小鼠子宫蜕膜化过程中细胞周期调控相关因子的研究进展

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摘要 多倍性细胞的产生作为小鼠子宫蜕膜化的标志之一, 其过程是受到细胞周期调控因子的严格调控的。目前对于细胞周期调控因子在蜕膜过程的研究已经很多, 但有一些分子机制尚不明确, 该文对近几年来小鼠子宫蜕膜化过程中细胞周期调控因子以及这些因子相互作用的研究做出综述, 以期对未来临床医学提供更多理论依据。

关键词 细胞周期蛋白; 细胞周期依赖性蛋白激酶; 细胞周期依赖性蛋白抑制剂; 蜕膜细胞; 核内复制周期

The Research Progress of Cell Cycle Regulators in Mouse Uterine Decidualization

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Abstract The formation of polyploidy cells, as one of the remarkable events in mouse decidua, is strictly regulated by the cell cycle regulators. At present, there are many researches about cell cycle regulators in deciduas, but the molecular mechanism is unclear. This paper reviewed the research progress about cell cycle regulators and interaction of these factors in mouse uterine decidualization. These results will provide more theoretical basis for clinical medicine in the future.

Key words cyclin; cyclin-dependent kinases; cyclin-dependent kinases inhibitor; decidual cells; endoreplication

胚胎着床是哺乳动物妊娠过程的关健步骤, 而子宫基质细胞蜕膜化对于着床的成功和胚胎的存活是必需的[1]。蜕膜过程中, 蜕膜细胞以间隙连接的方式传递信息, 并在雌激素和孕酮的作用下发生一系列形态、生化、脉管的变化, 从而维持蜕膜功能[2-3], 可以说子宫内膜蜕膜化是胚胎的生物传感器[4]。

在哺乳动物中, 多倍体化通常发生在某些特定的组织细胞中, 如胎盘、脊髓、心脏和肝脏等[5]。细胞通过有丝分裂细胞周期转变成为核内分裂周期, 即细胞停滞在G-S期, 连续进行DNA复制却没有胞质分裂, 导致多倍体的产生。因为多倍体细胞核内复制的特点改变了细胞核的空间构象, 减少了基因组的稳定性, 所以多倍体化能够增加遗传多样性, 还能够保护细胞不受基因毒性的损伤[6], 因此细胞多倍体的发生必然有其独特的生理意义。在小鼠围着床期, 多倍体化是基质细胞蜕膜化的一个重要标志[7],

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当基质细胞的多倍性减少时, 蜕膜化过程就会受到抑制。多倍体细胞作为一种末端分化细胞, 其意义在于通过不断增加基因拷贝数转录来确保高水平的蛋白合成, 支持胚胎发育和调控。同时, 多倍体化能够限制蜕膜细胞的寿命, 以便蜕膜细胞及时退化利于胚胎的后续发育和胎盘形成[8]。这个过程涉及核分裂周期、线粒体活性、代谢系统、ATP结合等调控。多倍体细胞的高速生长、发育和信号调节, 很多方面类似于癌细胞, 但是多倍体细胞中线粒体活性很高, 而癌细胞缺乏线粒体活性[9]。因此, 对基质细胞多倍性机制的研究可能为癌细胞的研究提供参考。

目前, 对于蜕膜化的分子机制及其细胞周期调控了解得还很少。不过已有的研究表明, 子宫内膜基质细胞分化成多倍体细胞在启动蜕膜化的过程中起重要作用。特别是近几年来, 通过基因型小鼠模型的应用、定量PCR、基因芯片、生物信息学等一系列现代生物学研究技术的应用, 蜕膜过程中细胞周期调控因子的作用机制也取得了一些研究进展[10-11]。本文将对这方面的研究进展进行综述。

1 核内复制作用机制及细胞周期调控因子的相互作用

真核细胞的细胞周期受细胞周期蛋白(Cyclin)、细胞周期依赖激酶(cyclin-dependent kinases, CDK)和细胞周期依赖激酶抑制剂(cyclin-dependent kinase inhibitors, CKI)的严格调控[8]。Cyclins、CDKs和CKIs在哺乳动物新陈代谢、精子发生、子宫蜕膜化、干细胞再生等过程中都是必不可少的[12]。多倍体细胞特殊的核内复制方式使细胞周期不断重复G_1期和S期, 因此, G_1-S期的细胞周期调控因子就成为了研究多倍体细胞模型的重点。CyclinD在G_1期积累, 并与CDK4、CDK6结合激活其蛋白激酶活性, 使CyclinD/CDK的下游蛋白成视网膜细胞瘤蛋白(retinoblastoma protein, Rb)磷酸化, 导致转录激活因子E2F解阻遏, 促使一些与DNA复制有关的基因表达来启动DNA复制, 从而利于细胞进入S期。随后, CyclinE/CDK2结合, 使Rb由低磷酸化状态变为高磷酸化状态并且直接参与中心体复制的起始调控, 促进DNA复制, 完成G_1-S期的转化[13-14](图1)。多倍体细胞重复性进行这种调控需要Cyclin/CDK复合物保持周期性震荡的活性和负调控因子的抑制作用。因此, 这些正负细胞周期调控因子之间的平衡是核内复制周期的关键, 也是蜕膜细胞区别于癌细胞的关键。

