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·综　述·

睾丸支持细胞糖脂代谢在生精细胞发育中的作用及机制

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［**摘　要**］ 睾丸支持细胞在精子发生过程中起重要作用。精子发生的异常与睾丸支持细胞糖脂代谢紊乱密切相关。睾丸支持细胞的代谢环境为缺氧，其主要的代谢方式包括糖酵解和脂肪酸β氧化，其中糖酵解是睾丸支持细胞为生精细胞提供能量的经典途径，而脂肪酸β氧化可能是睾丸支持细胞产生腺苷三磷酸的主要途径。目前睾丸支持细胞糖脂代谢与生精细胞发育的关系、糖代谢与脂代谢之间的联系尚不明确。包括性激素在内的多种激素可以通过调控内分泌影响睾丸支持细胞糖代谢。AMPK、mTOR、Akt等信号通路的激活或抑制可以改变糖酵解相关转运蛋白和基因的表达水平以及脂肪酸生成，影响睾丸支持细胞糖脂代谢过程。一些转录因子如PPARγ可通过直接与响应元件结合来调节下游脂肪酸代谢相关基因，促进睾丸支持细胞脂肪酸氧化。本综述基于睾丸支持细胞糖脂代谢过程以及相关的实验研究结果，阐述了睾丸支持细胞中糖代谢和脂代谢的关键影响因素及其联系，并对男性不育症的临床潜在治疗方向进行了讨论，以期为男性不育症的精准靶向治疗提供参考。

［**关键词**］ 睾丸支持细胞；生精细胞；糖代谢；脂代谢；精子发生；机制；综述
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Research progress on glycolipid metabolism of Sertoli cell in the development of spermatogenic cell

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[**Abstract**] Sertoli cells play an important role in the process of spermatogenesis, and the abnormalities in spermatogenesis are closely related to disruptions in glycolipid metabolism. The metabolic environment of Sertoli cells is hypoxic, with glycolysis and fatty acid β-oxidation being the primary metabolic pathways. In Sertoli cells, glycolysis produces lactate to provide energy for spermatogenic cells, while fatty acid β-oxidation generates ATP. Currently, the relationship between glycolipid metabolism in Sertoli cells and spermatogenic cell development, as well as the interplay between glucose and lipid metabolism remain unclear. Various hormones, including sex hormones, can affect glucose metabolism in Sertoli cells by endocrine regulation. The activation or inhibition of signaling pathways such as AMPK, mTOR, and Akt can alter the expression levels of glycolysis-related transporter genes and the synthesis of fatty acids, thereby affecting glycolipid metabolism in Sertoli cells. Some transcription factors such as PPARγ can regulate downstream fatty acid metabolism-related genes by directly binding to their response elements and promoting the oxidation of fatty acids in Sertoli cells. In this article we elaborate on the key factors influencing glycolipid metabolism in Sertoli cells and their interconnections, as well as their potential clinical implications, offering new insights for precisely targeted treatments of male infertility.

[**Key words**] Sertoli cell; Spermatogenic cell; Glucose metabolism; Lipid metabolism; Spermatogenesis; Mechanism; Review

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[**缩略语**] 腺苷三磷酸(adenosine triphosphate,ATP);葡萄糖转运蛋白(glucose transporter,GLUT);丙酮酸脱氢酶复合体(pyruvate dehydrogenase complex,PDC);乳酸脱氢酶(lactate dehydrogenase,LDH);单羧酸转运体(monocarboxylate transporters,MCT);肉碱脂酰转移酶(carnitine acyl-transferase,CPT);6-磷酸果糖-2-激酶/果糖-2,6-双磷酸酶2(6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase,PFKFB);丙酮酸脱氢酶磷酸酶(pyruvate dehydrogenase phosphatase,PDP);胰岛素受体底物(insulin receptor substrate,IRS);磷脂酰肌醇3激酶(phosphoinositide 3-kinase,PI3K);蛋白激酶B(protein kinase B,Akt);胰高血糖素样肽(glucagon-like peptide,GLP);褪黑激素受体(melatonin receptor,MTNR);热休克蛋白(heat shock protein,HSP);缺氧诱导因子(hypoxia-inducible factor,HIF);腺苷一磷酸(adenosine monophosphate,AMP);AMP活化的蛋白质激酶(AMP-activated protein kinase,AMPK);哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR);蛋白激酶AMP激活的催化亚基(protein kinase AMP-activated catalytic subunit,PRKA);腺苷二磷酸(adenosine diphosphate,ADP);乙酰辅酶A羧化酶(acetyl-coenzyme A carboxylase,ACC);UNC-51样激酶(UNC-51 like kinase,ULK);线粒体分裂因子(mitochondrial fission factor,MFF);结节性硬化症(tuberous sclerosis,TSC);mTOR调节相关蛋白(regulatory-associated protein of mTOR,RAPTOR);S期激酶相关蛋白

