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代谢稳态在早发性卵巢功能不全中的作用及相关干预措施研究进展

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摘　要

早发性卵巢功能不全(Premature Ovarian Insufficiency, POI)指女性在40岁以前出现卵巢功能减退，严重影响患者的身心健康和生育能力。颗粒细胞及卵母细胞的糖类、脂质及氨基酸的代谢紊乱在POI的发病中具有重要作用。本文综述了糖类、脂质及氨基酸的代谢在维持正常卵巢功能中的作用并讨论了代谢异常对卵巢储备功能的影响以及基于代谢重塑的相关药物或潜在分子对卵巢功能的调控机制。

关键词

早发性卵巢功能不全，糖酵解，脂肪酸β氧化，氨基酸代谢，颗粒细胞，卵母细胞

The Role of Metabolic Homeostasis in Premature Ovarian Insufficiency and Related Treatment Measures

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Abstract

Premature ovarian insufficiency (POI) is defined by loss of normal ovarian function before the age of 40 years, which can severely affect the physical and mental health of women. The metabolism of

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carbohydrates, amino acids, and lipids in oocytes and granulosa cells plays a significant role in the pathogenesis of POI. This review article provides a summary of glucose metabolism, amino acid and lipid metabolism in maintaining ovarian normal physiological function and homeostasis, the potential impact of metabolic disorder on ovarian reserve and the regulatory mechanisms in repair of ovarian function based on metabolic remodeling.

Keywords

Premature Ovarian Insufficiency, Glycolysis, Fatty Acid β-Oxidation, Amino Acid Metabolism, Granulosa Cells, Oocytes

1. 引言

早发性卵巢功能不全(Premature Ovarian Insufficiency, POI)是指女性在 40 岁以前出现卵巢功能减退，主要表现为月经异常(闭经、月经稀发或频发)、促性腺激素水平升高(FSH > 25 U/L) [1]。该疾病严重影响患者的身心健康和生育能力，目前治疗仍以激素补充治疗为主，其他前沿治疗方法尚处于研究阶段。POI 的发病涉及多种机制，包括原始卵泡池减少，卵泡闭锁加速以及卵泡功能障碍[2]。目前多项研究表明颗粒细胞及卵母细胞的糖类、脂质及氨基酸的代谢稳态和代谢调控与维持卵巢储备功能密切相关。卵泡中的糖代谢主要分为糖酵解、氧化磷酸化、磷酸戊糖途径及己糖胺生物合成途径[3]，其中糖酵解与氧化磷酸化之间相互调控，在卵母细胞发育及卵泡成熟过程中具有重要作用[4]。异常的葡萄糖代谢损害线粒体功能，导致卵母细胞衰老加速及卵泡质量下降[5]。脂质作为重要的储能物质，其代谢为卵泡生长和卵母细胞成熟提供了必要的能量来源[6]。脂肪酸是脂类物质的重要成分[7]，在卵泡环境中可观察到脂肪酸的广泛分布，脂肪酸代谢失调会导致卵泡发育受损及相关生育问题[6]。氨基酸作为蛋白质和核酸的前体，参与蛋白质合成、能量产生及其他过程，以调节卵母细胞的发育[8]。各种天然蛋白质水解的 α 氨基酸及非蛋白质氨基酸和支链氨基酸的代谢稳态均对卵巢功能有重要影响[9]-[12]。本文综述了糖类、脂质及氨基酸的代谢在维持正常卵巢功能中的作用及 POI 中的发病机制，为 POI 的发病机制研究提供了新的视角，并从改善卵巢功能的角度为 POI 治疗提供了新的治疗靶点，并具有提高 POI 患者的生育能力和辅助生殖的临床结果的潜在临床价值。

2. 葡萄糖代谢对卵巢功能的影响

在卵泡发育过程中，卵巢颗粒细胞由于血管供应少而处于相对低氧的状态，这使得卵巢颗粒细胞更倾向于通过糖酵解来产生能量；卵母细胞则更多地依赖线粒体氧化磷酸化供能[13]。糖酵解是细胞能量产生的基本途径，该代谢过程将葡萄糖转化为丙酮酸，产生一定量的 ATP 以满足细胞即时能量需求。颗粒细胞可以通过与卵母细胞间的细胞通讯为其提供糖酵解途径中的中间产物，例如丙酮酸和乳酸[14]。

