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多囊卵巢综合征与卵泡扩张的关系及调控机制研究进展

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【摘要】 卵泡扩张是卵泡生长发育为优势卵泡的重要环节,受多种分子及信号调控,主要包括卵泡腔形成、卵泡液积累及颗粒细胞增殖。多囊卵巢综合征(polycystic ovary syndrome, PCOS)是女性最常见的生殖内分泌疾病,患者主要表现为由卵泡扩张不足引起的窦前卵泡增多及卵巢多囊样变。本文综述了近年来有关卵泡扩张生理过程、相关调控因子及机制的新进展,并阐述了 PCOS 患者卵泡扩张受限的可能因素,以期为卵泡扩张异常导致的卵泡发育不良、排卵障碍等疾病提供理论依据。

【关键词】 卵泡扩张;卵泡腔形成;卵泡液积累;颗粒细胞增殖;多囊卵巢综合征
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Research progress in relationship between polycystic ovary syndrome and ovarian follicle expansion and its regulatory mechanism

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【Abstract】 Ovarian follicle expansion is an important part of their growth and development into dominant follicles, and is regulated by a variety of molecules and signals, including follicular cavity formation, follicular fluid accumulation, and granulosa cell proliferation. Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine disease in women, and patients mainly present with increased preantral follicles and polycystic ovarian lesions caused by inadequate ovarian follicle expansion. This review summarizes recent research developments concerning the physiological process of ovarian follicle expansion and the related regulatory factors and mechanisms.

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We also consider the possible factors restricting ovarian follicle expansion in patients with PCOS, to provide a theoretical basis for follicular dysplasia, ovulation disorders and other diseases caused by abnormal ovarian follicle expansion.

【**Keywords**】 ovarian follicle expansion; follicular cavity formation; follicular fluid accumulation; granulosa cell proliferation; polycystic ovary syndrome

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卵泡是雌性哺乳动物的基本生殖功能单位。卵泡发育是一个连续的、有选择性的过程[1-2],主要受到下丘脑-垂体-卵巢(hypothalamic-pituitary-ovarian, HPO)轴内分泌机制的动态调控[3]。卵泡扩张是卵泡有效发育的重要基础,伴随着卵泡直径增大及颗粒细胞增殖和功能分化,主要包括卵泡腔的形成与扩张、卵泡液积累以及卵泡内颗粒细胞增殖[4]。关于卵泡生长的体外研究大多集中在颗粒细胞增殖上,而利用超声技术的体内研究则集中在卵泡腔及其液体扩张上。与卵泡整体发育过程相类似,内分泌信号在调节卵泡扩张中的重要性早已被认识到[3,5]。除此之外,卵泡内局部微环境对卵泡扩张过程发挥关键调节作用[6]。卵泡发育不良和扩张不足可能导致排卵障碍性不孕,如育龄期女性常见的排卵障碍性疾病多囊卵巢综合征(polycystic ovary syndrome, PCOS),其与生殖、内分泌和代谢功能紊乱有关[7]。因此,本文重点探讨卵泡扩张的主要生理过程及相关信号的调控,为治疗卵泡扩张受限所导致的女性疾病提供新的策略及靶点。

1 卵泡扩张的生理过程

1.1 卵泡腔形成与发育

卵泡腔形成是卵泡发育为三级卵泡阶段的重要标志,也是卵泡获得对促性腺激素全面应答能力的分水岭[8]。当颗粒细胞层发生分离时形成窦腔,颗粒细胞与卵母细胞运输液体并迅速汇集到腔内,随着这些液体的扩张和合并,窦腔逐渐扩大相连形成半月形的腔,其内充满液体,即卵泡腔的形成过程[9]。同时,形成的小窦卵泡在促性腺激素的作用下急剧扩张,窦状卵泡得以形成[10]。研究发现,窦前卵泡阶段正常的颗粒细胞偶尔会发生少部分角质化后凋亡,这类细胞凋亡事件可能是窦腔或空腔形成的原因,凋亡的颗粒细胞释放高分子量的 DNA,为液体的渗入提供渗透梯度[8]。这个阶段水通道蛋白(aquaporin, AQP) 4 在颗粒细胞低表达。在 *AQP* 4 基因敲除小鼠中,窦状卵泡数量减少,考虑 AQP 4 可能参与卵泡腔的形成[10]。

