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Mini-review

Metabolic reprogramming links chronic intestinal inflammation and the oncogenic transformation in colorectal tumorigenesis

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ABSTRACT

The causal connections between chronic inflammation and tumorigenesis are well established and supported by a great deal of evidence and research results over recent decades. Still, many mysteries remain in our understanding of tumor metabolism, not to mention inflammatory-oncogenic transformation. In this review, we examined the Warburg effect and the process of inflammation during tumorigenesis and attempted to extend the knowledge about metabolic reprogramming. This review may establish a useful conceptual framework for understanding the complex pathophysiological process of inflammatory-oncogenic transformation from the metabolic perspective.

1. Introduction

Multiple studies have shown that colorectal cancer (CRC) is one of the most common intestinal malignant tumors, and millions of new cases of CRC are diagnosed worldwide every year [1]. In recent decades, there have been advances in our understanding of the genetic contributions to CRC, including historical changes in risk factors (e.g., reduced smoking and red meat consumption and increased use of aspirin), the introduction and dissemination of screening tests, and improvements in treatment (in mortality rates), resulting in a dramatic decline in the incidence of and mortality from CRC [2,3]. In particular, chronic inflammation has been increasingly shown to contribute to all steps of colorectal tumorigenesis. Old evidence has illustrated that patients who have long-standing inflammatory bowel disease (IBD) are at a high risk of colitis-associated cancer (CAC), which is more likely than any clear-cut genetic predisposition to trigger chronic inflammation of the gastrointestinal mucosa [4,5]. CAC, which is the CRC subtype that is associated with IBD, is difficult to treat and has a high mortality rate [6]. CRC may represent a paradigm for the relation between chronic inflammation and oncogenic transformation of cancer.

The connections between inflammation and cancer are becoming clearer and indicate that inflammation can drive tumorigenesis and tumor progression. Inflammation is a normal physiological response that allows an injured tissue to heal. The cause of the continued inflammation remains elusive. In the case of chronic inflammation, however, the inflammatory process may begin even in the absence of an injury. The hallmarks of cancer-related inflammation include the presence of inflammatory cells and inflammatory mediators (such as chemokines, cytokines, and prostaglandins) in tumor tissues, tissue remodeling, angiogenesis similar to that seen in chronic inflammatory responses, and tissue repair [7].

It is well known that tumorigenesis involves various alterations in cellular metabolism. For instance, cancer cells metabolize glucose in a manner that is distinct from that of cells in normal tissues; this phenomenon is termed the "Warburg effect" [8,9], which is also called aerobic glycolysis [10]. This metabolic switch to aerobic glycolysis is a hallmark of cancer because it facilitates the incorporation of nutrients into cell building blocks (nucleotides, lipids, and amino acids) and into the antioxidant glutathione to produce a new cell [11,12]. Indeed, the metabolic characteristics of cancer cells are not passive responses to damaged mitochondria; rather, they result from oncogene-directed metabolic reprogramming, which is necessary to support anabolic growth [13]. Although the rationale for glycolytic reprogramming in cancer cells remains elusive, enhanced glycolysis may promote the diversion of glycolytic intermediates into various biosynthetic pathways, and this change is important for provision of sufficient amounts of nucleotides, proteins, and lipids for cell proliferation.

Although the notion of metabolic reprogramming in tumor tissues

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seems more convincing and reasonable with increasing evidence, very few studies have addressed the connection between metabolic alterations and chronic inflammation. To gain a better understanding of the role of metabolic reprogramming in the process of chronic inflammation during colorectal tumorigenesis, the connections between metabolic alterations and inflammation-oncogenic transformation are discussed in this review. This review is based on the increasingly sophisticated understanding of tumor metabolism that is derived from works over the last decades. We attempt to convey the emerging paradigms and questions to guide future research and to promote novel therapeutic strategies from the perspective of metabolism to improve patient care.

2. IBD and CRC

Recent evidence suggests that about 20% of all human cancers are linked to pre-cancerous inflammation, and chronic inflammation in the gut in the form of IBD also significantly increases the risk of CRC [14]. IBD, including ulcerative colitis (UC) and Crohn's disease, is characterized by chronic intestinal inflammation, and growing evidence suggests that chronic mucosal inflammation is a key factor in the onset of carcinogenesis in patients with IBD. Although the etiology of IBD remains poorly understood, certain studies suggest that an individual's genetic susceptibility [15], an external environment [16], intestinal microbial flora [17], and immune responses [18] are all involved and are functionally integrated into the pathogenesis of IBD [19,20]. It will be important to determine how specific immune cells, cytokines, chemokines, and microflora members affect intestinal stem cells and epithelial–mesenchymal interactions during tumorigenesis.

