Cancer mutations convert an inhibitory protein into an accelerator for tumor growth

Cancer-inhibiting proteins, so-called tumor suppressors, play an important role in the prevention of uncontrolled cell division. This prevents tumor formation; similar to a brake in a car. Researchers from the UMC Utrecht have now shown that the generation of a fragment of these proteins leads to a switch in their function, turning the brake into a gas pedal. These insights generate a better starting point for new and more precise treatments.

A general assumption is that tumor suppressors in cancer are turned off by changes (mutations) in the DNA. This would cause the brake to disappear to drive the development of tumors. However, mapping the mutation landscape of different cancer types shows that mutations do not always completely eliminate tumor suppressors. Sometimes a fragment of the protein is still produced. The role of these defective proteins in cancer is so far unknown. Researchers from the UMC Utrecht now show that these protein fragments can play a new role in cancer cells and can function as an accelerator for cancer growth. The research was published in EMBO journal on August 11.

Mutations drive colon cancer growth

Previous studies showed that the tumor suppressor RNF43 inhibits the growth of colon stem cells thereby preventing the formation of precancerous tumors. Since then, multiple cancer types were found to carry changes in the RNF43 gene. The loss of this gene makes cells hypersensitive to the growth signal Wnt, which stimulates tumor growth. Therefore, patients that carry these mutations possibly can be treated with inhibitors of these growth signals: anti-Wnt therapy.

Converting brake into gas pedal

The research group of professor Madelon Maurice of the UMCU Center for Molecular Medicine and Oncode Institute now discovered an aberrant group of mutations that do not cause RNF43 loss, but rather mediate shortening of the protein. These shortened proteins acquire new properties that enable them to actively stimulate cell division even in the absence of Wnt growth signals. By applying these mutations in cultured mini intestines (intestinal organoids), the researchers showed that tumor cells with these mutations become insensitive to anti-Wnt therapy. “Our findings show that it is important to understand how the range of mutations that occur in patients' tumor tissues promote tumor growth,” Maurice says. "This allows us to better predict sensitivity to therapies and to develop more personalized treatment strategies for patients in the long term."