卵泡腔形成的时间与卵泡的发育程度呈正相关,这一过程依赖颗粒细胞产生的 kit 配基和卵母细胞缝隙连接蛋白 Cx37 的参与[11]。近期研究表明,卵泡刺激素(follicle-stimulating hormone, FSH)-雷帕霉素(mTOR)-C 型钠肽(natriuretic peptide C-type,NPPC)信号轴调控卵泡液的形成和颗粒细胞增殖,促使卵泡腔形成。同时,此研究还发现卵泡腔形成过程中糖酵解速率加快,ATP 生成增多,可为卵泡腔形成提供能量[12]。体外培养卵泡的研究表明,敲降紧密连接相关基因表达水平能够显著降低卵泡体积及卵泡腔占比,这提示紧密连接是促使卵泡腔扩张的重要结构基础[13]。通常卵泡腔是否形成以及形成后的大小可以作为评定卵泡发育程度的依据,这对于卵母细胞的成熟与排出至关重要。

1.2 卵泡液积累

卵泡腔内的卵泡液由血浆渗出物和卵巢局部分泌物构成,内含促性腺激素、雌激素、抗中肾旁管激素、类固醇激素、透明质酸、囊性纤维化跨膜调节因子(cystic fibrosis transmembrane regulator, CFTR)及多种生物活性物质[13]。这些组分能够促进卵泡扩张,调节健康的卵泡环境,进而对卵母细胞获得生殖发育能力起支持作用。CFTR 是一种氯离子(Cl^-)通道蛋白,具有介导离子和水分子在细胞中的分泌和转运的作用。CFTR 镶嵌在颗粒细胞膜上,使得颗粒细胞膜通透性增加,Cl^-、HCO_3^-以及水分子进入卵泡腔,进而促进卵泡液积累[14]。卵泡液对卵泡发育、卵母细胞成熟、排出及受精后胚胎的形成起着直接调控作用[15]。卵泡膜血管通透性升高能够引起卵泡液积累,但卵泡液汇聚的相关机制不止于此。

早期的研究认为,颗粒细胞膜上的钠泵和卵泡液中断裂的葡聚糖等渗透活性分子建立卵泡液渗透梯度,这是排卵前卵泡液体升高的机制[16]。之后的研究找到了卵泡液中存在大渗透活性分子的证据:从卵泡液中去除葡聚糖、透明质酸、硫酸软骨素以及 DNA 会造成卵泡渗透压降低,表明这些分子可能有助于维持卵泡液的渗透压,进行卵泡液积累[16]。此外,在卵巢中敲低编码钠钾泵的基因后,卵巢内水分显著减少,因此离子泵为卵泡液的集聚提供了动力来源[17]。还有研究表明,AQP 可能调控卵泡液的集聚,因为 AQP 8 的缺失促进卵泡液积累,而敲低 *AQP* 3 抑制卵泡液积累,降低卵泡直径,说明跨细胞转运是卵泡液进入卵泡的重要方式[10]。

综上所述,紧密连接为卵泡腔形成提供了结构基础、离子泵为卵泡液集聚提供动力来源,水通道蛋白为卵泡腔扩张及卵泡液积累提供了运输通道。实际上,卵泡液积累的本质是为卵泡腔形成及扩张提供驱动力。随着卵泡液分泌的增多,卵泡腔会不断扩张,导致卵泡体积增大,卵泡壁变薄,只有当卵泡腔内的卵泡液体积增加到足够大的情况下,才可以排卵。因此,卵泡腔扩张以及卵泡液积累对排卵过程至关重要。

