Cancer Letters 356 (2015) 273–280

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

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

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ARTICLE INFO

Article history:
Received 30 November 2013
Received in revised form 5 February 2014
Accepted 28 February 2014

Keywords:
Colorectal cancer
Diet
Microbiota
Butyrate
Mitochondria
Energy metabolism

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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http://dx.doi.org/10.1016/j.canlet.2014.02.026
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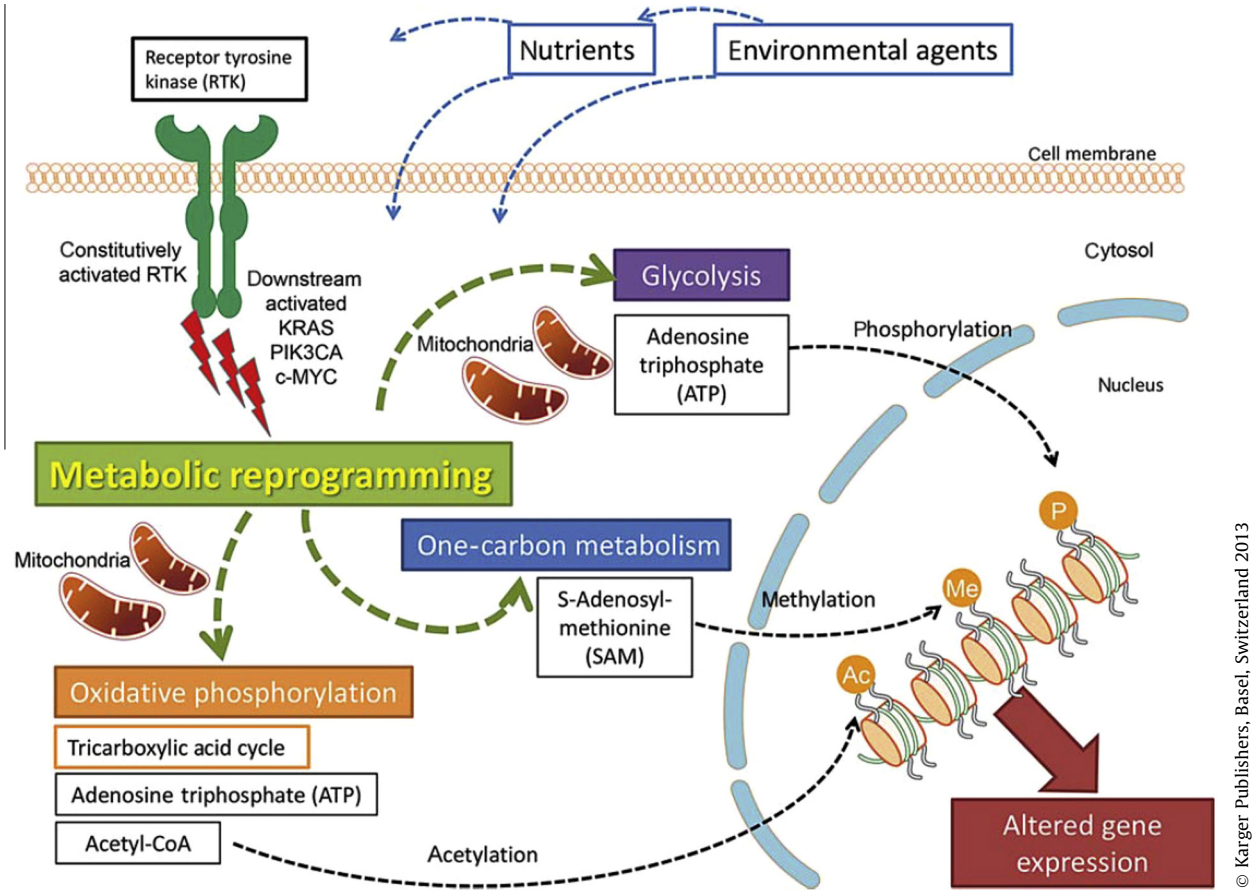

Fig. 1. Altered cellular energy metabolism in cancerogenesis. Reproduced with permission from Hagland et al. in Digestive Surgery, 2013.

