No. 05 January 30, 2015 (Koh)

Surface molecule promotes pancreatic cancer aggressiveness

A protein on the surface of pancreatic cancer cells promotes metastasis and the ability to initiate new tumors, as scientists from the German Cancer Research Center have now reported. When the researchers used a specific agent to block this surface protein in mice, tumors grew more slowly and formed fewer metastases.

To this day, pancreatic cancer is one of the most challenging types of cancer to treat. Only about five percent of patients live past the five-year mark following initial diagnosis with the disease. Poor prognosis can be attributed to extremely aggressive growth behavior of pancreatic tumors and their tendency to spread and form metastases at very early stages of disease.

When cancer cells leave a tumor, they undergo a specific, complex change in characteristics "They undergo a major transformation by which they change their shape, increase their mobility and cease to attach to each other," says Professor Ana Martin-Villalba of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ). "At the same time, they also acquire stem cell properties, namely, the capability to form new tumors or metastases."

A whole series of growth factors can induce this transition. In 2008, Martin-Villalba discovered that in glioblastoma, the most dangerous form of brain cancer, a surface protein called CD95 can act on brain tumor cells like a growth factor by increasing their aggressiveness. She suspected that CD95 might also be the culprit that promotes malignant transformation and metastasis in pancreatic cancer.

Studying tumor tissue samples, the researchers in Martin-Villalba's team discovered that pancreatic cancer cells exhibit significantly higher levels of CD95 on their surface than healthy pancreatic cells do. Cancer cells that expressed extremely high quantities of CD95 also displayed the most distinct characteristics of the transition towards malignancy. Additionally, cancer cells derived from metastatic sites expressed more CD95 than cells from the primary tumor.

Not every cancer cell is capable of generating a new tumor or a metastasis; this is an unique characteristic of so-called "cancer stem cells", or "tumor-initiating cells". If cancer cells that have been transferred into immunodeficient mice are able to grow into a new tumor, they are considered to be cancer stem cells. When CD95-bearing pancreatic cancer cells were transferred into immunodeficient mice, they formed tumors, implying that they had cancer stem cell-like properties.

Taken together, these results strongly suggest that CD95 plays a causal role in the aggressiveness of pancreatic cancer – but they alone are not sufficient proof of this. In order to definitively prove this theory, the scientists used a specific reagent called APG101 to inhibit the activation of CD95. Mice that had received the tumor cells and were also treated with APG101 developed smaller tumors, as well as fewer and smaller metastases than animals that did not receive the treatment.

CD95 has historically been known as a "death receptor" because it induces a cell death program called apoptosis. Therefore, it was initially thought to play a role in suppression of

tumor growth. The agent APG101 that Martin-Villalba's team successfully used to slow down cancer growth inhibits contact between the CD95 found on the surface of cancer cells and its specific binding partner. Thus, APG101 prevents activation of downstream CD95-dependent reaction pathways within the cell.

Furthermore, the DKFZ researchers found that in the case of pancreatic cancer cells, CD95 utilizes an adaptor protein called Sck to activate specific signaling pathways known to fuel cell growth and migration.

"Cancer researchers are urgently searching for marker molecules that they can use to identify tumor cells with metastatic potential in the blood of cancer patients," says Martin-Villalba. "CD95 qualifies as a candidate for this. This might help clinicians to better predict the course that the disease will take. Additionally, CD95 is also a very promising target that we might use very specifically to slow down the growth and spread of pancreatic cancer."

APG101 is being developed by the Heidelberg-based biotechnology company Apogenix, which is a spin-off company of DKFZ. The highly promising substance has already been successfully tested in a Phase II trial on the treatment of recurrent glioblastoma, where it significantly prolonged the survival of patients participating in the study.

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