1.3 卵泡内颗粒细胞增殖

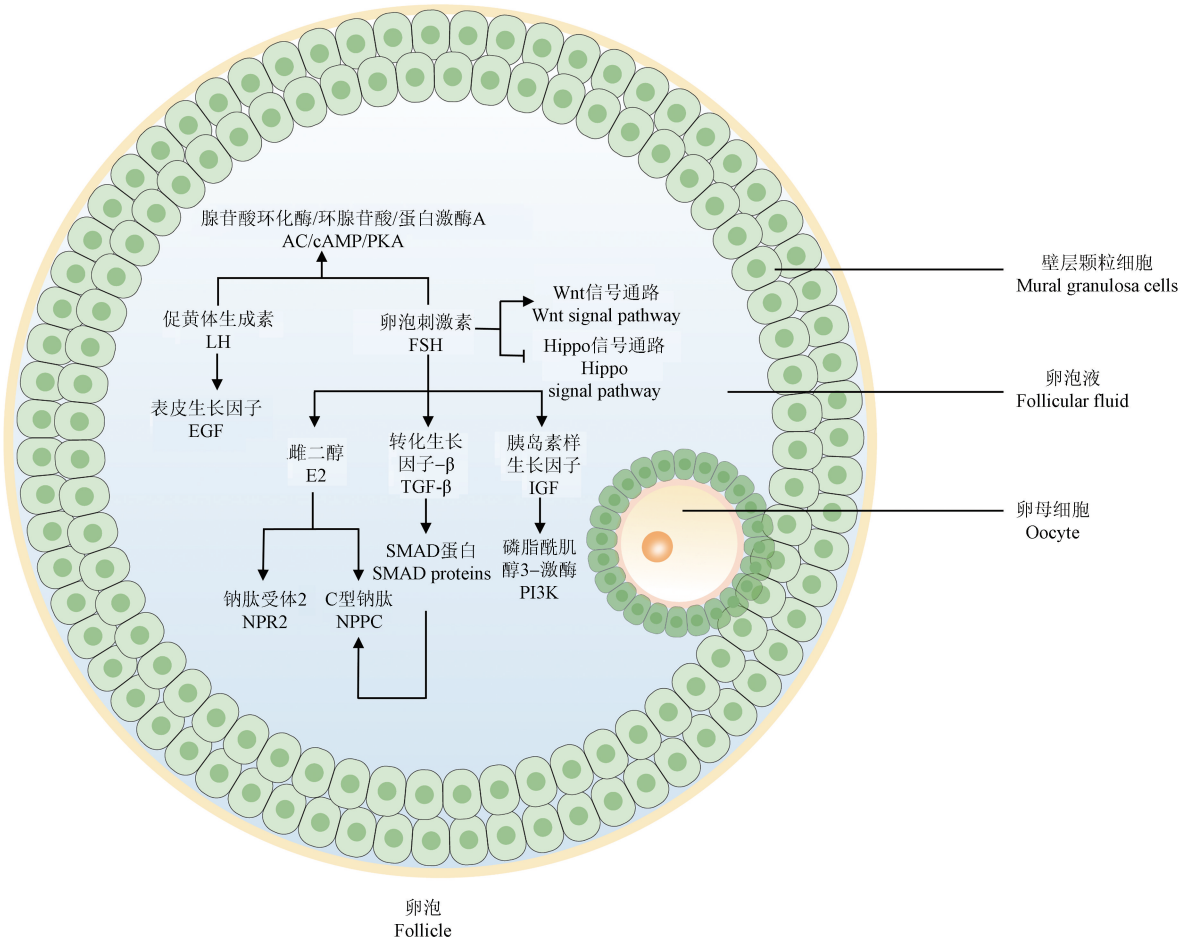
卵泡扩张与颗粒细胞增殖密切相关。在卵泡募集阶段,颗粒细胞由扁平状变为立方体状并获得有丝分裂的能力。在一个优势卵泡中,颗粒细胞在三级卵泡阶段迅速复制增殖(高达 100 倍),颗粒细胞数目不断增多。当颗粒细胞增殖分化到一定程度会表达各种促性腺激素受体包括 FSH 受体、促黄体生成素(luteinizing hormone, LH)受体等,这些受体与类固醇激素结合,更进一步促进卵泡扩张[18]。研究认为,颗粒细胞增殖速度与卵泡腔扩张及卵泡液积累速度之间并不存在紧密或协调调节[19]。颗粒细胞的复制一方面涉及到细胞周期等相关基因的调控,同时受到内环境的刺激,另一方面,在生物化学上卵泡液的形成是非常不同的,涉及多种复杂结构及渗透机制。卵泡腔初始形成有赖于颗粒细胞凋亡,之后的扩张阶段不太可能因颗粒细胞凋亡引起,因为这需要大量的颗粒细胞凋亡,但卵泡腔扩张的具体机制目前还不清楚[12,17]。因此,颗粒细胞复制、卵泡腔扩张、卵泡液积累可以受到不同的调节。关于颗粒细胞复制增殖相关生理过程已有文献详细描述[20-21],本文不再赘述。