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

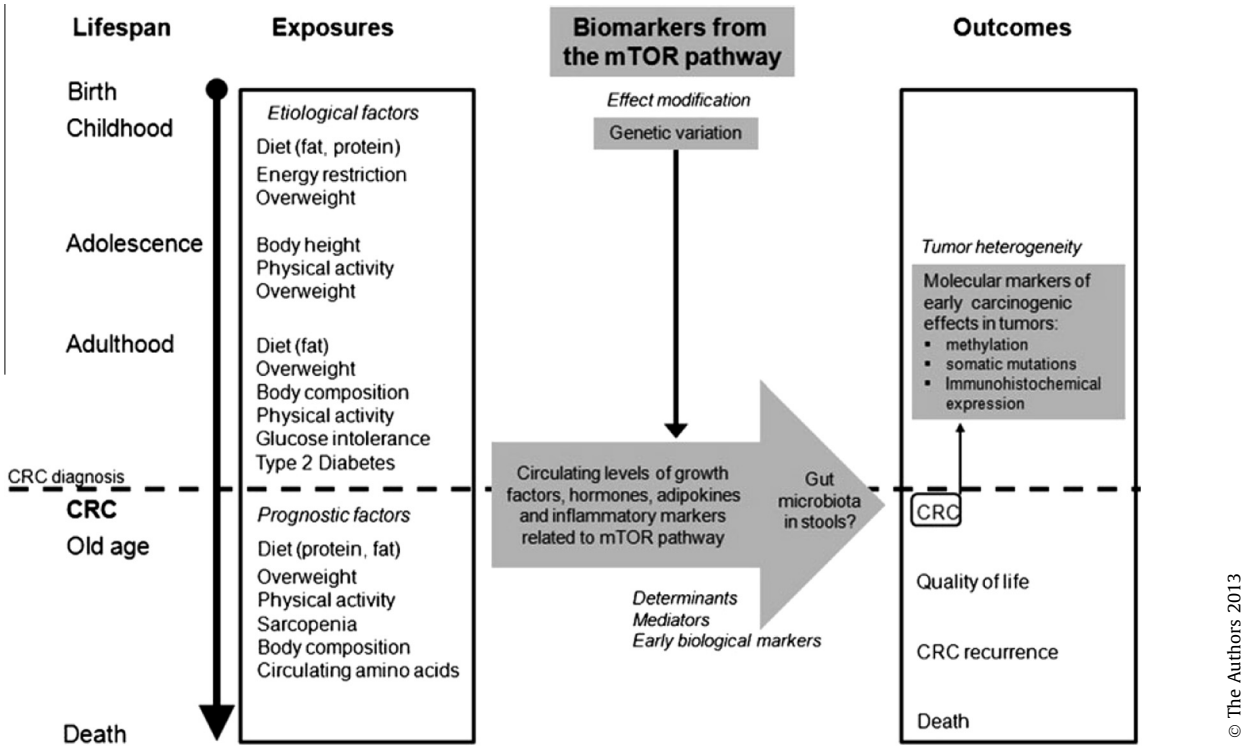

Fig. 2. Multidimensional, complex interplay between lifespan, exposure and outcome. Illustration of the multidimensional, complex interplay between lifespan exposures related to eventual outcomes, which underlies the investigation of potential biomarkers or risk mediators, illustrated here by the mTOR pathway. Curr. Nutr. Rep. 2013 March;2(1):19–26.

during childhood and adolescence has been associated with a low risk of developing a CIMP tumor [34]. Energy restriction and its protection against cancer is not a new phenomenon, as this association has been reported in a number of studies over the years, although many are experimental studies performed in rodents (for an extensive review, see [35]). Studies investigating obesity in relation to epigenetic molecular metabolic profiling and cancer risk have also been published [36]. However, it appears that the timing of energy restriction, i.e., during childhood, adolescence or adulthood, influences cancer prevalence [37]. The precise molecular mechanism behind this phenomenon has yet to be defined, although some candidate pathways have been suggested [38–42]. Investigation into the complex field of molecular epidemiology and risk assessment of the relationship between lifestyle and exposure and the eventual outcome are challenging, as shown for the mTOR pathway in Fig. 2. Nonetheless, increased knowledge in this area may address whether the timing of exposure to energy intake (be it excessive or restrictive) and the resultant BMI values influence epigenetic changes in cancers later in life. Indeed, a multidisciplinary and integrated research field has been created to better understand the biology of disease [43,44]. While metabolic syndrome, insulin resistance and adiponectines serve as risk modifiers for neoplasia development in obesity, other proposed mechanisms (such as gut microbiota and bile acids) continue to be controversial [45], as outlined in the summary model in Fig. 3.

