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综 述

胚胎植入的调控机理

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摘 要：胚胎植入对于妊娠的建立和维持至关重要，需要活化的胚泡和接受态的子宫之间进行同步。在辅助生殖技术中，子宫接受态的判断仍是制约妊娠率的一个关键限制性因素。已有数据显示，胚胎植入涉及一系列信号分子的激活和失活，进而影响子宫腔上皮细胞的增殖与分化、上皮极性、宫腔闭合、胚胎定位、上皮基质反应、腺体发育等。本文就雌激素、孕酮、白血病抑制因子(leukemia inhibitory factor, LIF)、microRNA (miRNA)、通道蛋白、信号转导通路等在胚胎植入过程中的作用及其调控网络作一综述，以期为不孕症的治疗及安全有效的避孕药开发提供理论依据。

关键词：子宫接受态；胚胎植入；调控机理
中图分类号：Q492.6；S852.1

Regulatory mechanism of embryo implantation

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Abstract: Embryo implantation is crucial for the establishment and maintenance of successful pregnancy and requires the synchronization between implantation-competent blastocyst and receptive uterus. In assisted reproductive technologies, recognition of uterine receptivity is the limiting factor for improving pregnancy rate. It has been previously reported that embryo implantation involves the activation and inactivation of numerous signaling molecules which may influence the proliferation and differentiation of uterine epithelial cells, epithelial polarity, luminal closure, embryo orientation, epithelial-stromal interactions, gland development, etc. Here we summarize the function of estrogen, progesterone, leukemia inhibitory factor (LIF), microRNA (miRNA), channel protein and signaling pathways in embryo implantation and explore their regulatory network to provide theoretical basis for the treatment of infertility and development of safe and efficient contraceptives.

Key words: uterine receptivity; embryo implantation; regulatory mechanism

世界卫生组织预测，不孕不育将成为仅次于肿瘤和心脑血管疾病的严重危害人类健康的第三大疾病[1, 2]。在全球育龄妇女中，妊娠失败比例高达25%~40%，已成为当今一个全球性的医学 - 社会问题[2, 3]。近年来基础和临床医学的研究显示：多数妊娠失败患者的病因都起源于胚胎植入的异常。胚胎植入是正常妊娠建立的一个关键环节，需要活化的胚泡和接受态的子宫之间进行同步。如果胚胎植入发生延迟，将导致小鼠胚胎在子宫内分布不均、胎盘发生受阻、胚胎吸收、胎儿发育延迟等不良后果，最终使早期妊娠失败的几率大大增加[4, 5]。在辅助生殖技术中，子宫接受态的判断仍是制约妊娠率的一个关键限制性因素[4, 5]。同时，子宫内膜炎、子宫内膜息肉、子宫内膜异位症、输卵管积水、子宫肌瘤以及多囊卵巢综合征等妇科疾病均可减弱子宫接受性，导致胚胎植入失败[6]。已有数据显示，

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雌激素和孕酮是调控胚胎植入的关键激素，在它们的协同作用下，生长因子、转录因子、通道蛋白、microRNA (miRNA) 及 Wnt、Notch 和 IHH 信号通路等被激活并相互对话。本文就胚胎植入的分子机制及调控网络作一综述。

1 雌激素

雌激素主要由卵巢合成，在小鼠妊娠第 4 天 (接受期)，雌激素水平显著增加，低剂量的雌激素可延长子宫接受态窗口期，而高剂量的雌激素则可关闭窗口，促使子宫进入不应期 [7]。将囊胚移植到接受期大鼠子宫中，胚胎植入正常发生，而移植到不应期子宫中，植入失败 [8]。在多囊卵巢综合征小鼠模型中，由于血清中雌激素水平异常升高而导致囊胚不能植入到子宫中 [9]。作为一种脂溶性小分子，雌激素可直接穿过细胞膜进入细胞内，与雌激素受体 (estrogen receptor, ER) 结合，ER 可分为 ERα 和 ERβ。ERα 在植入前胚胎高表达，而 ERβ 仅表达在桑椹胚和囊胚中；在活化的胚泡中降解 ERα 则会导致胚胎植入失败 [10]。在小鼠子宫接受期和植入期，ERα 高表达于子宫腔上皮和腺上皮，而 ERβ 仅在接受期子宫腺上皮表达；敲除 ERα 可导致子宫发育不全，而在 ERα 过表达转基因小鼠中，子宫腔上皮细胞凋亡率增加，胚胎植入位点数减少；敲除 ERβ 后，子宫腔上皮细胞增殖活性增强，腺体分泌增多而使子宫腔变大，对雌激素的敏感性增加，但胚胎植入仍能正常发生 [5, 11]。进一步研究显示，雌激素可诱导早期生长反应因子 1 (early growth response 1, EGR1) 在子宫腔上皮中的表达，而缺失 ERα 可阻碍这一效应 [12, 13]。在子宫中阻断或敲除 EGR1 后，因血管通透性减弱而使胚胎植入位点数减少 [13, 14]。