2 卵泡扩张的主要调控机制

卵泡扩张受多种因子及信号分子调控(如图 1 所示)包括 FSH、LH、胰岛素样生长因子(insulin-like growth factor, IGF)、表皮生长因子(epidermal growth factor, EGF)以及促性腺激素释放激素(gonadotropin releasing hormone, GnRH)信号通路等。

2.1 FSH、LH 调控卵泡扩张

GnRH 可刺激垂体分泌 FSH 和 LH,它们是参与卵泡生长发育最主要的糖蛋白激素,与存在于颗粒细胞、内膜细胞上的受体结合并激活经典的腺苷酸环化酶(adenylyl cyclase, AC)/环腺苷酸(cyclic adenosine monophosphate, cAMP)/蛋白激酶 A(protein kinase A, PKA)信号转导通路[22]。有研究发现,在 *FSHR*、*FSHβ* 基因敲除的雌性小鼠中,出现卵巢内 LH 含量升高,卵巢体积变小,卵泡发育受阻,不能形成卵泡腔等症状,且出现不孕的现象[23]。因此,在卵泡发育过程中,FSH 对于调节卵泡扩张起着必不可少的作用。FSH 与膜上的受体蛋白结合,产生有活性的刺激型 G 蛋白 α 亚基-鸟苷三磷酸复合体(stimulatory G protein α subunit-guanosine triphosphate complex, αGs-GTP),随后与其效应蛋白 AC 作用分解 ATP 产生 cAMP,激活 PKA 使底物蛋白磷酸化,刺激颗粒细胞有丝分裂并促进卵泡液产生[24]。因此,FSH 对颗粒细胞增殖及卵泡液的分泌均具有促进作用。另外,FSH 还可刺激颗粒细胞将雄激素转化为雌激素,FSH 与卵泡液中的雌二醇(estradiol, E2)通过协同作用刺激颗粒细胞产生 FSHR,增强颗粒细胞对 FSH 的敏感性,促进颗粒细胞增殖,从而促进卵泡扩张[25]。此外,有研究表明,FSH 可以通过 E2 及其受体上调 NPPC/钠肽受体(natriuretic peptide receptor, NPR)2 的表达,刺激窦前卵泡发育和小窦卵泡扩张[26]。FSH 也能够通过诱导颗粒细胞中转化生长因子-β(transforming growth factor-β, TGF-β)相关信号及其下游 SMAD 蛋白,上调 NPPC 的表达,进而增加窦状卵泡数量,促进卵泡扩张[27]。近几年的研究



注:在卵泡扩张过程中,LH、FSH 激活 AC/cAMP/PKA 信号通路,刺激颗粒细胞有丝分裂及卵泡液生成,促进卵泡扩张。同时,LH 通过刺激 EGF 的表达,诱导卵泡腔扩张;FSH 通过刺激 IGF 的表达激活 PI3K 信号通路,促进颗粒细胞增殖。FSH 还通过 E2 上调 NPPC/NPR2 的表达,促进窦前卵泡和小窦卵泡扩张。FSH 也能够促使 TGF-β 及其下游 SMAD 蛋白,上调 NPPC 的表达,促进卵泡扩张。此外,FSH 通过促进 Wnt 信号、抑制 Hippo 信号,使颗粒细胞数量增多、促进雌激素生成,从而促进卵泡扩张。

图 1 卵泡扩张的主要调控机制

Note. During the process of ovarian follicular expansion, LH and FSH activate the AC/cAMP/PKA signaling pathway, stimulating the mitosis of granulosa cells and the production of follicular fluid, thereby promoting ovarian follicular expansion. Meanwhile, LH induces the expansion of the follicular cavity by stimulating the expression of EGF. FSH activates the PI3K signaling pathway by stimulating the expression of IGF, promoting the proliferation of granulosa cells. FSH also upregulates the expression of NPPC/NPR2 through E2, promoting the expansion of preantral and small antral follicles. FSH can also promote the expression of NPPC by upregulating TGF-β and its downstream SMAD proteins, thereby promoting ovarian follicular expansion. Additionally, FSH promotes ovarian follicular expansion by increasing the number of granulosa cells and promoting estrogen production through promoting Wnt signaling and inhibiting Hippo signaling.

