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In colorectal cancer, lipid metabolism is a targetable metabolic vulnerability

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Abstract

According to the World Health Organization, Colorectal Cancer (CRC) is the second biggest cause of cancer-related deaths. It is still a major public health issue around the world. Despite recent breakthroughs in early detection tests and treatment choices that have lowered CRC mortality in industrialized countries, the global incidence of CRC has been continuously rising. CRCs have recently been diagnosed in a growing proportion of people under the age of 50. The causes of this disturbing trend are unknown, but recent evidence suggests that dietary fat intake and obesity may be key contributors to the rising risk of early-onset CRC. Multiple investigations have shown the link between CRC and lipid changes, suggesting that lipid metabolism has a significant impact on the onset and course of CRC and is a targetable vulnerability in this illness.

Fatty Acids (FAs), glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids, and polyketide are hydrophobic macromolecules divided into eight categories based on the presence of ketoacyl and isoprene groups. FAs are structural components of complex lipids that have numerous functions in the human body. FAs are crucial energy metabolism substrates, as well as necessary components for maintaining the structure and fluidity of all cell membranes. They also serve as building blocks for more structurally complex lipids. Lipids are involved in a variety of tasks, including signal transduction, intracellular trafficking, cell secretion, and motility, in addition to their role as energy substrates and structural components.

In CRC, dysregulation of lipid metabolism in cancer cells, which is becoming more well recognized as one of the hallmarks of aggressive cancer, is linked to a worse prognosis and shorter disease-free life. Fatty acid production was shown to be increased in 86 percent of aberrant crypt foci from patients with sporadic CRC or familial adenomatous polyposis, indicating its importance from the earliest stages of colonic neoplasm formation. Patients with locally advanced, unresectable, or metastatic CRC had different sphingolipid and glycerophospholipid profiles than healthy volunteers, according to research. In general, CRC cell lines and tumour cells extracted from CRC patients have greater total levels of all phospholipid classes than cells produced from normal mucosa.

FAs are readily absorbed into cellular triglycerides, which are the predominant type of lipid storage and a major source of energy in the human organism, whether by endogenous synthesis or external uptake. Excess triglycerides and cholesterol are retained in lipid droplets in cancer cells, and CRC has been found to have a higher number of lipid droplets than normal colonic tissues. Raman spectroscopic imaging indicated that CRC stem cells have more lipid droplets than differentiated counterparts, and the number of lipid droplets directly correlates with well-accepted CRC stem cell markers like CD133 and Wnt pathway activation. Interestingly, lipid droplets are utilised to supply a valuable source of Adenosine Triphosphate (ATP) and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) during metabolic stress, in addition to maintaining lipid homoeostasis and preventing lipotoxicity.

Serum lipid profiling is also a promising route for finding new cancer biomarkers. Several studies have shown that

blood lipid profile can distinguish CRC patients from healthy people and can be used as a diagnostic tool for early-stage CRC. CRC patients can be identified from healthy controls and individuals with colorectal polyps based on serum levels of linoleic and linolenic acid, according to an analysis of 234 serum samples from three groups of patients (66 with CRC, 76 with polyps, and 92 healthy controls). CRC patients had about 50% lower serum concentrations of linolenic acid than healthy controls in another study, leading the authors to propose it as a biomarker for CRC risk. Triglyceride levels are higher in advanced-stage CRC patient's plasma than in early-stage CRC patients' plasma, according to an analysis of plasma from CRC patients.

Determining the variations in lipid metabolism and lipid profiles between CRC patients and healthy people can lead to the development of not just biomarkers and diagnostic tools, but also treatment targets for CRC.

FAs can be acquired from the food or generated from carbohydrate precursors in mammalian cells. In contrast to normal epithelial cells, malignant cells generate the bulk of FAs from scratch, regardless of the availability of extracellular lipids. FASN, a major enzyme in lipid biosynthesis, catalyses the conversion of acetyl-CoA, malonyl-CoA, and NADPH to palmitoyl-CoA. Through the activity of stearoyl-CoA desaturase and the elongation of very long chain fatty acid proteins, palmitate can be extended and desaturated to form other FA species such as stearate and oleate, which can then be used to make more complex lipids.