

doi: 10.13241/j.cnki.pmb.2017.02.049

子宫腺肌病发病与干细胞关系的研究进展*

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摘要:子宫腺肌病(adenomyosis,AM)是一种常见的严重影响女性身心健康及女性生育并伴有恶性侵袭性的妇科良性疾病。以子宫内膜的腺体和间质异位至深部子宫肌层,并伴随相邻肌细胞增生和肥大特征,其临床特点特殊,近期统计研究发现其发病率正逐渐升高,而且趋向年轻化。现有报道子宫腺肌病发病涉及多方面的因素,但具体发病机制尚不明确。近期研究发现子宫内膜存在的基底层干细胞可能与子宫内膜随月经周期发生脱落、增殖相关,其功能紊乱可能导致子宫内膜增生异常性疾病包括子宫腺肌病的发生,子宫内膜干细胞侵入子宫肌层,在局部环境的诱导下增殖、分化或可形成子宫内膜的异位病灶。子宫内膜干细胞的研究可能为子宫腺肌病发病和治疗带来新的思路 and 希望。本文参考国内外文献,就近年来子宫腺肌病发病机制及与干细胞相关研究进展进行综述并提出展望。

关键词:干细胞;子宫干细胞;子宫腺肌病;发病机制

中图分类号:R711.74 **文献标识码:**A **文章编号:**1673-6273(2017)02-393-03

Stem Cells and Their Relationship with Adenomyosis*

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ABSTRACT: Adenomyosis is a common gynecological benign disease which affects women's physical and mental health and fertility. It is characterized by endometrial glands and interstitial deeply ectopic to uterine muscle layer, and with adjacent muscle cell hyperplasia and hypertrophy. By statistical study Its incidence is found increased gradually and trend younger in recent years, because of special clinical characteristics. There are many factors involved in the pathogenesis of the adenomyosis, But the specific pathogenesis is not clear. Recent studies have shown that basal layer of endometrial stem cells and endometrial with menstrual cycle occurred off, the proliferation and its dysfunction may lead to abnormal endometrial hyperplasia disease, including the occurrence of uterine adenomyosis, endometrial stem cells invading the myometrium, in the local environment induced proliferation, differentiation and the formation of ectopic endometrial lesions. The study of endometrial stem cells may bring new ideas and hopes for the pathogenesis and treatment of adenomyosis. This paper gave a review on the resent research at home and abroad.

Key words: Stem cell; uterine stem cell; adenomyosis; pathogenesis

Chinese Library Classification(CLC): R711.74 **Document code:** A

Article ID: 1673-6273(2017)02-393-03

前言

子宫腺肌病被定义为子宫内膜腺体和间质浸润至深部子宫肌层同时伴有周围临近平滑肌细胞的肥大和增生的良性疾病,可形成弥漫性病变或局限性病变^[1]。但具有恶性肿瘤的浸润、种植、血管增殖、与周围组织的粘连等生物学行为。Bird 于 1972 描述其显微镜下病理学特征为为肥大增生的子宫肌层环绕着异位、非恶性的内膜样腺体和间质^[2]。其病理过程涉及多方面的因素包括粘附、侵袭、子宫内膜与肌层的变化、新生血管的发生、激素的异常等。国外文献报道子宫腺肌病确诊困难、容易漏诊^[3]。2013 年 Levy 提出新的成像技术发现子宫腺肌病患者约 1/3 无症状,即使有临床症状也无特异性^[4]。子宫腺肌病的发

病机制继基底层子宫内膜直接侵入肌层生长学说之后,近年在组织细胞和分子水平对子宫腺肌病发病机制又相继从子宫间质组织分化异常、甾体激素的作用、遗传因素、免疫因素、基因水平改变等方面进行了大量的基础研究,子宫腺肌病发病涉及因素较多,彼此间相互补充、论证和发展。虽然近年关于子宫腺肌病发病机制的研究不断深入,子宫腺肌病的发病机制仍未明确。

子宫腺肌病和盆腔子宫内膜异位症常同时存在^[5],目前研究认为子宫腺肌病和盆腔子宫内膜异位症是两种发病原因和发病机制并不完全相同的疾病。关于子宫内膜异位症发病机制郎景和教授提出了“在位内膜决定论”学说^[6],在此学说基础上有人提出子宫内膜异位症可能是一种干细胞疾病^[7],有研究报道子宫腺肌病发病与恶性侵袭有可能也与子宫干细胞相关

* 基金项目:国家自然科学基金青年科学基金项目(81401203);黑龙江省自然科学基金项目(H201433);

哈尔滨市科学技术局科技创新人才基金项目(2013RFLYJ003);黑龙江省教育厅面上项目(12541339)