The most recent meta-analysis of CRC included a total of 31,287 patients with UC and a total of 293 reported CRCs; the overall prevalence was 0.85% (95% confidence interval [CI] 0.65–1.04). The risks of CRC were 0.02% (95% CI 0.00–0.04) at 10 years, 4.81% (3.26–6.36) at 20 years, and 13.91% (7.09–20.72) at 30 years. In addition, the risk of CRC among Asian patients with UC has been shown to be similar to recent estimates in Europe and North America [21,22]. These rates are lower than those reported in a meta-analysis published in 2001, in which the overall prevalence of CRC among any patients with UC, according to 116 studies, was estimated to be 3.7% (95% CI 3.2–4.2%), and the incidence rates corresponded to cumulative probabilities of 2% by 10 years, 8% by 20 years, and 18% by 30 years [23]. The decrease in risk may be attributed to the widespread use of aminosalicylates (such as 5-aminosalicylic acid, 5-ASA), which are believed to have anti-inflammatory and chemoprotective effects in IBD, to the more liberal and early use of colectomy for medically refractory UC, and possibly, to the use of surveillance colonoscopies [24]. Although only 1% of all cases of CRC occur in patients with IBD, these patients represent one of the highest risk groups for developing this dreaded complication [25].

IBD is widely accepted as one of the important risk factors of CRC, but the pathogenesis of CRC in IBD is poorly understood. Extensive data suggest that the risk of CRC in IBD increases with the duration and extent of colitis, with a familial history of CRC, coexistent primary sclerosing cholangitis, and a greater degree of inflammation [26,27]. Furthermore, other evidence indicates that similar to sporadic CRC, IBD-associated CRC is a consequence of sequential episodes of genomic alteration. Multiple inter-related pathways, including the immune response via mucosal inflammatory mediators, oxidative stress, and the intestinal microbiota, are also involved in the pathogenesis of IBD-associated CRC [28–30].

3. Pathogenesis of colorectal tumorigenesis

The pathogenesis of CRC in patients with IBD involves genetic and epigenetic changes, but the exact process and underlying molecular mechanisms are not clear. The typical molecular pathogenesis of colorectal tumorigenesis is shown in Fig. 1. In general, some of the essential stages of cancer development, including formation of aberrant crypt foci, polyps, adenomas, and carcinomas, are similar between noninflammatory CRC and CAC. Indeed, the progression of CRC typically follows several consecutive steps, which occur in a chronically inflamed mucosa and are believed to take place in the following sequence: no dysplasia-indefinite, dysplasia-low-grade, dysplasia-high-grade, and dysplasia-carcinoma. Tumor progression in patients can skip one or more of these steps [5]. For instance, the “normal mucosa-adenoma-dysplasia-carcinoma” sequence that is typical during sporadic-CRC progression has not been confirmed in CAC, which arises in an inflamed mucosa and develops in the “inflammation-dysplasia-carcinoma” sequence [31,32]. Several studies suggest that many of the genetic alterations that are associated with the development of spontaneous CRC also play roles in IBD-associated CRC [33,34]. The pathogenesis of IBD-associated colorectal tumorigenesis is thought to be similar to the typical sequence found in sporadic CRC, but the primary difference between them is that tumorigenesis promotion via the colitis-affected mucosa usually develops from multifocal dysplasia, which Ullamn and Kulaylat called the “field change effect” [4,35]. Multiple studies have revealed that aneuploidy is a key indicator of genomic instability and that aneuploidy is more expanded in IBD patients compared with dysplasia, present in 20%–50% of cells in the dysplastic lesion and 50%–90% of cancers; in addition, aneuploidy is detected in long-standing UC [33,36,37].

Many of the cellular defects that are associated with the progression of sporadic colorectal carcinomas are also associated with inflammation-related CRC carcinogenesis [38]. The two major types of genomic instability found in CRCs are chromosomal instability and microsatellite instability. For example, in CAC, the frequencies of chromosomal instability and microsatellite instability are 85% and 15%, respectively, which are approximately the same as those in sporadic colorectal carcinomas; however, these types of genomic instability differ in the timing and frequency from the pattern seen in sporadic CRC [33,39,40]. The functional loss of the adenomatous polyposis coli (*APC*) gene is an early event in the progression of sporadic CRCs; however, this loss is less frequent and usually occurs later in the development of colitis-associated dysplasia and carcinomas [41–43]. Loss of p53 function is a key step in the progression of IBD-associated CRC; in contrast, the loss or mutation of the *p53* gene often occurs in the early stages of IBD-associated CRC but is believed to be a late event during the development of sporadic colorectal carcinomas [44,45]. In addition, DNA methylation plays key roles in the development of CAC, in which methylation of CpG islands in several genes precedes dysplasia and can be detected throughout the mucosa of patients with UC [46]. In sporadic CRCs, methylation of the human *MLH1* (*hMLH1*) promoter, which leads to the transcriptional silencing of *hMLH1*, is the most frequent event; in contrast, methylation of the *hMLH1* promoter is unusual in IBD-associated CRC [47]. Other key factors of the progression of CRC in IBD are involved in chronic inflammation, e.g., proinflammatory cytokines and chemokines, and the induction of cyclooxygenase 2 (COX-2) [48], which produces a suitable inflammatory microenvironment for tumor formation and progression.

