

Specific diets may help prevent colorectal cancer in high-risk groups

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Colorectal cancer is the most prevalent malignant tumor in Spain. It is known that factors such as diet and intestinal inflammation play an important role in its occurrence, but direct links between nutrients, inflammation and colorectal cancer are poorly described. Researchers at the Spanish National Cancer Research Centre (CNIO) have discovered that the amount of protein in our diet may be an important factor in the prevention of colorectal cancer in different risk groups. People already suffering from inflammatory bowel disease could benefit from a high-protein diet; however, in contrast, low protein consumption may be the best option for those people who have a genetic predisposition to develop colon cancer.

Furthermore, the article reveals that a certain type of drug used against colorectal cancer, mTORC1 inhibitors, would be more effective in patients with a genetic predisposition, which “opens up avenues for optimising and personalizing treatments,” the researchers write in their publication in the *Cell Metabolism* journal.

Every year, more than 40,000 new cases of colorectal cancer are diagnosed in Spain, a deadly disease that is highly resistant to the treatments currently being used. Over 75% of cases of colorectal cancer are attributable to environmental causes since they are not associated to genetic risk factors.

Everything suggests that habits such as a poor diet, a lack of physical exercise and smoking may affect the digestive system and trigger inflammatory conditions, such as Crohn's disease

and ulcerative colitis, illnesses which often lead to colorectal cancer. However, the precise mechanisms linking diet, inflammation and colorectal cancer are not very well known.

In order to study them, Nabil Djouder, head of the Growth Factors, Nutrients and Cancer Group at the CNI0, focused upon mTORC1, a protein complex which works like a nutrient sensor. The researchers produced several genetically-modified mice in order to understand the function of this sensor in the body, and they verified the results using human samples of intestinal inflammation (derived from Crohn's disease and ulcerative colitis) and colorectal cancer.

Some treatments for colon cancer act upon mTORC1, specifically to inhibit its activity, but at the clinic, it was observed that in certain patients, mTORC1 inhibitors are practically ineffective.

Djouder's work shows that the inactivation of mTORC1 can better be beneficial in colorectal cancers with a significant genetic basis, specifically in those patients with mutations in the APC gene, which represent less than 5% of the total.

The dual function of mTORC1

This new study also provides information about colorectal cancers, which encompass the vast majority and which occur in people with intestinal inflammation and without hereditary mutations in the APC gene. The researchers state that the strategy for preventing tumors in patients with intestinal inflammation should be to promote mTORC1 activity.

Researchers have found that if mTORC1 is inactivated in mice with an inflammatory disease, the cancer spreads.

When there are hereditary mutations in the APC gene and mTORC1 is inhibited, "it is likely that the combination of both types of damage generates such high chromosomal instability in the

cells that they die, and the tumor does not progress,” explains Djouder. However, when the inactivation of mTORC1 alone limits the damage to low chromosomal instability, an excessive inflammatory response ensues, which increases proliferation of cells with low chromosomal instability, triggering the regeneration of the damaged tissue and the development of this type of cancer.

As such, the key to this dual effect of mTORC1 may lie in the amount of damage inflicted on the cell in both situations. In other words, if the colorectal cancer is due to APC mutations, it is advisable to inhibit the mTORC1, and if it is associated to intestinal inflammation, this protein should be activated. This is where diet comes into play, since the activation of mTORC1 can be regulated through food.

High-protein or low-protein diet

Researchers describe how a high-protein diet, using whey protein supplement, a source of high proteins, for example, promotes mTORC1 activity and reduces the formation of tumors in mice with chronic gastrointestinal inflammation.

On the other hand, “a low-protein diet may be an option for preventing colorectal cancer in patients with a genetic predisposition, for example, those who have APC mutations, whereas high-protein diet may protect patients of developing colorectal cancer with inflammatory bowel disease”, they state in *Cell Metabolism*.

“Our results may have important implications for the clinical use of mTORC1 inhibitors, such as opening up new avenues for optimising and personalizing colorectal cancer treatments,” they add.