(S phase kinase associated protein,SKP);过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor,PPAR)

据统计,全球有8%~12%的人群受不孕症影响,其中男性不育约占50%[1]。男性不育的原因很多,主要涉及精子发生,可由先天性发育异常、后天获得性因素或特发性因素等多种病理因素引起[1]。目前,基于精子发生的研究仍是评估和诊治男性不育症的关键科学问题[1]。在过去的30年里,全球范围内男性青春期启动时间呈现提前趋势[2],精子发生的提前启动可能与男性性早熟相关[3]。随着精子发生相关基因研究的不断深入,由精子发生阻滞引起的少精子症和无精子症也受到广泛关注[4],但其调控机制仍未完全阐明。睾丸支持细胞通过形成血-生精小管屏障、营养和保护生精细胞、分泌雄激素结合蛋白和抑制素、吞噬凋亡的生精细胞和残余体、促进精子释放等方式共同维持精子发生过程的正常进行[5-8]。睾丸支持细胞间紧密连接构成的血-睾屏障将生精小管分为基底室和近腔,为精子发生提供独特的微环境。此外,睾丸支持细胞可将大部分葡萄糖代谢为乳酸,而乳酸是生精细胞发育的主要能量底物且对生殖细胞具有抗凋亡作用,对精子发生具有重要意义[9]。而且,睾丸支持细胞产生的ATP明显高于生精细胞和间质细胞,这一特性主要依赖于脂肪酸β氧化的代谢途径[10]。多项研究表明,睾丸支持细胞糖脂代谢紊乱与精子发生异常密切相关[11-15]。本文重点介绍睾丸支持细胞糖脂代谢在生精细胞发育中的调控作用及其分子机制,深入探讨睾丸支持细胞糖脂代谢的关键影响因素及其联系,旨在为男性不育症的临床诊治提供潜在的治疗方向。

