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Cd24a 和前列腺素代谢相关酶在 PCOS 小鼠模型卵巢颗粒细胞中表达水平的实验研究 *

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摘要 目的：探讨 *Cd24a* 分子和前列腺素代谢相关酶在多囊卵巢综合征（polycystic ovary syndrome, PCOS）小鼠模型卵巢颗粒细胞中的表达水平。**方法**：取 20 只雌性 C57BL/6 小鼠，随机分为对照组（正常小鼠）和实验组（应用脱氢表雄酮建立 PCOS 小鼠模型），每组各 10 只。对照组小鼠于颈背部连续皮下注射 20 天芝麻油溶液（0.1 mL/100 g）。实验组应用脱氢表雄酮（6 mg/100 g）联合芝麻油溶液（0.1 mL/100 g）连续颈背部皮下注射 20 天。经苏木精一伊红染色观察两组小鼠卵巢组织病理学改变。应用实时荧光定量 PCR 法对小鼠卵巢颗粒细胞中 *Cd24a* 分子和前列腺素代谢相关酶 mRNA 表达量进行检测。**结果**：实验组体重显著高于对照组（$P<0.05$）；实验组小鼠卵巢呈多囊样改变，卵泡中颗粒细胞数量减少，闭锁卵泡增多，闭锁卵泡直径明显大于对照组；实验组 *Cd24a* 分子和前列腺素代谢相关酶 mRNA 表达量较对照组存在显著差异（$P<0.05$）。**结论**：PCOS 小鼠卵巢颗粒细胞中 *Cd24a* 分子和前列腺素代谢相关酶表达量异常，提示 *Cd24a* 分子可能与 PCOS 疾病发生相关。

关键词：小鼠；多囊卵巢综合征；卵巢颗粒细胞；*Cd24a*；前列腺素代谢相关基因

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Expression Levels of *Cd24a* and Prostaglandin Metabolism Related Enzymes in Ovarian Granulosa Cells of PCOS Mice*

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ABSTRACT Objective: The purpose of this research is to study the expression levels of *Cd24a* molecules and prostaglandin metabolism related enzymes in ovarian granular cells of polycystic ovary syndrome (polycystic ovary syndrome, PCOS) mouse mode. **Methods:** Twenty female C57BL/6 mice were randomly divided into the control group (normal mice) and the experimental group (dehydroepiandrosterone was used to establish PCOS mouse model), with 10 mice in each group. Control group was given sesame oil solution (0.1 mL/100 g). In the experimental group, dehydroepiandrosterone (6 mg/100 g) combined with sesame oil solution (0.1 mL/100 g) was injected subcutaneously in the neck for 20 days. Ovarian histopathological changes were observed by hematoxylin-eosin staining. mRNA expression levels of *Cd24a* molecule and prostaglandin metabolism related enzymes in mouse ovarian granule cells were detected by real-time fluorescent quantitative PCR. **Results:** The body weight of the experimental group was significantly higher than that of the control group ($P<0.05$). The ovary of the experimental group showed polycystic changes, the number of granulosa cells decreased, the number of atresia follicles increased, and the diameter of atresia follicles was significantly larger than that of the control group. mRNA expression levels of *Cd24a* molecule and prostaglandin metabolism related enzymes in the experimental group were significantly different than those in the control group ($P<0.05$). **Conclusion:** Abnormal expression of *Cd24a* molecule and prostaglandin metabolism related enzymes in ovarian granulosa cells of PCOS mice suggested that *Cd24a* molecule was associated with PCOS disease.

Key words: Mice; Polycystic ovary syndrome; Ovarian granulosa cells; *Cd24a*; Prostaglandin metabolism related enzymes

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前言

多囊卵巢综合征（polycystic ovary syndrome，PCOS）是育龄女性最常见的生殖内分泌紊乱综合征，发病率为 9%～18%[1,2]，目前有关该病的具体发病机制仍未完全明确[3-5]。排卵是由黄体生成激素（luteinizing hormone，LH）激增引发的复杂连续性过程[6,7]。源自多不饱和脂肪酸的前列腺素（prostaglandin，PGs）属于二十碳烷酸（花生酸）类物质，由 20 碳多不饱和脂肪酸酶解衍生而来，在卵巢功能调控中具有重要作用[8-10]。PGs 是哺乳类动物排卵卵泡中关键的调节介质，特别是 PGE_2 是介导排卵过程的关键性 PG[11-13]。LH 刺激的卵泡颗粒细胞中，激活表达环氧合酶 -2（COX-2）和前列腺素合酶（PGES）可促进颗粒细胞合成

