How metastases develop in the liver

14 October 2014

In order to invade healthy tissue, tumor cells must leave the actual tumor and enter the bloodstream or lymphatic system. For this purpose, they use certain enzymes, proteases that break down the tissue surrounding the tumor, thus opening the way for tumor cells to reach blood or lymphatic vessels. To keep the proteases in check, the body produces inhibitors such as the protein TIMP-1, which thwart the proteases in their work.

But during development of metastases, the control function of this inhibitor appears not only to fail but to swing in the opposite direction and to actually promote the formation of metastases. Observations in numerous cancer patients have shown that high levels of the inhibitor TIMP-1 in the blood did not slow the spread of cancer. On the contrary, it actually hastened the progression of the disease. The research group led by Prof. Achim Krüger at the Institute for Molecular Immunology and Experimental Oncology of Klinikum rechts der Isar has now been able to explain this contradiction experimentally, thus shedding light on a mechanism that leads to the formation of metastases in the liver.

Niche for cancer cells

Together with his team, he discovered that a high concentration of the inhibitor TIMP-1 induces local inflammation in liver tissue. In response, immune cells known as neutrophils migrate into the organ. Tumor cells circulating through the body in the bloodstream then take advantage of these cellular and molecular changes to lodge in the liver and form metastases. "TIMP-1 creates a zone in liver tissue in which favorable conditions for cancer cells prevail – a fatal development for the very early spread of the primary tumor," Krüger explains.

After the scientists discovered this metastasis-promoting effect of TIMP-1, they succeeded in elucidating the mechanism further and even preventing it. Using an animal model, they found that TIMP-1 recruits immune cells by increasing the levels of a specific signaling molecule in the liver. This signaling molecule binds to a receptor, creating ideal conditions for cancer cells. Using pharmacological substances and antibodies, the researchers were able to block this interaction between the signaling molecule and its receptor, thus inhibiting the metastatic process experimentally.

Kruger summarizes the research results as follows: "The early metastasis of tumor cells usually constitutes the critical step in cancer development. If we can prevent the formation of metastases in the liver, at least in an animal model, that is a major step towards developing new treatments for cancer patients."

More information: *Hepatology*, 2014. DOI: 10.1002/hep.27378

Provided by Technical University Munich