4. Infections-inflammation-carcinogenesis

The connections between inflammation and cancer were first reported in the 1800s by Rudolf Virchow, who suggested that a “lymphoreticular infiltrate” reflected the origin of cancer at sites of chronic inflammation [49]. Based on this hypothesis, subsequent studies suggested that tumors often arise at sites of chronic inflammation and that inflammatory cells are present in biopsy samples from tumors [50]. Likewise, in a broader definition, inflammation is a process that involves tissue remodeling events that are caused by changes in the functions of the cells of the vascular and immune systems. Such changes are orchestrated by a series of specific signaling pathways, including a variety of cytokines, chemokines, growth factors, and lipid mediators

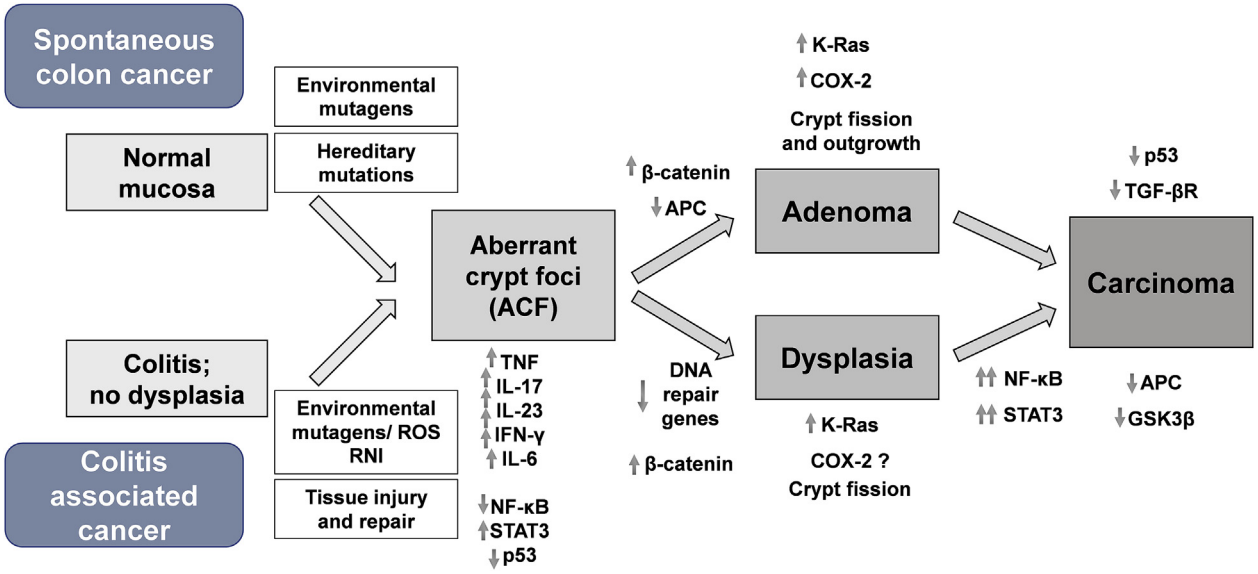

Fig. 1. Molecular pathogenesis of colorectal tumorigenesis, including sporadic colon cancer (top) and CAC (bottom). There is a considerable overlap between the mechanisms of CRC and CAC. Many of the genetic alterations associated with the development of sporadic colon cancer also play a role in CAC. Sporadic colon cancer is caused by accumulation of mutations in oncogenes and tumor suppressor genes, among which *APC*, β-catenin, and other components of this pathway mediate the transition of single preneoplastic cells to ACF and then to adenoma and carcinoma. Chronic inflammation, characterized by production of proinflammatory cytokines, can induce mutations in oncogenes and tumor suppressor genes (*APC*, *p53*, and *K-ras*) and genomic instability. Persistent inflammation causes tumor promotion by activating proliferation and antiapoptotic properties of premalignant cells as well as tumor progression and metastasis. APC, adenomatous polyposis coli; ACF, aberrant crypt foci; RNI, reactive nitrogen intermediates; GSK-β, glycogen synthase kinase β; TGF, transforming growth factor.

Table 1
Cancers associated with chronic inflammatory stimuli.

Inflammation	Associated cancer	References
IBD (UC and Crohn's disease)	CRC/CAC	[5]
Chronic gastritis (*H. pylori*)	Gastric cancer	[54,55]
Barrett's esophagitis	Esophageal cancer	[56]
Infection with HBV/HCV	Hepatocellular carcinoma	[57,58]
Liver fluke infection and primary sclerosing cholangitis	Cholangiocarcinoma	[59]
Endometriosis	Endometrial carcinoma	[60]
Escherichia coli infection of the prostate	Prostate cancer	[61,62]
Inflammation caused by asbestos, infections, smoking, or silica	Lung cancer	[63–65]
Pancreatitis	Pancreatic cancer	[66–68]
Gall bladder stone–associated chronic cholecystitis	Gall bladder carcinoma	[69,70]
UV irradiation–associated skin inflammation	Melanoma	[71]

[51]. Recent studies suggest that the majority of cancers arise from sites of chronic irritation, persistent infections, and long-term inflammation (including injury- and death-induced inflammation), and of course, senescence-inflammatory responses caused by chronic stress. Equally important is the notion that decompensation for chronic inflammation is also a critical factor for the progression of tumors (Table 1) [52,53].