4. GI tract microbiome and influence on colorectal cancer

A healthy human body contains at least tenfold more bacterial cells than human cells, and the most abundant and diverse microbial community resides in the intestinal tract. The GI tract harbors the largest quantity of microbes by far, estimated at approximately 100 trillion, as much as tenfold more than all of the somatic and germ cells in our body [46,47]. The symbiotic relationship between the human cells and microbiota in the human body is not well understood and clearly requires further investigation. An increasing body of knowledge suggests that the microbiota play an important role in "lifestyle-related illnesses". Several studies have suggested that the microbiota of the GI tract is "inherited" and subsequently modified throughout life by diet or exposure [48–52]. Symbiosis in this multifaceted organ is thus crucial to maintaining a healthy balance within the host-diet-microbiota triangle, and accordingly, changes to any of these three factors may drive a healthy situation into a state of disease. The first exposure to GI microbiota is from the mother through birth [48], whereas babies born by cesarean delivery may experience the microbiota of the hospital as their first encounter to microbes [49]. The intestinal microbiota develop in symbiosis with the cells of the GI tract, and although the precise species and variability of existing microbiota are unknown, there is a general consensus that the human intestinal "core microbiota" at the phylum level are composed of Proteobacteria, Bacteroidetes, Firmicutes and Actinobacteria [53–57]. However, identifying and understanding what makes and distinguishes "good" from "bad" bacteria and how the microbiome may influence human health are considerable challenges.

The influence of some bacteria and viruses on cancer development is well known. It has been estimated that approximately 20% of the global cancer burden is linked to infectious agents [58], and two well-known examples are the induction of cervical cancer by human papillomaviruses and of gastric cancer by Helicobacter pylori [58,59]. Indeed, an increasing amount of recent data supports the hypothesis that CRC can be initiated by bacteria "driving" cancer development, while other "passenger" bacteria strains promote the cancer [60]. Mechanisms of microbial influence on cancer development in the intestinal tract [61–63] include the balance of pro- and anti-inflammatory signals, the direct effects of bacterial enterotoxins on mucosal cells and intracellular pathways and the indirect potential of bacteria in the conversion of pro-carcinogenic dietary factors into carcinogens [64–67]. A thorough understanding of these processes will provide directions