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PGE_2，导致排卵前卵泡液中 PGE_2 明显增加，并于排卵时到达高峰[14,15]。已有研究显示，应用绒毛膜促性腺激素（hCG）促进排卵后 36 h，颗粒细胞中 PTGs 合酶（PTGS2、PTGES）相关基因表达量显著上调[16]。然而这些前列腺素代谢相关酶表达量改变的具体机制并不清楚。最近一项研究利用单细胞测序技术，分析了两名健康女性数百个颗粒细胞，结果显示颗粒细胞可分为三个亚群，同时 CD24 分子与前列腺素代谢相关酶具有一定的相关性。实验研究进一步表明，CD24 分子通过 EGFR-ERK1/2 信号通路激活前列腺素合成酶（ARK1C1, PTGS2, PTGES, PLA2G4A）以及前列腺素转运蛋白（SLCO2A1，ABCC4）的表达，进而影响排卵过程[17]。然而，有关 CD24 分子和前列腺素代谢相关酶在 PCOS 患者卵巢颗粒细胞中表达水平及相关研究报道并不多见。为此，本研究通过建立 PCOS 小鼠模型，探讨 *Cd24a* 分子及前列腺素代谢相关酶 mRNA 在 PCOS 小鼠模型中的表达水平，旨在为该病的病理机制和临床诊断及治疗提供实验依据。

1 材料方法

1.1 实验动物

选取 21 日龄 SPF 级雌性 C57BL/6 小鼠 20 只，随机分为 2 组：对照组（n = 10）、实验组（n = 10）。这些小鼠均购自上海斯莱克实验动物有限公司。实验动物于海军军医大学实验中心 SPF 级动物房中进行饲养，自由饮水、自由进食。饲养动物房环境温度为 20~24 ℃，饲养环境湿度为 40%~60%，每日光照及黑暗时间各 12 h。

1.2 药物和试剂

脱氢表雄酮（DHEA）购自于美国 Cayman 公司。Trizol 试剂盒购于 Takara 公司。逆转录试剂盒购于 Invitrogen 公司。TBGR Green 试剂盒购于 Takara 公司。孕马促性腺激素（PMSG）试剂购于 Sigma 公司。绒毛膜促性腺激素（hCG）试剂购于 Sigma 公司。透明质酸酶购于 Sigma 公司。

1.3 方法

1.3.1 动物模型建立 在小鼠适应性饲养 7 天（d）后，实验动物随机分为对照组（正常组）、脱氢表雄酮组（实验组），每组 10 只。其中，对照组给予芝麻油（0.1 mL/100 g），实验组应用脱氢表雄酮（6 mg/100 g）联合芝麻油（0.1 mL/100 g）连续颈背部皮下注射 20d。对照组和实验组给予正常饮食。

1.3.2 小鼠超排及样本收集 向建好后的 PCOS 雌性小鼠模型腹腔内注射（5IU/ 只）孕马血清促性腺激素（PMSG）（Sigma-Aldrich，USA），以刺激卵泡生长。48 h 后注射（5 IU/ 只）绒毛膜促性腺激素（hCG）（Sigma-Aldrich，USA）诱发排卵。

在给予 hCG 后的不同时间间隔（0 和 3 h），颈椎脱臼处死小鼠，无菌条件下迅速取出不同时间间隔的一侧卵巢，用 PBS 清洗 3 次，在体视显微镜下去除其周围脂肪和被膜，用 1 mL 注射器针头刺破卵泡使颗粒细胞和卵母细胞释放出来，加入 1 g/ L 透明质酸酶（Sigma-Aldrich，USA）消化使颗粒细胞与卵母细胞分离，用孔径为 0. 074 mm 筛网过滤，1 000 r/ min 离心 5 min。弃上清，用 PBS 清洗 3 次。收集卵巢颗粒细胞以用于后续实验。

