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Mini Review

Cytokines-Regulated Glycolytic Metabolism in Sertoli Cells: A Mini Review

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ABSTRACT

During spermatogenesis, germ cells cross a series of differentiation stages. Germ cells at each stage are provided with suitable metabolic substrates. The Sertoli Cell (SC) is commonly known as the main energy and nutritional supporter of the developing germ cells. SCs produce lactate, the central energy substrates for germ cells, and several other important nutrients *via* a glycolytic metabolism comparable to tumor cells. The maintenance of normal spermatogenesis is highly dependent on the tight regulation of SC glycolytic metabolism. Cytokines are widely reported as main factors responsible for the modulation of SC glycolytic metabolism. Herein, we review the impact and regulatory mechanism of cytokines on the glycolytic metabolism of SCs, with special focus on IL-1, TNF-α, HIF, bFGF and TGF-β

Keywords: Sertoli cells; Glycolytic metabolism; Cytokines; Metabolic modulation

INTRODUCTION

Spermatogenesis is a complex and highly regulated process occurring in the seminiferous tubules that involves the transformation from spermatogonial stem cells to spermatogonia, spermatocytes, spermatids and eventually mature spermatozoa [1]. Sertoli cells (SCs), as the principal somatic cells in the seminiferous tubules, play pivotal roles in spermatogenesis. In addition to forming the Blood-Testis Barrier (BTB) and physically supporting the germ cells, SCs are also responsible for the nutrient and energy supply to the germ cells during spermatogenesis [2]. Lactate secreted by SCs is the main energy substrate for the developing germ cells. It has also been reported to stimulate RNA and protein synthesis and inhibit apoptosis in germ cells [3,4]. Besides lactate, SCs also produce high quantities of acetate, the intermediate for the synthesis of lipids, and transferrin which mediates the iron transport to the germ cells, as well as other factors and proteins essential for the development and differentiation of germ cells [5,6].

The nutritional function of SCs depends on their own metabolic rate and protein expression activity. Notably, SCs mainly rely on glycolytic metabolism, which is analogous to tumor cells and described as a "Warburg-like" metabolism [7]. SCs import Glucose through Glucose Transporter (GLUT) members, mainly GLUT 1, 2 and 3 [8], and convert it into pyruvate through a high flux of glycolysis. Most of the pyruvate can then be reduced into lactate by Lactate Dehydrogenase (LDH) isoenzyme system and exported to the germ cells by Mono Carboxylate Transporters (MCTs); some pyruvate is oxidized into acetyl-CoA by Pyruvate Dehydrogenase Complex (PDC) in the mitochondria to produce acetate [9]. The metabolic behavior of SCs is precisely regulated by a network of endocrine and paracrine factors. Cytokines are small secreted proteins with multiple biological functions. Accumulating evidence has demonstrated the important roles of cytokines in the regulation of SC glycolytic metabolism, withinterleukin-1 (IL-1), Tumor Necrosis Factor-Alpha (TNF-α), Hypoxia-Inducible Factor (HIF), Basic Fibroblast Growth Factor (BFGF) and Transforming Growth Factor-Beta (TGF-β) being described as dominant regulators of the glycolytic metabolism in SCs. In this mini-review, we summarize our current understanding of the cytokines and mechanisms involved in the modulation of SC glycolytic metabolism.