Infections are among the best-understood activators of inflammation, in that microbes can trigger colorectal tumorigenesis by disturbing the homeostasis between a protective (tolerogenic) and aggressive (proinflammatory, protumorigenic) microflora or by altering the number, diversity, and stability of commensal bacterial cells (dysbiosis) [5,72]. Studies have shown that CAC development depends qualitatively and quantitatively on the intestinal microflora [73,74]. In many rodent models of IBD, commensal bacteria or specific bacteria (such as *H. hepaticus*) have been shown to be required for the initiation of inflammation and the development of dysplasia or cancer. Without these bacteria, neither colitis nor neoplasia develops [5,31].

More and more studies indicate that inflammation may result from persistent mucosal- or epithelial-cell colonization by microorganisms, including hepatitis B and C viruses (which can cause hepatocellular carcinoma [75,76]), certain human papilloma virus subtypes (which cause cervical cancer [77]), and the bacterium *Helicobacter pylori* (which can cause gastric cancer [76,78]). However, the connection between chronic inflammation and cancer does not operate only in one direction. For example, there is evidence that DNA damage may also result in inflammation because inflammation and DNA damage induce cell death by necrosis, which leads to more inflammation [79–83]. Furthermore, the activation of oncogenes, including *Ras*, *Myc*, and *RET*, may cause inflammation by activating the signaling pathways involved in the production of proinflammatory cytokines and chemokines [50,84]. Such negative effects may be attributed to stimulation by the external environment, such as persistent microbial colonization by viruses, bacteria, nematodes, or other pathogens that incite chronic inflammation. Furthermore, a recent study published by Pribluda and colleagues suggests that chronic stress initiates a senescence-inflammatory response, which can promote tumorigenesis in the absence of exogenous inflammatory triggers [53]. The same study characterized a distinct low-grade inflammatory process (in a stressed epithelium) that was related to parainflammation; this process was shown to either repress or promote tumorigenesis, depending on p53 activity [85,86].

Tumor promotion via injury- and death-induced inflammation should be mentioned. The hypothesis that tissue injury can promote tumorigenesis has already been advanced by Haddow, who suggested that “tumor production is a possible over-healing” [87,88], and by Dvorak, who stated that “tumors are wounds that do not heal” [89,90]. Many cancers develop in response to chronic tissue injury, in which the resulting cell death increases the tumorigenic potential of neighboring cells. Thus, it can be concluded that chronic injury can result in aberrant healing and a regenerative response that ultimately promotes the expansion and progression of initiated cells. Meanwhile, the key roles of mutagenesis, genomic instability, and epigenetic modifications are also important in this relation. In addition, persistent inflammation leads to increased cellular turnover, especially in an epithelium, and applies selection pressure that results in the emergence of cells that are at a high risk of malignant transformation. In effect, if the inflammation

cannot be eliminated or is chronically provoked by repetitive injury or other factors, the resulting unchecked wound healing process promotes oncogenic transformation. Accordingly, injury causes inflammation, which in turn orchestrates wound healing and tissue regeneration.

5. Energy metabolism reprogramming in carcinogenesis

In contrast to normal differentiated cells, which primarily depend on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, most cancer cells and certain rapidly proliferating cells instead rely on aerobic glycolysis, despite the presence of sufficient oxygen; this phenomenon is termed the "Warburg effect." This anomalous characteristic of cancer cell energy metabolism, also termed "aerobic glycolysis," was first reported by Otto Warburg in the 1920s [8] and was subsequently listed by Hanahan et al. as one of the 10 hallmarks of cancers [91]. Interestingly, this type of glucose metabolism is an inefficient method for generating adenosine 5′-triphosphate (ATP) and is characterized by an increase in glucose uptake and lactate production as well as a decrease in oxygen consumption. The advantage that this type of metabolism confers on cancer cells remains unclear; however, a common characteristic of metabolism in tumor cells is that these cells must acquire the necessary nutrients from a usually nutrient-poor microenvironment and utilize these nutrients to both maintain viability and build new biomass.

