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间充质干细胞在复发性自然流产中治疗潜能的研究进展

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[**摘　要**]　复发性自然流产(RSA)是妊娠早期最常见的并发症之一,影响2%~5%的育龄期女性,其发病率呈逐年上升趋势,不仅对女性的身心健康造成了影响,也给社会和家庭造成沉重的经济负担。间充质干细胞(MSCs)是一类源于多种组织的中胚层间充质的非造血成体多能干细胞,具有多向分化和自我更新等特性,对于RSA患者的生育结局具有改善作用,已成为近年研究的热点。因此,本文探明了不同来源的MSCs改善RSA患者妊娠结局的作用与机制,并分析其研究现状及存在的问题。

[**关键词**]　间充质干细胞;复发性自然流产;干细胞治疗

Research progress on therapeutic potential of mesenchymal stem cells in recurrent spontaneous abortion

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[**Abstract**]　Recurrent spontaneous abortion (RSA) is one of the most common complications in early pregnancy, affecting about 2%~5% of women of childbearing age, and its incidence is increasing year by year, which not only affects women's physical and mental health, but also causes a heavy economic burden to the society and the family. Mesenchymal stem cells (MSCs) are a class of non-hematopoietic adult multipotent stem cells derived from mesodermal mesenchymal cells of a variety of tissues. They have the characteristics of multi-directional differentiation and self-renewal, and can improve the fertility outcome of RSA patients, which has become a research hotspot in recent years. Therefore, this paper explores the roles and mechanisms of MSCs from different sources in improving pregnancy outcomes in RSA patients, and analyzes their research status and existing problems.

[**Key words**]　Mesenchymal stem cells;Recurrent spontaneous abortion;Stem cell therapy

复发性自然流产(recurrent spontaneous abortion,RSA)是指与同一性伴侣在妊娠20周前连续流产2次或以上的经历,发病率为1%~5%,在已知病因中,最重要的4种病因为母体免疫学因素、易栓因素、女性生殖道解剖结构异常(包括子宫粘连)以及内分泌异常(包括卵巢早衰)[1]。约50%的RSA是突发性的,定义为不明原因复发性流产(unexplained recurrent spontaneous abortion,URSA)[2]。目前对于URSA的治疗有静脉注射免疫球蛋白、环孢菌素A、泼尼松、羟氯喹、淋巴细胞主动免疫治疗、粒细胞集落刺激因子(granulocyte colony-stimulating factor,G-CSF)等,其安全性及有效性尚存争议,故不建议作为URSA的常规治疗方案[3]。间充质干细胞(mesenchymal stem cells,MSCs)属于非终末分化细胞,它有间质细胞、内皮细胞及上皮细胞的特征,因其突出的免疫抑制潜能已在众多免疫介导的疾病中展开广泛研究。近年来,MSCs治疗改善RSA患者妊娠结局已成为生殖医学领域的热点内容,为妊娠相关疾病的治疗提供了新靶点,本文就MSCs在妊娠母胎界面调节作用机制及其在RSA等疾病治疗中的应用研究进展做一综述。

1　MSCs的概述

1.1　MSCs的生物学特性　MSCs具有自我更新修复、增殖能力强、产生克隆细胞群、造血支持和促进干细胞植入的特性[4]。MSCs的低免疫原性并非完全的免疫豁免,主要与表达主要组织相容性复合体Ⅰ(major histocompatibility complexⅠ,MHCⅠ)以及

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不表达MHC Ⅱ、CD40、CD80、CD86有关。MSCs可从多种组织中分离出来[5]。在伦理上MSCs比胚胎干细胞更易接受，MSCs在免疫性疾病治疗中展现出巨大的潜力，如COVID-19、移植物抗宿主病（graft-versus-host disease，GVHD）、肝硬化、系统性红斑狼疮和克罗恩病等[4,6-9]。MSCs具有旁分泌及归巢作用，这些生物学特性使MSCs成为RSA的潜在治疗方案。