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LITERATURE REVIEW

Interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α)

Urinary IL-1 is widely known as a pro-inflammatory cytokine involved in immune and inflammatory responses. There are two isoforms of IL-1 detected in testis: IL-1α expressed by germ cells and SCs, and IL-1β expressed by Leydig cells and interstitial macrophages, both of which are considered as key regulators of SC glycolytic metabolism [10]. IL-1α has previously been reported to promote lactate production in porcine SCs by enhancing the expression and activity of LDHA. The uptake of glucose by SCs was also shown to be increased by IL-1α, but the underlying mechanism was not further investigated [11]. IL-1β was found to elevate the lactate production level in porcine SCs in the same study. The impact mechanism was later investigated in studies using rat SCs, which indicated IL-1β could enhance the activity of LDH and was capable to redistribute the expression of LDH isozymes by increasing the proportion of LDH-4 and LDH-5 while reducing the proportion of LDH-1 and LDH-2 [12]. Moreover, IL-1β can stimulate the transcription of GLUT1, but not GLUT3, to facilitate the glucose uptake of SCs [13]. TNF-α is another pro-inflammatory cytokine involved in the regulation of SC glycolytic metabolism. In porcine SCs, TNF-α has been proved to induce SC lactate production through up-regulating the expression of LDHA [14]. However, no such effect of TNF-α is found in rat SCs [12], implicating different regulation patterns of SC metabolism among mammals. Since IL-1 and TNF-α are both related to immunity and inflammation, it is worth to further explore their functions in SC metabolism under inflammatory conditions.

Hypoxia-Inducible Factor (HIF)

HIF is a transcription factor required in the cellular response to low oxygen. It consists of two subunits: HIFβ with constitutive expression and HIFα whose expression is oxygen-dependent. Active HIF functions as a transcription stimulator by interacting with a consensus Hypoxia Response Element (HRE) in the promoter region of target genes [15]. Two isoforms of HIFα, HIFα1 and HIFα2, have been detected in SCs, interacting with HIFβ to form HIF1 and HIF2, respectively [16,17]. HIF is recently indicated as a major regulator of SC glycolytic metabolism. Hyper-activated transcription of HIF results in a stronger activity of LDH, as well as higher expression of GLUT1, Pyruvate Kinase M2 Splice Isoform (PKM2) and LDHA that have a HRE in their promoter region, and thereby increases the glucose uptake and lactate production of SCs [18]. HIF also functions as a downstream factor of follicle-stimulating hormone (FSH) in its regulation of SC lactate production through promoting the transcription of GLUT1, PKM2 and LDHA [18]. Moreover, HIFα1 is recently indicated as a target of nonylphenol, a typical endocrine disruptor, during its inhibition of SC glycolysis [19]. Nevertheless, HIF may also participate in the modulation of SC metabolism by other hormones or chemicals. Also, since the expression of HIF is hypoxic-dependent, it may involve in the modulation of SC metabolism under oxygen stress. The upstream regulation of HIF and its roles in SC metabolic regulation under oxidative stress remain largely unknown.

Basic fibroblast growth factor (bFGF)

bFGF is one of the best-known growth factors secreted by both SCs and germ cells. It acts as a central regulator of glycolytic metabolism *via* its specific receptors in SCs [20].bFGF improves the lactate secretion of SCs through distinct mechanisms. Firstly, it stimulates the glucose uptake of SCs in two patterns: a short-term stimulation with the underlying mechanism remaining elusive and a long-term stimulation by increasing the transcription level of GLUT1 [21]. The activation of phosphatidyl inositol 3-kinase/protein kinase B (PI3K/PKB) signaling pathway is reported to involve in the regulation of bFGF on the glucose transport into SCs [22]. Moreover, bFGF can raise the transcription level of LDHA in SCs [21]. It is also proved to enhance the activity of LDHA by activating the mitogen-activated protein kinase (MAPK) signaling pathway [22]. Besides lactate secretion, MAPK signaling pathway also participates in the acceleration of transferrin production in SCs by bFGF [22]. bFGF also facilitates SC glycolysis by increasing the expression of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB), an enzyme required for the activation of 6-phosphofructokinase-1 (PFK1) [23]. In addition, bFGF can elevate the levels of all the four isoforms of pyruvate dehydrogenase kinase (PDK) in SCs. Phosphorylation by PDK results in the inactivation of PDC. bFGF in this way lowers the activity of PDC to reduce the conversion of pyruvate to acetyl-CoA, hence augments the availability of pyruvate that can be converted into lactate [23]. Furthermore, bFGF has been described earlier to affect the number of FSH receptors in SCs [24], and the observation of a synergistic promoting effect of FSH with bFGF on both lactate and transferrin secretion of SCs [25] further proves the participation of bFGF in the modulation of SC metabolism by FSH. The production of estradiol and γ-Glutamyl Trans Peptidase (γ-GTP), a key enzyme in glutathione metabolism, in SCs can also be raised by bFGF [25], indicating pleiotropic effects of bFGF on SC metabolism. In summary, bFGF exert its effect on SC glycolytic metabolism through various mechanisms, while the intermediate molecules and signalings involved in each mechanism still need further investigation.

