



• 生育力下降现状的生殖医学对策 •

|| 文献综述 ||

## 线粒体功能异常在子宫内膜异位症相关不孕中的研究进展

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**【摘要】** 子宫内膜异位症(endometriosis, EMT)作为一种常见的妇科良性疾病,是导致女性不孕的重要原因,从多个方面影响女性生育力。线粒体被称为“细胞动力工厂”,在细胞能量代谢、钙稳态、氧化应激、自噬、调控细胞周期及细胞死亡等生理过程中扮演重要角色,参与多种疾病的发生、发展。线粒体具有高度动态性,不断进行着分裂和融合的循环,以满足细胞活动所需,线粒体动力学平衡对正常女性生殖功能十分重要。此外,线粒体还是细胞内活性氧类(reactive oxygen species, ROS)的主要来源,EMT患者体内氧化-抗氧化系统失衡,其介导的细胞损伤、细胞死亡、纤维化等可以导致卵母细胞质量下降、卵巢储备降低。目前,EMT相关不孕的发病机制及其治疗仍是一个具有挑战性和争议性的话题。本文就线粒体功能异常在EMT相关不孕中研究进展及潜在治疗靶点进行综述。

**【关键词】** 子宫内膜异位症 不孕 线粒体 氧化应激 综述

**Research Progress in the Role of Mitochondrial Dysfunction in Endometriosis-Associated Infertility** GONG Xue, HUANG Jin, WANG Chichiu<sup>△</sup>. Department of Obstetrics and Gynaecology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR 999077, China

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**【Abstract】** Endometriosis (EMT), a common benign gynecological disease, is a leading cause of infertility in women. EMT affects female fertility in various aspects. However, the underlying mechanisms have not been fully elucidated. Mitochondria are known as the "powerhouse" of a cell. They play pivotal roles in the physiological processes of cellular energy metabolism, calcium homeostasis, oxidative stress, autophagy, the regulation of cell cycle, and cell death, and are involved in the pathophysiology of many diseases. Cellular mitochondria are highly dynamic, continuously undergoing cyclic fission and fusion to meet the demands of cellular activities. Balanced mitochondrial dynamics are critical for maintaining normal reproductive function in women. In addition, mitochondria are the major source of reactive oxygen species (ROS). Cell damage, cell death, and fibrosis mediated by the imbalance in the oxidative-antioxidant system in EMT patients lead to decreased oocyte quality and ovarian reserve. Currently, the treatment of EMT-associated infertility remains a challenging and controversial topic. We herein reviewed the latest findings on the role of mitochondrial dysfunction in EMT-associated infertility and the potential therapeutic targets.

**【Key words】** Endometriosis Infertility Mitochondria Oxidative stress Review

子宫内膜异位症(endometriosis, EMT)是一种雌激素依赖性的慢性炎症性疾病,其特征为子宫内膜组织在子宫腔以外的部位异常种植和生长<sup>[1-2]</sup>,影响约10%的育龄期女性<sup>[3]</sup>。EMT是导致女性不孕的主要原因之一,其在不孕患者中的发病率高达50%,而约30%的EMT患者合并不孕<sup>[4]</sup>。近年来,EMT相关不孕的发病机制及其治疗受到了学者的广泛关注和研究,然而,目前EMT与不孕之间的联系尚未完全阐明,研究表明炎症反应、氧化应激、免疫紊乱、内分泌异常以及盆腔解剖结构改变等可能参与其中<sup>[5-6]</sup>。

线粒体是一种具有双膜结构的细胞器,除进行氧化磷酸化(oxidative phosphorylation, OXPHOS)、合成三磷酸腺苷(adenosine triphosphate, ATP)提供细胞活动所需

能量外,其在细胞代谢、钙稳态、自噬、炎症、氧化应激等生化过程中也起着枢纽作用<sup>[7-8]</sup>,此外,线粒体还携带有自身遗传物质——线粒体DNA(mitochondrial DNA, mtDNA)。线粒体功能异常与多种疾病密切相关,包括代谢性疾病、心血管疾病、癌症和神经退行性疾病等<sup>[9]</sup>。近年来,研究发现线粒体功能异常在EMT及EMT相关不孕的发生、发展中起着重要作用。本文就线粒体功能异常在EMT相关不孕中的发病机制及其潜在治疗靶点进行综述。