多项研究表明，糖酵解过程的激活或抑制对颗粒细胞增殖、卵泡发育、卵巢功能的影响并非单向调控，而是涉及多种调节途径的复杂调节网络。颗粒细胞内高水平的糖酵解代谢途径对卵泡发育具有重要影响[15]。颗粒细胞中高水平的糖酵解代谢通过 mTOR 信号通路，介导其下游通路 Akt 和 FOXO3a 的磷酸化，从而促进原始卵泡的激活[16]。同时，颗粒细胞的增殖依赖于 HIF1α-VEGF-Akt-mTOR 通路的上调

以及糖酵解的上调[17]。然而，糖酵解水平的过度激活则会导致颗粒细胞过度增殖、卵泡发育加速，使得卵巢中有限数量的原始卵泡提早耗竭，发生卵巢早衰[18]。Shang [19]等人研究发现，富含亮氨酸的重复序列蛋白 4 (Leucine Rich Repeat Containing 4, LRRC4)是卵泡发育的关键调节因子，在细胞增殖、分化和发育中具有关键作用。LRRC4 可通过增加 Yes 相关蛋白(Yes-associated Protein, YAP) K48 连接的泛素化并抑制 K63 连接的泛素化促进 YAP 的降解，从而抑制线粒体过度自噬，维持糖酵解的代谢稳态。LRRC4 缺乏导致糖酵解过度增加和线粒体有氧呼吸减弱，乳酸积累并加剧线粒体损伤，引发卵母细胞成熟障碍、卵泡过度激活和闭锁。

微小 RNA 通过细胞的 Warburg 效应调控糖酵解，控制关键糖酵解酶，包括己糖激酶 2 (Hexokinase2, HK2)，乳酸脱氢酶 A (Lactate Dehydrogenase A, LDHA)和丙酮酸激酶 M2 (Pyruvate kinase M2, PKM2)的表达[20]。卵泡液来源的外泌体 miR-143-3p 的表达的上调和 miR-155-5p 表达的下调导致 HK2，LDHA 和 PKM2 的表达下降，拮抗糖酵解过程，加速颗粒细胞的凋亡；卵泡发育的能量供应不足，继而导致卵泡发育异常[21]。此外，另一项研究则表明，人脐带间充质干细胞来源的外泌体可以通过 Hippo 信号通路增强卵巢功能储备，改善环磷酰胺诱导的早发性卵巢功能不全[22]。在缺氧和常氧条件下分别从人脐带间充质干细胞中分离并鉴定外泌体，研究发现两者均通过 SIRT3/PGC-1α 信号通路调节线粒体功能和氧化应激，且缺氧条件下间充质干细胞来源的外泌体与正常条件相比展现出更显著的卵巢功能改善效果[23]。Li [24]等人的研究同样发现在缺氧条件下分离并鉴定的股骨骨髓间充质干细胞来源的外泌体比在常氧条件下表现出了更强的靶向卵巢组织颗粒细胞的递送能力和更显著的卵巢储备功能改善效果。同时，该研究表明缺氧条件下分离的外泌体中富集的环状 RNA hsa-circ-0002142 通过靶向结合 LDHA 调控其催化活性并增强 LDHA 介导的糖酵解，从而恢复卵巢颗粒细胞糖酵解能力并修复卵巢功能障碍。然而，在实际临床应用中，间充质干细胞会受到免疫原性、恶变、栓塞、细胞植入不足以及移植后的存活率等问题的限制[25]。

长链非编码 RNA ZNF674-AS1 在能量应激状态诱导下直接参与糖酵解过程的第四种酶——果糖-1,6-二磷酸醛缩酶 A (Aldolase A, ALDOA) [26]，并调控其活性，并通过 ALDOA/v-ATPase 依赖的途径激活 AMPK 相关通路，从而参与卵泡颗粒细胞的糖酵解和葡萄糖代谢并调控颗粒细胞的增殖[27]。二甲双胍激活卵巢中的 AMPK/SIRT1 信号通路[28]并增加 LDHA 和 PKM2 的表达[29]，可提高卵巢颗粒细胞的糖酵解活性和整体代谢功能。另一方面，二甲双胍对 mTOR 信号通路具有抑制作用，可减少卵巢中过多的能量累积[30]。研究发现，白藜芦醇和罗汉果苷 V (Mogroside V, MV)可以通过上调 LDHA、HK2 和 PKM2 的表达促进糖酵解过程，增加乳酸和 ATP 水平，从而改善细胞能量代谢，维护正常卵巢功能[31]。

