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Mini-review

Cellular metabolism in colorectal carcinogenesis: Influence of lifestyle, gut microbiome and metabolic pathways

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ABSTRACT

The interconnectivity between diet, gut microbiota and cell molecular responses is well known; however, only recently has technology allowed the identification of strains of microorganisms harbored in the gastrointestinal tract that may increase susceptibility to cancer. The colonic environment appears to play a role in the development of colon cancer, which is influenced by the human metabolic lifestyle and changes in the gut microbiome. Studying metabolic changes at the cellular level in cancer be useful for developing novel improved preventative measures, such as screening through metabolic breath-tests or treatment options that directly affect the metabolic pathways responsible for the carcinogenicity.

1. Introduction

Historically unparalleled access to excessive amounts of food and a predominantly sedentary lifestyle in modern society has resulted in an increasing epidemic of "metabolic syndrome". Metabolic syndrome is a complex of interrelated risk factors for cardiovascular disease (stroke and cardiac infarction) and diabetes. Risk factors include dysglycemia, high blood pressure, elevated triglyceride levels, low high-density lipoprotein cholesterol levels, and obesity. Many suggested definitions exist, but a recent consensus proposed that 3 abnormal findings out of 5 would qualify a person for metabolic syndrome [1]. Notably, the associations between and clustering of these factors have been known for decades. More recently, interest has focused on the involvement of insulin resistance as a linking factor, although the pathogenesis remains unclear and diagnostic criteria have not been established. Central to the understanding of metabolism and cancer is the relationship between epidemiological metabolic risk factors and diet, the relationship between diet and changes in metabolism per se and how alterations in metabolism may occur through changes in the gut microbiome, which is also affected by dietary intake [2–6]. Eventually, these external influences may have internal effects on cellular metabolism, and the mitochondria may be key players [7–9], in the increased susceptibility of cells to becoming cancerous (Fig. 1). Recently, high-throughput sequencing of the human microbiota inhabiting the gastrointestinal (GI) tract has demonstrated that specific gut microbiomes are correlated with specific metabolomic markers [10]. Furthermore, understanding the gut microbiome, which can be altered with lifestyle changes, such as changes in diet and body weight [11], has the potential to elucidate the interconnectivity between these conditions and improve the prevention, diagnosis and treatment of diseases, including cancer.

In this review, we investigate some of the current concepts in cancer development with respect to metabolism in the human body and within cells. In particular, we focus on the effects that certain nutrients and metabolic alterations have on colorectal cancer cells. This knowledge may improve preventive measures, diagnosis and treatment and provide a better understanding of the disease.

2. Colorectal carcinogenesis

Colorectal cancer (CRC) is one of the most frequently occurring forms of cancers worldwide, causing as many as 600,000 deaths annually, and represents a high disease burden to society [12–14]. The lifetime risk of CRC in the Western population is estimated

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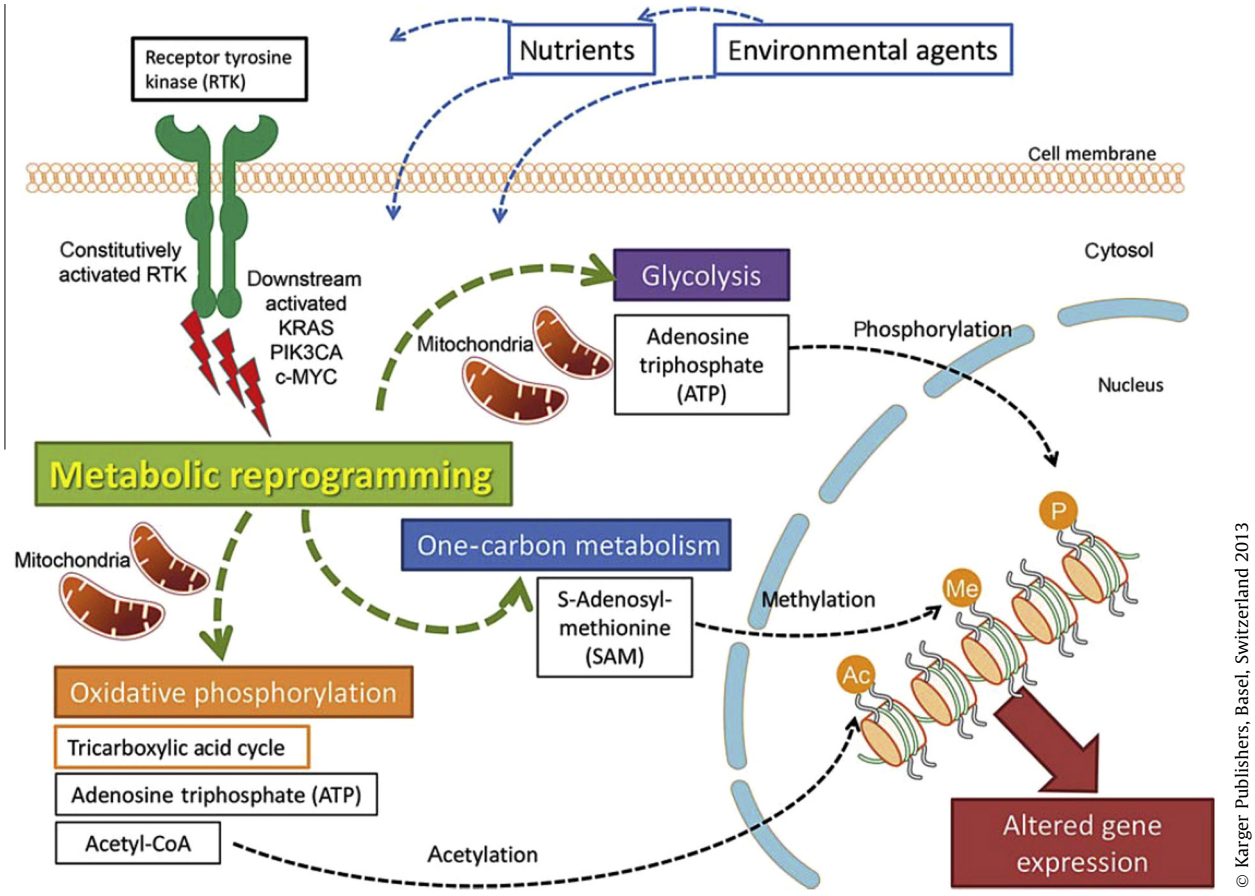

