Therapeutic vaccines against brain tumours

Therapeutic cancer vaccines have the potential to boost the immune system's ability to destroy tumour cells. Cancer researchers around the world are intensively studying the potential of this therapeutic concept and initial positive results have been obtained. Cancer researchers from Heidelberg have developed a vaccine that triggers an immune response against a protein that is mutated in brain cancer. The vaccine, which successfully arrested tumour growth in animals, is now undergoing phase I clinical testing.

A prerequisite for the development of a tumour vaccine is to find specific protein structures (tumour antigens) in cancer cells that differ from those of healthy cells. The immune system is then able to recognise and eliminate the cells. Cancer cells, advanced stage ones in particular, are characterised by a larger number of mutations than healthy cells. However, due to the huge heterogeneity and variability of tumours it is difficult to identify stable, specific tumour characteristics that would be suitable for vaccine development.

“Every cancer is different,” is a dogma frequently repeated by oncologists. In fact, tumours not only differ between individuals, but different tumour cells can also show distinct profiles.

A tumour-specific mutation

Prof. Dr. Michael Platten
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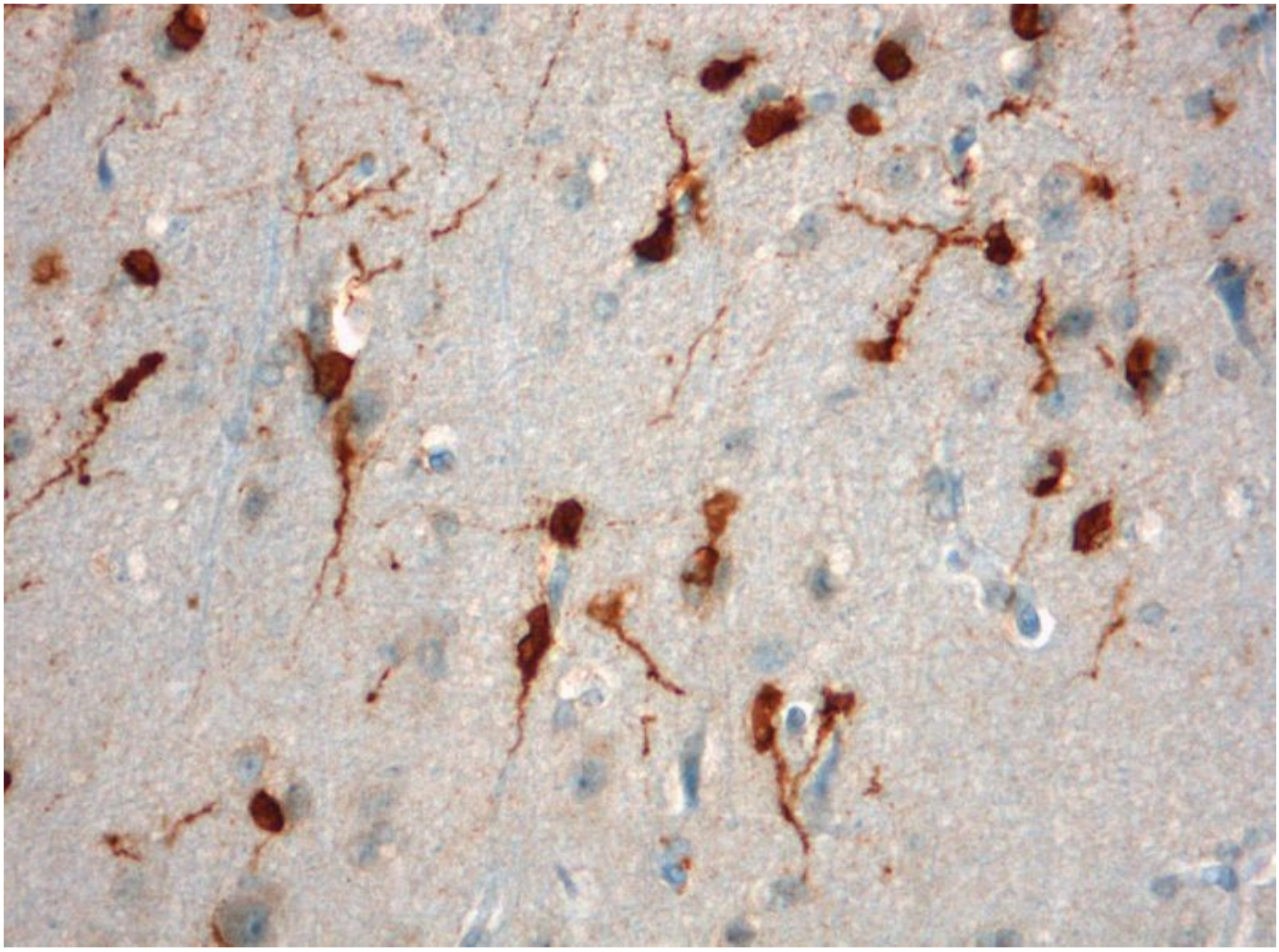
“The discovery that more than 70% of all low-grade gliomas, which are brain tumours that can develop into extremely aggressive glioblastomas, exhibit the same mutation in a particular protein,

attracted our attention as immunologists," says Prof. Dr. Michael Platten from the German Cancer Research Center (DKFZ) and the University Hospital of Heidelberg. The researchers found a point mutation in an enzyme called isocitrate dehydrogenase 1 (IDH 1). As a result, the amino acid at the 132nd position of the protein sequence is replaced by the amino acid histidine. No other type of tumour displays the same mutation with such frequency. This gives the protein in the cancer cells novel immunological properties that can be recognised by the body's immune cells.