Transforming growth factor-beta (TGF-β)

Three isoforms of TGF-β (TGF-β1, TGF-β2 and TGF-β3) belonging to the transforming growth factor-beta superfamily have been detected in testis [26]. TGF-β1 and TGF-β3 are worth mentioning among the cytokines regulating SC glycolytic metabolism. TGF-β1 has been observed in an earlier study to directly stimulate the lactate production of porcine SCs [27]; however, the exact mechanism remains unclear. TGF-β3 is generally accepted as a vital regulatory factor of BTB. It is recently found to also play central roles in facilitating lactate secretion of SCs. Through the inhibition of Notch signaling pathway, TGF-β3 up-regulates multiple factors affecting the efficiency of SC lactate secretion including the glucose uptake of SCs, the expression of MCT4 and the activity of both PFK and

LDH [28]. Increments in glutamine consumption and glutaminase activity have also been detected in SCs exposed to TGF-β3, indicating a regulatory function of TGF-β3 in glutaminolysis, another important way of energy providing in SCs [28].TGF-β1 has been shown to induce glutaminolysis in human endothelial cells [29], hence it is possible that TGF-β1 can also to some extent affect the glutaminolysis in SCs.

DISCUSSION

To our knowledge, no evidence has been presented regarding the regulatory role of TGF-β2 on SC metabolism. However, as it is expressed predominantly in the fetal and neonatal testis [26], it is probably associated with the metabolic behavior of immature SCs. Besides the above-mentioned cytokines, several other cytokines, for example epidermal growth factor (EGF) [30], also play important roles in the modulation of SC glycolytic metabolism with their impact mechanism remaining to be discovered [31].

CONCLUSION

Cytokines play crucial roles in spermatogenesis that depends on SCs as the source of energy and nutrient substances. Several cytokines are indicated as major regulators of SC glycolytic metabolism. We have herein presented an up-to-date overview of the impact mechanism of cytokines on SC glycolytic metabolism. However, the current evidences are mainly based on studies *in vitro*. More *in vivo* studies are highly expected to provide a better understanding regarding the modulation of SC glycolytic metabolism by cytokines and its relevance to spermatogenesis. In addition, many diseases, drugs and environmental toxicants are reported to induce spermatogenetic disorders. Most of them have been found to disrupt SC metabolism. Abnormal expression of cytokines in testis was usually reported with diseases and toxicants' influence. For instance, IL-1, TNF-α and TGF-β are found to be overexpressed in the testes of patients or animal models with varicocele. Efforts on disclosing the participation of cytokines in the regulation of SC metabolism under the influence of diseases or toxicants may shed new light on the protection of spermatogenesis and male fertility under abnormal conditions. Furthermore, in the past decade the metabolic cooperation between testicular cells and its relevance to male infertility have attracted mounting attentions. Some cytokines are produced by not only SCs but also germ cells and other testicular cells. Their potential functions in the metabolic cooperation between testicular cells are worth further revealing. The function of cytokines in testis is not restricted to metabolic regulation; their multifarious roles during spermatogenesis deserve deeper studies.

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CONFLICT OF INTEREST

None of the authors has potential conflicts of interest to declare.

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