Figure 1 Main regulatory mechanisms of ovarian follicular expansion

发现,Hippo 通路也参与了卵泡扩张的调节。FSH 可通过阻碍 Hippo 信号传导减轻其对卵泡生长的抑制,同时也可促进颗粒细胞合成雌激素,供卵泡发育所利用[28]。无翅型 MMTV 整合位点家族(wingless type MMTV integration site family, Wnt)信号通路促进颗粒细胞增殖和雌激素分泌,有利于卵泡扩张。利用 Wnt 信号通路选择性抑制剂 1(inhibitor of Wnt response-1, IWR-1)体外培养颗粒细胞,发现 IWR-1 的存在使颗粒细胞中一种黏附连接蛋白(beta catenin, CTNNB1)降解,令 FSH 诱导的雌激素生成酶基因 mRNA 含量降低,抑制了 FSH 通过 Wnt 信号通路调节颗粒细胞合成类固醇的作用[29]。因此,抑制 Wnt 信号将致使卵泡扩张受限。综上表明,FSH 通过作用于颗粒细胞,促进其增殖、激素分泌等过程,从而促进卵泡扩张。

在卵泡发育的中晚期,LH 同样通过 G 蛋白偶联信号转导通路,协助 FSH 促进卵泡发育,刺激卵泡生长。在排卵前卵泡阶段,高浓度的 LH/人绒毛膜促性腺激素(human chorionic gonadotropin, hCG)可以激活 PKA 途径,PKA 调控蛋白激酶 B(protein kinase B, AKT)、Tuberin、mTOR 等信号通路,刺激颗粒细胞复制周期及类固醇激素的生成[30]。有研究表明,LH 诱导 EGF 相关生长因子的瞬时和连续表达,且 EGF 相关的生长因子作为旁分泌介质,在卵泡中传播 LH 信号[31]。另外,LH-EGFR 信号可诱导卵泡腔扩张,且 TGF-β 参与了这一过程[32]。卵泡通过上述调控机制使卵巢组织发生重塑,这对动物的排卵和繁殖具有重要作用。

2.2 IGF、EGF 调控卵泡扩张

卵泡液中含丰富的生长因子,它们在颗粒细胞增殖、卵丘扩张和卵泡腔扩张过程中发挥着关键作用,如 IGF、EGF 等。IGF1 已被证实是卵泡发生所必需的局部生长因子[33]。研究显示,小鼠颗粒细胞中的 *Igf* mRNA 水平在卵泡腔形成阶段达到峰值,缺乏 IGF1 的小鼠会出现不育,这是因为它们的卵泡发育在窦腔形成阶段受阻,无法进一步扩张为窦状卵泡[34]。因此,IGF1 具有促使卵泡腔扩张的作用。此外,IGF1 还能增加颗粒细胞中 E2 的分泌。E2 或 FSH 可促进 IGF1 合成,这表明这三种生长因子具有协同放大效应,相互作用可明显促进卵泡扩张。同时,IGF1 还能通过启动磷脂酰肌醇 3-激酶(phosphatidylinositol 3-kinase, PI3K)信号转导,促进颗粒细胞增殖并抑制颗粒细胞凋亡,进而促进卵泡扩张[35]。EGF 主要在窦状卵泡的颗粒细胞中表达,其受体主要在卵丘细胞中表达。研究发现,在牛卵泡腔初始形成阶段的培养液中添加 EGF 培养 6 d 后,可显著提高卵泡活力、增加卵泡直径、促进雌激素和孕酮的分泌[36]。EGF 还能通过提高卵丘细胞内钙离子浓度、进而加快卵母细胞减数分裂恢复进程、促进卵丘扩张,调控卵丘扩张基因的表达,从而参与卵泡扩张[37]。