NCOA6 (nuclear receptor coactivator-6) 是 ERα 的辅助激活因子，可与 ERα N 端的 LXXLL 基序结合，进而增强 ERα 的转录活性。敲除 NCOA6 可因胎盘、心脏和肝脏发育异常而导致胚胎致死；在子宫上皮和基质中敲除 NCOA6 后，上皮细胞持续增殖，子宫对雌激素的敏感性增加，雌激素靶基因表达异常，进而导致胚胎植入失败 [15]。进一步研究显示，NCOA6 可促进 ERα 的泛素化并加速其降解，下调核受体辅助激活因子 SRC3 (steroid receptor coactivator-3) 在子宫腔上皮中的表达，缺失 SRC3 可使雌激素反应性减低，造成妊娠障碍。敲除 NCOA6 后可使 ERα 堆积在细胞中，添加 ER 拮抗剂 ICI182780 可拯救 NCOA6 缺失造成的胚胎植入缺陷 [15]。

REA (repressor of estrogen receptor activity) 是 ER 的辅助调节性伴侣蛋白，可竞争性地抑制 ER 转录活性。REA 条件性敲除纯合小鼠卵巢功能正常，但由于子宫内膜细胞增殖周期停滞、凋亡率增加、DNA 复制受损及腺体发生紊乱，子宫发育受阻，进而导致雌性小鼠不孕；而在杂合小鼠中，雌激素过度刺激，子宫腔上皮细胞持续增殖，宫腔内液体吸收增加，生育率降低 [16]。

SHP2 (Src homology 2 domain containing protein tyrosine phosphatase) 是蛋白酪氨酸磷酸酶家族中的一员，可通过 SH2 结构域与 ERα 相互作用来促进 ERα 的转录活性。在植入期小鼠子宫中，SHP2 高表达于子宫腔上皮和上皮下基质细胞中，子宫特异性敲除 SHP2 后，可阻断雌激素信号，诱使子宫腔上皮分支及微绒毛数量增多，上皮和基质细胞增殖异常，宫腔闭合受阻，进而导致胚胎植入失败 [17]。

2 孕酮

孕酮对于妊娠的建立和维持至关重要，在胚胎植入期，血清孕酮水平升高，可促使增殖的子宫内膜转化为分泌期，补充孕酮可改善女性的子宫内膜容受性，提高黄体功能不全患者的妊娠率，而孕酮的这一生理效应依赖于孕酮受体 (progesterone receptor, PR)[18]。PR 可分为 PRA 和 PRB，将 PRB 敲除后，雌性小鼠可正常生育，而缺失 PRA 可因胚胎植入失败而导致雌性小鼠不孕；添加 PR 拮抗剂 RU486 后，因抑制人子宫内膜容受性而导致植入失败 [5, 19, 20]。

CYP11A1 (cytochrome P450 family 11 subfamily A member 1) 是孕酮合成的一个关键酶，敲除 CYP11A1 后，小鼠因类固醇激素合成障碍而在出生后死亡，而在转基因过表达 CYP11A1 小鼠中，胚胎发育正常，但由于胚胎植入受损，妊娠率和产仔数显著减少，其原因是过表达 CYP11A1 可延迟卵巢颗粒细胞分化为黄体细胞，孕酮合成关键酶 StAR (steroidogenic acute regulatory protein) 和 HSD3B1 (hydroxy-δ-5-steroid dehydrogenase, 3β- and steroid δ-isomerase 1) 表达减少，胆固醇利用率减弱，最终导致孕酮水平显著下降；补充孕酮可恢复胚胎植入缺陷 [21]。