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(收稿日期:2016-03-25 接受日期:2016-04-16)

^[8]。接下来对查阅的国内外关于子宫腺肌病发病与子宫干细胞关系相关研究进展的文献进行归纳综述。

1 传统子宫腺肌病发病机制学说及相关因素研究

传统子宫腺肌病理论即 Cullen^[9]于 1908 年提出的基底层内膜侵袭学说即正常的子宫内膜与子宫肌层交界处出现薄弱破损,子宫内膜腺体和基质由此侵入子宫肌层,同时引起子宫平滑肌细胞的肥大和增生。Panganamanmla^[10]的调查也发现宫腔内操作史与子宫腺肌病发病相关。支持子宫内膜及肌层连接处受损后,异常子宫内膜基底层细胞侵入子宫肌壁间形成子宫肌壁间的异位子宫内膜病灶。但是调查发现,具有多次宫腔内操作史及多产史的妇女并非一定会患此病,并且动物实验研究也发现子宫内膜的侵入并不一定需要子宫内膜与子宫肌层之间的边界被破坏,与此学说相悖^[11],说明其发病或还涉及其他因素的参与。NATSUKI KOIKE^[12]等总结已有文献概况子宫腺肌症发病机制涉及子宫肌层功能不良与子宫腔内压力增大、子宫内膜间质变化与上皮-间质转换、多能周细胞成血管、肥大细胞激活等理论,另外子宫腺肌病具有家族聚集性、基因、免疫因素、生长因子可能亦参与其发病^[13]。动物实验显示,他莫昔芬可诱导小鼠子宫发生子宫腺肌症^[14]。但在人类中尚无类似实验研究,但临床上常见子宫腺肌病经常与子宫肌瘤及子宫内膜异位症共发,且该病好发于绝经前期的生育年龄女性,绝经后病灶逐渐萎缩同时症状逐渐消退,提示此病是一种雌激素依赖性疾病。另外在光镜下多年前就有学者观察到子宫腺肌病患者的子宫内膜毛细血管增生活跃^[15],提示血管生成的异常可能与子宫腺肌病发病相关,血管生成在子宫腺肌病异位内膜病灶的存活中可能起到重要作用。

2 子宫干细胞

2.1 子宫干细胞标志物的表达和其基底层分布

干细胞能够自我更新,具有高度增殖、多向分化的潜能,具有克隆、集落形成能力,分为胚胎干细胞和成体干细胞。存在于人和动物成年组织中的干细胞为成体干细胞。子宫作为孕育胚胎、胎儿和产生月经的器官,其子宫内膜功能层受卵巢性激素的影响发生周期性的增值、分泌和脱落,具有惊人的再生能力,提示子宫内膜中少数细胞具有强大的增殖潜能和克隆形成能力。早年就有研究提出具有这种再生能力的细胞可能是子宫内膜干细胞^[16],这一学说最先被 Chan 等^[17]通过细胞克隆形成实验鉴定证实,并且提出为子宫内膜上皮和基质来源。最近的研究报道子宫内膜干细胞可以从月经血^[18,19]或从活检子宫内膜组织分离出来^[20]。Chan^[17]的研究还发现在月经周期的不同阶段上皮细胞和基质细胞的克隆形成能力并无明显变化,提示干细胞可能于特定的微环境中处于相对稳定静止的状态。另有研究通过 BrdU 标记小鼠子宫内膜细胞,即标记滞留细胞(label-retaining cell,LRC)实验发现子宫内膜上皮干细胞主要存在于内膜肌层交界处的腺腔、血管旁^[21]。但人体尚无 LRC 技术研究,所以目前人子宫内膜干细胞无法通过 LRC 技术确切定位。

关于子宫内膜干细胞标记物研究有 Cho 等^[22]学者对女性不同生理时期包括胎儿及育龄期子宫内膜不同时相通过免疫组织化学技术研究其造血干细胞标志物 CD117 和 CD34 的表达,结果发现子宫内膜干细胞主要存在于基底层,不随月经周

期中卵巢激素分泌的变化,不发生周期性脱落。Schwab 等^[23]报道从子宫内膜中分离出的 CD146 和 PDGFR β 阳性间质细胞具有间充质干细胞表型和特性。并且具有多向分化潜能,表达与血管形成相关的基因,分布在功能层和基底层的血管周围,近期 Masuda 等^[24]发现 W5C5 一个新的子宫内膜间充质干细胞(eMSC)标记物。分离提取的 W5C5 阳性 eMSC 与 CD146+PDGF-R 具有相似的特性。