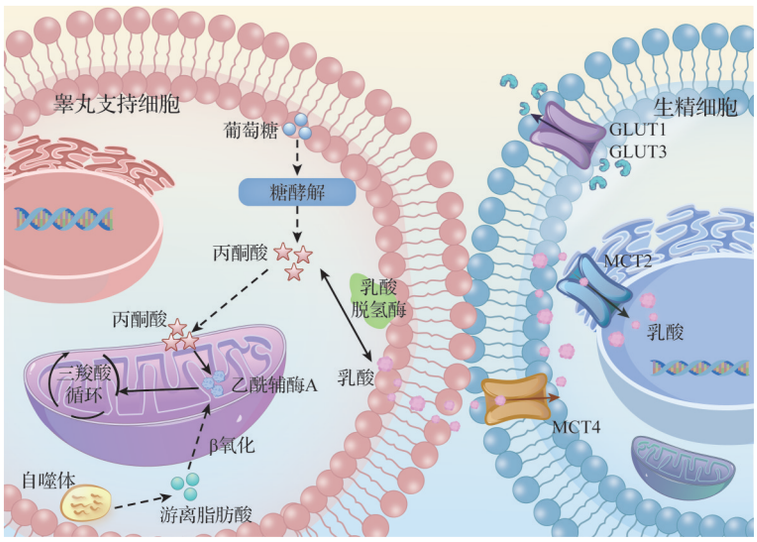
1 睾丸支持细胞糖脂代谢过程及其对生精细胞的作用

在精子发生过程中,生精细胞发育所需能量有赖于睾丸支持细胞,睾丸支持细胞通过糖酵解产生乳酸,为生精细胞提供能量[16-17]。研究表明,睾丸支持细胞通过细胞膜上GLUT来摄取葡萄糖[18]。被摄取的葡萄糖在己糖激酶、6-磷酸果糖激酶-1和丙酮酸激酶等一系列酶的催化作用下进行糖酵解反应生成丙酮酸[19]。一小部分丙酮酸进入线粒体,在PDC催化下变为辅酶A,进入三羧酸循环[20-21];另一部分丙酮酸则通过LDH转化为乳酸,为生精细胞发育提供能量底物,由MCT调控乳酸的运输和生精细胞的能量供应[22-24]。研究显示,睾丸支持细胞在营养生精细胞时所需要的大量能量并不是完全依赖于糖酵解[9],而是主要通过脂肪酸β氧化获得[10]。睾丸支持细胞中的脂肪酸首先在脂酰辅酶A合成酶的作用下活化成脂酰辅酶A,接着脂酰辅酶A在线粒体内膜外侧CPT1的催化下转化为脂酰肉碱,然后借助线粒体内膜上的转位酶转运到内膜内侧,在线粒体内膜内侧CPT2的催化下释放肉碱,肉碱进入线粒体基质后又转变为脂酰辅酶A,进入线粒体后的脂酰辅酶A经过脱氢、加水、再脱氢、硫解四个步骤进行氧化分解供能[25-27]。睾丸支持细胞糖脂代谢过程见图1。

2 影响睾丸支持细胞糖代谢的关键因素

2.1 激 素

激素水平可明显影响睾丸支持细胞的糖代谢过程。研究表明,5α-二氢睾酮处理的睾丸支持细胞葡萄糖消耗量增多,但乳酸产量减少,可能是由于GLUT1、LDHA、MCT4表达水平降低所致[28-29]。而17β-雌二醇处理的睾丸支持细胞MCT4表达水平上升,乳酸生成增多[30]。促卵泡激素可以提高LDH活性,促进LDHA、GLUT1、PFKFB1、PFKFB3表达,下调PDC表达,抑制三羧酸循环,也可使乳酸生成增多[31]。除性激素外,其他激素在睾丸支持细胞糖代谢调控中也能发挥重要作用。例如,在糖皮质激素皮质酮处理后的睾丸支持细胞中,乳酸代谢相关基因*PDP1*、*PDP2*上调,*GLUT1*、*GLUT3*、*LDHB*、*MCT4*下调,导致乳酸生成减少,最终导致精子发生障碍[32]。而胰岛素能诱导睾丸支持细胞生成乳酸。在胰岛素剥夺的情况下,睾丸支持细胞*GLUT3*、*LDHA*、*MCT4*表达减少,睾丸支持细胞对葡萄糖、乳酸的摄取减少,进而影响糖酵解过程[33]。最近的研究揭示,热应激可以通过IRS2-PI3K-Akt信号通路提高胰岛素敏感性,促进睾丸支持细胞生成乳酸[33]。Martins等[34]研究发现,在乳酸生成过程中,虽然GLP-1使LDH表达略有下降,但LDH活性明显增加,糖酵解增



睾丸支持细胞通过糖脂代谢途径为生精细胞提供能量和代谢前体物质:通过糖酵解将葡萄糖转化为丙酮酸,一部分丙酮酸在乳酸脱氢酶作用下转化为乳酸,并通过MCT转运至生精细胞,另一部分丙酮酸则进入三羧酸循环产生能量;还通过脂肪酸β氧化将游离脂肪酸转化为乙酰辅酶A,后者同样进入三羧酸循环产生能量.生精细胞利用GLUT摄取葡萄糖、通过MCT摄取乳酸为其提供能量和合成代谢的前体物质,从而支持其生长和发育.GLUT:葡萄糖转运蛋白;MCT:单羧酸转运体.