1.2 不同来源MSCs的优势与缺陷　不同组织来源的MSCs可能具有不同临床特性，骨髓间充质干细胞（bone marrow derived-mesenchymal stem cells，BMSCs）已被广泛使用，但骨髓的抽吸是侵入性的，细胞产量相对较低，并且随着年龄的增长，骨髓细胞产量显著下降[10]。脂肪间充质干细胞（adipose-derived mesenchymal stem cells，ADSCs）来源广泛，可通过脂肪抽吸术安全获得，比BMSCs体量大且安全性提高，体外扩增速度远高于BMSCs，易于自体移植，同样是干细胞移植的良好选择[11]；月经血间充质干细胞（menstrual blood-derived mesenchymal stem cells，MenSCs）表面标志物与BMSCs一致，可从经血中无创分离获得，增殖能力强、免疫原性低、无伦理限制[12]。由于子宫内膜薄且容易被污染，可用的数量有限，MenSCs在临床上的应用存在局限性。与BMSCs相比，脐带间充质干细胞（umbilical cord-mesenchymal stem cells，UCMSC）具有克隆形成、增殖、迁移、旁分泌的潜力，特别是其易于扩增和传代的特性，使UCMSC可大规模生产用于临床研究的MSCs[13-14]。

2　MSCs改善RSA患者生育结局的可能机制

MSCs的作用机制涉及细胞分化、免疫调节、抗炎因子分泌、迁移和归巢、抗凋亡特性以及分泌细胞外囊泡（extracellular vesicles，EV）[15]。MSCs具有向损伤或炎症区域优势分布的能力，刺激或抑制宿主免疫系统发挥免疫调节作用，这种“定向迁移”即为归巢能力，对损伤修复至关重要[16-17]；旁分泌活动也是MSCs修复损伤的子宫内膜功能的重要方式之一，可通过分泌多种可溶性细胞因子，修复与再生受损组织，还可分泌EV作用于附近的受体细胞[18-19]。外泌体（exosomes，Exo）是旁分泌过程中重要的EV[20]。Exo介导的miR-340可对子宫内膜间质细胞进行表观遗传调控，抑制局部炎症反应，加速受损组织血管新生，参与调控子宫内膜的解剖与功能修复[21-22]。近年来研究发现，Exo具有与MSCs相似的治疗效果，在治疗女性生殖障碍方面的机制包括促血管生成、免疫调节、抗纤维化和抗氧化应激，功能内容值得进一步探索[23]。

2.1 改善子宫内膜容受性

2.1.1 修复子宫内膜　子宫内膜厚度已被普遍认为是评估子宫内膜容受性的重要指标，当排卵期子宫内膜厚度低于7 mm时，妊娠成功率极低[24-25]，子宫组织中的肌瘤、疤痕、手术、感染都会损伤子宫内膜，导致组织再生障碍、宫腔粘连（intrauterine adhesions，IUA）、宫腔变形，部分或完全阻塞子宫腔。一项研究表明，使用人脐带间充质干细胞的胶原支架（collagen scaffold seeded with umbilical cord mesenchymal stem cells，CS/UC-MSCs）治疗IUA，可使子宫内膜再生，促进子宫内膜结构重建和功能恢复，进而改善IUA患者的妊娠结局[26]。CS/UC-MSCs的作用机制可能是在体外通过旁分泌作用促进人子宫内膜间质细胞增殖并抑制凋亡，维持正常管腔结构，促进胶原重塑，诱导子宫内膜固有细胞增殖和上皮恢复，增加子宫内膜厚度，增加雌激素受体，孕激素受体的表达，修复子宫内膜，被干预的子宫内膜再生能力增强[27]。

2.1.2 降低纤维化　子宫内膜纤维化是造成RSA的获得性生殖道解剖异常因素之一，常因子宫内膜受损后胶原沉积导致，子宫内膜纤维化可能与刮宫次数过多有关[28]。研究表明，兔刮宫后立即注射BMSCs条件培养基可使兔子宫纤维化组织形成减少，并对纤维化组织形成具有预防作用。另一研究表明通过鼠尾静脉和宫腔灌注给予BMSCs的子宫内膜腺体数量增加，纤维化面积率下降[29]。BMSCs减少纤维化的机制可能与迅速促进新生子宫内膜腺形成，取代纤维化瘢痕有关。