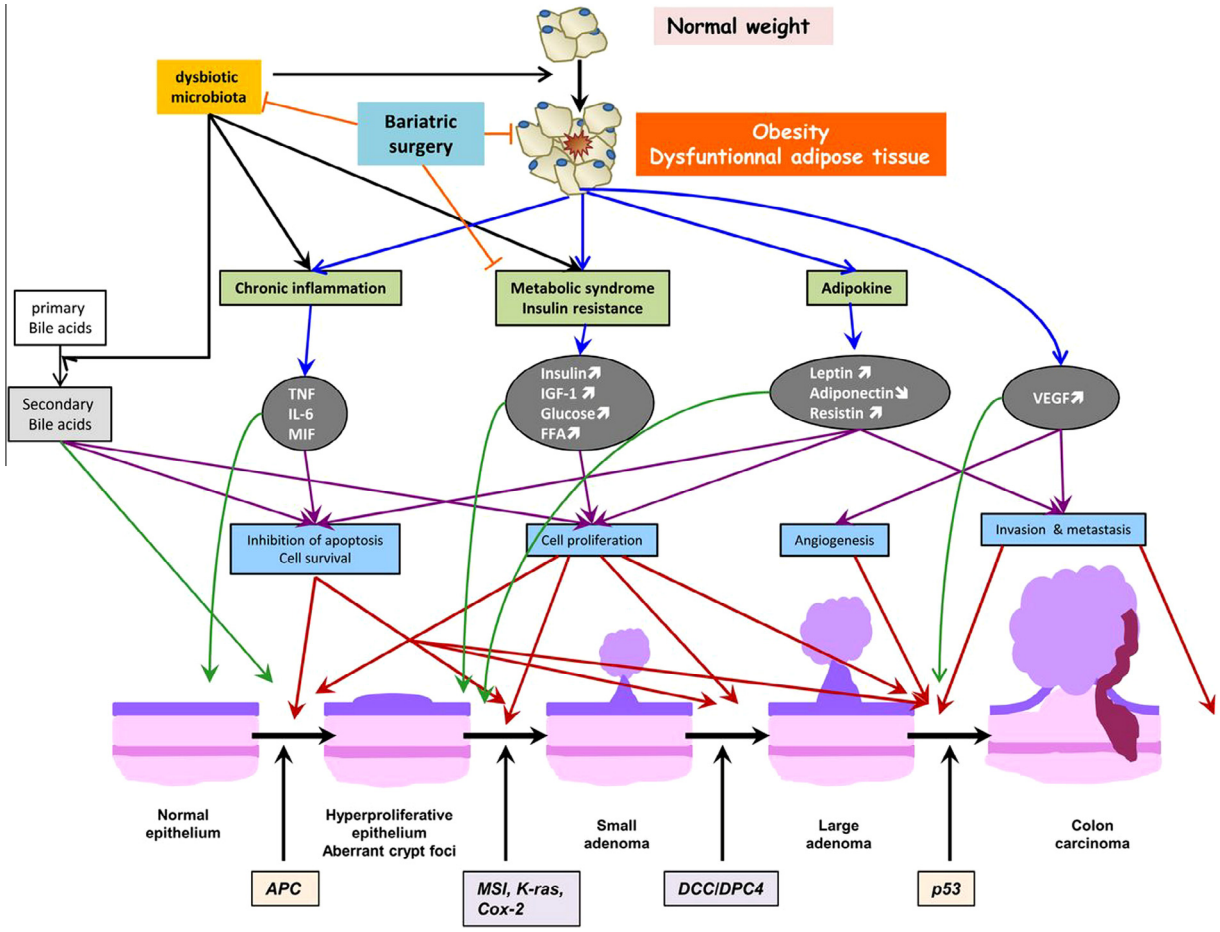

Fig. 3. Mechanistic summary of potential factors linked to obesity, inflammation and colorectal cancer. Blue arrows indicate the metabolic consequences of obesity. Black arrows represent suspected consequences of dysbiotic microbiota. Purple arrows represent cellular events induced by obesity-related metabolic changes. Red arrows localize these cellular events within the carcinogenic process. Green arrows represent the proposed stage of the normal epithelium-to-carcinoma sequence when the different biological factors may start to act. Orange lines indicate some suggested potentially beneficial effects of bariatric surgery. FFA, free fatty acid; IGF-1, insulin-like growth factor 1; IL, interleukin; MIF, macrophage migration inhibitory factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor. APC, Adenomatous polyposis coli; MSI, microsatellite instability, K-ras, Kirsten-rat sarcoma, Cox-2, cyclooxygenase-2; DCC (deleted in colorectal carcinomas), DPC4 (deleted in pancreatic carcinomas, locus 4). Reproduced from Obesity and colorectal cancer, Bardou et al., Gut 2013;62:933–947. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for future research and may ultimately aid in the development of new strategies for CRC diagnosis and prevention.

Metagenomics projects involving high-throughput/next-generation sequencing have been initiated to characterize the microbes within the human body [68–73], in which the gut microbiome is highly enriched for genes involved in energy production and metabolism [47,70]. The intestinal microbe population is heterogeneous and composed of more than 1000 different bacterial species [74]. The bacterial density in the large intestine is 12-fold higher than that in the small intestine. Interestingly, there is an estimated 12-fold increase in cancer risk in the large intestine compared with the small intestine [74]. Functional contributions of the gut microbiota that may influence cancer susceptibility in the broad sense include the following [75]:

- harvesting otherwise inaccessible nutrients and/or sources of energy from the diet (i.e., fermentation of dietary fibers and resistant starch);
- metabolizing xenobiotics, including those that are potentially beneficial and detrimental (i.e., dietary constituents, drugs, carcinogens, etc.);
- renewing gut epithelial cells and maintaining mucosal integrity; and
- affecting immune system development and activity [76].