1.3.3 小鼠体重监测 测量小鼠体重并记录数值，监测小鼠体质量变化，连续记录 20 天。

1.3.4 卵巢组织病理学的检测 解剖小鼠一侧卵巢，去除卵巢表面的脂肪组织及其覆盖包膜，随后用 PBS 冲洗 3 次，置于 4%多聚甲醛溶液中，固定 2 d。常规脱水、石蜡包埋。每个蜡块分别以 4 μm 厚度切片多次，随后行苏木精－伊红染色，于光镜（德国 ZEISS 公司）下对大鼠卵巢组织病理学改变进行观察，并拍照。

1.3.5 细胞 RNA 抽提及实时荧光定量 PCR 法的检测 将分离得到的颗粒细胞置于 PBS 中洗涤。离心处理，4500 r/min，10 min。去除上清液，保留沉淀。采用 Trizol 试剂盒（Takara 公司）对细胞总 RNA 进行提取，用逆转录试剂盒（Invitrogen 公司）逆转录为 cDNA，随后置于 -20℃保存。以 GAPDH 为内参照，对引物序列进行设计，应用 TBGR Green (Takara)试剂盒，仪器为 StepOne™ Real-Time PCR System (Applied Biosystems)，反应条件：95℃ 10 min，95℃ 15 s，60℃ 30 s，72℃ 30s 共进行 40 个循环。用 $2^{-\Delta\Delta Ct}$ 对基因相对表达量进行定量分析。

1.3.6 统计学方法 应用 SPSS 16.0 统计学软件对数据进行分析处理，以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 各组小鼠体重的比较

实验开始时，两组小鼠均发育正常，皮毛光滑润泽无破损，体征无明显差异。实验结束时，与对照组相比，实验组小鼠皮毛显著光滑润泽。体重测量的结果显示，两组小鼠实验开始时体重无显著性差异。实验结束时，PCOS 小鼠（实验组）体重与对照组小鼠相比，显著高于对照组（$P<0.05$，图 1）。

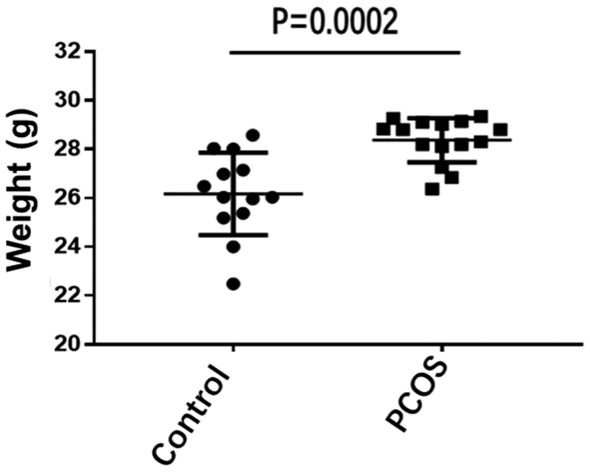

图 1 实验组小鼠和对照组小鼠体重的比较

Fig. 1 Comparison of body weight between experimental and control mice

2.2 卵巢病理学变化

对照组小鼠卵巢可见正常发育各级卵泡及多个黄体组织，卵泡内颗粒细胞排列整齐（图 2 左）。实验组小鼠卵巢中呈现大量囊性扩张卵泡且数量明显增多，卵泡内卵母细胞模糊且不可见，卵巢颗粒细胞数量显著减少，无成熟卵泡（图 2 右）。依此可见，实验组小鼠存在典型的 PCOS 卵巢改变，提示该实验小鼠 PCOS 动物模型构建成功。

2.3 两组小鼠 Cd24a 和前列腺素代谢相关基因 mRNA 表达比较

应用促绒毛膜性腺激素(hCG)模拟排卵过程,我们抽取扳机后 0 h、3 h 小鼠卵巢颗粒细胞,并通过 qRT-PCR 法对两组小鼠卵巢颗粒细胞 *Cd24a* 和前列腺素代谢相关基因(*Ptgs2*,*Ptges*、*Pla2g4a*、*Slco2a1* 和 *Abcc4*)表达情况进行检测,结果(图3)发现实验组 *Cd24a* 和前列腺素代谢部分相关酶(*Ptgs2*,*Ptges*、*Pla2g4a*)基因相对表达量较对照组显著降低,而扳机后 3 h,实验组中 *Slco2a1* 和 *Abcc4* 的表达量较对照组明显上调(P<0.05)。