FKBP52 (immunophilin FK506-binding protein 52)

为类固醇激素核受体辅助伴侣蛋白，在调节 PR 活性中起重要作用。FKBP52 缺失小鼠子宫接受态异常、PR 转录活性降低，从而导致胚胎植入失败，补充孕酮可缓解这一缺陷 [22, 23]。进一步研究显示，MAGE-A11 (melanoma antigen-A11) 可与 PRB 相互作用来稳定 PRB/FKBP5 复合物 [24]。与此同时，在 FKBP52 缺失小鼠子宫中，抗氧化蛋白 PRDX6 (peroxiredoxin-6) 表达显著减少；在百草枯诱导的氧化损伤模型中，孕酮并不能拯救因 FKBP52 缺失而导致的胚胎植入失败，而补充抗氧化剂可缓解这一缺陷 [25]，提示 FKBP52 涉及氧化应激介导的胚胎植入损伤。

SRC2 是 PR 另一经典共激活分子，可与 PR 相互作用并影响其功能，缺失 SRC2 使胎盘发育不良而导致胎儿生长迟缓，子宫特异性敲除 SRC2 使孕酮功能缺陷而导致植入失败 [26]。Klf9 (Kruppel-like factor 9) 也是 PR 的共激活因子，在子宫上皮细胞中可与 PR 相互作用并增强其转录活性。敲除 Klf9 后，因 Klf13 的补偿作用而使得胚胎植入位点数减少，子宫内膜细胞增殖功能及 PR 靶基因表达紊乱 [27–30]。Xin 等进一步研究发现，BMI1 (B cell-specific Mo-MLV integration site 1) 可通过 E3 泛素连接酶 E6AP 对 PR 进行泛素化修饰并影响其转录活性，缺失 BMI1 可阻断子宫对孕酮信号的应答，PR 转录活性减弱，子宫上皮功能紊乱，从而导致胚胎植入失败、雌性小鼠不孕；补充孕酮可改善胚胎植入率，恢复 PR 的泛素化 [31]。

雌激素可刺激上皮细胞的增殖，而孕酮可拮抗雌激素效应并促进其向接受态分化，为胚胎和上皮的黏附反应做好准备。缺失 PRA 可使孕酮拮抗雌激素诱导的上皮细胞增殖效应失败，导致子宫腔上皮增生。进一步研究显示，转录因子 Hand2 (heart and neural crest derivatives expressed 2) 是 PR 下游靶基因，通过 FGF/FGFR-ERK 通路调控 ERα 进而抑制上皮细胞的增殖 (图 1)，子宫特异性敲除 Hand2 可致上皮增殖过度，进而导致胚胎植入失败 [32]。

3 白血病抑制因子(leukemia inhibitory factor, LIF)