图1　睾丸支持细胞糖脂代谢示意图

Figure 1　Chematic diagram of glycolipid metabolism in Sertoli cell

强,从而增加乳酸生成。还有研究发现,生长激素释放肽能够以剂量依赖的方式作为人睾丸支持细胞的能量状态传感器调控精子发生,在生长激素释放肽处理的支持细胞中,尽管LDH表达量略有上升,但其活性明显下降,丙酮酸消耗量也下降,最终导致乳酸生成减少[35]。同样作为能量状态传感器的脂肪组织激素瘦素可通过提高GLUT2表达水平和LDH活性使乳酸生成增多[36-37]。褪黑素能够通过MTNR1B-HSP90-HIF-1α轴改变睾丸支持细胞糖代谢相关基因表达,上调糖酵解过程中*GLUT3*、*GLUT4*、*LDHA*、*MCT1*表达,从而促进乳酸生成[38]。Rossi等[39]发现前列腺素D2可通过前列腺素D1和D2受体诱导LDH相关基因表达,使乳酸生成增多。甲状腺激素可通过上调睾丸支持细胞GLUT1表达水平来促进乳酸生成[9]。因此,包括性激素在内的多种激素对睾丸支持细胞糖代谢有重要的影响。

2.2　AMPK及相关信号通路

既往研究表明,睾丸支持细胞中AMPK、mTOR、Akt等多种信号通路参与精子发生[40-42]。其中,AMPK信号通路在睾丸支持细胞糖代谢过程中发挥关键的调控作用[43-44]。AMPK是一个三聚体复合物,由催化亚基α和调节亚基β、γ组成。在哺乳动物中,基因*PRKAA1*、*PRKAA2*编码催化亚基β1、β2,基因*PRKAB1*、*PRKAB2*编码调节亚基β1、β2,基因*PRKAG1*、*PRKAG2*、*PRKAG3*编码调节亚基γ1、γ2、γ3[45]。AMPK不仅具有经典的AMP/ADP依赖的激活机制,还具有非经典的激活机制——通过感知1,6-二磷酸果糖缺失来触发AMPK激活[46]。AMPK作为关键的细胞能量传感器,还能调控多种下游效应分子,包括ACC、ULK1、MFF、TSC2、RAPTOR、H2B、SKP2、PDHA等[47]。研究表明,大鼠睾丸支持细胞在葡萄糖剥夺的条件下,通过激活AMPK信号通路上调GLUT1表达水平,从而加速葡萄糖的摄取,确保葡萄糖剥夺条件下乳酸生成[48]。腺苷能够通过AMPK信号通路上调GLUT1、LDHA、MCT4表达,促使乳酸生成增加[49]。AMPK激活剂氨基咪唑甲酰胺核苷通过激活AMPK信号通路可使大鼠睾丸支持细胞GLUT1、MCT4表达增加,GLUT3、MCT1表达减少,葡萄糖摄取增加,从而增加了乳酸生成[50]。睾丸支持细胞中Smtnl2是糖代谢的新型调节因子,可编程调控葡萄糖代谢,抑制Smtnl2可使LDHA表达明显减少;可通过激活AMPK来调节乳酸代谢和清除凋亡的生殖细胞[51]。此外,铅暴露可通过抑制AMPK信号通路干扰睾丸支持细胞的糖酵解代谢,导致青春期睾丸损伤和精子质量下降[52]。Dong等[53]发现葛根素可通过AMPK信号通路逆转镉暴露诱导的睾丸支持细胞糖酵解代谢紊乱。鉴于AMPK信号通路的重要作用,与其相关的mTOR和Akt等各种信号通路对精子发生过程的影响也可能有一定的研究意义。