### 1 线粒体动力学异常

#### 1.1 线粒体动力学概述

线粒体具有高度可塑性和动态性,通过其自身的分裂和融合来维持和调控细胞内线粒体的形态、质量、数量、功能以及分布,并形成动态的线粒体网络,以适应能

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出版日期: 2024-05-20

量需求并维持细胞稳态,这种线粒体动态分裂和融合的过程被称为线粒体动力学<sup>[10]</sup>。线粒体融合指两个线粒体的外膜和内膜相互融合,形成一个线粒体的过程,线粒体融合可以增加线粒体内膜的面积,改善能量供应<sup>[11]</sup>,同时促进线粒体之间的物质交换,有助于维持线粒体功能及mtDNA的完整性<sup>[12]</sup>。线粒体分裂则是指一个线粒体分裂成两个的过程,在线粒体质量控制中起着重要作用,通过分裂可以将线粒体内正常和受损的成分分别分离到子线粒体内,含受损成分的子线粒体将进一步由线粒体自噬选择性消除<sup>[13-14]</sup>,避免受损线粒体累积进一步导致细胞损伤和死亡。目前已知的参与哺乳动物线粒体分裂和融合过程的关键蛋白都属于发动蛋白相关三磷酸鸟苷酶(dynammin-associated GTPases),包括动力相关蛋白1(dynamic-related protein 1, DRP1)、线粒体融合蛋白1(mitofusin1, MFN1)、线粒体融合蛋白2(mitofusin2, MFN2)和视神经萎缩蛋白1(optic atrophy 1, OPA1)<sup>[10, 15]</sup>。DRP1是一种胞质蛋白,通常位于细胞质中,经过特定的翻译后修饰后与线粒体外膜上的受体线粒体动力学蛋白49/51(MiD49/51)、线粒体分裂蛋白1(FIS1)和线粒体分裂因子(MFF)结合,易位到线粒体外膜,聚合并形成收缩环,诱导线粒体分裂;MFN1/2位于线粒体外膜,介导线粒体外膜的融合;OPA1位于线粒体内膜,参与线粒体内膜的融合<sup>[10]</sup>。近年来,越来越多的研究表明线粒体动力学失调参与多种疾病的发病机制。

### 1.2 线粒体动力学与卵泡发育障碍

最近的研究表明,线粒体动力学在女性生殖中也发挥着重要作用。卵子是哺乳动物体内线粒体数量最多的细胞,线粒体在卵泡发生的过程中不断生成,直至卵子成熟,此时每个成熟卵子内的线粒体数量高达十万个<sup>[16]</sup>,在受精后到胚胎植入前这段时间,线粒体的生物发生将会暂停,胚胎发育所需能量由卵子提供的线粒体供应,因此卵子的线粒体对植入前胚胎发育也至关重要<sup>[17]</sup>。线粒体结构在卵母细胞发育过程中变化显著,在始基卵泡中,卵母细胞中的线粒体呈现长约1.2~1.9  $\mu\text{m}$ 的棒状;初级卵泡时期,卵母细胞中哑铃状线粒体明显增加;至排卵前,卵母细胞中的线粒体呈直径0.4~0.6  $\mu\text{m}$ 的圆形空泡状,并具有拱形和同心排列的嵴,这种线粒体形态的改变提示在卵泡发生过程中,线粒体动力学可能发生了改变<sup>[18-19]</sup>。研究人员发现在特异性敲除卵母细胞DRP1(DRP1 KO)的小鼠中,卵母细胞线粒体因分裂障碍而伸长,并表现出卵泡成熟障碍、卵母细胞的分泌和减数分裂受损<sup>[20]</sup>,进一步支持了线粒体动力学参与调控卵泡发生。此外,卵母细胞MFN1特异性缺失(MFN1<sup>-/-</sup>)也会导致卵母细胞成熟和