以上结果说明卵泡扩张受卵泡液中的生长因子以及多种促性腺激素的调节。除以上调控因子外,卵泡扩张还受到许多其他调控因子的调节,如环鸟苷酸(cyclic guanosine monophosphate, cGMP)-蛋白激酶 G(protein kinase G, PKG)信号、GnRH 信号通路都参与了卵泡扩张的部分环节。然而,对于雌性哺乳动物卵泡扩张的具体机制现在还未完全被阐明。

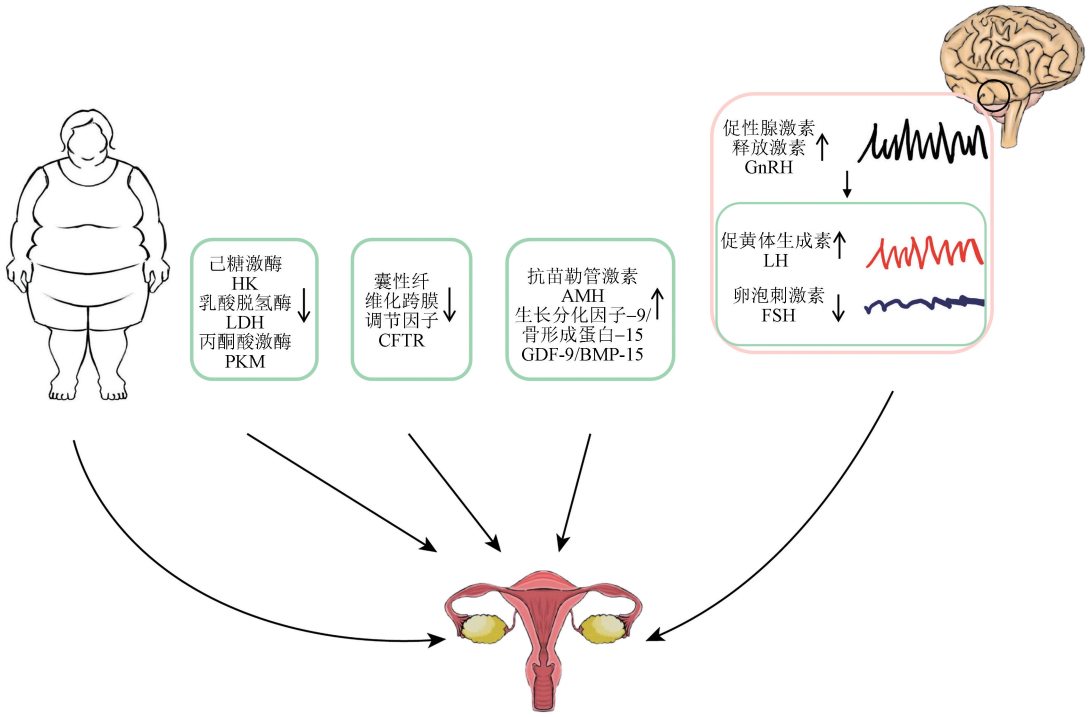
3 PCOS 卵泡扩张受限

PCOS 是一种常见的女性生殖内分泌疾病,通常表现为卵巢多囊样病变、排卵障碍或不排卵,伴有内分泌紊乱和代谢障碍,这严重损害了育龄期女性的生殖及心理健康[38](图 2)。PCOS 患者的窦前及窦状卵泡数量较多,但卵泡体积却较小,难以扩张成为优势卵泡,因此无法发育成为成熟卵泡,患者稀发排卵或无排卵[39]。PCOS 患者 HPO 轴发生紊乱,出现神经内分泌异常,包括 GnRH 脉冲频率增加,随之而来的 LH 分泌过多,FSH 水平降低,阻碍卵泡正常扩张、导致卵泡发育停滞,从而引起排卵障碍[40]。

据流行病学调查显示,PCOS 在全球育龄期妇女的发病率为 6%~10%,随着环境因素的持续恶化,其发病率还在不断上升[41-42]。这充分说明了 PCOS 严重威胁育龄期妇女的生育能力,严重干扰我国二孩、三孩生育政策的落实,故研究 PCOS 患者卵泡扩张受限的可能因素对女性生殖健康至关重要。

