Press release of the German Cancer Consortium

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DKTK Essen: Dangerous Merkel cell skin carcinoma exposed

Merkel cell carcinoma are one of the most dangerous skin carcinoma types. However, the human immune defense system often fails to recognize them as cancer cells. Scientists at the German Cancer Consortium (DKTK) have now found a way to make the tumor visible to the immune system. Present therapies could thereby become a lot more effective. The DKTK brings together the German Cancer Research Center (DKFZ) in Heidelberg with seven partner sites across Germany. This long-term partnership is now eager to implement the results of basic research and to bring on new approaches in prevention, diagnostics and the development of more effective cancer therapies as quickly as possible.

Merkel cell carcinoma (MCC) is one of the most dangerous skin cancer types because of its ability to grow and frequently metastasize. Around a third of patients diagnosed with MCC will die from the disease. Up to now, this type of skin cancer was relatively rare and affected mainly those patients over 70 years old. But for some years now, it has started to occur more often in the younger population.

The disease is caused by an infection with the Merkel cell polyomavirus. Most viruses including those that trigger cancer, provoke violent immune responses aimed at destroying the infected cells. The Merkel cell carcinoma cells however remain unaffected.

The DKTK scientists at the Essen partner location have now uncovered how Merkel cell carcinoma manage to evade destruction by the immune system, and how to lift their camouflage. The tumor uses so-called epigenetic mechanisms to silence relevant genes of the immune system. Jürgen Becker is the head of the DKTK working group for translational cancer research at the University Hospital in Essen. He explains that 'normally, a viral infection and the conversion into a malignant tumor cell would signal danger and thus activate defense cells. In the re-programmed cancer cells however, the virus removes the histone acetylation process and thus turns off various immune genes. This phenomenon is also known as epigenetic silencing.'

Histones are spherical proteins that wrap our DNA into chromosomes. If the histones are labeled with acetyl groups, this will signal the cell to read the DNA. In Merkel cell carcinoma, the acetyl groups are removed. This in turn switches off a gene of the immune defense that encodes a crucial stress molecule. As a result, the cells of the immune defense, so called T-cells, no longer recognize the tumor and fail to attack.

The scientists from Essen have now succeeded in making the tumor susceptible to the immune response again. They use inhibitors to block the histone deacetylase, which is the key enzyme responsible for the inactivation. As a result, the signal genes are reactivated and can be read again. The scientists were able to show in cell cultures that the treated tumor cells were consequently attacked by specialized T-cells and destroyed.

'We already knew that epigenetic silencing plays a role in cancer. But we were surprised at how central this mechanism is to the escape of the tumor cells', explains Cathrin Ritter, who

did this work as part of her thesis at the DKTK. She will probably also be part of the next steps towards clinical trials.

The research team has every reason to be optimistic as this work is extremely interesting for the current immune therapeutics that big pharmaceutical companies are developing. These are based on improving the patients' immune responses. In some patients however, this approach is unsuccessful because the tumor is not even recognized as such. Jürgen Becker is confident that this may change: 'We have managed to show that the epigenetic inactivation of genes is an important camouflage mechanism in Merkel cell carcinoma, and that we can reverse it. We therefore see a good chance to combine current therapies with our results.'

The cooperation within the DKTK alliance has been an important source of inspiration for him. 'As a dermatologist I always have the clinical application in mind. Through networking with basic researchers at the DKTK, I have discovered completely new details that open up new avenues for therapy.'

Ritter C, Fan K, Paulson KG, Nghiem P, Schrama D, Becker JC. Reversal of epigenetic silencing of MHC class I chain-related protein A and B improves immune recognition of Merkel cell carcinoma. Scientific Reports 2016, DOI:10.1038/srep21678

The German Cancer Consortium (DKTK) is a joint long-term initiative of the Federal Ministry of Education and Research (BMBF), the federal states concerned, German Cancer Aid (Deutsche Krebshilfe) and the DKFZ and was founded as one of six German Centers for Health Research (DZGs). The consortium brings together high-ranking institutes from Berlin, Dresden, Essen/Dusseldorf, Frankfurt/Mainz, Freiburg, Heidelberg, Munich and Tübingen, working jointly toward the main goal of enhancing the translation of research from bench to bedside. The Consortium promotes interdisciplinary research at the interface between basic and clinical research, as well as clinical studies on innovative therapeutic and diagnostic methods. A further key focus is on building research platforms in order to expedite personalized cancer therapies and to improve the diagnostics and prevention of cancer.

More information is available at http://www.dkfz.de/de/dktk/

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