2 at 1 stroke -- how cells protect themselves from cancer

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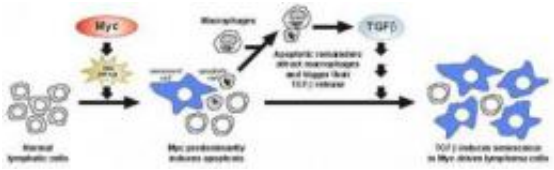

Researchers have known for some time that -- paradoxically -- oncogenes themselves can activate cell protection programs in an early developmental stage of the disease. This may explain why some tumors take decades to develop until the outbreak of the disease. Credit: Clemens Schmitt

Cells have two different protection programs to safeguard them from getting out of control under stress and from dividing without stopping and developing cancer. Until now, researchers assumed that these protective systems were prompted separately from each other. Now for the first time, using an animal model for lymphoma, cancer researchers of the Max Delbrück Center (MDC) Berlin-Buch and the Charité - University Hospital Berlin in Germany have shown that these two protection programs work together through an interaction with normal immune cells to prevent tumors. The findings of Dr. Maurice Reimann and his colleagues in the research group led by Professor Clemens Schmitt may be of fundamental importance in the fight against cancer.

Researchers have known for some time that - paradoxically - oncogenes themselves can activate these cell protection programs in an early

developmental stage of the disease. This may explain why some tumors take decades to develop until the outbreak of the disease. The Myc oncogene triggers apoptosis (programmed cell death), inducing damaged cells to commit suicide in order to protect the organism as a whole. By means of chemotherapy, physicians activate this protection program to treat cancer.

The second protection program - not as well understood as apoptosis - is senescence (biological aging). This program is triggered by another oncogene, the ras gene. Senescence stops the cell cycle, and the cell can no longer divide. But in contrast to apoptosis the cell continues to live and is still metabolically active. Professor Schmitt, physician at Charité University Hospital and research group leader at the MDC, was able to show on an animal model for lymphoma that senescence can block the development of early-stage malignant tumors.

Myc oncogene triggers cascade to activate both protection programs

Now, for the first time, Dr. Reimann, Dr. Soyoung Lee, Dr. Christoph Loddenkemper, Dr. Jan R. Dörr, Dr. Vedrana Tabor and Professor Schmitt have provided evidence that the Myc oncogene plays a key role in the activation of both protection programs - without the presence of the ras oncogene. "What is remarkable about this finding is that an oncogene can first trigger apoptosis and interact with the tumor stroma - the tissue that surrounds the tumor which also contains healthy cells - and with the immune system and then is able to switch on signals which lead to tumor senescence," Professor Schmitt said, summarizing how the interaction works.

"Fundamental significance"

According to the researchers' findings, the cascade occurs as follows: First the Myc oncogene triggers apoptosis in the lymphoma cells. The dying, apoptotic cells attract macrophages of the immune system, which devour and dispose of the dead lymphoma cells. The thus activated macrophages in turn secrete messenger molecules (cytokines), including the cytokine TGF-beta. It can block the growth of cancer cells in the early stage of a tumor disease. The MDC and Charité researchers discovered that the cytokines in the tumor cells that had escaped apoptosis switch on the senescence program and suppress the cancer cells.

"Our findings promise to have fundamental significance for elucidating the pathogenesis not only of lymphoma cancers, but of cancer in general. Our results indicate that senescence triggered by the immune system's messenger molecules may be a further important active principle, apart from apoptosis induced by chemotherapy."

At present the researchers in Professor Schmitt's group are focusing intensively on chemotherapy-mediated senescence. "If by inducing senescence we could obtain a sustained suppression of the cancer cells we can no longer destroy, this would mean exciting new possibilities for therapy," Professor Schmitt said.

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