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dr. christiane menzfeld

tel.: +49 89 8578-2824

fax: +49 89 8578-2943

menzfeld@biochem.mpg.de

www.biochem.mpg.de/news

The needle in the haystack

Immunotherapy for cancer: identifying suitable target antigens by mass spectrometry.

The immune system can fight specifically against cancer by tumor-specific T cells although suitable altered target structures are currently mostly unknown. A team at the the Max Planck Institute of Biochemistry and Technical University of Munich (TUM) has developed a method that allows for the first time the reliable identification of suitable antigens directly from patients` tumor cells by mass spectrometry. These structures proved to be immunogenic. This procedure therefore opens up new possibilities for individualized targeted cancer treatments.

Through evolution, the immune system has developed sophisticated mechanisms for fighting illnesses associated with viruses and tumors. T cells play an important role in this setting. They can identify peptides, small protein structures, presented by the body`s own cells that may indicate a viral infection or a genetic alteration as for example a mutation – a characteristic of tumor cells. Peptides identified by immune cells are known as antigens. T cells that recognize antigens can trigger a reaction that destroys the targeted cells. In recent years research teams, including TUM researchers, have successfully utilized this characteristic for cancer treatments. Different approaches have emerged. Vaccinating a patient with an antigen can stimulate the body to enhance the production of specific T cells. Another possibility is to enrich T cells that are "trained" for certain antigens and transfer them to the patient.

A method, that identifies the antigen structures of patient specific tumors has now been developed by a team led by Angela M. Krackhardt, a professor of translational immunotherapy at the Third Medical Clinic at TUM's Klinikum rechts der Isar, and Professor Matthias Mann of the Department of Proteomics and Signal Transduction at the Max Planck Institute of Biochemistry. Krackhardt and Mann have described their approach in an article published in the Journal Nature Communications. Unlike former applied methods, it is not based on predictive models. Instead, a mass spectrometer is used to identify the peptides actually present on the tumor surface.

For a therapy, it is important to know which antigens derived from viruses or tumors are recognized by the T cells. Many different peptides can be found on the body's own cells and cancer cells.



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Consequently, the pool of potential candidates when searching for suitable antigens is very large. The authors of the new study identified approximately 100,000 different peptides from tumor tissue samples derived from only 25 melanoma patients. The T cells are particularly good at identifying peptides on tumor cells with mutations, i.e. structural changes. The peptides that mutate and the type of mutations they undergo generally varies from one patient to another.

Time-consuming and error-prone search for antigens

In the past, the search for mutated peptides truly presented on the tumor was a time-consuming and error-prone process. Scientists had to start by sequencing the DNA from tumor cells. That process alone takes one to two weeks. The sequencing data is then fed into Computer-based prediction algorithms to determine which mutated peptides might be found on the surface of the cell. Subsequently, time-consuming laboratory experiments had to be performed in order to find out whether these molecules actually existed and were presented on the cell surface.

Accurate and time-saving

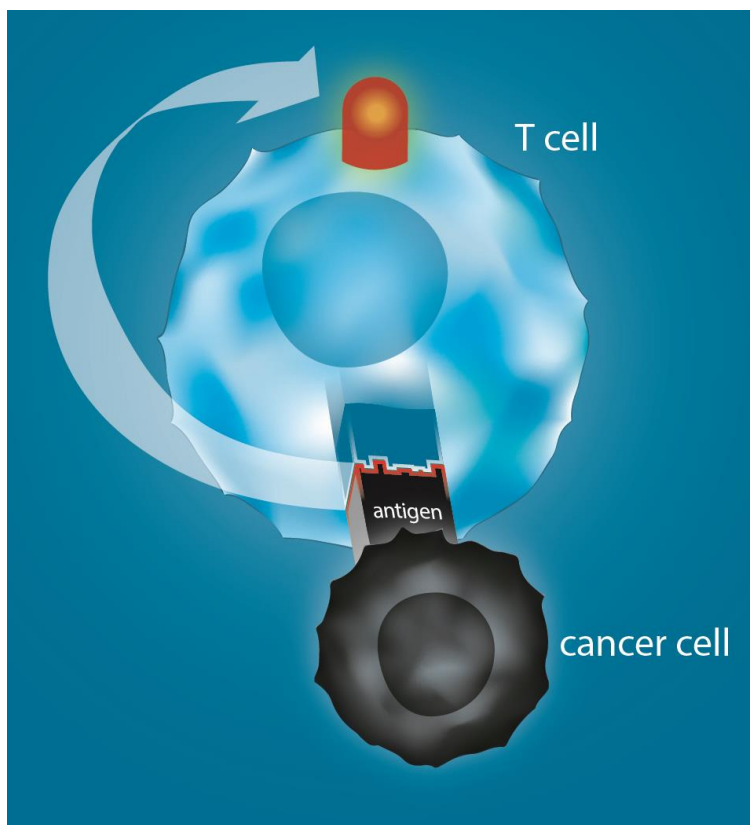
The genomic sequence, or blueprint, of the tumor cells is also required for the new method. At the same time, surface structures of the malignant cell – in this case presented peptides – are removed directly from tumor tissue and investigated by mass spectrometry. Thus, the mass spectrometer directly identifies those components presented on the tumor tissue surface. Combining both analyses by bioinformatics results in the identification of mutated antigens actually presented on the cells with considerable accuracy.

The team headed by Krackhardt and Mann was also able to demonstrate the clinical relevance of the new method: In the blood of melanoma cancer patients they found T cells that recognized tumor cells by means of antigens identified with mass spectrometry.

The new approach offers numerous advantages. By avoiding time-consuming simulations and laboratory experiments, information on mutated peptides on the tumor cells is much faster available. "For the first time, we have used the mass spectrometer to investigate not just expanded, clonal cells, but rather heterogenous tumor tissues of real patients," adds Matthias Mann. "That gives us much more detailed information about the molecular characteristics of the tumor." Moreover, the method is highly sensitive. The results of the study are already serving as the starting point for promising research initiatives, for example on the role of phosphorylated peptides.

Angela Krackhardt doesn't see major obstacles for clinical translation of the method. "Our approach opens up new possibilities for the personalized treatment of cancer," says Krackhardt. "Identification of suitable antigens by this method will allow us to provide individualized vaccines or adoptive T-cell therapies for our patients within weeks to a few months".





Caption:

T cells recognize antigens, small protein structure, on the surface of different cells. These structures may indicate for mutated DNA, characteristic for tumor cells. Which antigens are located on cancer cells can now be analysed patient specific by mass spectrometry.
Sinitcyn, Krause © MPI für Biochemie

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M. Bassani-Sternberg, E. Bräunlein, R. Klar, T. Engleitner, P. Sinitcyn, S. Audehm, M. Straub, J. Weber, J. Slotta-Huspenina, K. Sprecht, M. E. Martignoni, A. Werner, R. Hein, D. H. Busch, C. Peschel, R. Rad, J. Cox, M. Mann & A. M. Krackhardt: Direct identification of clinically relevant neoepitopes presented on native human melanoma tissue by mass spectrometry, *Nature Communications*, November 2016

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Contact:

Prof. Dr. Matthias Mann
Proteomics and Signal Transduction
Max Planck Institute of Biochemistry
Am Klopferspitz 18
82152 Martinsried
Germany
E-Mail: mmann@biochem.mpg.de
www.biochem.mpg.de/mann

Dr. Christiane Menzfeld
Public Relations
Max Planck Institute of Biochemistry
Am Klopferspitz 18
82152 Martinsried
Germany
Tel. +49 89 8578-2824
E-Mail: pr@biochem.mpg.de
www.biochem.mpg.de