The occurrence of this anomalous metabolic switch in cancer cells has been substantiated in the ensuing decades. Investigation of the reprogramming of metabolic properties in cancer cells has been a rapidly growing area in cancer research. Such metabolic reprogramming is seemingly counterintuitive, in that cancer cells become "greedy" for glucose and use glycolysis preferentially for energy production, even under normoxic conditions [92]. Therefore, cancer cells must compensate for the approximately 18-fold lower efficiency of ATP production afforded by glycolysis relative to mitochondrial oxidative phosphorylation. Notably, the activity of this type of energy metabolism in the presence of sufficient oxygen is distinct from normal anaerobic glycolysis, which is active in healthy cells under hypoxic conditions [93]. Aerobic glycolysis can be observed most readily by noninvasively visualizing glucose uptake by positron emission tomography (PET) with a radiolabeled analog of glucose (^{18}F-fluorodeoxyglucose) as a reporter. Pavlova et al. have summarized the known cancer-associated metabolic changes into the following six hallmarks: (1) deregulated uptake of glucose and of amino acids, (2) the use of opportunistic modes of nutrient acquisition, (3) utilization of glycolysis or tricarboxylic acid (TCA) cycle intermediates for biosynthesis and NADPH production, (4) an increased demand for nitrogen, (5) alterations in metabolite-driven gene regulation, and (6) metabolic interactions with the microenvironment [94]. Enhanced glycolytic flux is now known to allow for the increased synthesis of intermediates for sustaining the anabolic pathways critical for cancer cell growth. Along with the enhancement of glycolysis, cancer cells transform their mitochondria into biosynthesis machines that are supported by augmented glutaminolysis, thereby promoting lipid production, amino acid synthesis, and the pentose phosphate pathway. Thus, as Vander Heiden et al. generalized earlier, the metabolism of cancer cells and, indeed, all proliferating cells, is adapted to facilitate the uptake and incorporation of nutrients into the biomass (e.g., nucleotides, amino acids, and lipids), which is needed to produce a new cell [95]. Moreover, metabolic adaptation in tumors extends beyond the Warburg effect. In general, the alterations to metabolism balance the need of the cell for energy with its equally important need for macromolecular building blocks and maintenance of the redox equilibrium [96].

Cancer-related metabolic reprogramming has been shown to be associated with activated oncogenes (e.g., *Ras*, *Myc*) [97] and mutant tumor suppressors (e.g., *TP53*) [98]; the alterations of these genes that lead to tumorigenesis are numerous and heterogeneous. Indeed, cancer-related driver mutations affect a dozen or more core signaling pathways and processes that are responsible for tumorigenesis [99] and have been selected primarily for their ability to confer the hallmark capabilities of cell proliferation, avoidance of cytostatic controls, and attenuation of apoptosis. It is increasingly accepted that this metabolic switch is a consequence of defects in cellular respiration, of oncogenic alterations, and overexpression of glycolytic enzymes and metabolite transporters [100]. For instance, target genes that are activated by hypoxia-inducible factor (HIF) decrease the dependence of the cell on oxygen, whereas *Ras*, *Myc*, and *Akt* can also upregulate glucose consumption and glycolysis. One of the principal mechanisms underlying aerobic glycolysis involves the activation of HIF, a transcription factor that is induced not only by hypoxic stress but also by oncogenic, inflammatory, metabolic, and oxidative stressors [101–103]. In addition to a decrease in O_2 tension, HIF1 can be activated under normoxic conditions by oncogenic signaling pathways, including PI3K [104] and by mutations in tumor suppressor proteins, such as (Von Hippel-Lindau) VHL [105], succinate dehydrogenase (SDH) [106], and fumarate hydratase (FH) [107]. Once activated, HIF1 amplifies the transcription of genes that encode glucose transporters and most of glycolytic enzymes, thereby enhancing the glycolytic capacity of the cell [108]. The loss of p53 may also recapitulate the features of the Warburg effect, that is, the uncoupling of glycolysis from oxygen levels. Furthermore, recent additional evidence suggests that in addition to the core factors mentioned above (including HIF-1, c-Myc, p53), metabolic reprogramming is induced by (Pyruvate kinase) PKM2 [109], (isocitrate dehydrogenase) IDH [110–112], (Glutaminase) GLS [113,114], and other molecules that act both independently and in concert with one another. The alterations of core signaling pathways induced by mutations in these key cancer-associated genes that are implicated in cell proliferation also regulate metabolic pathways that incorporate nutrients into biomass.

Almost all mammalian cells require amphibolic glucose metabolism via glycolysis and the TCA cycle to meet catabolic demands and support anabolic carbon needs, especially the high level of lactate production via glycolysis in cancer cells, independently of O_2 availability. After searching the public database of the NIH, dbEST, for the expression of genes and expressed sequence tags (ESTs), Altenberg et al. reported that genes involved in the glycolysis pathway were found to be overexpressed in a set of 24 cancers representing more than 70% of human cancer cases worldwide [115]. The findings concerning the overexpression of these genes along with the exploitation of increased glucose uptake of cancer cells for tumor diagnostics by positron emission tomography with ^{18}F-fluorodeoxyglucose have contributed to the renewed interest in this topic. In particular, the major glycolysis-related genes, including *GLUT*, *HK*, *PFK*, *PK*, and *LDH*, are overexpressed in cancer cells [115–117], both at mRNA and protein levels. For example, lactate dehydrogenase A (LDH-A), which catalyzes the last step of anaerobic glycolysis, is abnormally expressed in many types of human cancers. It has been reported that the inhibition of LDH-A prevents the Warburg effect and forces cancer cells to revert to oxidative phosphorylation to reoxidize NADH and produce ATP [118,119].

