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Scientists discover how to stop the spread of metastasis

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A group of researchers from the Institute of Bioorganic Chemistry of the Russian Academy of Sciences and Queen's University (Canada), in conjunction with the Institute of Macromolecular Compounds of the Russian Academy of Sciences, has studied the role of sialic acid in cancer development. The results of their research show that cancer cells can be manipulated by properly adjusting the acid's levels, and this can possibly halt the spread of metastases. Their findings were published in the *Oncotarget* magazine.

Tumor cell surfaces are often filled with large quantities of sialic acid. This acid gives cell membranes a negative charge, and due to the repulsive forces thus created, contributes to their separation from the primary tumor. As a result, tumor cells can spread throughout the body, forming secondary lesions of the disease in a process called metastasis.

However, until now, an important aspect of this process, which involves the role that sialic acid plays in the biochemistry of cancer cells, was not yet clear. Under the direction of Elena Arnoldovna Markvicheva, researchers at the M.M. Shemyakin and Yu. A. Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, in collaboration with scientists from Queen's University (represented by Ronald J. Neufeld, Myron R. Szewczuk), were able to clarify the role that sialic acid plays in the development of cancer and in the interaction of cancer cells with each other.

"We looked at two different ways in which sialic acid can be attached to

cell surfaces – either via α-2,3 or α-2,6 linkages," explains Roman Akasov, junior researcher at the Institute of Bioorganic Chemistry's 'Polymers for Biology' Laboratory of the Russian Academy of Sciences, one of the authors of the article. "Both of these linkage options are present in the cells, and despite the fact that their structures appear similar, even a slight difference may be important for the cell itself. We decided to carry out an experiment on tumor spheroids. Tumor spheroids are dense, bead-like substances from cells that simulate the growth and behavior of the actual tumor cells. To this end, my colleagues and I developed a method that we can use to create such spheroids. Their formation is not associated with physical strength, but with the changes in cell behavior—a small amount of a special peptide is added to them as they begin to migrate, and they independently stick together in neat little balls, each of which consists of several hundred individual cancer cells. Since this method does not require mixing the environment or any other severe physical intervention in a cell's life, it is well suited for studying the very minute biochemical factors that influence the cells' ability to form spheroids."

Roman and his colleagues found that increasing the number of α-2,3 linkages and reducing the level of α-2,6 sialic acid linkages leads to a greater adhesion of cells in spheroids. Within the human body, this is most likely a good sign, since the stronger the tendency of cells to fuse together, the less likely that one of them will break away and begin forming new tumors. If, under these conditions, the enzymes that the sialic acid gets rid off are suppressed, the cells are also more likely to stick together.

This is exactly how the oseltamivir antiviral drug acts. Queen's University researchers demonstrated that this drug affects the formation of metastases. In an experiment that involved a very malign, highly dangerous type of breast cancer, they injected the drug into the blood of mice in order to block the enzymes that remove sialic acid from the cell

surface, and managed to suppress the formation of secondary tumor lesions. Interestingly, everyone is skeptical about osetalmivira's antiviral effect (Osetalmivira can be bought at any local pharmacy under the brand name Tamiflu) because it has not yet been conclusively proven that it can deal with cancer.

In another method that involves manually removing the acid from the surface of a cell, or blocking its linkages, the tumor spheroids are not formed.

"In this way, we learned that by adjusting the total amount of sialic acid on the surfaces of cancer cells and changing the ratio of α-2,3 and α-2,6 linkages, we can manipulate the cells to achieve either their aggregation (i.e. sticking to the balls) or suppression . For cancer treatment, we will probably need to enhance the aggregation of cells to prevent the formation of metastases," concludes Roman.

Using tumor spheroids as a testing system will be essential in searching for and developing new drugs that will be used to modulate cell aggregation. This will bring us closer to understanding the biology of cancer.

More information: Sialylation transmogrifies human breast and pancreatic cancer cells into 3D multicellular tumor spheroids using cyclic RGD-peptide induced self-assembly. *Oncotarget*. DOI: 10.18632/oncotarget.11868

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