Warburg Effect in Colorectal Carcinogenesis

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Colorectal cancer is one of the most leading causes of death worldwide. The Hallmark of colorectal cancer is the increase of glucose uptake and lactate production even in the presence of oxygen, a phenomenon known as the “Warburg effect”.

Keywords: colorectal cancer ; Warburg effect ; epigenetic alterations ; ncRNA ; genetic mutations ; anti-glycolysis therapy

1. Introduction

Colorectal cancer (CRC) is the fourth most common type of cancer, with more than 1.84 million new cases reported annually. Despite improvements in diagnosis and treatment, CRC causes approximately one million deaths per year and accounts for the third-highest cancer-related deaths worldwide [1]. Recently, anti-cancer drugs targeting dysregulated cancer cell metabolism have been gaining greater attention in the scientific community [2][3]; therefore, understanding the metabolic pathways in CRC cells may provide a key for developing novel diagnostic and therapeutic options to overcome this disease.

Glucose is metabolized by oxidative phosphorylation (OXPHOS) when oxygen is available to normal cells. Under hypoxic conditions, cells undergo anaerobic glycolysis to produce lactate [4], but even in the presence of oxygen, cancer cells adapt to metabolize a high amount of glucose into lactate to fuel uncontrolled cell growth. This phenomenon is the “Warburg effect”, which is a hallmark of nearly all types of cancer, including CRC [5][6]. CRC is a heterogeneous disease in which numerous oncogenes and tumor suppresser genes are mutated in an adenoma-carcinoma sequence that facilitates CRC progression [1]. Several genetic mutations may lead to the upregulation of enzymes and transporters involved in the Warburg effect. Indeed, CRC cells prefer glycolysis over OXPHOS even under normoxic conditions, leading to mitochondrial dysfunction [7]. Still, it is unclear whether OXPHOS is completely turned off by genetic and epigenetic alteration or whether mitochondria continue to function to generate the energy required by the CRC cells. The former might be true because the net ATP yield generated by OXPHOS is higher than that generated by aerobic glycolysis, but glycolysis is 100 times faster [8]. Moreover, glycolysis protects CRC cells against the toxic byproducts of OXPHOS and provides an acidic environment to enhance the cellular uptake of the essential intermediate metabolites required for proper cancer cell growth [9]. Regardless of the significance of the Warburg effect, some types of cancer depend on more than 90% OXPHOS [8], but some cancer metabolisms are a mixture of OXPHOS and glycolysis [9]. Kaldma et al. reported that in situ human CRC cells use glycolysis in the same way as healthy cells; nevertheless, in malignant cells, increased OXPHOS might be due to stimulation of the mitochondrial biogenesis [10].

2. Metabolic Reprogramming in CRC: Genetic Mutations and ncRNA-Mediated Epigenetic Alteration

Recent studies have suggested that numerous genetic mutations and epigenetic alterations causing abnormal activation of several oncogenes (*KRAS* [11][12], *c-Myc* [13], *PIM1* [14]), and the inactivation of several tumor suppresser genes (*APC* [15], *TP53* [16], *SMAD4* [17], *PTEN* [18]), reprogram the metabolic pathway in CRC, mediating the Warburg effect. For instance, *KRAS* expression can be downregulated by the overexpression of miR-143, while the lncRNA (glycolysis-associated lncRNA of colorectal cancer) GLCC1 directly increases *c-Myc* expression [19][20]. In addition, miR-135, miR-150-5p, miR-34a, and miR-21 target *APC*, *TP53*, *SMAD4*, and *PTEN* expression to promote CRC progression [19][21]. Also, aberrant activation of various signaling pathways, such as the Wnt/β-catenin, FYN-HIF2A, Receptor Tyrosine Kinase (RTK)/Ras GTPase/MAP kinase (MAPK), and PI3K pathways, modulates CRC cell metabolism [22]. Activation of the Wnt/β-catenin pathway accounts for almost 90% of sporadic CRC and is usually associated with a high rate of aerobic glycolysis [15][23]. Also, the Hippo pathway induces glycolysis via upregulation of yes-associated protein 1 [24]. Mutations in transcription factors such as forkhead box (*FOX*) [6] and *HIF1A* [5] genes, which could alter the expression of the enzyme-coding genes involved in glycolysis, have been widely reported in CRC. Those enzymes include phosphoglycerate kinase 1 (PGK1) [25], glucose transporter 1 (GLUT1), hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), and lactate

dehydrogenase (LDH) [23]. Furthermore, the cytokine-mediated pro-inflammatory microenvironment may enhance the Warburg effect in CRC [26].