6. Metabolic interaction with the inflammatory and tumor microenvironment

Tumor cells, stromal cells, and the stroma constitute the tumor microenvironment, which is now considered crucial for promoting tumorigenesis and metastasis. Multiple studies have revealed that stromal cells can promote tumor progression and metastasis not only through the paracrine secretion of cytokines or chemokines but also via intermediate metabolites [120]. However, cancer cells must reprogram and readapt their microenvironment strategically to support tumor progression and dissemination, which involves secretion of growth factors and alterations to the extracellular matrix and cell–cell interactions; this altered metabolism of cancer cells confers a selective advantage in survival and proliferation within the unique tumor microenvironment. Under normal conditions, the cellular microenvironment can suppress

malignant cell growth, whereas tumor–stroma interactions modulate the microenvironment to be more permissive of malignant cell proliferation, motility, and adhesion.

Hypoxia is a hallmark of both the inflammatory microenvironment and tumor microenvironment, and most cancer cells are exposed to chronic hypoxia from the early stage of carcinogenesis [121]. One compelling explanation of the Warburg effect is that the altered metabolism of cancer cells confers a selective advantage in survival and proliferation within the unique tumor microenvironment. As the early tumor expands, it outgrows the diffusion limits of its local blood supply, leading to hypoxia and the stabilization of hypoxia-inducible transcription factor HIF [122]. Indeed, measurements of oxygen tension in tumors have confirmed the occurrence of severe hypoxia in many types of cancer [123], thereby resulting in a shift in cellular metabolism toward glycolysis through the increased expression of glycolytic enzymes, glucose transporters, and inhibitors of mitochondrial metabolism. In addition, HIF stimulates angiogenesis (the formation of new blood vessels) by upregulating several factors, including most prominently, vascular endothelial growth factor (VEGF) [124]. Nonetheless, the blood vessels that are recruited to the tumor microenvironment are disorganized, may not deliver blood effectively, and therefore do not completely alleviate hypoxia [10]. The hypothesis that hypoxia can induce inflammation has gained general acceptance based upon studies of the hypoxia signaling pathway. In the context of inflammation, for example, mechanisms leading to HIF induction can be oxygen-independent and mediated by other transcription factors, such as STAT3 [125] and NF-κB [126]. In addition, HIF can directly contribute to the inflammatory response, by inducing several proinflammatory chemokines and cytokines [127]. Importantly, many of the genes that are transcriptionally activated by HIF are also targets of NF-κB and are involved in tumorigenesis, e.g., IL-6, MMP9, and COX2 as well as prosurvival genes, such as Bcl-2, among others [128]. The development of inflammation in response to hypoxia is clinically relevant, just as hypoxia can induce inflammation, and inflamed lesions in turn often become severely hypoxic. In IBD, not only does the entire mucosa become even more hypoxic [129], but also surgical specimens of the inflamed intestine contain elevated amounts of HIF-1 [130]. This phenomenon may be due to the steep oxygen gradient between the anaerobic intestinal lumen and the metabolically active lamina propria mucosae; this arrangement causes intestinal epithelial cells to become normally hypoxic. Importantly, in the case of an inflamed tissue, hypoxia is not a bystander but rather an influence on the environment of the tissue, particularly via regulation of oxygen-dependent gene expression.

Another commonality between the inflammatory microenvironment and tumor microenvironment that has a significant role in neoplastic progression is the expression of specific cytokines. In general, cytokines are low-molecular-weight proteins that mediate cell-to-cell communication and can be divided into proinflammatory cytokines (such as IL-1, -6, -11, −12, −18, and −23; IFN-γ; TNF-α; and MIF) and anti-inflammatory cytokines (such as IL-4, IL-10, INF-α and -β, and TGF-β); in addition, it has become increasingly clear that many of these cytokines can have dual roles [131]. These cytokines are synthesized by both immune and stromal cells (such as fibroblasts and endothelial cells), and their effect is similarly important for sustaining chronic inflammation, promoting the progression and proliferation of tumor cells, and for inhibiting immune-system–mediated tumor surveillance. Under normal conditions, such as wound healing, an influx of cytokines and chemokines functions in a self-limiting manner to heal the wound. However, dysregulation of this process can lead to abnormalities in the inflammatory response and ultimately to tumorigenesis. Depending on the tumor microenvironment, cytokines can modulate an antitumor response, but during chronic inflammation, they can also induce cell transformation and malignancy, depending on the balance of pro- and anti-inflammatory cytokines; their relative concentrations, cytokine receptor expression, and the activation state of the surrounding cells [132]. For example, IL-6, which is a proinflammatory cytokine with a typical protumorigenic effect, has been shown to stay at elevated levels in the serum of patients with systemic cancers as compared to healthy controls or patients with benign diseases. Given the tight link of IL-6 to NF-kB, IL-6 is an early candidate for the myeloid-derived factor that may promote tumorigenesis by binding to its receptor (IL-6Rα) and coreceptor gp130 (glycoprotein 130), thereby activating the JAK–STAT signaling pathway [133]. Indeed, STAT3 activation in human tumors is often observed at the invasive front of tumors adjacent to inflammatory cells.