卵泡发育障碍,使得小鼠卵泡发育停滞在窦前阶段,并导致小鼠卵巢储备功能下降<sup>[21]</sup>。MFN1<sup>-/-</sup>小鼠始基卵泡耗竭的机制可能与卵泡募集加速有关,AMH是临床上常用的反映卵巢储备功能的指标之一,由窦前和小窦卵泡中的颗粒细胞分泌<sup>[21]</sup>,具有限制卵泡募集、维持卵泡储备的作用<sup>[22]</sup>,其中直径4~8 mm的小窦卵泡为AMH的主要来源<sup>[23]</sup>。由于MFN1<sup>-/-</sup>小鼠无窦卵泡形成,AMH降低,进而可能加速卵泡募集,导致卵巢储备耗竭。与输卵管因素或男性因素不孕的患者相比,EMT相关不孕患者在IVF周期中的获卵数、卵母细胞成熟率和受精率均更低<sup>[24-25]</sup>。研究发现,EMT患者卵子中的线粒体数量显著低于输卵管因素/男性因素不孕患者,且结构异常的线粒体数量显著增加,提示卵母细胞线粒体数量和质量异常与EMT患者IVF/ICSI周期中不良妊娠结局密切相关<sup>[26]</sup>。然而,目前对EMT相关不孕患者的卵巢中的线粒体动力学改变仍知之甚少,亟须更多的研究来探索其潜在关联。

### 1.3 线粒体动力学与子宫内膜容受性

子宫内膜容受性指子宫内膜允许囊胚定位、黏附、侵入并着床的能力<sup>[27]</sup>,目前尚缺乏评估子宫内膜容受性的可靠标准。关于EMT是否通过改变子宫内膜容受性导致女性不孕尚存争议。据SIMON等<sup>[28]</sup>的报道,在接受供卵的IVF周期中,EMT患者的着床和妊娠率与非EMT患者相当,这一发现对EMT患者的子宫环境可能对着床过程产生负面影响的观点提出了质疑。与之相反,另一项回顾性研究分析了3071个IVF周期,发现与输卵管因素不孕患者相比,EMT患者的获卵数、卵母细胞成熟率、临床妊娠率、活产率和累积活产率均显著降低,并提示其可能与EMT患者卵泡液中炎症因子水平升高、免疫微环境紊乱影响卵母细胞发育和质量相关<sup>[29]</sup>。因此,EMT对子宫内膜容受性的影响似乎有限。YE等<sup>[30]</sup>检测了EMT患者在位和异位子宫内膜中线粒体动力学相关基因的表达,结果显示,与患其他妇科良性疾病的在位内膜相比,EMT患者在位子宫内膜基质细胞中DRP1表达上调,而EMT患者异位子宫内膜基质细胞中DRP1、OPA1、MFN1/2的表达均显著下调,且观察到异位子宫内膜中线粒体数量减少、颗粒或短杆状线粒体增加,线粒体网络的平均分支长度减少,提示部分线粒体可能处于病理状态。然而,子宫内膜线粒体动力学改变是否以及如何影响子宫内膜容受性仍需进一步研究。

