

Key piece identified for slowing a colorectal cancer subtype

August 2 2018

Inhibiting the Jagged 1 protein in mice prevents the proliferation and growth of colon and rectal tumours. What is more, this approach to the disease permits the removal of existing tumours. This is the conclusion of a study led by the Molecular Mechanisms of Cancer and Stem Cells research group from the Hospital del Mar Medical Research Institute (IMIM), directed by Dr. Lluís Espinosa, who is also a member of CIBERONC (the Network Centre for Biomedical Research into Cancer), in collaboration with the Pathological Anatomy and Medical Oncology Units at Hospital del Mar, and the IDIBELL-Catalan Oncology Institute. The work has been published in *Nature Communications*.

The researchers took tumours from patients and then implanted them into mice in order to analyse the role of this protein in [cancer](#) cell proliferation. Jagged 1 is essential for cancer cells due to its role in activating the so-called Notch cell-signalling pathway. Generally speaking, Notch inhibits cell differentiation—in other words, a cell's ability to become a mature cell that can no longer proliferate. In the case of colorectal tumours, the activation of this signaling pathway favours their proliferation and growth. In this study, the researchers discovered that the intestinal tumours of mice lack a protein known as Fringe, implying that Jagged 1 is essential for activating Notch. "The fact that Fringe is present in the normal cells of the small intestine represents a significant therapeutic opportunity for treating patients with colorectal cancer," says Dr. Espinosa, since by inhibiting Jagged 1 you can halt [tumour](#) growth without affecting the function of normal tissue.

In fact, researchers have been able to see how, in the case of healthy mice, the colon and rectum do not need Jagged 1, since in the presence of the Fringe protein there are other mechanisms for activating Notch. This need to have Jagged 1 in order to activate Notch in the absence of Fringe was observed in 239 of the cases of human tumours that were analysed. Therefore, inhibiting this protein could enable doctors to combat the disease without affecting the functioning of the body. Dr. Espinosa explains that "we implanted human tumours with Jagged 1, without Fringe, into mice and then we treated them with antibodies. Post-treatment, the tumours were very small and had necrosed." In the study, the tumours had shrunk after 10 weeks of treatment.

Prognostic factor

The study also enabled the researchers to demonstrate that Jagged 1 protein levels in patients with colorectal cancer is a prognostic indicator. Where levels are high, the disease rapidly becomes worse. The researchers believe that this way of treating the cancer is very promising and there are already several pharmaceutical companies working with specific antibodies to inhibit Jagged 1. Even so, the work that has just been published is a preclinical trial, and not yet transferable to patient treatment.

In this regard, Dr. Joan Albanell, one of the authors of the study, head of the Medical Oncology Unit at Hospital del Mar, and director of the IMIM's Cancer Research Programme, points out that "these results lead the way towards therapeutic strategies for selectively deactivating the properties of malignant multipotent stem cells in colon cancer. It is now very important to continue this research so that in the next few years it can culminate in clinical trials for patients with [colorectal cancer](#). For these people, the identification of new therapeutic targets is essential."

Colorectal cancer

This is the most common type of cancer in Catalonia, with more than 6,000 new cases every year, and the second leading cause of cancer death. The frequency of colon cancer is similar in men and women, while rectal cancer is more common in men.

In 2017, 6,201 people were diagnosed in Catalonia and 2,700 died. For Spain as a whole, the number of patients diagnosed exceeded 34,000, making it the most prevalent cancer in the country. Mortality, however, has gone down 5.3% in men and 6.7% in women since 2012, thanks to the success of early detection programmes, like the Early Detection Programme for Colorectal Cancer, a joint action between Hospital del Mar and Hospital Clínic that has been running since 2009.

More information: Erika López-Arribillaga et al, Manic Fringe deficiency imposes Jagged1 addiction to intestinal tumor cells, *Nature Communications* (2018). [DOI: 10.1038/s41467-018-05385-0](https://doi.org/10.1038/s41467-018-05385-0)

Provided by IMIM (Hospital del Mar Medical Research Institute)

Citation: Key piece identified for slowing a colorectal cancer subtype (2018, August 2) retrieved 24 April 2024 from <https://medicalxpress.com/news/2018-08-key-piece-colorectal-cancer-subtype.html>

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