LIF 是一个具有多种生物学功能的细胞因子，

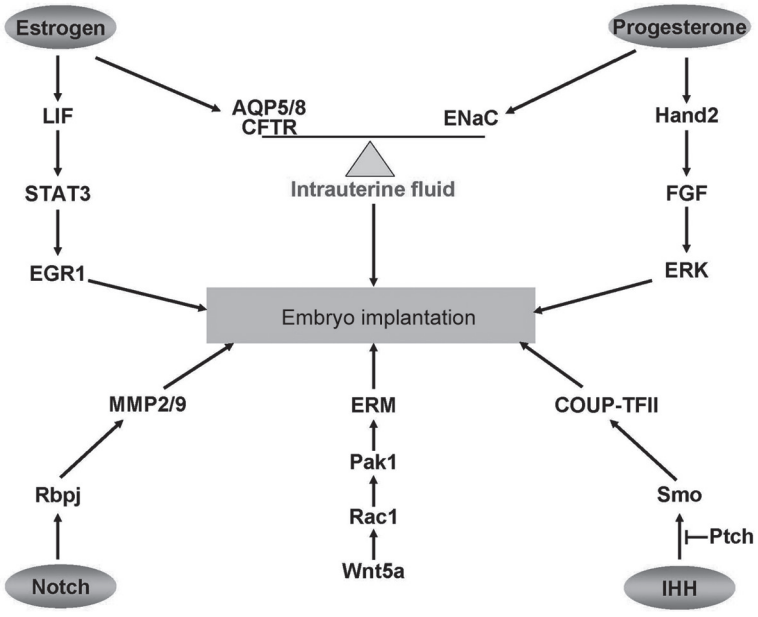

图 1. 胚胎植入的分子调控网路

Fig. 1. Molecular regulatory network of embryo implantation. Schematic diagram unravels the linear pathways involving estrogen, progesterone, Notch, Wnt5a and IHH signaling in embryo implantation, respectively. LIF, leukemia inhibitory factor; STAT3, signal transducer and activator of transcription 3; EGR1, early growth response 1; AQP, aquaporin; CFTR, cystic fibrosis transmembrane conductance regulator; ENaC, epithelial Na^+ channel; Hand2, heart and neural crest derivatives expressed 2; FGF, fibroblast growth factor; IHH, Indian hedgehog; COUP-TFII, chicken ovalbumin upstream promoter transcription factor II; Rac1, Ras-related C3 botulinum toxin substrate 1; Pak1, P21 activated kinase 1; ERM, Ezrin-Moesin-Radixin; Rbpj, recombination signal binding protein for immunoglobulin κ J region; MMP, matrix metalloproteinase; Smo, smoothened; Ptch: Patched.

高表达于小鼠接受期子宫腺上皮；在人月经周期中，LIF 表达于分泌中期子宫内膜腔上皮和腺上皮，而在不明原因不孕和反复性植入失败妇女中，LIF 表达显著降低 [5, 33]。注射 LIF 抗体可减少小鼠胚胎植入位点数，而在恒河猴植入前期注射 LIF 抗体则会导致妊娠率降低；将 LIF 敲除后，小鼠胚胎发育正常但不能植入子宫，将其移植到野生型小鼠子宫中，胚胎植入正常启动，但将野生型小鼠囊胚移植到 LIF 缺失子宫，胚胎植入失败，提示 LIF 主要影响子宫接受态 [4, 5]。在糖尿病小鼠模型中，子宫吞饮泡成熟受阻，Th1 型细胞因子干扰素 γ (interferon-γ, IFNγ) 分泌显著增加，LIF 表达减弱，胚胎植入率和妊娠率显著减少，补充 LIF 重组蛋白可改善胚胎植入率 [9, 34]。进一步研究显示，LIF 可通过整合素 β3 和 β5 来调节胚胎上皮黏附反应 [35]。

雌激素作用于子宫腺上皮 ER 后可促腺体中 LIF 分泌增加，与腔上皮细胞膜上的受体 LIFR 和 Gp130 结合后，激活胞内 JAK 酶并磷酸化下游 STAT3 (signal transducer and activator of transcription 3) 蛋白，通过与核内靶基因位点结合而完成其生物学效应 [4, 5](图 1)。LIFR 主要表达于妊娠第 4 天 (接受期) 小鼠子宫腔上皮，而 Gp130 则定位于子宫腺上皮细胞中。敲除 Gp30 可致造血和心脏功能异常，进而导致胚胎致死，而缺失 STAT3 会引起胚胎降解，导致其在植入后死亡 [36, 37]。子宫特异性敲除 Gp130 或 STAT3 后，血管通透性减弱，子宫对雌激素的应答增强，上皮基质反应及上皮细胞分化受损，胚胎植入失败 [38]。条件性敲除 LIFR 可抑制 STAT3 磷酸化，补充 LIF 可缓解这一效应 [39]；子宫腔上皮敲除 STAT3 可致上皮细胞极性及其完整性改变，进而导致胚胎不能黏附于子宫腔上皮 [40]。进一步研究显示，EGR1 启动子区域存在 STAT3 结合位点，可作为雌激素 -LIF-STAT3 的下游靶基因来调控环加氧酶 2 (cyclooxygenase-2, Cox-2)、血管内皮生长因子 (vascular endothelial growth factor, VEGF)，进而影响植入位点的血管通透性 [12, 13]。