2 Cyclin在核内复制周期和子宫内膜蜕膜化中的作用

CyclinD3在G_1期聚集, 对于G_0-G_1期的转换是必需的, 其本身不呈周期性表达, 只要生长因子持续刺激细胞就可以合成[8,15], 但在核内复制周期中呈周期性波动。在哺乳动物中, CyclinD3是子宫内膜细胞增殖和蜕膜多倍体化过程的关键因子[16-17]。目前, CyclinD3的水平已经成为体外诱导基质细胞蜕膜化是否成功的一个度量标准。在胚胎着床的过

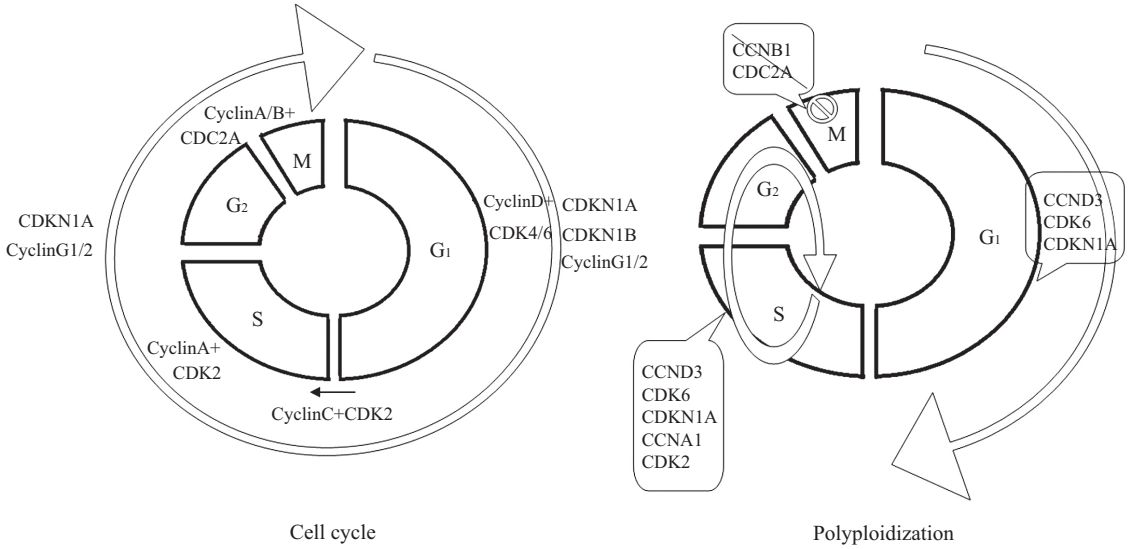

图1 细胞周期调节因子在细胞周期进程中的作用模式图(根据参考文献[8])

Fig.1 A model for role of cell cycle regulators in cell cycle (modified from reference [8])

程中, *CyclinD3* mRNA在小鼠围着床期表达水平随子宫内膜蜕膜化进程逐渐上调, 具有时空和细胞特异性[18]。CyclinD3$^{-/-}$小鼠可导致蜕膜多倍体化障碍, 使着床点处蜕膜结构受损, 胚胎着床数量明显减少, 但不能完全抑制着床的发生, 其具体机制研究尚不完全, 可能是因为CyclinD3的功能与CyclinD1和CyclinD2的功能存在冗余性[19-20]。在利用CyclinD3过表达代替Hoxa10$^{-/-}$小鼠模型中, 小鼠可正常着床并且形成胎盘, 直到妊娠D10时会出现流产现象。可见, CyclinD3能够促进小鼠围着床期子宫蜕膜细胞增殖, 是子宫蜕膜细胞多倍体化的主要调节者, 在小鼠子宫蜕膜化过程中CyclinD3能够补偿Hoxa10的作用[16], 但对于妊娠后期的维持作用还有待进一步研究。

CyclinE在G_1期合成, 但比CyclinD3稍晚[21], 对G_1-S期转换和细胞周期的再进入是必需的。有人认为在核内复制周期中, CyclinE完成Rb的磷酸化是依靠CyclinD/CDK复合物作用来启动的[22]。CyclinE是子宫内膜细胞增殖的调节因子。*CyclinE* mRNA在妊娠D5的小鼠子宫中表达水平达到峰值, 随后逐渐下降。子宫角注射抗CyclinE单克隆抗体干扰CyclinE, 小鼠的胚泡着床受到明显抑制, 但不能完全抑制着床。可见, CyclinE能促进着床窗口期子宫内膜细胞增殖, 在胚胎着床过程中起作用, 但并不是唯一的决定因素[23]。另外CyclinE缺失的细胞对于癌变的敏感性大大降低, 具有一定的抗癌性, 这也为癌症的预防和治疗提供新的思路和启示[22]。目前对于CyclinE在小鼠子宫内膜蜕膜化和多倍体化过程中的作用机制和信号通路还不够完善, 有待进一步研究。