Prof. Dr. Andreas von Deimling, a neuropathologist at the University Hospital and the DKFZ, and his team have developed an antibody for reliably identifying the altered enzyme IDH1(R132H+). The researchers found the altered form of IDH1 on the surface of all tumour cells in the brain, and only there, not on healthy cells.



Immunohistochemical staining of glioma cells (brown) with mutated forms of the protein IDH1; the nuclei are shown in blue. The altered protein is found in the cytoplasm and in the cell protrusions of the tumour cells.

"This suggested that we might be able to use a vaccine to alert the patient's immune system to mutant IDH1 and fight the tumour without damaging healthy cells," Platten explains.

A vaccine against slow-growing, aggressive brain tumours

Low-grade gliomas (astrocytomas, oligodendrogliomas and oligoastrocytomas) are slow-growing brain tumours that are very difficult to treat. Gliomas can develop into extremely aggressive glioblastomas. They arise from the support cells of the central nervous system and are the most common brain tumours in children and adolescents. Since they spread in a diffuse manner in the brain, they cannot be completely eliminated with surgery and the effectiveness of chemotherapy and

radiotherapy is also very limited. Gliomas therefore recur frequently. Patients would therefore benefit enormously from a vaccine that prevents the tumour from recurring.

Prof. Dr. Andreas von Deimling, director of the Department of Neuropathology at the University Hospital of Heidelberg and head of the clinical cooperation unit Neuropathology at the DKFZ.

In collaboration with physicians and scientists from the universities of Mainz, Tübingen and Heidelberg, Platten and his co-workers are working on the development of an IDH1(R132H+)-specific vaccine. The researchers constructed an artificial version of the IDH1 segment that contained the characteristic mutation. They synthesised a peptide consisting of 15 amino acids, which fitted exactly into the peptide-binding pocket of an MHC class II molecule on the so-called antigen-presenting cells (i.e. dendritic cells). This complex synthesis procedure was necessary because immune cells only respond to targets, in this case tumour antigens, that are presented on the surface of MHC II molecules.

The researchers knew that the IDH1 protein with the characteristic mutation was immunogenic, i.e. able to mount an immune response by forming specific antibodies, as they had previously discovered spontaneous immune responses against altered IDH1 in a number of patients with low-grade glioma.

The researchers used transgenic mice to prove that the IDH1(R132H+) peptide vaccine was effective in gliomas. Instead of carrying their own mouse-specific MHC molecules, the cells of the transgenic mice were equipped with human MHC molecules. Dr. Theresa Schumacher, first author of the study published in Nature in 2014, explains: “After vaccinating the animals with the peptide, we were able to detect immune cells and antibodies that specifically recognised the altered IDH1 of tumour cells rather than the normal form of the enzyme in healthy cells.”

Dr. Theresa Schumacher, Department of Neuroimmunology and Brain Tumour Immunology at the DKFZ

Immunohistochemical experiments also showed that T cells entered the tumours after vaccination. In the experimental animals, this specific immune response induced by the vaccine arrested the growth of cancer cells that exhibited the IDH1(R132H+) mutation. The vaccine did not disrupt the functioning of the normal IDH1 enzyme, which plays a role in the energy metabolism of all healthy cells in the body.

The animal experiments have shown that vaccines based on the peptide can support the body's immune system in the fight against cancer cells. These results have paved the way for a clinical phase I trial to test the safety of the vaccine in humans.

The clinical trial, which is scheduled for early 2015, will be supported by the German Consortium for Translational Cancer Research (DKTK), a platform that was initiated by the German Federal Ministry of Research and Education (BMBF) and which brings together its core center, the German Cancer Research Center (DKFZ) in Heidelberg, with seven partner sites across Germany.

Original publication:
Schumacher T, Bunse L, Pusch S, Sahm F, Wiestler B, Quandt J, Menn O, Osswald M, Oezen I, Ott M, Keil M, Balß J, Rauschenbach K, Grabowska AK, Vogler I, Diekmann J, Trautwein N, Eichmüller SB, Okun J, Stefanovic, Riemer AB, Sahin U, Friese MA, Beckhove P, von Deimling A, Wick W, Platten M: A vaccine targeting mutant IDH1 induces antitumour immunity. Nature 2014; 512: 324-7.

Article

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