New inhibitor has potential as cancer drug

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Laboratory experiments have previously shown that cancer cells overproduce an enzyme, heparanase, which splits the body's own polysaccharide heparan sulfate into shorter fragments. The amount of enzyme is related to the degree of malignancy. Today a study is being published in the journal *Nature Chemical Biology* in which Uppsala University researchers show, on the basis of animal models, that an inhibitor for heparanase would be extremely interesting as a drug candidate.

Heparan sulfate is a polysaccharide, that is, a chain of linked sugar units, with sulfate groups in different positions. These chains are found on the surface of practically every cell in the body. The sulfate groups enable binding to a number of proteins, such as inflammation proteins and growth factors. Heparan sulfate can thereby regulate different processes in the body, during embryonic development, for example, but also in various conditions of sickness. The capacity for protein-binding generally increases the more sulfate groups there are on the polysaccharide.

The enzyme heparanase splits heparan sulfate at certain points and converts the long chains into shorter fragments. Research at other laboratories has shown that cancer cells in many cases overproduce heparanase and that the amount of heparanase correlates with the degree of malignancy of the cancer cells and their capacity to metasthesize. The connection is believed to have multiple explanations. Heparanase helps cancer cells make their way through tissue barriers, but it also stimulates the heightened generation of blood vessels that is necessary for tumor growth. The fragments function as carriers of growth factors that can promote tumor growth in many ways.

In the current project the scientists introduced the gene for human heparanase into a mouse, so that the enzyme would be overproduced in several organs. Besides the expected splitting of heparan sulfate, they found that the metabolism of the polysaccharide was stimulated, but that the number of sulfate groups increased at the same time. The 'high-sulfated' fragments released by the enzyme evince dramatically increased binding to certain growth factors of potential importance to tumor growth.

When they examined heparan sulfate from authentic cancer cells instead, or from cancer tissue that had overproduced heparanase, it was found that here too there was an increase in the number of sulfate groups compared with heparan sulfate from corresponding normal cells/tissues. The findings indicate that producing an inhibitor for heparanase is an urgent step in discovering new drugs for cancer.

Source: Uppsala University