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Review

How glycosylation aids tumor angiogenesis: An updated review

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ABSTRACT

Glycosylation is an enzymatic process in which a carbohydrate is attached to a functional group from another molecule. Glycosylation is a crucial post translational process in protein modification. The tumor microenvironment produces altered glycans that contribute to cancer progression and aggressiveness. Abnormal glycosylation is widely observed in tumor angiogenesis. Despite many attempts to decipher the role of glycosylation in different aspects of cancer, little is known regarding the roles of glycans in angiogenesis. The blood vessels in tumors are often used to transport oxygen and nutrients for tumor progression and metastasis. The crosstalk within the tumor microenvironment can induce angiogenesis by manipulating these glycans to hijack the normal angiogenesis process, thus promoting tumor growth. Abnormal glycosylation has been shown to promote tumor angiogenesis by degrading the extracellular matrix to activate the angiogenic signaling pathways. This review highlights the latest update on how glycosylation can contribute to tumor angiogenesis that may affect treatment outcomes.

1. Introduction

Glycosylation is a process in which carbohydrate molecules known as glycans become attached to other biological molecules such as proteins and lipids, thus affecting different biological pathways. These biological processes require glycans for cell adhesion [1], molecular trafficking and clearance [2], receptor activation [3], signal transduction [4] as well as endocytosis of molecules [5]. In cancer, glycans are implicated in cell dissociation & cell invasion [6], cell-cell interaction, and cell signaling through cell matrix interaction [7]. Glycan have been demonstrated to play a role in endothelial cells by ensuring the survival of endothelial cells [8], regulating vascular permeability [9] and influencing connection of blood and lymphatic vessels [10]. In addition, glycosylation is also implicated in immune modulation and cancer metastasis [11].

Although mounting evidence has reported the role of glycosylation in tumor progression [12–14], there is limited information on how glycosylation affects the tumor vasculature. However, recent studies have shed light on glycosylation crosstalks with cellular metabolism and related kinases. These glycosylation crosstalks include post-translational modifications on the FoxO3 protein that may lead to the onset of various cancers [15] and activation of Akt/tuberous sclerosis complex (TSC2)/mammalian target of rapamycin (MTOR) cell signaling pathway that affect cancer cell proliferation and tumor growth [16]. In prostate cancer, androgen has been reported to induce glycosylation that subsequently modified receptor tyrosine kinase (RTK) to support prostate tumor growth [17], In addition, relocation of *O*-glycosylation initiating glycosyltransferases from the golgi apparatue to endoplasmic reticulum has been demonstrated to enable matrix degradation and liver tumor expansion [18].

Tumor angiogenesis is the propagation of endothelial cells which infiltrate the solid neoplasm, leading to the sprouting and maturation of new blood vessels from already existing blood vessels [19]. Tumor cells can crosstalk with the tumor microenvironment by releasing angiogenic molecules that bind to their respective receptors in the neighboring cells or through paracrine signaling which promote blood vessels sprouting [20,21]. These blood vessels are essential to supply nutrients and oxygen to aid tumor growth [22]. Tumor metastasis occurs when cancer cells travel through the blood circulation system and form secondary tumors at distant sites [23].

2. *O*-linked glycosylation in tumor angiogenesis

2.1. Hyper-O-GlcNAcylation regulates tumor angiogenesis

O-linked glycosylation is the addition of oxygen atom to the glycans. Cancer requires transformed mechanisms of glycosylation to sustain its malignant phenotype. Hexosamine biosynthesis pathway (HBP) is a sub-branch of glucose metabolism responsible for generating substrates used for protein glycosylation in order to produce glycoproteins and glycolipids. The glycosylation process is essential in retaining proper function of proteins. The HBP pathway has been shown to be involved