2.2 子宫内膜干细胞与子宫内膜再生

人类的子宫内膜不仅随月经周期增殖、脱落,在分娩后,行子宫内膜切除术后和绝经后服用雌激素替代治疗仍可以再生^[25]。有实验证实将行人子宫内膜切除术后获得的组织制成未分选的单细胞悬液接种到免疫缺陷小鼠肾包膜下,可以产生细胞角蛋白和 CD9⁺腺体样结构,CD10⁺和 CD13⁺的基质样组织与 aSMA 阳性的子宫平滑肌样组织。这种异种移植产生的内膜组织对模拟人月经周期的雌孕激素产生反应^[26]。把从人子宫内膜分离的 SP(Side Population,侧群细胞)细胞接种到小鼠肾包膜下也能形成内膜组织^[27]。这些研究表明,子宫内膜中存在可以体内产生内膜组织的干细胞。对于这些细胞的特性和类型特别是 SP 细胞需要更进一步的研究来明确。

3 子宫腺肌病异位内膜组织生物学行为

子宫内膜基底层位于子宫肌层与内膜交界处,早期有研究发现子宫内膜基底层少部分细胞细胞可以向上皮、间质或平滑肌细胞分化^[28],后有实验研究子宫腺肌病病灶组织,发现该病灶组织包含腺体、基质和平滑肌成分,提示子宫腺肌病病灶为异位生长的内膜,该内膜细胞具有重建类似于子宫内膜与肌层交界处组织结构的能力^[29],说明子宫腺肌病病灶与基底层内膜之间具有紧密的联系。

4 子宫内膜异位病灶相关干细胞研究

4.1 子宫内膜异位病灶干细胞的分离及鉴定

关于干细胞鉴定,研究者有采用标记滞留细胞的技术来分析识别体内静息状态的干细胞,但标记滞留细胞技术尚无法应用于人体。还有人利用干细胞的增殖更新能力,观察其在体外培养时表现出的克隆集落形成能力,来分析其干细胞特性。但是干细胞鉴定的金标准是体内组织的重建^[30]。关于子宫内膜异位症,kao 和 chan 的实验先后证实卵巢子宫内膜异位囊肿中存在具有可克隆能力、自我更新能力及多向分化潜能的间充质干细胞^[31-32]。对于子宫腺肌病,近期有研究者通过行子宫全切术患者提取人子宫腺肌病病灶组织制成单细胞悬液,进行磁珠分选出 CD45⁻和血型糖蛋白 A⁻的细胞进行培养,发现部分细胞能够形成集落,具有克隆形成能力,增殖周期为 56.3 小时左右。同时该研究团队还通过了流式细胞分仪分析其表面标志物,发现能表达间充质干细胞标志物,进行体外诱导分化实验发现能够诱导分化形成脂肪细胞,骨细胞和肝细胞。提示这类细胞具有干细胞特性,可能为干细胞^[33]。

4.2 子宫内膜异位病灶干细胞的来源

郎景和教授提出的“在位内膜决定论”,强调了子宫内膜异位症患者的在位内膜与无子宫内膜异位症健康的女性子宫

内膜相比,具有更强的粘附、侵袭、种植能力,更容易形成异位内膜病灶。提示异位内膜干细胞主要来源于子宫内膜细胞。但还有其他实验研究发现骨髓干细胞能够向异位子宫内膜组织分化,所以骨髓干细胞或许也参与了子宫内膜异位病灶的形成^[34,35]。

5 从干细胞壁龛学说看子宫腺肌病发病

关于干细胞研究史上的一个突破是 Schofield 提出干细胞壁龛的假说,首先假想了一个称为壁龛的环境,由壁龛细胞构成,干细胞位于壁龛中,并对壁龛细胞的信息作出应答反应。在机体正常情况下壁龛的微环境阻止干细胞增殖、分化、及凋亡,使干细胞处于一种静息的状态,但在某些外界因素的刺激诱导下或内在机体病理条件下将出现不同程度的增殖、再生和分化,这在某些增殖分化异常性疾病如肿瘤和机体自我修复中起到重要甚至决定性作用。Gargett 提出:在组织损伤时成体干细胞常被激活,这可能与异位组织的重建相关,子宫内膜干细胞的壁龛结构似乎定位于基底层中^[36],基底层干细胞在不同的壁龛调控下可能发生于子宫肌层的浸润侵袭^[37]。

6 小结与展望

综上所述,虽然干细胞与子宫腺肌病发病机制及恶性侵袭之间确切的关系尚未能明确,需要进一步的实验研究。但是干细胞理论为子宫腺肌病发病及恶性侵袭机制的研究提供了一个新的思路,或许能帮助我们子宫腺肌病的源头解释其病理起因,对于子宫腺肌的认识和治疗具有重大意义。

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