The fact that the microbiota found in the colon is enriched for genes involved in energy production and extraction, in which carbohydrate metabolism is particularly overrepresented in the family of glycoside hydrolases and polysaccharide lyases [77], begs the question of how these particular microbiota influence colon cell metabolism. Dietary carbohydrates, specifically starches and fiber, are substrates for fermentation by microbes in the colon, which results in short chain fatty acids (SCFAs), such as acetate, propionate and butyrate [78]. Whereas acetate enters the peripheral circulation to be metabolized by peripheral tissues, propionate is largely taken up by the liver, and butyrate is the major energy source for colonocytes [78]. The proximal colon contains the highest number of bacteria and shows the highest fermentation ratios and highest proliferation rates, most likely because substrate availability is best [79]. The total amount of SCFAs in the proximal colon is estimated to range from 70 to 140 mM, and the amount of SCFs falls to 20 to 70 mM in the distal colon [80]. The production of SCFAs is highly dependent on the substrate source and the dietary intake of non-digestible carbohydrates in the form of starches and fiber varies. The colon absorbs water, lipids and minerals from food, and the quantity of substrates available for fermentation decreases from the proximal to distal side [79]. Total SCFA and regional differences in concentration are implicated in colonic diseases, especially in cancer and GI disorders that most often occur distally

[78]. High animal protein intake and a high-fat diet are known risk factors associated with colon cancer. Such diet is common in the western world, whereas in Africa, where the prevalence of colon cancer is relatively low, the staple diet consists of maize meal, which is rich in resistant starch [81]. A study analyzing the colon contents of native Africans, African Americans and Caucasian Americans found that the butyrate concentration was significantly higher in native Africans compared with the two American groups [82]. This supports the notion that the Western diet, which has a higher dietary intake of animal products, may alter the gut microbiota and thus play a key role in carcinogenesis.

The intestinal bacteria composition is relatively stable throughout adult life; however, the strain composition varies from person to person [60]. The "core microbiome" hypothesis states that there are many microbial functions that are genetically similar, but the strains of bacteria may vary at the species level [53,83]. Furthermore, increasing evidence suggests that there is a correlation between the type of bacteria found in the colon and the risk of developing colon cancer [60]. Analysis of microbes in non-tumor sites compared with sites within tumors in the colon of CRC patients has led to the development of the "driver" and "passenger" theory of tumorigenesis, as previously mentioned [60]. The commonly found bacterial strains at tumor sites were Fusobacterium, which function as "passenger" bacteria. Enterotoxigenic Bacteroides fragilis (ETBF) strains of bacteria were found at non-tumor sites and are characterized as "driver" bacteria [84–86].

5. Cellular metabolism and relationship to cancer

Nearly a century ago, the German physiologist and Nobel laureate Otto Warburg made the discovery that cancer cells secreted more lactate than normal cells under aerobic conditions, indicating higher glucose usage compared with normal cells [87]. This discovery was later termed the "Warburg effect" and was initially believed to be caused by a hostile tumor microenvironment that had damaged mitochondria, resulting in higher glycolysis [88,89]. This theory has later been disproven, as most tumor cells still harbor functional mitochondria and use oxidative phosphorylation and glycolysis to support cell growth [89,90]. However, the observation of higher glucose flux through cancer cells remains valid and is also exploited in the 2-fluorodeoxyglucose positron emission tomography (2-FDG PET) scan used to identify metastasis in the clinic today.

This glucose preference and metabolic switch observed in cancer cells is now recognized as one of the hallmarks of cancer [91]. The increase in glycolysis is necessary to support rapid cell growth, and pathways emerging from the breakdown of glucose include the pentose phosphate pathway. This pathway involves the conversion of glucose-6-phosphate and fructose-6-phosphate to ribose-5-phosphate, which is the precursor for nucleotide biosynthesis, and glyceraldehyde-3-phosphate, a precursor for the phospholipids needed to build new membranes. The entire metabolic shift is required to maintain a high proliferation rate, which is predetermined by the different activating mutations in oncogenes and subsequent deactivating mutations in tumor suppressor genes. While the basic metabolic currency is universal to all cells (e.g., NADH, NADPH, ATP, acetyl coenzyme A, GTP), the specific metabolic requirements are controlled by the cellular environment and tissue function. Consequently, highly proliferative cells, such as lymphocytes activated by an immune response, must maintain a high carbon flux to sustain the high use of energy and require biomolecules to support the biosynthesis of new cells [92,93], which explains why common mutations in cancers genes are related to metabolism [94].

