Researchers discover how melanoma cells circumvent the immune system

October 10 2012

Melanoma is so dangerous because it tends to metastasize early on. New treatment approaches utilize, among other things, the ability of the immune defense to search out and destroy malignant cells. Yet this strategy is often only temporarily effective. A research team under the direction of Bonn University has discovered why this is the case: In the inflammatory reaction caused by the treatment, the tumor cells temporarily alter their external characteristics and thus become invisible to defense cells. This knowledge forms an important foundation for the improvement of combination therapies.

The results have been published online in the renowned journal *Nature*.

In Germany, approximately 15,000 people develop melanoma annually and approximately 2,000 people die from it every year. Malignant melanoma is the most frequently fatal skin diseases. The particular malignancy is based on the fact that small tumors can spread via the lymphatic vessels and the bloodstream. For many years, the working group under Prof. Dr. Thomas Tüting, Director of the Laboratory for Experimental Dermatology at the Bonn University Hospital, has investigated the effect of a targeted immune therapy with tumor-specific defense cells.

Tumor cells behave like a wolf in sheep's clothing

In trials on mice who congenitally develop melanoma, the researchers

were able to destroy advanced tumors using so-called cytotoxic T-cells. "But they recover after some time - just as they do in patients in the hospital," explain Dr. Jennifer Landsberg and Dr. Judith Kohlmeyer, lead authors of the study. This form of therapy triggers inflammation. Now the researchers have discovered that the melanoma cells change their external characteristics precisely via this accompanying inflammatory reaction. "They behave like wolves in sheep's clothing and thus evade detection and destruction by defense cells," says Marcel Renn, also a lead author of the study.

The immune system can fight tumors – but it can also protect them

On the search for the underlying mechanisms, the researchers pointed histological investigations of tumors in the right direction: Therapy-resistant melanomas demonstrated a significantly stronger inflammatory reaction with many scavenger cells of the immune system, the so-called macrophages. A messenger primarily released from these immune cells - the tumor necrosis factor-alpha - was able to bring about the change in character of the melanoma cells directly in the Petri dish in the laboratory. Cells treated in this way were subsequently hardly detected by the defense cells. "The immune system is like a double-edged sword," explains Prof. Tüting. "It can fight the tumor – but it can also protect it." Such changes in the tumor tissue are probably of great importance for the formation of resistance to therapy. "According to more recent discoveries, treatment with inhibitors which prevent signal transmission in tumor cells is also affected by this," remarks Prof. Tüting.

Melanoma cells lose their typical characteristics

Molecular genetic investigations revealed that melanoma cells from therapy-resistant tumors had lost the characteristics typical for pigment

cells. Instead, they demonstrated traits of connective tissue cells. "It is possible that melanoma cells undergo this change in character so easily because they originate from the embryonic development of cells in the neural crest which can also form connective tissue and nerve cells," says Prof. Dr. Michael Hölzel, co-author from the Institute for Clinical Pharmacology and Clinical Chemistry at the Bonn University Hospital.

Results can also be transferred to humans

Findings initially gained from laboratory mice were also able to be reproduced by the team of researchers with human melanoma cells and various associated defense cells in the Petri dish. The melanoma cells likewise reacted to the messenger tumor necrosis factor-alpha with a loss of pigment cell characteristics and could then no longer be detected by pigment-cell-specific defense cells. "Detection by other defense cells which can search out specific genetic changes in the melanoma cells was not affected by this, however," stresses Prof. Dr. Thomas Wölfel, director of a working group involved in the study at the Medical Clinic III of the Mainz University Hospital.

Important findings for new treatment strategies

As soon as the tumor necrosis factor alpha no longer had an effect on the human and mouse melanoma cells, however, the cells regained their pigment-cell characteristics. Then they were also able to be detected and fought against by all immune defense cells once more. All of these findings yield important information for new treatment strategies. Thus in the future, defense cells against antigens of various categories and specificity should be used and at the same time, the inflammation utilized by the tumor cells should be therapeutically inhibited. "Our experimental model system will help us to develop optimally effective combination therapies as rapidly as possible," says Prof. Tüting.

"However, it will still take several years until the clinical application of strategies of this type."

More information: Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation, *Nature*, DOI: 10.1038/nature11538

Provided by University of Bonn