## 2 线粒体氧化应激

### 2.1 氧化应激与卵巢储备功能减退

氧化应激(oxidative stress, OS)指细胞内活性氧类

(reactive oxygen species, ROS)生成过多,超过了抗氧化系统的清除能力,从而导致一系列细胞功能障碍的状况<sup>[31]</sup>。细胞内的ROS主要来自于线粒体,是OXPHOS过程中呼吸链复合物电子泄漏形成的副产物,包括过氧化氢( $H_2O_2$ )、羟自由基( $OH\cdot$ )和超氧阴离子( $O_2^-$ )等<sup>[32]</sup>。ROS具有高度的化学反应活性,在正常生理平衡的状况下,ROS参与多种细胞信号通路的信号传导,高水平的ROS会对细胞内DNA、蛋白质和脂质等结构造成氧化损伤,进而引发一系列病理过程<sup>[33]</sup>。OS已被证明与多种疾病有关,包括动脉粥样硬化、阿尔茨海默病、EMT和癌症等,然而其参与不同疾病病理程度具有高度异质性<sup>[34]</sup>。OS在EMT发病机制中的关键作用已被广泛报道和深入研究<sup>[35]</sup>,参与异位子宫内膜在宫腔外存活、黏附、生长及血管生成等过程<sup>[36]</sup>。现有研究表明EMT本身及其治疗方式均可能对卵巢储备功能产生不利影响<sup>[37]</sup>。在卵巢型EMT中,有证据表明PI3K-PTEN-Akt-Foxo3信号通路的过度激活可以加速始基卵泡募集,导致卵泡储备减少。ROS不仅可以激活PI3K-PTEN-Akt-Foxo3信号通路,还可以通过累积DNA损伤导致细胞凋亡,从而降低卵巢储备功能<sup>[36, 38]</sup>。此外,OS和慢性炎症介导的卵巢组织纤维化也是导致卵巢储备下降的重要原因<sup>[39]</sup>。

## 2.2 氧化应激与配子和胚胎质量

腹膜液(peritoneal fluid, PF)及卵泡液(follicular fluid, FF)的微环境与卵母细胞的生长、发育及其质量,以及受精和胚胎发育等过程密切相关。如前所述,EMT患者在IVF周期中获卵数较少、卵母细胞质量降低、胚胎数量、质量及囊胚形成率较低<sup>[40]</sup>。研究发现,EMT相关不孕患者PF和FF中ROS和炎症因子水平显著高于非EMT相关不孕的女性,而其维生素C、维生素E、过氧化物歧化酶和谷胱甘肽等抗氧化剂的含量显著低于非EMT相关不孕的患者<sup>[41-43]</sup>。暴露于高ROS环境中,可能导致卵母细胞纺锤体异常、染色体错位和非整倍体发生率增加,从而导致卵母细胞成熟障碍、减数分裂异常,甚至发育停滞和凋亡<sup>[44-46]</sup>。OS对精子质量的影响同样不容小觑。研究显示,将健康男性的精子与EMT患者和健康对照组的PF共同孵育,与EMT患者PF共孵育的精子表现为DNA碎片显著增多<sup>[47]</sup>。DING等<sup>[48]</sup>将小鼠精子与EMT患者和对照组的PF共孵育后行IVF,EMT孵育组的受精率显著下降。在小鼠胚胎培养基中添加EMT或健康对照患者的PF或FF,添加EMT患者PF或FF的小鼠胚胎显示出囊胚形成率降低、DNA断裂、发育停滞和细胞凋亡增加<sup>[48-49]</sup>。由此可见,OS对配子及胚胎质量的影响在EMT相关不孕中也发挥着重要作用。

## 3 类固醇激素合成

类固醇激素又称甾体激素,主要由肾上腺、卵巢和睾丸分泌,包括糖皮质激素、盐皮质激素、雄激素、雌激素和孕激素。线粒体是类固醇激素合成的关键场所,原料胆固醇运送至线粒体后,由线粒体外膜上的在类固醇生成急性调节蛋白(StAR)协调转运至内膜,该过程是类固醇激素合成的限速步骤,到达线粒体内膜后,胆固醇在胆固醇侧链裂解酶细胞色素P450(CYP11A1)的作用下生成孕烯醇酮,这一步是类固醇生成的酶促限速步骤,它们共同决定了线粒体合成类固醇激素的能力和速率,孕烯醇酮将继续参与雌、孕激素的合成<sup>[50-51]</sup>。在卵巢中,颗粒细胞和卵泡膜细胞参与类固醇激素的合成。雌二醇(estradiol,  $E_2$ )由卵巢颗粒细胞合成,在调节卵泡发生中发挥着重要作用,是协调优势卵泡的发育和选择的决定性因素<sup>[52]</sup>。正常在位内膜基质细胞中几乎检测不到StAR的表达或类固醇激素的产生,然而,在异位子宫内膜基质细胞可以检测到StAR、芳香酶以及其他必需的类固醇生成酶同时表达,使得异位子宫内膜组织能够以胆固醇为底物合成 $E_2$ ,从而促进异位子宫内膜的生长和炎症反应<sup>[53-54]</sup>。OS和炎症反应会损伤EMT患者卵巢颗粒细胞中的线粒体,导致线粒体断裂增加和膜电位降低,影响胆固醇的转运与合成,血清和卵泡液中 $E_2$ 水平显著降低,从而进一步导致卵母细胞成熟障碍、质量下降以及受精率降低<sup>[55]</sup>。此外,EMT患者StAR水平显著降低,并与 $E_2$ 水平高度相关。