3. 脂质代谢对卵巢功能的影响

在卵母细胞在减数分裂及成熟过程中，除葡萄糖代谢外，其他代谢方式也是该过程重要的能量来源。既往关于卵母细胞内源性脂肪酸和甘油三酯的研究表明，β 氧化在卵母细胞成熟和早期胚胎发育的能量代谢中起重要作用。脂肪酸 β 氧化过程的限速步骤是肉碱棕榈酰转移酶 1 (Carnitine Palmityl Transferase 1, CPT 1)将肉碱连接到脂肪酸上生成形成脂酰肉碱，使其进入线粒体基质。在经腹腔注射人绒毛膜促性腺激素后，在小鼠卵丘–卵母细胞复合体(COC)中观察到 CPT1B mRNA 表达显著上调，诱导卵母细胞成熟和排卵。在卵母细胞成熟过程中抑制 β-氧化会导致卵母细胞发育能力下降，影响胚胎发育。而 COC 中的 β 氧化则显著提高了卵母细胞发育能力和胚胎发育至囊胚阶段的比例[32]。甘油三酯是卵母细胞细胞质脂滴的主要成分，可被激素敏感性脂肪酶水解为 2 个游离脂肪酸和 1 个甘油分子。研究发现 HSL 抑制剂 CAY10499 明显降低了猪卵母细胞的成熟率、卵裂率及囊胚成熟率，而 HSL 激活剂异丙肾上腺素可拮抗这一作用[33]。乙酰辅酶 A 羧化酶(Acetyl-CoA Carboxylase, ACAC)是脂肪酸合成步骤的限速酶，可催化

乙酰 COA 生成对 CPT I 具有抑制作用的丙二酰辅酶 A [34]。在排卵前，LH 和 HCG 激活磷酸二酯酶，导致 cAMP 的分解并促进减数分裂[35]以及 camp-AMP-PrKA 途径的激活，这一过程会导致线粒体中乙 ACAC 的磷酸化和失活[36]，从而减少丙二酰辅酶 A 对脂肪酸 β 氧化的抑制作用。小鼠卵母细胞中的 AMP 激酶(AMP-activated Protein Kinase, AMPK)可介导 ACAC 的磷酸化并使其失活，降低丙二酰辅酶 A 水平，促进脂肪酸进入线粒体进行 β-氧化并诱导减数分裂[37]。

白蔹水提物通过上调脂蛋白脂肪酶、二酰甘油磷酸胆碱转移酶和胆碱/乙醇胺磷酸转移酶 1 的表达，调节异常的甘油酯和甘油磷脂代谢，减少颗粒细胞凋亡并改善排卵功能障碍[38]。青蒿素可激活 AMPK 信号通路，使 AMPK 磷酸化，进而启动下游的代谢调控机制。通过 AMPK 的激活，增强脂肪酸氧化并改善脂质代谢，从而改善卵巢功能[39]。左旋肉碱是一种人体内天然存在的氨基酸类似物，可以促进脂质代谢并保护线粒体膜免受脂质过氧化的损伤。研究发现，在卵母细胞体外成熟系统中加入左旋肉碱有利于促进脂肪酸 β-氧化，诱导卵母细胞的发育并改善卵母细胞质量[40]。

卵丘－卵母细胞复合体中脂质积累过多则会引发脂肪毒性反应，引起卵母细胞线粒体功能障碍，颗粒细胞内质网应激和细胞凋亡显著增加[41]。内质网应激抑制剂 salubrinal 能够逆转内质网稳态失衡导致的卵母细胞线粒体功能障碍，促进卵母细胞成熟和胚胎发育[42]。氨基酰-tRNA 合成酶(Aminoacyl-tRNA Synthetase, AARS)可介导肉碱棕榈酰转移酶 2 (Carnitine Palmityl Transferase, CPT2)乳酸化，使其失活，导致游离脂肪酸积累，激活过氧化物酶体增殖物激活受体 γ，过高的乳酸化信号导致卵泡耗竭和 POI。β-丙氨酸可抑制 AARS 活性，对 POI 具有治疗作用[18]。

