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How immune cells destroy cancer cells: Researchers elucidate mechanism

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In the treatment of large tumors, how effective is adoptive T cell therapy in comparison to drug-based cancer treatment? To answer this question, Dr. Kathleen Anders and Professor Thomas Blankenstein of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch and researchers of the Beckman Research Institute of the City of Hope Cancer Center in Duarte, California, USA designed and carried out a study comparing the two methods. Based on a mouse cancer model, the researchers elucidated the mechanisms of the two different treatments. The researchers showed that both forms of therapy are highly effective against large tumors. However, the T cells not only kill cancer cells – they additionally destroy the tumor blood vessel system, thus impeding the supply of nutrients to the tumor. Consequently, quasi as a side effect, "escapee" mutant tumor cells are eradicated that have become resistant to drug-based treatment and are responsible for tumor recurrence. The researchers hope that their insights in defining optimal conditions for T cell therapy may help improve future clinical trials and thus the treatment of cancer patients.

The researchers transplanted tumor cells into mice that express SV40 large T antigen (Tag), the oncogene that is critical for tumor growth. The researchers were thus able to target and inactivate the oncogene using the antibiotic drug doxycycline (dox), which has an effect similar to modern drugs currently in clinical use. Since the oncogene is also present as antigen on the surface of the tumor cells, the researchers were also able to target these tumors with oncogene-specific T cells. Thus, for the first time the effect of the two completely different therapy approaches could

be compared directly with each other.

Moreover, a special feature of the study was that the tumors in the mice were large – bigger than one centimeter and containing about one billion cancer cells, comparable to clinical-size tumors in patients. Only then, according to the researchers, is the development of the tumor tissue (tumor stroma), which also includes the tumor vasculature, complete. The tumor is then considered "established". The aim of tumor therapy is to kill all cancer cells to prevent the recurrence of cancer disease.

The researchers showed in mice that the tumor is destroyed by the drug-mediated inactivation of the oncogene, but that the tumor vasculature and thus the blood supply of the tumor remains intact. In addition, due to a high mutation rate, some cancer cells become resistant to the drug and quickly generate new tumors despite continual administration of the anti-cancer drug.

Adoptive T-cell therapy, the researchers noted, is more effective in the mice in the long term, because it destroys the blood supply of the tumor. In addition, it evidently intercepts cancer cells that have altered their characteristics via mutations and thus escape drug treatment. In adoptive T-cell therapy, the researchers modulate the cytotoxic T cells (immune cells toxic for the cell) in the test tube in such a way that the T cells recognize certain features on the surface of cancer cells and specifically destroy the tumor cells. Then these primed immune cells are transferred back into the mice. The researchers point out that techniques to produce highly specialized T cells against human tumors have recently been developed following previous studies by Professor Blankenstein's research group. Now it will be important to determine exactly how these immune cells can be used in future clinical trials.

*Oncogene-targeting T cells reject large tumors, while oncogene inactivation selects escape variants in mouse models of cancer

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