Cancer cells have altered epigenetic mechanisms to manipulate the gene expression for abnormal cell growth and metastasis [27]. These epigenetic mechanisms include DNA methylations, histone modifications, and ncRNA-mediated regulation of gene expression [28][29]. Regulation of gene expression by ncRNAs can happen at multiple levels by interacting with DNA, RNA, or proteins. Moreover, the ncRNAs can modulate chromatin structure and the transcription of adjacent or faraway genes. However, the best of the known mechanisms of ncRNA-mediated gene repression is interference with the transcription machinery, which leads to alteration of the recruitment of transcription factors. The ncRNAs mediate transcriptional regulation on an epigenetic level through interaction with chromatin modifiers, either directly via chromatin looping or by sponging a diversity of miRNAs [30]. Recently, accumulating evidence has also proven the role of regulatory ncRNA in metabolic remodeling of CRC [31][32][33]. These molecules can either function as tumor inducers or suppressers by targeting different players of CRC metabolism genes such as transcription factors, enzymes, and transporters of glycolysis. Profiling those ncRNAs in CRC metabolism is further required, paving the way to identify novel targeted therapies and diagnostic, prognostic, and predictive tests.

Mutations cause aberrant expression of c-Myc via different pathways, such as the Wnt and PI3K/AKT/mTOR signaling pathways [34]. When c-Myc is inhibited, various glycolysis enzymes, such as PDK1, LDH, and GLUT1, are downregulated, resulting in tumor growth suppression [13]. The upregulation of c-Myc indirectly promotes glycolysis in CRC cells through the overexpression of polypyrimidine tract binding protein 1 (PTB1)—a protein that plays a role in pre-mRNA splicing. PTB1 facilitates glycolysis by promoting the splicing of PKM2 in CRC cells [35]. In addition, c-Myc can also facilitate CRC progression by upregulating genes relating to other metabolic pathways. For instance, c-Myc has been shown to tip the balance of CRC metabolism from glycolysis toward OXPHOS by upregulating mitochondrial-related proteins such as PGC-1, CPT1A, and TFAM [36]. c-Myc boosts CRC progression through various mechanisms, such as OXPHOS and glycolysis, allowing the identification of novel molecules in its activity. Unfortunately, targeting c-Myc through small molecules such as antibodies is difficult because it is a nuclear protein without a deep surface binding pocket [34]. Therefore, further studies are required to identify other target therapies downstream of c-Myc or examine different epigenetic mechanisms that modulate its expression in CRC cells.

The mRNA splicing of PKM to form PKM1 or PKM2 is mediated by the three heterogeneous nuclear ribonucleoproteins (hnRNPs)—PTB1, hnRNAPA1, and hnRNAPA2. Recently, studies have demonstrated that PKM2 levels can be epigenetically altered by targeting PKM splicers. Both miR-1 and miR-133b have been shown to inhibit CRC progression by targeting PTBP1. When inhibited, PTBP1 tipped the balance of PKM2 towards PKM1, thereby inhibiting glycolysis [37]. In addition, miR-124, miR-137, and miR-340 have been observed to reduce the growth of CRC cells by inhibiting PKM2 splicing, thereby counteracting the Warburg effect [38]. A newly discovered miR-206 has been shown to target hnRNPA1 and inhibit PKM2 splicing. The reduced PKM2 splicing inhibited glycolysis in CRC cells [39]. The lncRNA MEG3 has also been reported as a tumor suppressor in CRC cells by inhibiting the c-Myc expression and indirectly reducing PKM2 activity, resulting in reduced glycolysis activity [40]. Another study showed that PKM2 levels were elevated by the lncRNA FEZF1-AS1, which improves PKM2 stabilization and thus enhances glycolysis in CRC cells [41]. Together, these studies prove that miRNAs and lncRNAs may impair CRC progression by targeting the Warburg effect and altering the PKM2/PKM1 ratio.

With regard to epigenetic regulation, Gregersen et al. reported that HK2 is the main target for miR-143 and that miR-143 loss is significantly associated with increased glycolysis activity in CRC cells [42]. Moreover, lncRNAs (such as MEG3 and KCNQ1OT1) were also reported to regulate HK2 activity [31][40]. Both these lncRNAs play an important role in regulating the Warburg effect in CRC cells. CRC cells overexpressing MEG have shown a reduced expression of HK2 and an inhibition of glycolysis metabolism [40]. On the other hand, KCNQ1OT1 acts as a proteasome inhibitor to increase the stability of HK2, thereby increasing aerobic glycolysis in CRC cells [31].