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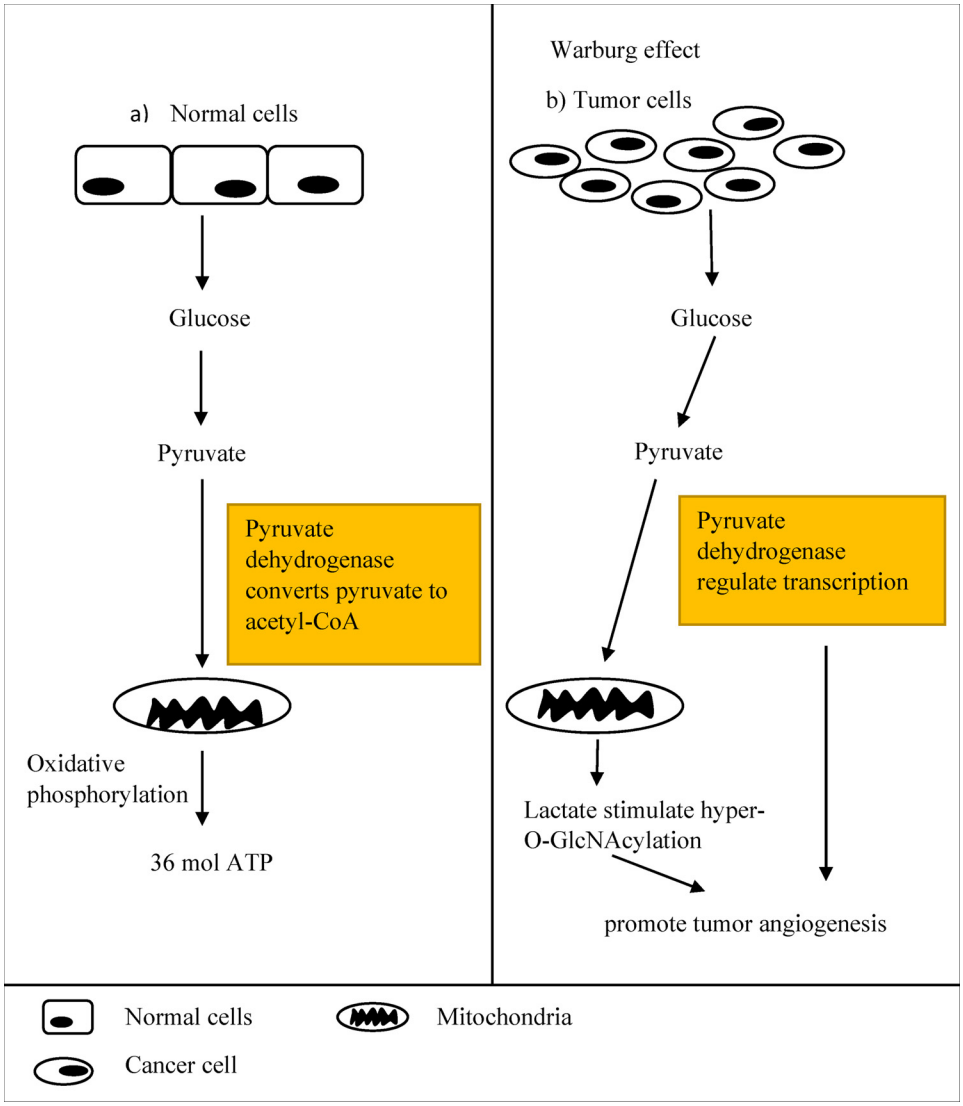

Fig. 1. Diagram depicting the difference in energy production between normal cells and tumor cells. (a) In normal cells, pyruvate dehydrogenase converts pyruvate to acetyl-CoA in citric acid cycle to produce adenosine 5′-triphosphate (ATP) through oxidative phosphorylation whereas (b) in tumor cells, pyruvate is converted to lactate resulting in hyper-*O*-GlcNacylation. This event, together with regulation of gene transcription by pyruvate dehydrogenase can increase tumor angiogenesis.

in glycosylation of angiogenic factors [24–26].

The HBP pathway metabolizes glucose to produce uridine diphosphate GlcNAc (UDP-GlcNAc) as an end product. The GlcNAc group in UDP-GlcNAc is then utilized in both *O*- and *N*-linked protein glycosylation processes to make glycosaminoglycans, proteoglycans, and glycolipids [27]. In cancer, energy metabolism changes from conventional mitochondrial oxidative phosphorylation to a less efficient glycolysis pathway and this phenomenon is known as the Warburg effect [28]. The Warburg effect occurs within the tumor microenvironment where high lactate production is observed even though there is adequate O_2 (Fig. 1) [29]. Moonlighting proteins are proteins containing a single polypeptide chain that performs multiple functions [30]. Pyruvate dehydrogenase (PD), one of the key enzymes in glycolysis, is an example of a moonlighting protein with reported ability to bind to DNA to regulate gene transcription [30,31]. A majority of cancer does not employ PD to generate ATP in citric acid cycle. However an elegant study by Koukorakis and colleagues showed that abunandt expression of PD in primary cell lung carcinomas and lung adenocarcinomas positively correlated with high angiogenic activity and poor prognosis in patients [32]. In addition, other studies have uncover the role of PD in regulating gene transcription may be related to tumor angiognesis [33,34], which could explain the abnormal high expression of PD found in lung cancer.

Lactate stimulates the production of hyper-*O*-GlcNAcylation to promote angiogenesis in tumor. This phenomenon is known as the Warburg Effect.

Recent studies have shown that lactate produced by tumor cells may have pro-angiogenic effects. This requires higher glucose uptake to generate the same amount of energy which increases HBP influx. The Warburg effect is a cancer-specific biological pathway that is also linked to a condition known as hyper-*O*-GlcNAacylation. Hyper-*O*-GlcNAcylation is a type of *O*-linked glycosylation. The increased uptake of glucose and glutamine due to Warburg effect drives high HBP influx leading to elevated level of *O*-GlcNAcylation in human prostate carcinoma *in vitro* [35]. In addition, O-GlcNAcylation has been found to upregulate the oncogenic transcription factor FoxM1 which regulates tumor invasion and angiogenesis [35]. Abnormalities in hyper-*O*-GlcNAcylation also have been shown to contribute to tumor progression in breast cancer, prostate cancer and colon cancer ;[28,35–39].

Downregulation of hyper-*O*-GlcNAcylation has been shown to reduce tumor angiogenesis in prostate cancer [35]. Gene knockdown of *O*-GlcNAc transferase (OGT) in PC-3ML, a prostate cancer cell line resulted in reduced hyper-*O*-GlcNAcylation leading to the inhibition angiogenesis *in vitro* through the downregulation of vascular endothelial