3.1 PCOS 与糖酵解

卵泡的扩张与成熟离不开能量的供应,其中颗粒细胞糖酵解产生的能量物质是其过程最重要的来源之一,同时颗粒细胞糖酵解也为颗粒细胞增殖复制提供能量基础[43]。临床案例显示,PCOS 患者体内雄激素含量较正常水平高出几倍之多,并且具有明显的胰岛素抵抗现象[39]。而近年的研究发现,高雄激素和胰岛素抵抗可以抑制卵巢颗粒细胞乳酸生成,减少其为卵泡发育供应能量[44]。与此同时,HARRIS 等[45]研究发现,PCOS 患者卵泡扩张较正常女性需要更多的能量供应。有学者还发现 PCOS 大鼠卵巢中糖酵解关键酶——己糖激酶(hexokinase, HK)、乳酸脱氢酶(lactate dehydrogenase, LDH)、丙酮酸激酶(pyruvate kinase, PKM)表达明显减少[46],说明 PCOS 大鼠对葡萄糖的利用能力下降,需求的增多与供应的减少共同导致了卵泡扩张与成熟过程能量缺乏,这可能是 PCOS 发生的重要机制之



注:PCOS 患者 GnRH 脉冲频率增加,随之而来的 LH 分泌过多,FSH 水平降低,阻碍卵泡正常扩张。PCOS 颗粒细胞糖酵解关键酶 HK、LDH、PKM 表达下降,抑制颗粒细胞增殖复制,进而致使卵泡扩张受限。此外,CFTR 低表达于 PCOS 颗粒细胞上,影响颗粒细胞功能,减少卵泡液积累,导致生殖激素紊乱。PCOS 患者 AMH 过度分泌导致卵泡扩张停滞,同时,GDF-9/BMP-15 比值升高可能成为 PCOS 新的生物标志物。

图 2 PCOS 患者卵泡扩张受限相关因素

Note. PCOS patients have an increased GnRH pulse frequency, leading to excessive LH secretion and reduced FSH levels, which impede normal ovarian follicular expansion. In PCOS, the expression of key glycolytic enzymes in granulosa cells, such as HK, LDH, and PKM, is decreased, inhibiting granulosa cell proliferation and thus limiting ovarian follicular expansion. Moreover, CFTR is low-expressed in PCOS granulosa cells, affecting their function, reducing follicular fluid accumulation, and causing reproductive hormone disorders. The over-secretion of AMH in PCOS patients halts ovarian follicular expansion, and an increased ratio of GDF-9/BMP-15 may serve as a new biomarker for PCOS.

Figure 2 Factors associated with limited ovarian follicular expansion in patients with PCOS

一。值得注意的是,糖代谢紊乱与脂代谢紊乱两者相互影响,糖代谢紊乱后大量糖类化合物积累,加重肝负担,从而导致脂代谢异常;脂代谢异常导致游离脂肪酸过多,可促使糖异生及糖原分解,胰岛 β 细胞分泌胰岛素负担过重,严重可造成细胞死亡,进而影响糖代谢[47]。两者息息相关,但具体联系机制还不明确,需要进一步深入研究。

3.2 PCOS 与 CFTR

CFTR 基因缺失可导致囊性纤维化(cystic fibrosis, CF),而 CF 患者在临床上表现为卵泡体积小且呈囊状结构、排卵出现障碍,症状与 PCOS 相似。同时 CHEN 等[48]发现 PCOS 大鼠体内 CFTR 表达降低,利用 PCOS 大鼠模型和颗粒细胞原代培养发现,*CFTR* 的下调伴随着增殖细胞核抗原(proliferating cell nuclear antigen, PCNA)的表达降低。利用颗粒细胞进行原代培养的实验也发现,敲除或抑制 *CFTR* 会导致细胞活性下降,同时也会使得 PCNA 表达降低,说明 *CFTR* 下调可能会抑制颗粒细胞增殖,从而导致纤维多囊化和 PCOS 卵泡扩张异常。另外,有研究发现 CFTR 特异性抑制剂 CFTRinh-172 可抑制人源卵巢颗粒肿瘤细胞(COV434)中肿瘤坏死因子相关基因诱导配体(tumor necrosis factor-related apoptosis-inducing ligand, TRAIL)的表达[49]。因此,CFTR 功能缺失可能影响颗粒细胞功能,进而造成 PCOS。这一发现为理解 PCOS 的发生机制提供了新的视角。PCOS 患者常伴随雌激素代谢异