4 通道蛋白

子宫腔液在胚胎植入前期可作为一个介质将胚泡运送到子宫中，而在接受期因被吸收而减少，这将有助于子宫腔闭合和胚泡在子宫腔中的定位，使子宫腔上皮与胚泡紧密接触。在小鼠和大鼠中，雌激素可刺激液体的分泌，而孕酮则诱导黏附前液体的吸收 [41]。妊娠第 4 天小鼠皮下注射雌激素或宫腔内注射生理盐水后，宫腔液增多而导致胚胎植入位点数减少、妊娠率降低 [42, 43]。

水通道 (aquaporin, AQP) 是位于细胞膜上的一种与水转运有关的跨膜蛋白，在雌激素诱导的宫腔液增多模型中，子宫中 AQP5 和 AQP8 表达增强，孕酮可拮抗此效应，缺失 AQP5、AQP8 或 AQP5/8 可导致宫腔液显著减少，胚胎植入异常得到明显缓解 [43]。同时，CFTR (cystic fibrosis transmembrane conductance regulator) 和 ENaC (epithelial Na^+ channel) 可相互作用来调控子宫腔液的分泌与吸收 (图 1)。CFTR 是一个 cAMP 激活的氯离子通道，主要定位在子宫基质细胞中，雌激素可诱导 CFTR 表达，导致液体在子宫腔积累 [41]。在小鼠中，炎症引起的 CFTR 上调可导致异常的宫腔液积累及植入失败 [41]。ENaC 主要定位于子宫腔上皮和腺上皮的顶部，孕酮可刺激 ENaC 表达，引起离子浓度改变形成渗透压力梯度，进而促进水分子的重吸收。在体外受精 (*in vitro* fertilization, IVF) 处理前，反复植入失败妇女子宫中 ENaC 表达明显降低 [44]。将子宫中 ENaC 敲低后，胚胎植入失败 [44]。进一步研究显示，激活 ENaC 可促使钠离子内流，引起上皮细胞膜去极化、钙通道激活、胞内钙离子浓度升高、转录因子 CREB 磷酸化，导致 Cox-2 表达上调，释放上皮中 PGE_2，并激活胚胎植入相关因子过氧化物酶体增殖物激活受体 δ (peroxisome proliferators-activating receptor δ, PPARδ) 和 RXR (retinoid X receptor)[41, 44]。

SGK1 (serum- and gulcocoticoid-induced protein kinase 1) 是一种丝氨酸 / 苏氨酸蛋白激酶，可通过抑制泛素连接酶 NEDD4-2 来促进 ENaC 表达，进而调节上皮钠离子的转运。SGK1 在接受期子宫腔上皮中表达较低，而在不孕妇女子宫中表达增强。在子宫腔上皮中持续激活 SGK1，因子宫腔液吸收紊乱而导致胚胎植入失败；敲除 SGK1 并不影响胚胎植入，但会导致蜕膜 - 胎盘界面出血、胎儿生长受限及死亡等 [45]。

5 miRNA

miRNA 为 21~24 个核苷酸的非编码 RNA，可通过抑制翻译或降解 mRNA 来调控下游靶基因的表达。在接受期子宫中，miR-101a 和 miR-199a* 高表达，可在转录后水平调控 Cox-2 的表达，影响前列腺素的产生，避免过度的炎症反应 [46]。与非植入

位点相比，小鼠子宫植入位点 13 个 miRNA 表达上调，2 个 miRNA 下调，其中 miR-21 可通过 Reck 来调控基质金属蛋白酶 2/9 (matrix metalloproteinases 2/9, MMP2/9) 的表达，促进细胞外基质的降解进而影响胚胎植入 [47]；在子宫内膜异位症女性子宫中，miR-21 表达紊乱 [48]。miR-181a/b 转基因过表达小鼠胚胎发育正常，但子宫接受态异常，导致着床位点减少，补充 LIF 重组蛋白可缓解这一缺陷 [49]。miR-145 在反复性植入失败妇女子宫中高表达，可通过抑制 IGFR 来阻碍胚胎黏附于子宫腔上皮；miR-200a 可降低 PR 转录活性，上调酮代谢酶 200α-HSD 的表达进而阻止胚胎植入；let-7a、miR-30d、miR-181、miR-125b、miR-451、miR-429、miR-661、miR-223-3p 等 miRNA 均在胚胎植入过程中起重要作用 [50–52]。