3 讨论

PCOS 的表型具有异质性,包括高雄激素血症,排卵功能障碍,多囊卵巢形态和代谢紊乱(肥胖,胰岛素抵抗和糖尿病)[18-20]。生殖系统方面的表现包括卵巢囊肿及多囊性改变、卵泡发育障碍、不排卵或稀发排卵、高雄激素血症等[21]。

颗粒细胞在促进卵巢卵泡的形成和构建卵丘复合体过程中起关键作用[22]。卵母细胞的质量对女性的生育能力至关重要[23]。在卵子的正常发育中需要颗粒细胞 - 卵母细胞之间双向信号传递[24]。一方面,颗粒细胞为卵母细胞的发育提供支持;同时,卵母细胞对颗粒细胞的分化、发育也起着重要的调节作用。卵子的成熟是生殖细胞与体细胞构成的微环境中各种类型的细胞相互作用的结果。因此,不难理解健康、高质量的卵子,对应着 " 正常的颗粒细胞 ", 而 " 异常的颗粒细胞 " 对应着异常的、低质量的卵子。颗粒细胞可作为评估卵子质量的 " 窗口 "。

已有研究[25,26]表明,应用绒毛膜促性腺激素(hCG)促进卵泡成熟及排卵过程中,与激素生物合成及排卵相关的多个基因在人卵巢颗粒细胞中发生显著的改变。最新研究显示,正常人卵巢卵泡发育过程中,应用 hCG 可促进 CD24 分子上调表达[17,27],并且可能通过 EGFR-ERK1/2 通路,调控前列腺素合酶(PTGS2,PTGES 和 PLA2G4A)和前列腺素转运蛋白(SLCO2A1 和 ABCC4)表达的上调。因此,CD24 可能是介导卵泡发育以及排卵的重要分子。

我们应用脱氢表雄酮构建 PCOS 小鼠模型实验发现,实验组小鼠体重比对照组明显增高,符合人类 PCOS 特征[28-31]。卵巢

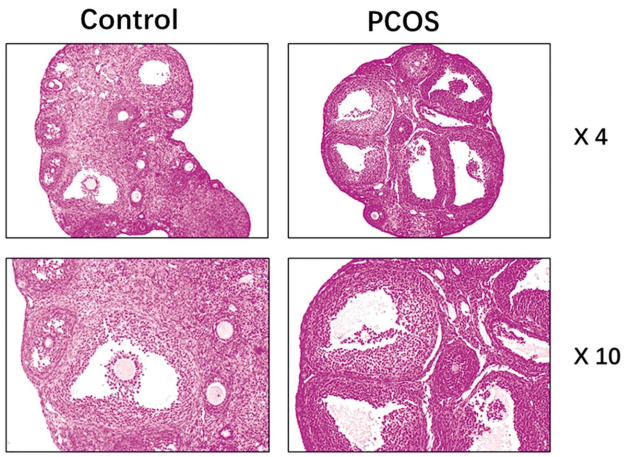

图 2 实验组和对照组小鼠卵巢组织 HE 染色。图中右侧标记的数字为物镜放大倍数

Fig. 2 HE staining of ovarian tissue in mice of the experimental group and control group. The number marked on the right is the magnification of the objective lens