Fig. 1. Altered cellular energy metabolism in cancerogenesis. Reproduced with permission from Hagland et al. in Digestive Surgery, 2013.

to be 5–6% [15,16], with >90% of cases of sporadic or unknown origin and <10% caused by known hereditary cancer syndromes [17,18]. Most sporadic cases (85%) present with chromosomal instability (CIN), which results in cell aneuploidy, whereas the remaining cases (15%) have microsatellite instability (MSI) phenotypes [19]. MSI tumors are characterized by single nucleotide mutations in repetitive DNA sequences found throughout the genome [20]. Affected genes include MLH, MSH2 and MSH6, which control the DNA mismatch repair machinery [20]. Another common observation in colon cancer is the hypermethylation of CpG islands, most often found in the promoter areas of genes. Hypermethylation of CpG islands affects gene transcription epigenetically. In sporadic MSI cases, hypermethylation of the promoter regions of MLH1 is often observed and causes the nucleotide mutations typical of MSI [21,22]. These tumors are characterized by proximal location, poor differentiation, mucinous histology and lymphocytic infiltration [19]. In addition, MSI tumors have a pronounced susceptibility to PI3K inhibitors, suggesting that they are particularly dependent on this pathway [23]. The localization of a CRC tumor appears to dictate commonalities that have been suggested as classification markers for CRC, such as MSI, CIN and CpG island methylation (CIMP). The macromolecular milieu in the colon may therefore play a significant role in the development of these tumors, which is why lifestyle-related factors are being heavily investigated as instigators of tumorigenesis in sporadic CRC [24–27]. Finally, CRC may develop in an inflammatory background resulting from severe and chronic activity in inflammatory bowel disease (Crohn's disease or ulcerative colitis). Contrary to the early reports of a very high cancer risk in these patients, primarily populations with severe disease investigated in tertiary referral centers, many later epidemiological follow-up studies have demonstrated only a moderately increased risk of cancer development, which is likely greater for Crohn's disease than ulcerative colitis [28]. However, compared with sporadic or hereditary CRC, risk is increased, and the mechanisms appear to be different. The involvement of microbiota in the damaged epithelium has garnered interest and serves as an investigational model for inflammation carcinogenesis. A recent overview, including proposed molecular mechanisms, has been reported in this Journal [29] and is beyond the scope of this review.

3. Diet, lifestyle and cancer risk

Risk factors for developing colon cancer include age, male sex, previous colonic polyps, previous CRC and environmental factors [19], such as diet, weight and general lifestyle. An increasing number of patients are being diagnosed with metabolic syndrome, including obese patients and patients with type 2 diabetes, cardiac disease and GI disorders in the Western world. High caloric intake and reduced activity are the main contributors to the development of these metabolic syndromes, and genetic predispositions are also risk factors. A high body mass index (BMI) and waist circumference are clear risk factors for CRC, although little is known about the connection between these parameters and the different molecular disease subsets. The epigenetically modified CIMP in CRC was recently investigated to determine the associations between BMI and known methylation patterns. No significant association was observed between high BMI and CIMP or non-CIMP status [30], which was somewhat surprising. However, other studies have demonstrated that childhood and adolescent height and weight play a role; energy restriction at a young age decreased the risk of CRC later in life [31–33]. Moreover, severe energy restriction

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