One of the most commonly deregulated pathways reported in cancer cells is the phosphoinositide-3-kinase (PI3K)–AKT pathway [95]. In CRC, the WNT/β-catenin pathway, transforming growth factor beta (TGFβ) and epidermal growth factor receptor (EGFR) pathway, with its downstream targets RAS, RAF, and PI3K–AKT [96], are often deregulated. All of the above-mentioned pathways interact with cellular metabolism at some level. Perturbations in the PI3K–AKT pathway in particular have been associated with increased glycolytic flux and glucose dependence [97]. This increase renders cells more resistant to conventional cancer treatments [98] but may make them more vulnerable to other types of treatment [99,100].

Furthermore, it has become evident that many tumor suppressor genes are epigenetically regulated [101,102]. This finding implies that in a state of high energy availability, which is often the case when a cell increases nutrient uptake in response to a growth factor, these genes may be silenced by mechanisms such as methylation. When the extracellular signal that triggers a proliferation event becomes self-autonomous, nutrient uptake and cellular energy will be maintained at a high level, causing the cell to lose the "on and off" epigenetic control of these tumor suppressor genes. The longstanding idea that growth factors directly trigger genetic events that require ATP, therefore shifting the ATP:ADP levels and causing the cell to adapt and increase its metabolic machinery to compensate, is under attack. This previous hypothesis is based on the classic model of single cell eukaryotic metabolism; however, under low nutrient availability, cells maximize the use of nutrients for ATP production, whereas when nutrients are plentiful, cells redirect their metabolism for growth. Thus, it has recently been suggested that the metabolic shift is the first event after growth factor binding and is not a result of ATP decrease. Instead, the shift is a means to increase the supply of reduced carbon, reduced nitrogen and NADPH for reductive biosynthetic reactions, which are critical for the macromolecular synthesis of nucleotides, proteins and lipids to make new daughter cells (Ward and Thompson [90]). Supporting this idea, seven glucose molecules are required to make sufficient NADPH for one fatty acyl molecule, whereas one glucose molecule can produce fivefold more ATP than required for this reaction to occur [103]. Although the value of ATP should not be underestimated, NADPH is also an essential co-factor in proliferating cells [104]. If all available glucose were funneled through glycolysis via the tricarboxylic acid (TCA) cycle to maximize ATP production, the production of NADPH via the pentose phosphate pathway would be stalled, further inhibiting the export of citrate for producing lipids. Conversely, all of the pathways involved in generating molecules for biomass production are dependent on high glucose flux through glycolysis, not ATP production. Furthermore, complete oxidation of each glucose molecule would result in high ATP levels that would induce feedback and shut down glycolysis, something that is avoided by the recycling of ATP to ADP via lactate dehydrogenase and lactate secretion in cancer cells [103].

These metabolic changes common in cancer cells are required for the cells to proliferate. The pathways controlling these changes are most often deregulated, as observed with the PI3K–AKT pathway, and EGFR controls nutrient uptake and intracellular distribution. Our increasing understanding of how intracellular pathways and key effector proteins orchestrate the required uncontrolled growth of cancer cells will allow new drugs to be tested for cancer treatment in the future.

6. The butyrate paradox

"The butyrate paradox" refers to the opposing effects that the metabolite butyrate has on the proliferation of normal versus cancerous colon cells [105]. Butyrate is predominantly produced by the colonic bacteria Clostridia clusters XIVa and IV of Firmicutes from food residues, such as dietary fiber or resistant starch [81]. The oxidation of butyrate in colonocytes supplies more than 70% of the required energy, thereby reducing glucose oxidation and saving pyruvate and glutamine. This phenomenon is likely due to