3　影响睾丸支持细胞脂代谢的关键因素

3.1　转录因子

PPAR是一种配体激活转录因子,包括PPARα、PPARγ和PPARβ/δ三种亚型。PPARγ

通过直接与响应元件(位于其靶基因的启动子区域)结合,调控下游脂肪酸代谢相关基因的表达[54],可见PPARγ在睾丸支持细胞脂肪酸代谢中的重要中介作用。Regueira等[55]研究表明,凋亡的生精细胞可以调控睾丸支持细胞脂肪酸的储存和分解;其作为PPAR配体激活PPAR转录活性,而不是简单改变PPAR表达水平,其中配体激活的PPARα、PPARβ/δ介导CPT1表达水平增加,导致脂肪酸氧化增加,而配体激活的PPARγ介导PLIN1表达水平增加,也可导致脂肪酸氧化增加。既往研究发现,睾丸支持细胞可通过吞噬凋亡的生精细胞作为脂质来源[10],且PPAR的内源性配体也是脂质[56]。综上,凋亡的生精细胞通过产生脂质来作为PPAR的配体,激活PPAR转录活性,从而调控睾丸支持细胞脂代谢稳态,同时脂质也作为PPAR参与脂代谢的底物。此外,研究表明其他与脂代谢相关的转录因子也会影响睾丸支持细胞的增殖能力,如E4F1是一种调控细胞增殖、代谢和干细胞命运决定的多功能蛋白,在*E4f1*条件性敲除的小鼠睾丸中,睾丸支持细胞增殖受损,生殖细胞凋亡增多,推测E4F1在调节睾丸支持细胞的增殖和生育能力方面发挥一定作用[57]。

3.2 AMPK信号通路

AMPK信号通路不仅在睾丸支持细胞糖代谢中扮演着重要角色,在脂代谢中也发挥着关键的调控作用。最新研究发现,睾丸支持细胞在葡萄糖剥夺的情况下,可通过激活AMPK信号通路促进脂肪酸氧化来获取能量[58]。Pinkosky等[59]研究证实了AMPK对脂肪酸代谢调节的重要意义:在正常代谢环境中,较低活性的AMPK足以维持脂肪酸代谢稳态;而在高脂条件下,AMPK的调节亚基β1Ser108位点磷酸化可以促进ULK1的磷酸化,进而维持线粒体功能和脂肪酸代谢稳态[60]。此外,研究发现自噬在精子发生过程中具有重要作用,自噬过程是通过吞噬细胞内容物,随后在溶酶体中进行消化来参与脂代谢过程[61]。最新研究表明,激活AMPK能抑制mTOR通路,使AMPK与ULK1相互作用增强,进而诱导生精细胞自噬[62]。AMPK也可通过直接磷酸化ULK1诱导自噬[63-64]。研究还发现,睾丸支持细胞吞噬凋亡的生精细胞和残余体后将其降解为脂质和其他代谢产物,并通过脂肪酸氧化产生能量,以满足营养生精细胞的需求,这一过程可以称为"脂噬"[65]。AMPK信号通路在睾丸支持细胞脂质自噬中的具体机制是一个潜在的研究方向。

3.3 脂肪酸

脂肪酸主要分为饱和脂肪酸、单不饱和脂肪酸和多不饱和脂肪酸,其中与睾丸支持细胞脂代谢有关的主要是饱和脂肪酸和多不饱和脂肪酸[66]。饱和脂肪酸和多不饱和脂肪酸对睾丸支持细胞的脂代谢有着截然不同的影响。过量饱和脂肪酸尤其是棕榈酸明显增加了睾丸支持细胞的代谢压力,导致溶酶体酸性下降和细胞内代谢产物包括脂质的累积。这表明饱和脂肪酸可能通过影响溶酶体功能来影响睾丸支持细胞的脂代谢[66]。还有研究表明,饱和脂肪酸可以增加内质网应激,进而破坏睾丸支持细胞间紧密连接及内分泌等功能,同时也影响睾丸支持细胞的脂代谢,从而导致男性不育[67]。然而,多不饱和脂肪酸可促进精子发生,有助于维持精子细胞膜的完整性,减轻脂质过氧化对精子细胞膜的损伤[68]。不同脂肪酸类型对睾丸支持细胞脂代谢具有不同的影响,这些研究结果对理解脂代谢紊乱与男性生殖障碍的关系提供了参考。