## 4 潜在治疗靶点

目前,EMT相关不孕的治疗在妇产科领域仍是一个具有争议和挑战性的问题。褪黑素是松果体分泌的一种激素,调节人体昼夜节律,近年来大量研究发现褪黑素还具有抗氧化、抑制细胞增殖和血管生成等作用<sup>[56-57]</sup>。研究表明褪黑素可以上调EMT小鼠模型中抗氧化酶的表达、减轻OS、延缓颗粒细胞衰老并提高生育力<sup>[58]</sup>。此外,褪黑素还可以改善卵母细胞治疗及卵巢储备,在小鼠的饮用水中添加30  $\mu\text{g}/\text{mL}$ 的褪黑素,持续21 d后,小鼠窦卵泡数量以及囊胚形成率较对照组明显升高<sup>[57]</sup>。目前为止,短期补充褪黑素被认为是安全的,且无明显生殖毒性<sup>[59]</sup>。因此,褪黑素可能是一种有前景的改善EMT中OS引起的生育力下降的辅助治疗方式。白藜芦醇是一种天然多酚化合物,具有抗衰老、抗氧化、抗炎等作用<sup>[60]</sup>,并能够抑制子宫内膜异位病灶的进展<sup>[61]</sup>。白藜芦醇可以通过激活SIRT1降低细胞内ROS水平,并改善线粒体功能<sup>[62]</sup>。同时,

白藜芦醇还能影响卵母细胞发育过程中的线粒体生物合成和自噬,通过清除受损的线粒体来维持卵母细胞和颗粒细胞的稳态<sup>[63]</sup>。这些效应提示白藜芦醇对EMT相关不孕可能具有潜在治疗作用。目前对EMT相关不孕的以线粒体为靶点的新型治疗模式的探索主要集中在抗氧化剂的应用方面,而关于线粒体动力学、类固醇激素合成方面仍有待研究。

## 5 总结与展望

EMT相关不孕的发病机制尚未完全阐明,以上内容讨论了线粒体在EMT相关不孕中的作用。线粒体动力学在女性卵巢储备、卵泡发育、卵母细胞成熟等过程中起着重要的调控作用,已有研究表明线粒体动力学异常参与了异位内膜的种植与生长过程。然而,目前关于EMT对卵巢线粒体动力学的影响知之甚少,亟须更多的研究来揭示其中的联系,探索EMT相关不孕的治疗的新靶点。EMT是一种慢性全身性炎症性疾病,慢性炎症介导的氧化应激可导致卵巢储备减退、配子及胚胎质量下降、颗粒细胞功能受损和类固醇激素合成障碍等,从而对女性生育力产生不良影响。需要注意的是,线粒体各个功能之间是相互关联和协调的,并且线粒体与其他细胞器,如内质网,存在相互作用和交流,需要动态、关联地看待和探索线粒体在疾病中的作用。针对EMT相关不孕的治疗,目前的研究主要集中于抗氧化剂的应用,研究发现褪黑素和白藜芦醇可以改善女性生殖功能,其在EMT相关不孕中的应用具有一定前景。尽管如此,EMT相关不孕的治疗目前仍是一个棘手的问题,迫切需要探索和开发新的治疗靶点。

\* \* \*

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**Author Contribution** GONG Xue is responsible for conceptualization, writing--original draft, and writing--review and editing. HUANG Jin is responsible for supervision, and writing--review and editing. WANG Chichiu is responsible for conceptualization, supervision, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

**利益冲突** 所有作者均声明不存在利益冲突

**Declaration of Conflicting Interests** All authors declare no competing interests.

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(2024-01-20收稿, 2024-05-07修回)

编辑 何学令



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