对比休眠期，活化期胚泡 45 个 miRNA 表达紊乱，其中 let-7 家族中 5 个 miRNA 在活化胚泡中表达下调，let-7a 在植入前胚胎中低表达，将 let-7a 前体 RNA 导入 8 细胞胚胎中，胚泡黏附反应减弱，胚胎植入率降低，补充整合素 β3 重组蛋白可缓解这一效应 [52]。miR-29b 可通过 DNMT3a/b 改变 DNA 甲基化水平进而阻止早期胚胎发育至囊胚，而 miR-34c 和 miR-135A 则可抑制受精卵卵裂 [51–53]。

Dicer 是 miRNA 形成过程中的一个关键酶，将 Dicer 敲除后，胚泡和子宫中 miRNA 表达紊乱，胚胎发育停滞在 D7.5 [54, 55]。利用 AMHR2 (anti-Mullerian hormone type 2 receptor)-Cre 系统构建的条件性 Dicer 敲除小鼠卵巢中闭锁卵泡增多，排卵和早期胚胎发育异常，输卵管系膜囊肿，导致胚胎不能通过输卵管进入子宫中，将野生型胚胎移植到萎缩的 Dicer 缺失子宫中，胚胎植入无法正常启动 [56–58]。利用 PR-Cre 将 Dicer 在小鼠子宫中敲除后，血清激素水平正常，子宫萎缩，腺上皮缺失，子宫基质细胞大量凋亡，IHH 和经典 Wnt 信号通路失调 [55]。

6 Wnt信号通路

β-catenin 是经典 Wnt 信号通路中的下游效应分子，表达于植入前胚胎中，抑制 β-catenin 信号后，胚胎可正常发育到囊胚，但因胚泡活化受损而使胚胎植入失败 [59, 60]。条件性敲除 β-catenin 后，子宫内膜上皮和基质细胞增殖异常，腺体发育延缓，上皮间质转化受损，形成子宫内膜基质肉瘤，因输卵管发育不全使胚胎停滞于输卵管进而导致雌性小鼠不孕 [61]；将野生型小鼠胚胎移植到 β-catenin 缺失小鼠子宫中，胚胎植入位点数显著减少 [62]。

Wnt5a 是非经典 Wnt 通路中的一个配体，可通过 Ror1/2 来调节细胞的定向运动及极性 [63]。子宫中缺失 Wnt5 后，上皮细胞极性及绒毛样突起形成受阻、着床小室和胚胎均匀分布发生紊乱，胚胎植入位点数减少，流产率增加 [64]。Rac1 (Ras-related C3 botulinum toxin substrate 1) 是 Wnt5a 信号的下游靶基因，在接受期小鼠子宫内皮上皮和基质细胞中高表达，条件性敲除 Rac1 可致子宫腔上皮极性及完整性改变，进而导致子宫接受态和胚胎植入异常。进一步研究显示，Rac1 可通过 Pak1-ERM (Ezrin-Moesin-Radixin) 通路来调节子宫腔上皮的完整性，激活 P38 MAPK 信号来确保着床小室处上皮细胞的凋亡 [65](图 1)。

Wnt4 和 Wnt7a 在胚胎植入过程中也起重要作用。将 Wnt4 在子宫中敲除后，腺体数目减少，柱状腔上皮下出现 P63 阳性的基底细胞层，上皮细胞分化异常，雌激素处理可使其分化成扁平上皮；胚泡可正常黏附于子宫腔上皮，但因侵入子宫基质能力受损而导致胚胎植入失败 [66]。敲除 Wnt7a 因子宫和输卵管发育异常而导致雌性小鼠不孕，而条件性敲除 Wnt7a 后，子宫腺体缺失，胚胎植入失败 [67]。在 Wnt7a 缺失小鼠子宫中，Msx1 表达显著减少；将子宫中 Msx1 缺失后，上皮基质反应受损，血管通透性减弱，植入位点数减少，流产率增加，产仔数减少。进一步研究显示，Msx2 可在一定程度上补偿 Msx1 的作用，缺失 Msx1/2 可导致胚胎植入完全失败 [68]。