7. Metabolic reprogramming of inflammatory-oncogenic transformation

The metabolic shift to aerobic glycolysis appears to be a common feature of cancer. Indeed, the chronic and often uncontrolled cell proliferation that represents the essence of neoplastic disease involves not only the deregulated control of cell proliferation but also the corresponding adjustments of energy metabolism to fuel cell growth and division. The prolonged and uncontrolled activation of inflammation is also a hallmark of many diseases, including cancer and obesity-associated metabolic disorders. Many decades ago, Warburg interpreted tumor lactate secretion as an indication that oxidative metabolism was damaged, but substantial follow-up studies failed to confirm defective respiration as a general characteristic of cancer cells [134]. In fact, respiration and other mitochondrial activities are required for tumor growth [135]. In addition, in nontransformed cells, the Warburg effect is a reversible phenomenon that is tethered to proliferation, suggesting that this effect reflects proliferation-associated shifts in metabolism rather than a unique feature of cancer. Meanwhile in our previous work, we for the first time found that under inflammatory conditions, the type of cell metabolism shifts toward aerobic glycolysis such that a series of glycolysis indicators, including glucose uptake, lactate production, and glycolytic enzymes, are maintained at high levels [136,137]. These results indicate that the type of cellular metabolism may have been reprogrammed in the process of inflammatory-oncogenic transformation instead of the later stages of tumorigenesis. Early in the neoplastic process, the inflammatory cells and the surrounding microenvironment are powerful tumor promoters, producing an environment conducive to tumor growth, facilitating genomic instability, and promoting angiogenesis. Another rational interpretation may refer to hypoxia, because hypoxia is not a unique feature of a tumor and is also present in inflammation [128,138]. As described above, hypoxia alters transcription through the stabilization of HIF, which increases the glycolytic capacity and decreases mitochondrial respiration [139]. Accordingly, under hypoxic conditions, glycolysis allows for continued ATP production without the need for O_2-dependent oxidative phosphorylation.

In addition to hypoxia, the inflammatory microenvironment including various cytokines and immune cells plays a dominant role in the process of inflammatory-oncogenic transformation. Additionally, as discussed above, a causal link between chronic inflammation and colorectal tumorigenesis has long been recognized, and substantial insight into the underlying molecular mechanisms and signaling pathways has been obtained in recent years. The studies by Grivennikov et al. and Bollrath et al. uncovered the importance of the interleukin 6 family of proinflammatory cytokines and their downstream effector STAT3 in CAC [140,141], suggesting that the IL-6–STAT3 axis may play a primary role in the process of inflammatory-oncogenic transformation. STAT3 is highly phosphorylated not only during DSS-induced colitis in mice but also in the mucosa and lamina propria of human patients with IBD [142]. Furthermore, STAT3 has been found to be activated in various adenomas and carcinomas, although the mechanisms underlying its activation are not clear [143,144]. Our previous studies have also verified this notion because we found that STAT3 is activated not only in a mouse model of DSS-induced colitis but in colon cell lines and