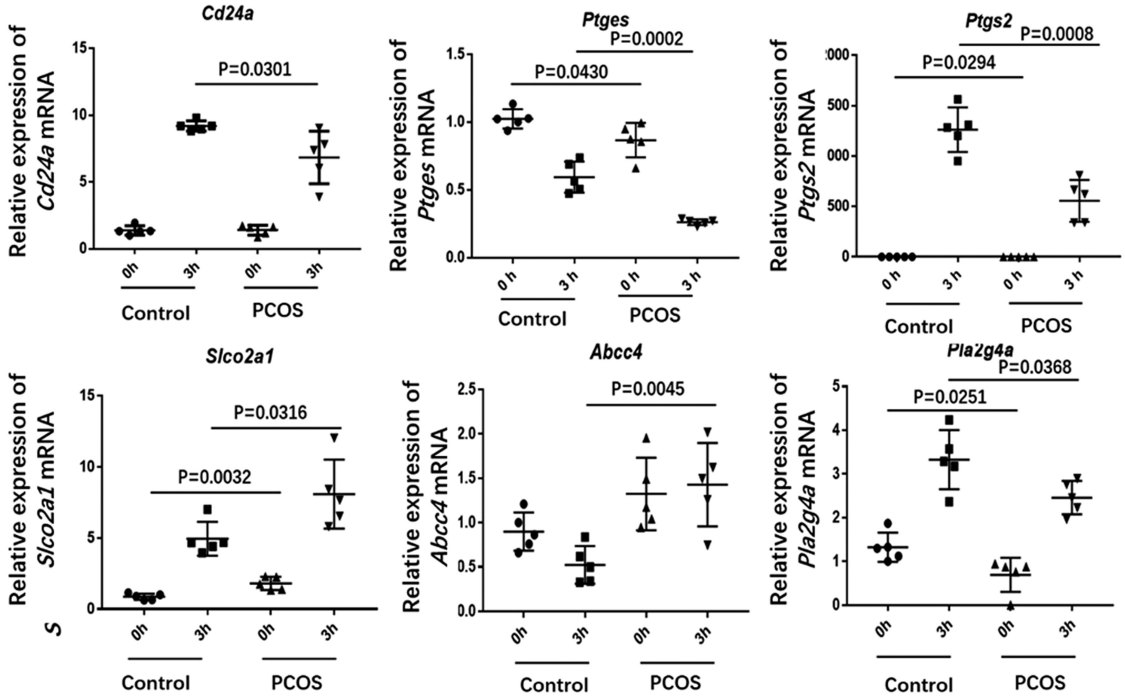

图 3 实验组和对照组小鼠颗粒细胞中 *Cd24a* 和前列腺素代谢相关酶表达情况的比较。0h:应用 hCG 促排后 0h 分离小鼠卵巢颗粒细胞;3h:应用 hCG 促排后 3h 分离小鼠卵巢颗粒细胞

Fig. 3 The expression of *Cd24a* and prostaglandin metabolism related enzymes in granulosa cells of experimental and control mice were compared. 0h: Mouse ovarian granulosa cells were isolated at 0h after induction with hCG; 3h: Mouse ovarian granulosa cells were isolated at 3h after induction with hCG.

HE 染色切片显示,实验组卵巢卵泡直径较大并呈现囊性扩张,卵巢呈多囊样改变,与 PCOS 患者卵巢病理改变特征相类似。因此,我们认为应用脱氢表雄酮造模,符合 PCOS 的卵巢特征性改变和主要内分泌变化。随后,我们使用造模成功后的 PCOS 小鼠模型,应用 hCG 进行 " 扳机 ",分离扳机后 0h 和 3 h卵泡中颗粒细胞,检验 *Cd24a* 及前列腺素代谢相关基因(*Ptgs2*、*Ptges*、*Pla2g4a*、*Slco2a1* 和 *Abcc4*)mRNA 表达。实验结果显示,*Cd24a* 分子在 0h 时实验组和对照组比较没有显著性差异,而 3h 时 PCOS 组颗粒细胞中的表达量明显低于对照组(P<0.05)。因此,我们认为 *Cd24a* 分子表达在 PCOS 小鼠排卵过程中受到了抑制。同时,我们发现前列腺素代谢相关的基因 *Ptgs2*、*Ptges*、*Pla2g4a* 表达在 0h、3h 均受到了抑制,而 *Slco2a1* 和 *Abcc4* 表达较对照组异常增高。

综上所述,在 PCOS 小鼠模型中,*Cd24a* 分子和前列腺素代谢相关酶基因表达异常,提示与 PCOS 疾病排卵障碍有关,并且 *Cd24a* 分子可能在 PCOS 的致病过程中起作用。因此,CD24 分子可作为排卵障碍的治疗靶点,同时为后续探讨 PCOS 的确切致病机制提供新的方向和依据。

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