4 睾丸支持细胞糖代谢与脂代谢有联系

睾丸支持细胞糖代谢和脂代谢之间有着密不可分的联系。睾丸支持细胞糖代谢过程中产生的乳酸不仅是生精细胞的主要能量来源,同时也是支持细胞脂代谢的重要调节因子,三羧酸循环和脂肪酸氧化是糖、脂质的代谢途径,释放的能量均以ATP化学能储存[69]。此外,糖代谢和脂代谢会受到相同关键因素的调控。如研究发现促卵泡激素在促进乳酸生成的同时抑制睾丸支持细胞脂肪酸氧化,还可以调节脂质酯化,刺激乙酸盐(乙酰辅酶A前体)掺入甘油三酯和磷脂中,促使睾丸支持细胞有效地储存能量,并在需要时通过脂肪酸氧化或磷脂分解来释放能量[70]。又如PPAR转录因子,除了影响脂代谢外,其部分亚型也可以促进睾丸支持细胞的糖代谢。研究表明PPARγ的激活可上调GLUT2表达,促进葡萄糖摄取,最终使乳酸生成增加[71]。这些研究都证实了睾丸支持细胞糖代谢和脂代谢在某些情况下受相同因素的调控。

5 结 语

阐明睾丸支持细胞糖脂代谢在生精细胞发育中的作用及分子机制对于探讨男性不育症的临床治疗方向有重要意义。研究显示,二甲双胍可在体外改变睾丸支持细胞间紧密连接和脂代谢,然而在大鼠血–生精小管屏障形成期间,二甲双胍暴露对血–生精小管屏障通透性影响很小,且不改变精子发生过程[72]。与此同时,研究发现,膳食补充二甲双胍可通过AMPK通路介导睾丸支持细胞糖脂代谢,改善哺乳动物的睾丸功能和精液质量[73]。吡格列酮可上调线粒体复合物Ⅱ的蛋白质表达水平,以提高睾丸支持细胞糖酵解通量和乳酸产生的效率,也能有效提升精子质量[74]。这些研究提示,临床上可使用抗糖尿病药物二甲双胍和吡格列酮来缓解男性不育症,尤其是青春期前的糖尿病患者。最新研究报道了多不饱和脂肪酸可有效减轻一些化疗药物对男性生育力的不良影响[75],这对青春期前的年轻肿瘤患者如白血病患者尤为重要。此外,很多经典代谢产物也影响着睾丸支持细胞糖脂代谢过程。研究发现,无精子症男性精浆中代谢产物乳酸和甘油磷酸胆碱的含量发生改变,这可能是由于活性氧过度产生导致细胞损伤和代谢紊乱,这种代谢紊乱导致了精浆中代谢产物含量改变,表明活性氧与不育症之间存在潜在联系[76]。肉碱是在体内发现的天然抗氧化剂,也是睾丸支持细胞脂代谢的产物,可抵消过量活性氧的不良影响,提升精子质量[77]。研究活性氧与睾丸支持细胞代谢产物之间的联系有助于改善男性精子质量,是临床上治疗男性不育症的潜在方向。基于睾丸支持细胞糖脂代谢产物的代谢组学与男性不育症之间的复杂关系也有待进一步探索,以促进男性不育症的精准靶向治疗[78]。

睾丸支持细胞糖脂代谢对精子发生具有重大影响,相关分子机制的研究表明多种因素可导致睾丸支持细胞糖脂代谢异常,然而如何有效逆转或预防这一现象的发生,目前尚不明确。GLUT、LDHA、MCT在糖酵解过程中的作用以及CPT1、CPT2在脂肪酸β氧化过程中的作用相关研究提示,这些分子有可能作为候选药物靶点来改善男性生育力低下。PPAR分子机制研究提供了一种很好的保护睾丸支持细胞糖脂代谢功能的示例,通过调节PPAR活性实现对睾丸支持细胞代谢功能的保护,从而改善精子发生过程,为开发针对男性不育症的治疗策略提供了新的思路。此外,多种环境污染物如空气中存在的细颗粒物2.5、增塑剂邻苯二甲酸二丁酯等对睾丸支持细胞糖脂代谢也有一定的影响[79-80],提示减少环境污染物的接触可能是预防男性不育症的关键环节之一。

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利益冲突 所有作者均声明不存在利益冲突

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