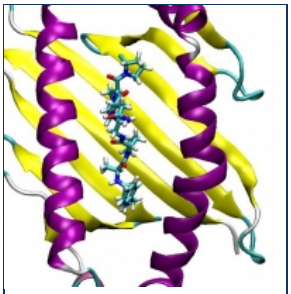
Controlling the immune reaction: New research project aims at developing a substance to boost or suppress the body's immune response



The newly discovered substance (middle) is able to keep the binding site (yellow area between the purple helices) open and thus enhances the binding process between MHC class I molecules and peptides.

A new research project led by Sebastian Springer, Professor of Biochemistry and Cell Biology at Jacobs University, is examining how the body's immune reaction to viruses, bacteria and cancer can be manipulated. In cooperation with Martin Zacharias, Professor of Theoretical Biophysics at the Technical University Munich, Springer aims at developing chemical substances to inhibit or enhance the response. These substances could then be used either in vaccines to boost the immune reaction or in drugs administered to transplant patients to suppress a possible rejection of the organ. The project, which combines bioinformatics and biochemistry approaches, is funded by the German Research Foundation (Deutsche Forschungsgemeinschaft DFG) with a total of 225 000 Euros over an initial three-year period.

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Vaccination to prevent diseases such as polio and seasonal influenza is commonplace in Europe today. Just a little needle-prick and one is protected from infections like flue or measles. Weakened or killed forms of the pathogen (the virus or bacterium) are contained in the vaccine to stimulate the body's immune response. White blood cells recognize the pathogen as foreign, destroy it, and remember its structure to be able to identify and kill the same kind of virus when encountered again. These facts have been known for a while. However, the chemical processes that take place inside each cell to trigger the immune reaction are still not understood in detail.

For almost ten years, Sebastian Springer, Jacobs University Professor of Biochemistry and Cell Biology, has been conducting research to better understand and influence these processes. His research focuses on the so called "major histocompatibility complex (MHC) class I molecules", which play a central role in the mammalian immune defense against viruses, intracellular bacteria, and cancer.

As a virus replicates inside a cell, it produces peptides (small pieces of proteins). These peptides bind to MHC class I molecules, which are present inside all cells. The binding process activates the molecule to travel to the cell surface, where they are surveyed by white blood cells called "cytotoxic T lymphocytes" (CTL). If the CTL detect that unusual peptides are bound to the molecules, they induce the infected cell to undergo controlled cell death. This way, the production site of the virus is eliminated and it can't spread out further.

During his studies, Springer discovered a chemical substance that enhances the binding process between MHC class I molecules and peptides. "Picture the part of the molecule that the peptide docks onto as the mouth of a venus flytrap," Springer explains. "The substance we discovered is able to keep this mouth - the binding site - open and thus makes it much easier for the peptide to bind to the molecule. As the binding rate increases, more molecules are triggered to travel to the cell surface and an infected cell can be faster detected and eliminated."

Although highly unstable and not yet ready for use in vaccines or other drugs, the newly discovered substance provides an ideal basis for further research. "By

understanding how the substance keeps the binding site open we can begin to develop similar but more stable substances for the use in therapeutic drugs," says Springer.

Combining bioinformatics and biochemistry approaches, Springer and his team will develop and analyze various chemical components in respect of their influence on the peptide-molecule binding process. In a first step, Martin Zacharias, Professor of Theoretical Biophysics at the TU Munich, will recreate the chemical structure of the substances in a computer simulation and imitate a possible interaction between substance and molecule. In a second step, the substances that accelerated or retarded the binding process will then be tested in living cells in Springer's laboratory and further developed.

"If we find a chemical substance that is stable enough to travel into cells when administered in combination with a vaccine or other drug," says Springer, "we could be able to control the immune reaction on a cellular level and thus enhance the affectivity of viral vaccination or, by suppressing the immune reaction, increase the success rate of organ transplantations and therapies used for autoimmune disease patients."

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