2.1.3 促进血管生成　子宫内膜复杂的血管供应与重塑是维持妊娠的基础，血管受损或重塑不良则会导致子宫内膜容受性不良，造成流产等妊娠并发症。MSCs能够促进子宫内膜血管生成、增殖和分化，这可能与MSCs上调子宫内膜微血管密度、增殖指数Ki67有关[30-31]。卵巢丰富的血管网维持稳态对于卵巢生殖与分泌功能起着至关重要的作用，卵巢血管受损可能与卵巢早衰有关。研究表明，MenSCs可通过分泌血管内皮生长因子/胰岛素样生长因子、粒细胞集落刺激因子、肝细胞生长因子（hepatocyte growth factor，HGF）等相关细胞因子促进卵巢血管再生，减轻间质纤维化，从而改善卵巢功能[32]。总

之，MSCs可通过多种方式促进子宫内膜、卵巢血管生成，增加子宫内膜厚度，修复受损的生殖功能。

2.2　调节母胎界面的免疫稳态　免疫异常是造成RSA的原因之一，已有报道体内外实验均证实MSCs对先天性和获得性免疫具有非特异性的免疫调节抑制免疫过激的能力，MSCs的免疫调控可能通过分泌可溶性因子和细胞间接触依赖机制减少妊娠丢失率，可诱导T细胞、巨噬细胞、树突状细胞（dendritic cells，DCs）、自然杀伤（natural killer，NK）细胞、B细胞水平维持稳态[33]。RSA与全身母体免疫炎症有关，淋巴细胞运输、补体沉积、共刺激分子的增加以及胎儿-母体组织中NK细胞、巨噬细胞和T细胞的激活均可导致子宫微环境呈炎症状态[34]。

2.2.1　巨噬细胞　巨噬细胞及其分泌的细胞因子可清除凋亡细胞、降解细胞外基质、促进子宫壁血管重塑[35-36]。研究表明，MSCs可诱导促炎巨噬细胞表型M1向抗炎巨噬细胞表型M2的转变，肿瘤坏死因子α刺激基因-6（tumor necrosis factor alpha stimulated gene-6，TSG-6）和CD200与之密切相关。MSCs与促炎巨噬细胞M1直接接触后，MSCs旁分泌产生的TSG-6和CD200表达增加，CD200与M1上的CD200R相互作用，促进巨噬细胞表型由M1转向M2，因此，TSG-6和CD200与促炎巨噬细胞M1接触参与MSCs对流产的免疫抑制。XIN等[37]采用外泌体和胶原支架结构（CS/Exos）治疗子宫内膜损伤的大鼠，结果表明CS/Exos能有效恢复生育能力，其机制可能与CS/Exos通过含有1个miRNA的外泌体从而促进$CD163^+$M2巨噬细胞极化、减轻炎症并增加体内和体外的抗炎反应有关。

2.2.2　子宫自然杀伤细胞　子宫自然杀伤细胞（uterine natural killer cell，uNK）是早期妊娠中主要的蜕膜淋巴细胞来源，约占90%，在维持妊娠过程中起重要作用[38]。有研究认为RSA可能与uNK数目异常有关[39]。在接种MSCs后，蜕膜表面uNK计数趋向正常化。既往研究表明，MSCs通过分泌可溶性因子，如血清前列腺素E2（prostaglandin E2，PGE2）、吲哚胺2，3双加氧酶（IDO1）和可溶性人类白细胞抗原G（soluble human leukocyte antigen，sHLA-G），以及细胞与细胞之间的接触，调节NK细胞的功能和表型[40]。在有流产倾向的小鼠母胎界面，uNK产生的IFN-γ明显高于正常妊娠小鼠，而MSCs给药后，怀孕小鼠蜕膜中产生IFN-γ的NK细胞频率降低，产生IL-4和IL-10的NK细胞频率增加，抑制NK细胞的增殖和功能，并进一步改变其细胞因子谱[41-42]。体外研究也表明，BMSCs与uNK共培养可下调IFN-γ和TNF-α表达，促进IL-4和IL-10产生[43]。MSCs可通过分泌sHLA-G发挥其免疫调节功能，抑制妊娠期间外周血自然杀伤细胞（peripheral natural killer cell，pNK）向子宫的过度募集及过度浸润。综上所述，MSCs主要通过调节多种免疫因子调节uNK分布，调节母胎界面的微环境，从而提高RSA患者妊娠率，防止流产。

