Unexpected role of mTORC2 protein in colorectal cancer

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New results from researchers at MedUni Vienna's Center for Pathobiochemistry and Genetics show that a protein called mTORC2, which is the target of newly developed cancer drugs, is not even active in colorectal cancer. mTORC2 activity was only found in certain immune cells, which actually need this protein to fight cancer cells.

In addition to cancer cells, tumors also contain a large number of different types of immune cells, which normally fight against the cancer cells. However, many tumors have developed strategies to reprogram immune cells so that they actually assist tumor growth. In the age of immunotherapy, which is very successful in reactivating the immune system, research into how tumor cells and immune cells interact is of major importance.

mTORC2 assists tumor growth—but not in colorectal cancer

The mTORC2 protein plays an important role in tumorigenesis and is currently the target of a series of new drugs that can successfully inhibit the growth of cancer cells in a test tube. In the future, mTORC2 inhibitors could be effective in many types of cancer, including colorectal cancer. A MedUni Vienna research team centered around Thomas Weichhart's group has now discovered that mTORC2 is actually not active in colorectal cancer cells, but only in certain immune cells, so-called macrophages, which normally fight cancer cells. These findings have now been published in the *Journal of Clinical Investigation Insight*.

Together with their colleagues, the three lead authors, Karl Katholnig, Birgit Schütz and Stephanie Fritsch, have shown that a high level of mTORC2 activity is important in macrophages to suppress the growth of colorectal cancer in an animal model. Karl Katholnig says, "When we deactivated mTORC2 specifically in macrophages in an animal model, the growth of the colorectal tumor accelerated in these mice."

Birgit Schütz says, "Surprisingly, an mTORC2 inhibitor also had the same effect in this colorectal cancer model." This correlation also prevails in humans. "We discovered that, in colorectal cancer patients, high mTORC2 activity in macrophages is associated with a favorable course," says Stephanie Fritsch. These results indicate that it could be therapeutically useful to maintain mTORC2 activity in colorectal cancer, rather than inhibiting it.

In conclusion, Thomas Weichhart says, "In order to safeguard their own survival, the cancer cells even try to deactivate mTORC2 in macrophages as soon as these cells penetrate into the tumor mass."

The researchers now want to find out how the tumor cells deactivate mTORC2 in macrophages. If that can be prevented, it may comprise a new immunotherapy approach. In any case, it appears that in order to have a full understanding of drug efficacy, it is also necessary to consider the immune system, and an efficient cancer treatment must also include the immune system.

More information: Karl Katholnig et al. Inactivation of mTORC2 in macrophages is a signature of colorectal cancer that promotes tumorigenesis, *JCI Insight* (2019). DOI: 10.1172/jci.insight.124164

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