the memory of the immune system works on the molecular level. “How does a cell manage to aggregate certain receptors on the cell membrane?” was one of the questions Schamel was interested in solving, after which he went on to look for a new protein. After years of trying, Schamel came up with the idea that the sought-after molecule was a component of the cell membrane into which TCRs are embedded. “We knew that cholesterol was a prominent component of cell membranes and decided to look at this molecule in greater detail,” said Schamel. This decision eventually led to a breakthrough. The researchers discovered that the composition of the lipids of a membrane is responsible for the clustering of the receptors. In fact, the teams led by Schamel and his colleague Professor Dr. Rolf Schubert from the Department of Pharmaceutical Technology at the University of Freiburg found that the presence of cholesterol and sphingomyelin, which is always bound to cholesterol, is responsible for the clustering of the TCRs. “We had not really considered this possibility as it is not widely known that lipids are able to control protein activity.”

Artificial membranes contribute to understanding TCR clustering

Schamel and Schubert are members of the Freiburg excellence cluster BIOSS, Centre for Biological Signalling Studies, and chose a synthetic biology approach for their investigations, entirely in the spirit of BIOSS. A synthetic biology approach does not involve destroying biological structures in order to analyse them. Instead, synthetic biologists create new artificial, biological systems, which helps reduce the complexity of organ systems. Working with his postdoc Dr. Eszter Molnar, his colleague Rolf Schubert, and Schubert's doctoral student Martin Holzer, Schamel started to produce artificial liposomes with the goal of integrating individual TCRs into synthetic membranes and examining the role of cholesterol and sphingomyelin in the formation of TCR clusters.

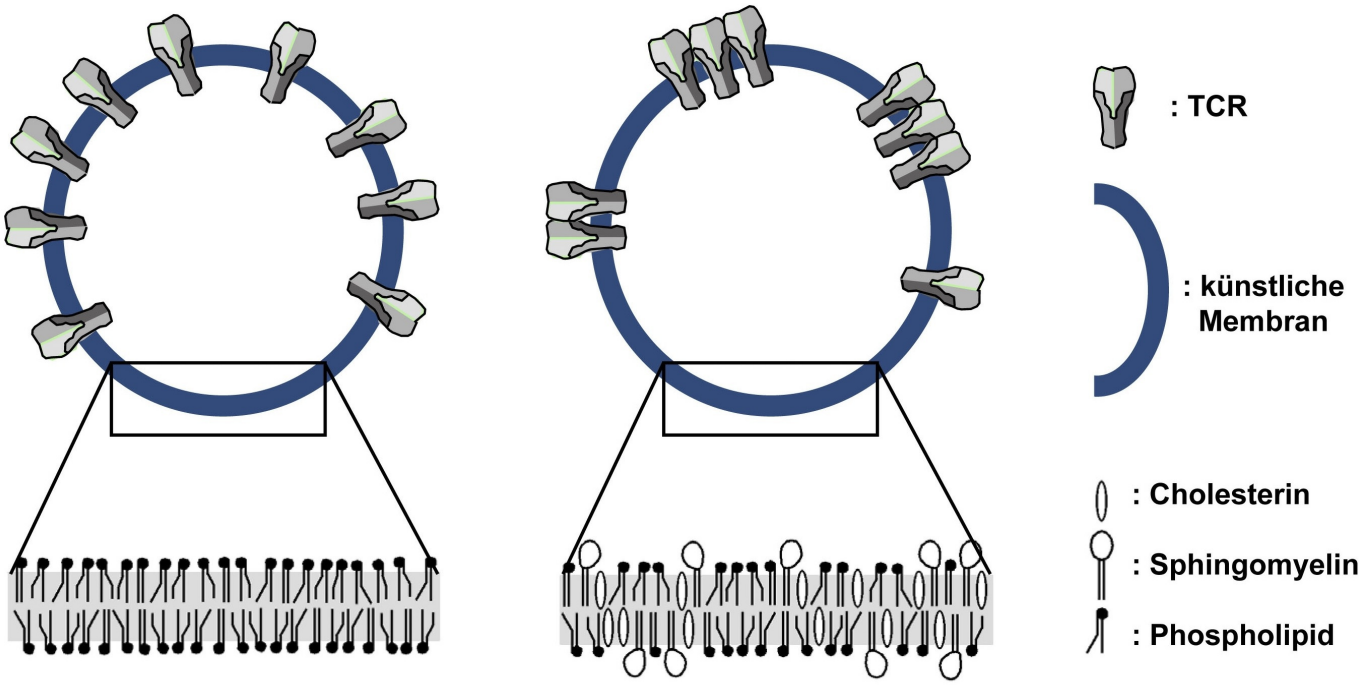


Fig.: Artificial liposomes with TCRs. Left: unclustered receptors in a membrane consisting of phospholipids only. Right: the membrane also contains cholesterol and sphingomyelin; the receptors are arranged in clusters.

Under certain conditions, lipids, which are the major constituents of cell membranes, are able to form membranes. They have hydrophobic and hydrophylic properties and form small vesicles in aqueous solutions in which the hydrophilic heads face away from the aqueous fluid. After working on this for around 18 months, Eszter Molnar managed to isolate the receptors and reconstruct them in a synthetic membrane. The addition of cholesterol and sphingomyelin led to the aggregation of receptors. The researchers also discovered a cholesterol-binding site in the transmembrane region of the TCR; when cholesterol binds to the TCR it becomes an integral part of the TCR cluster. The researchers concluded that the lipid composition of a naïve cell differs from that of a memory cell and the composition of the membrane lipids controls the aggregation of TCRs and hence the sensitivity of T cells.

Immune system memory increases cholesterol synthesis

Schamel and his team were able to substantiate their finding using real T cells. They extracted

cholesterol from the cells and found that the TCR cluster disintegrated into individual receptors and the cells lost their high sensitivity. Cholesterol therefore acts like glue.

Another interesting finding was that an activated T cell also increases its own cholesterol production, ensuring there is more of the compound available to enable the cluster to better remember the intruder.

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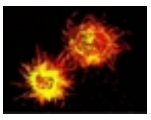

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