Inhibition of GLUT1 expression has been shown to be facilitated by a group of anti-cancer therapies, including DT-13, Oridonin, and Oxymatrine [2][3][43], and by butyrate, which functions as a glycolysis inhibitor in CRC cells [44]. However, it is still unclear whether butyrate affects GLUT1 expression as an HDAC inhibitor, thus warranting further studies. These studies, as mentioned earlier, may provide insights into the relationship between GLUT1 inhibition and chemoresistance in CRC cells.

4. Conclusions and Future Research

In summary, CRC cells benefit from the Warburg effect's ability to enhance their bioenergetic balance and obtain growth-related advantages from glycolysis-derived metabolites. Genetic analyses and ncRNA-mediated epigenetic research have provided insights into the molecular mechanisms of genes involved in regulating the Warburg effect and the development of tumorigenesis. In this review, we have presented molecular insights into the clinical impacts of oncogenic alterations and the effects of overexpression of transcription factors (KRAS, APC, c-Myc, P53, and HIF1-α), metabolite transporters (GLUT1), and glycolytic enzymes (HK2, PKM2, PDK1, and LDH) on the Warburg effect in CRC cells. For the first time, we have summarized recent pieces of literature showing the importance of miRNAs and lncRNAs as epigenetic mediators regulating the Warburg effect in CRC cells (**Table 1**). Genetic mutations and epigenetic alterations that deregulate transcription factors, metabolic transporters, and glycolytic enzymes have been associated with poor prognoses and may be associated with chemoradiotherapy resistance in CRC patients. Novel small molecules targeting these enzymes or transporters exert significant anti-proliferative effects. Hence, glycolytic enzymes and metabolite transporters may be used as biomarkers for predicting CRC prognoses and crucial therapeutic targets. Previous studies have demonstrated that the inhibition of epigenetic factors impacts cancer cell metabolism, although further studies are required to fully understand the effectiveness of these inhibitors on the underlying mechanisms in CRC cells. Future studies, particularly translational research, should incorporate ncRNA analysis of epigenomic biomarkers, allowing for personalized treatment using epigenetic modulators. Additionally, combining epigenetic and genetic targeting might be a more effective strategy for delaying CRC progression.

Table 1. Warburg effect-mediating molecules and their associated epigenetic alteration, resistance to chemotherapy, and tested anti-glycolytic drugs for CRC.

Genes	Function	Epigenetic Alteration			Therapy Resistance	Anti-Glycolysis Therapy
		Molecule	Expression in CRC	Effect on Glycolysis		
KRAS	Oncogenic activator of RAS/MAPK	UNC5B-AS1 [45]	Upregulated	Activating	Anti-EGFR [46] [47]	3-BrPA [12], ascorbic acid [11]
c-Myc	Oncogenic Transcription factor	MEG3 [40] GLCC1 [20] miR-181d [48] miR-124 [35]	Downregulated Upregulated Upregulated Downregulated	Inhibitory Activating Activating Inhibitory	N\A	vitamin D [40] Ketamine [49] Dioscin [50]
HIF1A	Hypoxia-inducible transcription factor	METTL3 [51] YTHDF1 [51] HIFAL [32]	Upregulated Upregulated Upregulated	Activating Activating Inhibitory	5-FU [52]	Rosmarinic acid [53]
APC	Tumor suppressor controlling beta-catenin	N\A		N\A	N\A	DT-13 [2] Metformin [54]
TP53	Transcription factor and tumor suppresser	N\A		N\A	N\A	DCA [16] FK866 [55]
PKM2	An enzyme of aerobic glycolysis	miR-1 [37] miR-133b [37] miR-124 [38] miR-137 [38] miR-340 [38] miR-206 [39] MEG3 [40] FEZF1-AS1 [41] miR-122 [56]	Downregulated Downregulated Downregulated Downregulated Downregulated Downregulated Downregulated Upregulated Downregulated	Inhibitory Inhibitory Inhibitory Inhibitory Inhibitory Inhibitory Inhibitory Activating Inhibitory	Oxaliplatin [56]	Butyrate [57] vitamin C [58] Oxymatrine [3]
HK2	An enzyme of aerobic glycolysis	miR-143 [42] MEG3 [40] KCNQ1OT1 [31]	Downregulated Downregulated Upregulated	Inhibitory Inhibitory Activating	Oxaliplatin [59] 5-FU [59]	N\A
GLUT1	Glucose transporter	miR-760 [60] miR-143 [61] circDENND4C [60] METTL3 [62]	Downregulated Downregulated Upregulated Upregulated	Inhibitory Inhibitory Activating Activating	5-FU [44]	DT-13 [2] Oridonin [43] Oxymatrine [3] Butyrate [44]

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