2.2.3　调节Th1/Th2与Th17/Treg平衡　越来越多的证据表明，母胎界面的调节性T细胞（regulatory T cells，Treg）偏移有利于子宫内膜接受作为同种异体的胚胎植入[44]。研究表明，Treg数量减少及功能缺失均是导致RSA及反复种植失败的危险因素[45]。MSCs治疗可促进$CD4^+Foxp3^+$Treg的产生，并且诱导Treg优先产生抗炎细胞因子IL-10和转化生长因子-β（transforming growth factor-β，TGF-β），增强dTreg抑制Th1和Th17相关炎症反应的能力，Th1型TNF-α、IFN-γ和Th17型IL-17A的产生明显减少[46]。Treg通过共抑制分子如细胞毒性T淋巴细胞相关蛋白4、T细胞免疫球蛋白和黏蛋白域3、肿瘤坏死因子受体和程序性死亡配体-1有效抑制效应T细胞[47]。缺乏Treg可导致效应T细胞过度增生，引起相关免疫反应导致胎儿排斥反应，最终导致妊娠失败[48]。研究发现与MSCs共培养时，Treg对效应T细胞的抑制活性会增强。与未经处理的Treg相比，MSCs诱导的Treg具有促进$dCD4^+$T细胞分泌Th样细胞因子的潜能[49]。Treg可以抑制$CD4^+CD5^-$效应T细胞的增殖，通过分泌IL-10减少IFN-γ的释放，增强滋养层细胞的侵袭力。另一研究表明小鼠BMSCs对$CD4^+$T、$CD8^+$T细胞和幼稚性T细胞、记忆性T细胞均有免疫抑制作用，这种抑制作用主要由诱导型一氧化氮合酶（inducible nitric oxide synthase，iNOS）、转化生长因子β1（TGF-β1）、前列腺素E（prostaglandin-E，PG-E）、肝细胞生长因子和可溶性HLA-G介导[50-51]，导致T细胞从促炎（产生IFN-γ）状态转变为抗炎（产生IL-4）状态。这说明MSCs可招募其他免疫细胞因子并发挥免疫作用，诱导Th1细胞向Th2细胞偏移、Th17细胞向Treg细胞偏移，从而维持妊娠。

2.2.4　DCs　子宫内膜树突状细胞（uterine dendritic cell，uDC）作为T细胞免疫的激活剂和调节剂，其分布、成熟状态和功能的任何紊乱都可能影响妊娠结局，从而导致妊娠紊乱[52]。正常妊娠中的uDC大多不成熟且对诱导免疫原性T细胞反应效率低下[53]。RSA患者uDC数量显著多于正常妊娠女性，

蜕膜DC^{-}SIGN^{+}细胞的数量显著减少[54]。研究表明，MSCs给药后显著降低uDC上DC成熟标志物（MHC-Ⅱ、CD86和CD40）的表达[55]。此外，MSCs具有产生粒细胞-单核细胞集落刺激因子（granulocyte-monocyte colony-stimulating factor，GM-CSF）等细胞因子和趋化因子的作用，GM-CSF可促进DCs的分化和扩增，并能调节免疫细胞（尤其是uDC）向子宫内膜转运[56]。MSCs对uDC的调节可能是MSCs在RSA治疗中产生积极作用的主要机制之一。