7 Notch信号通路

Notch 是一种进化上高度保守的跨膜受体蛋白，由胞外区、跨膜区和胞内区三部分所组成。当配体与相邻细胞表面的 Notch 受体结合后就会导致其胞外区酶解，随后 γ- 分泌酶复合物在跨膜区靠近胞膜内的位点进行切割，使其胞内区 (Notch intracellular domain, NICD) 释放入胞质，并进一步转移至细胞核，与转录调节因子 Rbpj (recombination signal binding protein for immunoglobulin κ J region) 和 MAML (mastermind like transcriptional coactivator) 形成转录激活复合物，通过与靶基因启动子区域中的 DNA 序列结合而调控下游靶基因的转录，进而影响细胞的增殖、分化及凋亡等生理过程 [69](图 1)。Notch1 定位

于子宫腺上皮和基质细胞中，在子宫内膜异位症妇女中，Notch1 表达减弱 [70, 71]。子宫特异性敲除 Notch1 后，子宫蜕膜化反应异常；而激活 Notch1 通路可致子宫接受态异常、腺体缺失和 PR 超甲基化，进而导致雌性小鼠不孕 [71, 72]。Notch2 主要表达于子宫蜕膜区，可调控子宫基质细胞的分化，在蜕膜化过程中起重要作用 [73]。

Rbpj 高表达于接受期子宫基质细胞中，而在习惯性流产女性子宫中表达减弱，条件性缺失 Rbpj，胚胎植入正常启动，但植入期子宫腔闭合受损、胚胎 - 子宫轴定向模式改变、子宫上皮和肌层再生能力出现缺陷、促炎细胞因子 IFNγ 分泌增加，导致妊娠中期胚胎吸收和流产。进一步研究显示，Rbpj 可与 ERα 结合，调节雌激素效应基因的表达进而促使子宫腔从分支样结构转变为狭缝状 [69, 71]。

MMP2 和 MMP9 是基质金属蛋白酶家族的成员，可参与细胞外基质的降解。在 Rbpj 缺失子宫中，MMP2 和 MMP9 表达显著减少，且 Rbpj 可与 MMP2 启动子区域结合，提示 MMP2/9 是 Rbpj 下游靶基因 [69]。MMP2 缺失小鼠可正常生育，而将 MMP9 敲除后可导致滋养层细胞的分化、侵入能力及胎盘成熟受损，胚胎发育和母 - 胎反应异常，宫内胎儿生长迟缓，产仔数减少，并伴随有先兆子痫症状 [74, 75]。

8 IHH信号通路

Hedgehog 是一种高度保守的分泌性糖蛋白，可分为 IHH (Indian hedgehog)、SHH (Sonic Hedgehog) 和 DHH (Desert hedgehog)。IHH 表达于接受期子宫腔上皮和腺上皮，而 SHH 和 DHH 在子宫中未见表达 [76]。将 IHH 在子宫中敲除后，胚泡不能黏附于子宫腔上皮，胚胎植入失败导致小鼠不孕 [77, 78]。进一步研究显示，孕酮刺激上皮产生的 IHH 扩散进入基质中，与其细胞膜受体 Ptch (Patched) 结合后，可解除 Ptch 对 Smo (Smoothened) 的抑制作用，活化的 Smo 进一步激活锌指转录因子 Gli (Glioma-associated oncogene homolog)，随后 Gli 进入细胞核，通过与靶基因启动子序列的特异元件结合而调控下游靶基因的转录 (图 1)。条件性敲除 Smo 可延迟胚胎植入，使胚胎吸收增加 [79]；而持续激活 Smo 可使子宫直径变大，腺体数目减少而基质增多，因受精和蜕膜化缺陷而导致小鼠不孕 [80]。

COUP-TFII (chicken ovalbumin upstream promoter transcription factor II) 是 IHH 信号的下游靶基因，表达于子宫基质细胞中。利用 PR-Cre 小鼠将其在子宫中敲除后，胚胎植入失败，并伴随有上皮微绒毛重塑受损及雌激素活性增强。进一步研究显示，COUP-TFII 可通过上调 ERα 及其辅助激活因子 SRC1 来调控雌激素活性 [81]。

总之，胚胎植入是一个多因素精密调节的复杂生理过程，深入研究其分子机理对于子宫接受态标志物的识别、IVF 临床妊娠率的改善、不孕症的治疗以及开发安全有效的避孕药等具有重要意义。

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