4. 氨基酸代谢对卵巢功能的影响

氨基酸代谢同样影响卵巢功能储备。氨基酸周转率与卵母细胞减数分裂进程相关。对不同发育阶段的卵母细胞的氨基酸谱分析显示，停滞在 GV 阶段的卵母细胞比 MII 阶段的卵母细胞消耗更多的缬氨酸和异亮氨酸，比停滞在 MI 阶段的卵母细胞消耗更多的异亮氨酸。在退化的 MII 阶段卵母细胞与正常 MII 卵母细胞之间的谷氨酸、谷氨酰胺、精氨酸、缬氨酸和异亮氨酸的消耗水平和含量均有显著差异[43]。丝氨酸合成的关键酶 3-磷酸甘油酸脱氢酶、磷酸丝氨酸氨基转移酶 1、磷酸丝氨酸磷酸酶和丝氨酸羟甲基转移酶-2 在卵巢储备功能减退患者的卵丘细胞中表达增加，丝氨酸的生物合成通路上调可能通过参与一碳代谢，介导 DNA 甲基化从而调控细胞增殖并影响卵巢功能[11]。Parimah Alborzi 等人研究发现，在培养小鼠卵巢组织时加入亮氨酸、谷氨酰胺、精氨酸或它们的组合可以加速原始卵泡的激活[44]。

一项基于非靶向气相色谱－质谱法的代谢组学研究显示，磷酸、N-乙酰-d-氨基葡萄糖、支链氨基酸(Branched Chain Amino Acid，BCAA)、脯氨酸、尿素和吡咯酸等血清代谢物的水平与抗缪勒管激素(Anti-Müllerian Hormone, AMH)的年衰减率呈正相关。氨基糖和核苷酸糖代谢、BCAAs 代谢以及氨酰 tRNA 生物合成是与 AMH 年下降率最显著相关的通路[45]。BCAAs 通过改变血脑屏障处的血清素(由色氨酸衍生)和儿茶酚胺(由酪氨酸和苯丙氨酸衍生)的转运，抑制下丘脑促性腺激素释放激素的合成和分泌[12]，从而影响排卵和黄体生成。高浓度的支链氨基酸可促进活性氧(Reactive Oxygen Species，ROS)的产生并导致线粒体功能障碍，激活 Akt-mTOR 通路[46]，mTOR 通路的过度激活导致原始卵泡募集和耗竭[47]，最终导致 POI。相反地，另一项研究则发现低支链氨基酸饮食的小鼠出现 POI 表型，该现象与 BCAAs 不足诱导神经酰胺升高，导致 ROS 相关基因上调，损害颗粒细胞功能，导致 POI。BCAAs 补充剂 N-乙酰半胱氨酸则可以部分恢复 BCAA 低水平导致的卵巢功能异常[48]。

5. 总结与展望

POI 已经成为现代女性生育健康的重大挑战。而其发病机制可能与多种物质的代谢稳态失衡相关，

各种代谢途径内在的复杂的调控网络和相关通路为 POI 发病机制与潜在治疗方案研究提供了新的视角。基于代谢重塑机制治疗 POI 的方案相比传统激素替代疗法更强调病因干预而非简单的对症治疗，同时，代谢调节副作用更小，血栓形成或乳腺癌风险减少；且具有针对不同原因的代谢紊乱患者提供个体化精准医疗的潜力。目前，各种代谢水平的精细调节和各种代谢途径间的相互影响尚需进一步研究，卵泡微环境中不同细胞类型(颗粒细胞、卵泡膜细胞、免疫细胞)间的代谢串扰机制和调控网络尚未完全明确，基于代谢重塑改善卵巢功能、治疗 POI 的相关靶点及治疗方案仍需大样本临床研究来验证其安全性及有效性。因此，未来的研究应深入探讨卵巢细胞的代谢稳态调控机制和各类治疗方案的干预靶点，聚焦于鉴定不同病因 POI 的特异性代谢标志物谱，以实现分型诊断和精准治疗。

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