2.3　促进卵巢颗粒细胞增殖、抑制凋亡　卵巢颗粒细胞是卵巢中主要的功能细胞，其凋亡可导致卵巢早衰。研究发现，将受损的卵巢颗粒细胞与BMSCs共培养后，B淋巴细胞瘤-2蛋白表达增加，颗粒细胞凋亡率降低[57]。在另一实验中，有学者将自然衰老的卵巢颗粒细胞与ADSCs共培养，细胞表面抗苗勒管激素、卵泡刺激素受体、叉头转录因子2、芳香化酶表达明显增加[58]，且PMSC可通过激活磷脂酰肌醇-3-激酶/蛋白激酶B信号通路减少早衰的卵巢组织中卵巢颗粒细胞凋亡[59]。以上研究表明，MSCs可通过调控卵巢颗粒细胞凋亡促进其增殖，恢复损伤的卵巢功能，并能促进人子宫内膜基质细胞增殖并抑制其凋亡，增强子宫内膜对激素的生物学反应[60-61]。

3　MSCs治疗RSA的研究进展

TAYLOR[62]首次发现非子宫来源的干细胞有助于损伤的子宫内膜再生，这一研究开启了干细胞修复受损子宫内膜的新篇章。NAGORI等[63]首次对1例33岁的重度IUA患者进行自体BMSCs移植，并辅以雌孕激素治疗，4个周期后子宫内膜厚度由3.6 mm增加至8.0 mm，该患者通过辅助生殖技术成功妊娠。动物实验已证实，在子宫内膜脱落或缺损后，MSCs可协助子宫内膜再生修复，显著提高IUA大鼠的妊娠率和活产率[64]。近期有学者证明了在脂多糖（lipopolysaccharide，LPS）诱导的流产模型和免疫反应介导的自然流产模型中，MSCs地过继转移可抑制LPS诱导的外周血CD4细胞活化和血清中高水平的促炎细胞因子产生，抑制巨噬细胞的促炎表型以及过度的补体激活和促进血管生成因子的产生，在降低流产率、防止妊娠丢失方面发挥关键作用[65-66]。以上结果证明了MSCs在预防流产方面的作用，表明MSCs在流产中的临床应用前景广阔。然而，很少有文章报道MSCs应用于RSA的临床研究。MSCs治疗的最佳应用途径尚无定论，文献报道的应用途径有子宫内膜下移植、经子宫动脉注射、联合胶原支架宫腔内放置以及宫腔灌注[67-70]。

有学者提出同种异体MSCs移植可引发免疫排斥的不良反应，为克服免疫排斥反应、延长同种异体MSCs的存活时间，可对MSCs进行预处理或装载生物制剂以增加表面受体的表达或免疫抑制细胞的产生，也可通过Exo处理提高同种异体MSCs的免疫耐受性[71-72]。为避免不良反应，自体MSCs移植已成为近年来的研究热点。尽管自体MSCs移植比异体MSCs更安全、更符合伦理道德，但在临床应用中仍存在一些问题。首先，提取的自体MSCs数量非常有限，因为它们只能从宿主体内提取。其次，自体MSCs提取后，体外培养周期长，可能无法完全满足机体的需要[73]。

4　总结与展望

综上所述，MSCs在女性生殖系统疾病诊疗方面具有巨大潜力，其作用机制包括修复子宫内膜、降低纤维化、促进血管生成、促进细胞增殖、抑制细胞凋亡、免疫抑制等，MSCs衍生的Exo表现出与其源细胞相似的功能，且Exo无低输注量、低保留率、移植后免疫排斥反应和致瘤性等缺陷，因而成为有待进一步研究的诊疗新靶点。目前大多数MSCs治疗女性生殖疾病的研究均为小样本临床试验，还需更多的多中心大样本随机对照试验以验证其确切疗效及安全性，此外，MSCs在RSA的临床应用前需要充分阐明MSCs治疗的确切机制、常规治疗方案、副作用及禁忌证，以便更好地应用于临床。

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