an evolutionary adaptation based on the most available substrate in this area. The highest butyrate oxidation occurs in the proximal colon [80], whereas butyrate was not detectable in stool samples after a whole gut transit time of greater than 50 h [80], likely due to colonic uptake. Butyrate levels have also been measured [106] by liquid chromatography–tandem mass spectrometry (LC–MS/MS) in the lumen of mouse colons, in which decreasing butyrate concentrations (3.5, 0.8 and 0.5 mM) were observed in the proximal, medial and distal segments, respectively. Butyrate is metabolized in the mitochondria of cells via the β-oxidation pathway in the matrix. It then enters the TCA as acetyl-CoA, which together with oxaloacetate generates citrate via citrate synthase. Citrate can be further metabolized in the TCA cycle to generate electrons for the electron transport chain, fueling ATP production; in cells in which the demand for ATP is relatively low, citrate can be exported out of the mitochondria and converted back to oxaloacetate and acetyl-CoA in the cytosol by ATP citrate lyase. ATP citrate lyase has also been identified in the nucleus, where it is involved in histone acetylation events via histone acetylase transferase (HAT) [101]. Acetyl-CoA is a precursor for building lipids de novo and also is the donor of the acetyl groups found on histones that render genes more readily accessible for transcription by opening the heterochromatin to the more relaxed euchromatin form. Hence, under conditions in which there is a high influx of nutrients generating metabolites, such as ATP and acetyl-CoA, such conditions will impact gene regulation via epigenetic events, such as phosphorylation and acetylation, respectively. Andriamihaja et al. observed that the concentration limit for butyrate metabolism was 2 mM in colon cancer cells [107]. Higher concentrations of butyrate were not metabolized but accumulated intracellularly in the nucleus to work directly as histone deacetylase inhibitors (HDACs) [106,107], causing epigenetic changes that turned on genes that regulate apoptosis rather than inducing proliferation [106]. In both cases, histones are regulated epigenetically by acetylation events, but the outcome differs according to nuclear-localized ATP citrate lyase [106]. In cancer cells, in which there is a metabolic shift towards glycolysis and glucose utilization, it is hypothesized that increased glucose uptake and lactate secretion [108] diminishes the utilization of oxidative phosphorylation and the use of butyrate as a substrate [77]. Therefore, butyrate accumulates in the nucleus and induces apoptosis via HDAC inhibition and the transcription of apoptotic genes [106]. Consistent with the oxidative metabolic capacity of the cells being studied, a concentration range of 0.5–1 mM butyrate corresponded with the acetyl-CoA/HAT mechanism, whereas higher concentrations (2–5 mM) shifted the mechanism to HDAC inhibition.

Furthermore, independent groups have demonstrated that long-term incubation of colon cancer cell lines in culture medium containing butyrate does not increase butyrate oxidation but does lead to its incorporation into cellular lipids, such as phospholipids and triacylglycerides. This effect was dependent on glucose in the culture medium [109]. In this study, glucose was channeled into the pentose phosphate pathway to generate NADPH, which could be used to increase the incorporation of butyrate into lipids. Interestingly, the fact that butyrate was not oxidized in the mitochondria but was stored as lipid droplets in the cells is consistent with another study that demonstrated that carnitine palmitoyl transferase 1 (CPT1) was translocated to the nucleus in CRC tumors while fatty acid synthase (FAS) was increased in the cytoplasm. This action would effectively prevent the fatty acid oxidation of stored lipids in the cytoplasm. Moreover, CPT1 in the nucleus co-immunoprecipitated with HDACs, suggesting an interaction between these proteins. This protein–protein interaction was not observed in normal mucosa tissues in which CPT1 was present in its usual form in the outer mitochondria and functioned as a long chain fatty acid transporter for fatty acid β-oxidation [110].

7. Future directions

The evidence discussed above clearly suggests that there are links between diet and lifestyle, metabolic syndrome and obesity and inflammation and the risk of cancer development. Exactly why, how and through what mechanisms remain to be clearly elucidated. However, the idea that the microbial content of the GI tract can be altered using pre- or probiotics is being tested, and new and improved strains of bacteria with beneficial effects are being developed for this purpose with hopes of influencing disease course and improving health [111]. If there is a symbiotic relationship between an already established tumor and its microbial climate, the notion that a change to this microclimate may also affect the growth of the tumor is intriguing.

Conflict of Interest

The authors have no conflicts of interest to disclose.

Acknowledgements

Work in our lab has been supported by funds from the Folke Hermansen Cancer Fund, the Institute of Surgical Sciences and the Mjaaland Cancer Fund.

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