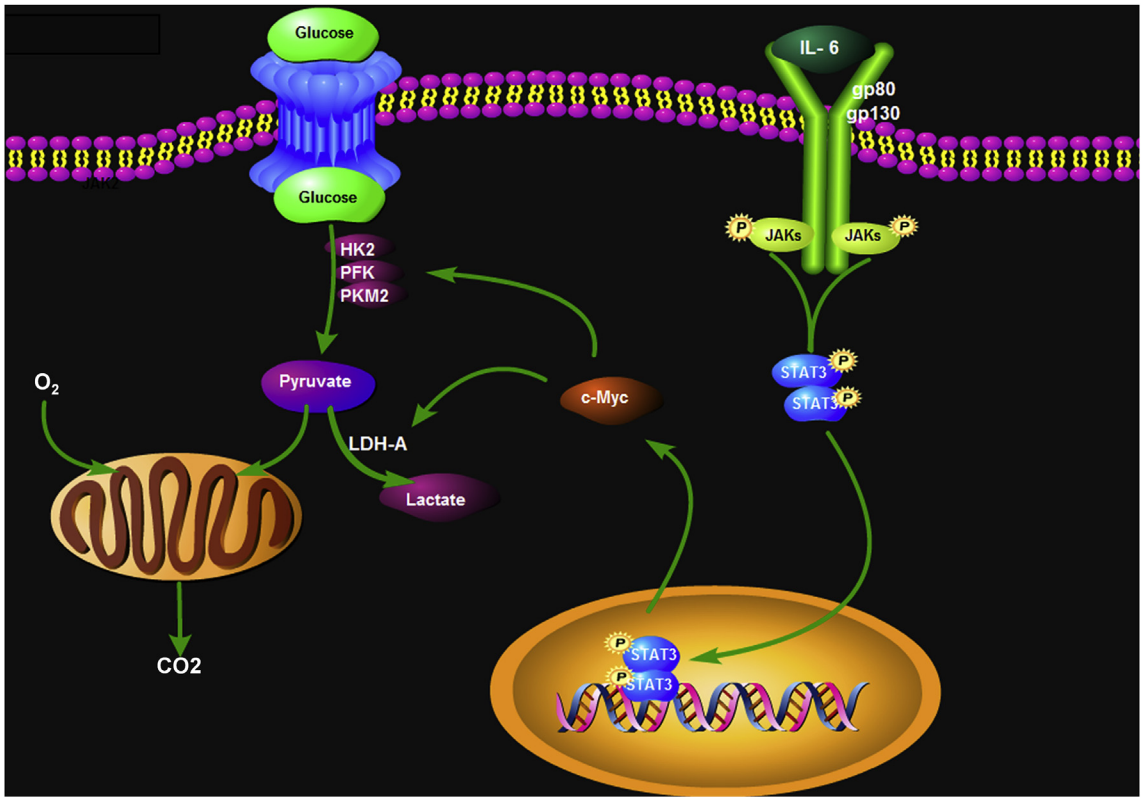

Fig. 2. Schematic representation of the molecular pathway involved in the inflammation-promoting metabolic reprogramming. This schematic shows our current understanding of metabolic alterations in the process of inflammatory-oncogenic transformation. IL-6, for example (as one of proinflammatory cytokines with a typical protumorigenic effect)—which is produced by inflammatory and stromal cells within the inflammatory microenvironment—binds to gp80 or gp130, thereby leading to JAK activation and phosphorylation of STAT3 and thus regulating the expression of c-Myc mediating proliferation and aerobic glycolysis. Key steps in glycolysis and lactate production can be promoted by the activation of the STAT3–c-Myc signaling pathways.

human intestinal epithelial cell (HIEC) lines pretreated with IL-6. Moreover, our studies determined that *c-Myc*, which is a multifaceted oncogene that exerts important regulatory actions on multiple parameters of cell transformation [145–147], is dramatically upregulated by inflammatory stimulation, accompanied by the upregulation of glycolysis and lactate production. The link between a member of the STAT3 family and the activation of c-Myc was first proposed by Kiuchi et al. in a study suggesting that upon stimulation with IL-6, STAT3 primarily mediates the rapid activation of *c-Myc* via binding to a region overlapping with the E_2F binding site in the *c-Myc* promoter [148]. On the basis of these results, we used small-molecule inhibitors to block STAT3–c-Myc signaling and found that a series of aerobic glycolysis indicators resulting from pretreatment with IL-6 were recovered to normal levels to varying degrees. Our previous studies indicate that in the inflammatory microenvironment dominated by hypoxia and inundated with numerous cytokines, the metabolism may be shifted to tumor-associated aerobic glycolysis through the activation of STAT3–c-Myc signaling. This phenomenon is precisely what we attempt to convey and clarify in this review (Fig. 2).

8. The uncharted territory and vision of the future

Many mysteries remain in our understanding of human tumor metabolism, let alone the process of inflammatory-oncogenic transformation. Still, we have sought here to revisit and extend the concept of metabolism reprogramming, especially during inflammation-transforming tumorigenesis, which may provide a useful conceptual framework for elucidation of the complex biology of inflammatory-oncogenic transformation from the metabolic perspective.

The causal link between inflammation and tumorigenesis is well established, and in the last decade, this link has received a great deal of supporting evidence from genetic, pharmacological, and epidemiological data. Throughout this period, hypoxia and the inflammatory microenvironment played leading roles in promotion of cancer-associated alterations in metabolism. As described above, under inflammatory conditions, cells tend to shift their metabolism toward tumor-associated aerobic glycolysis by activating the STAT3–c-Myc signaling pathway. However, exploring and understanding the underlying mechanisms and deeper connections will be our research focus in the future. Furthermore, more complex questions remain to be answered. For example, what are the similarities and differences in metabolism between cancer cells and normal cells during inflammation? What about normal cells and those in an inflammatory environment? Given that metabolism may be reprogrammed in the process of inflammatory-oncogenic transformation, does cellular metabolism recover to normal levels when the inflammation disappears? Alternatively, is this metabolic reprogramming irreversible? Are there unique inflammation-specific metabolic pathways, or combinations of pathways, utilized by the cells under inflammatory conditions but not by normal cells? Are different stages of metabolic adaptations required for cells to progress from inflammation to tumorigenesis?

From a therapeutic perspective, knowledge about the causes, benefits, and vulnerabilities of inflammatory-oncogenic transformation will hopefully enable identification of new drug targets. Several studies clearly suggest that inhibitors of IL-6 signaling, such as antibodies or JAK inhibitors, which are presently being tested in clinical trials for other diseases, should be considered for the treatment of patients with CRC. Furthermore, restraining the STAT3–c-Myc signaling pathways is likely to prolong the process of inflammatory-oncogenic transformation; this phenomenon may provide a novel therapeutic strategy involving early diagnostic biomarkers or may point to potential therapeutic targets in intestinal inflammation and tumors. Restraining

inflammatory-oncogenic transformation by ensuring metabolic homeostasis may be a new anticancer therapeutic opportunity.

Conflicts of interest statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled “Metabolic reprogramming links chronic intestinal inflammation and the oncogenic transformation in colorectal tumorigenesis”.

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