常,而 CFTR 可通过核可溶性腺苷酸环化酶放大 FSH 刺激的信号,恰巧 FSH 可调节将雄激素转化为雌激素的限速酶芳香化酶活性,进而影响雌激素合成[50]。所以 CFTR 缺陷将导致雌激素代谢紊乱,影响 PCOS 发病。胰岛素与胰高血糖素平衡紊乱是 PCOS 的另一大特征。SUN 等[51]通过双氢睾酮诱导的 PCOS 大鼠模型发现,当雄激素过多时 CFTR 会上调,并促进葡萄糖刺激的胰岛素分泌,导致高胰岛素血症。HUANG 等[52]利用同样的 PCOS 大鼠模型发现,胰岛 α 细胞中 CFTR 表达会上调,而空腹胰高血糖素水平却明显降低,且可以被 CFTR 抑制剂阻断。说明 CFTR 可影响胰岛细胞的功能与代谢,进而导致胰岛素与胰高血糖素的平衡紊乱。

3.3 PCOS 与 TGF-β 超家族

TGF-β 超家族主要包括 TGF-β 亚家族、抗苗勒管激素(anti-Müllerian hormone, AMH)、骨形成蛋白(bone morphogenetic protein, BMP)亚家族、生长分化因子(growth differentiation factor, GDF)亚家族等成员,其在调节窦状卵泡募集、卵泡扩张和卵巢功能中发挥重要作用[53]。有报道称 PCOS 患者与非 PCOS 患者之间卵泡扩张能力的差异可能是由于一个或多个 TGF-β 超家族成员的异常调节导致的[54]。有研究表明,PCOS 大鼠卵巢转化生长因子-β 受体Ⅰ(transforming growth factor-β receptor Ⅰ, TβRⅠ)和转化生长因子-β 受体Ⅱ(transforming growth factor-β receptor Ⅱ, TβRⅡ)mRNA 的表达较正常组明显升高,很可能直接影响到 TGF-β1 对卵泡扩张的调节作用,与卵泡成熟障碍有关[55]。与正常女性相比,PCOS 患者血清和卵泡液中的 AMH 水平较高。近年研究表明,PCOS 患者 AMH 水平升高是由于窦前卵泡与小窦卵泡的数量增加所致,并且其颗粒细胞本身就存在异常,从而致使 AMH 的过度分泌,导致卵泡扩张停滞。此外,AMH 的增加可能与血清 LH 水平升高及 LH/FSH 比例增加有关[56]。PCOS 患者卵泡内 GDF-9 和 BMP-15 浓度的变化呈负相关,反映了其内分泌环境的异常,同时 GDF-9/BMP-15 比值升高可能成为 PCOS 新的生物标志物[57]。WEI 等[58]研究发现,GDF-9 和 BMP-15 在 PCOS 患者卵巢的小窦卵泡中表达水平正常,这可能与 PCOS 的异常卵泡发育有关。

以上结果说明 PCOS 患者卵泡扩张受限受到生物化学过程、离子通道蛋白及相关转化生长因子的调控。但 PCOS 的发病机制较为复杂,目前还未完全被阐明。

4 结语

卵泡扩张是卵泡有效发育的重要基础。但卵泡扩张过程的具体调控机制仍不完善。PCOS 患者卵泡扩张障碍,是导致卵泡发育不良、排卵异常的关键因素。PCOS 的发病机制极为复杂,上述调控信号有望成为日后治疗 PCOS 患者卵泡发育不良、卵泡扩张受限的重要研究方向。未来,在卵泡扩张领域的机制研究应该更加精细化,为卵泡扩张异常导致稀发排卵或无排卵的育龄期妇女的治疗提供理论依据。

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