Open access to a potential new drug target for bowel cancer

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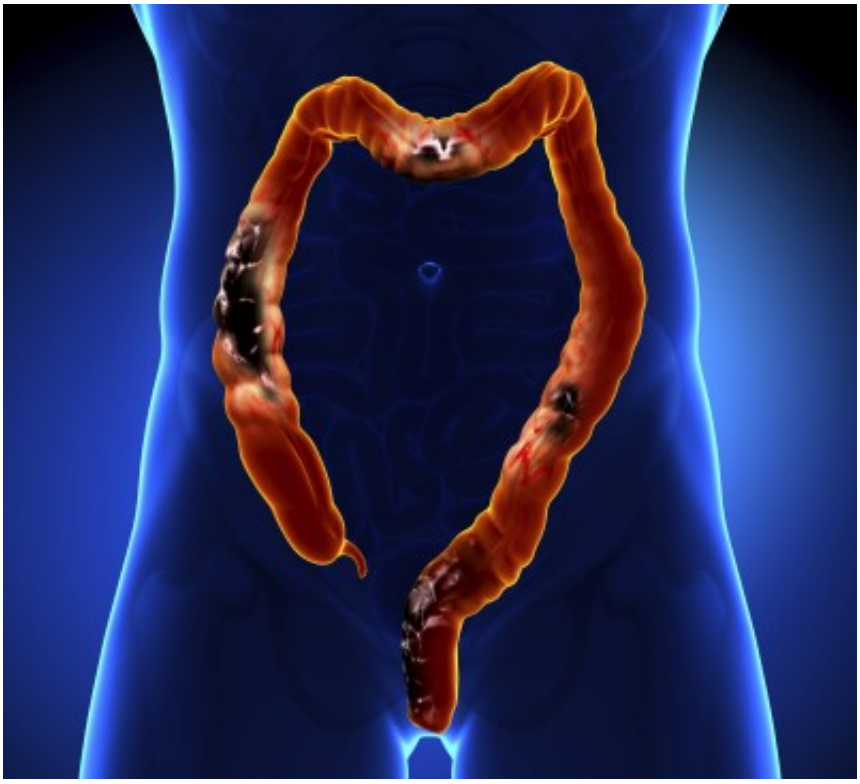

Monash and international researchers have discovered a protein that may be crucial in the development of 90 per cent of colon cancers, and may also be involved in the causation of several other cancers, including breast and liver cancers.

The study, published recently in *Developmental Cell*, is the work of an international collaboration between Australian, Japanese, US and Canadian researchers led by Professor Colby Zaph, from the Biomedicine Discovery Institute at Monash University.

The research is focused on a protein called SETD7, an enzyme that modifies other proteins to affect their function. SETD7 is a central regulator of two of the major pathways to tumorigenesis that merge to create cancerous cells. These two pathways, called the Hippo/YAP and Wnt/beta catenin pathways, have both been highly associated with causing the unlimited growth that is the hallmark of cancers. Research had previously shown that these pathways are related, but the mechanisms that linked them have remained elusive until now.

The study found that SETD7 is an important link between these pathways. SETD7 modifies YAP, which is a critical step in the activation of the Wnt pathway.

"In effect, SETD7 is an important molecular switch that controls two of the main pathways that lead to intestinal cancers," Professor Zaph said.

Professor Zaph and colleagues showed that in the absence of SETD7, tumours took significantly longer to develop and the tumours that did develop were much smaller.

"Inhibiting SETD7 does not cure cancer or completely stop its development, but it does significantly delay development and growth," said Professor Zaph.

In 2012, there were an estimated 15,840 cases of colon cancer diagnosed in Australia. This made up 7.6 per cent of all cancer cases, making bowel cancer second only in incidence to prostate cancer.

The study arose from a collaboration of international scientists, including some in pharmaceutical companies, called the Structural Genomics Consortium (the SGC), which provides chemical probes against disease-associated proteins in the hope this will lead to new therapeutic approaches for cancer, diabetes, obesity, and inflammatory and psychiatric disorders.

Aled Edwards, head of the SGC said, "This collaboration is a perfect example of how open-access research between academia and industry can work. Professor Zaph's research identified a possible new approach to colon cancer, and his open collaboration with Pfizer's world-leading chemists provided him with a new chemical probe to test his idea. Their findings provide a strong rationale to further develop his idea".

Professor Zaph cautioned that the results are preliminary and decades from being translated but that the patient group most likely to benefit from this research are those with Familial adenomatous polyposis (FAP), a genetic disorder that increases an individual's chance of developing colon cancer.

"At the moment, to the best of our knowledge, there aren't any drugs available to patients that directly target the Wnt or Hippo pathways, which we know can lead to cancer, so our discovery that SETD7 is involved in these pathways and that the protein can be inhibited by a small molecule may be a step towards a treatment for colon, and potentially, other cancers.

"What this study highlights is that the development of cancer is very complex and that through open-access sharing of information and reagents progress can be made," Professor Zaph said. "The identification of SETD7 as a potential novel drug target to treat cancer only happened because of the SGC and its open-access principles."

More information: Menno J. Oudhoff et al. SETD7 Controls Intestinal Regeneration and Tumorigenesis by Regulating Wnt/β-Catenin and Hippo/YAP Signaling, *Developmental Cell* (2016). DOI: 10.1016/j.devcel.2016.03.002