CyclinG是细胞周期调控因子中的负调控因子, 目前为止, 已被确定的有CyclinG1和CyclinG2两个亚型。CyclinG1表达贯穿整个细胞周期, 对G_2-M期停滞起关键作用[24]; CyclinG2在细胞周期中波动性表达, 与G_1-S期的停滞有关[25]。*CyclinG1*和*CyclinG2* mRNA在小鼠围着床期子宫内膜中的表达具有时空差异性, *CyclinG1* mRNA主要在妊娠D3-7的上皮细胞和SDZ中表达, 受孕酮的调控。而*CyclinG2* mRNA主要表达于D1-8的上皮细胞和PDZ中[26], 且不受孕酮调控。在小鼠子宫内膜蜕膜化过程中, CyclinG1主要是限制子宫基质细胞增殖, 而CyclinG2主要促进蜕膜细胞的终端分化和凋亡, 为胚胎生长提供空间。此外, Hoxa10$^{-/-}$的小鼠子宫中这些基因的表达是异常上调的, 表明*CyclinG1*和*CyclinG2*基因作为Hoxa10的下游靶基因对子宫细胞增殖产生负调控, 但Hoxa10$^{-/-}$对CyclinG的异常上调是否有直接的影响还有待进一步研究[26]。总之, 正、负细胞调控因子各司其职, 却又相互协作, 共同完成子宫内膜细胞在着床及蜕膜过程的特异性增殖、分化、凋亡过程。

3 CDK在核内复制和子宫基质细胞蜕膜化中的作用

CDK在整个细胞周期中的含量是平稳的, 在不同的细胞周期中, 只有CDK磷酸化特定Cyclin上的丝氨酸和苏氨酸残基, 使Cyclin变构后才会具有活性。有活性的Cyclin/CDK复合物才能启动或调控细胞周期的主要事件[27]。

CDK4、CDK6在G_1期被CyclinD3激活, 促进细胞进入S期[28]。S期的细胞数增加, 意味着子宫基质细胞增殖水平升高。*CDK4*、*CDK6*和*CyclinD3* mRNA的表达水平与基质细胞蜕膜化情况在时空上存在很大程度的重叠, 但在妊娠D8时, *CDK4* mRNA只在植入对侧表达, 而*CDK6* mRNA只在植入侧表达。CyclinD3/CDK4能够促进子宫基质细胞增殖, 随着CDK4表达水平的下调, CDK6上调, 进而促使基质细胞转向分化和多倍体化[29]。随着很多细胞周期调控因子敲除的小鼠模型的建立, 一些基因间代偿机制在近几年也被发现, CDK1能够单独驱动细胞周期。CDK2和CDK3参与调控G_1-S期的转变[30-31], 但CDK3对正常的小鼠发育是非必要的。另外, CDK2对于细胞有丝分裂并不是必需的, CDK4和CDK1能够代替CDK2执行其功能[27,32], 但因多倍体细胞特殊的核内复制方式, 所以CDK家族在核内复制的代偿机制还有待研究。

4 CKI在核内复制和子宫基质细胞蜕膜化中的作用

CKI是CDK的负调控因子, 一般来说, CDK的活性受到至少两种CKI的抑制, 分别是CDKN1A和CDKN2A, 其中CDKN1A对于CDK的抑制具有广泛的特异性, 如p21、p57、p27, 而CDKN2A特异地抑制CyclinD/CDK4和CDK6催化反应, 如p16、p18[8]。CKI通过N端的结构域与Cyclin对CDK竞争性结合, 拮抗Cyclin作用, 来调节细胞周期进程。此外, p21

的C端能与增殖细胞核抗原(proliferating cell nuclear antigen, PCNA)相互作用, 阻断PCNA活化DNA聚合酶的活性, 可以直接抑制DNA合成, 这是其他抑制剂不具备的特点。近些年来对于CKI的研究越来越受到重视, 越来越多的证据显示, CKI与DNA损伤修复、子宫内恶性肿瘤、癌症、细胞衰老凋亡、造血等病症有关[33-34]。

p21和p57都可以使细胞周期停滞在G_1期, 抑制细胞在G_1-S期的转变, 从而抑制DNA的合成。在小鼠子宫蜕膜化和多倍体化过程中, p21与p57虽然功能相似, 但上游调控基因却不同, 二者协同作用抑制Cyclin/CDK4, 使细胞脱离细胞周期[35]。小鼠妊娠D1-4, *p21* mRNA在子宫内未见表达, 着床后其表达水平随蜕膜细胞脱离细胞周期过程而上调, 直到妊娠D8, 随着*CyclinD3*/*CDK4* mRNA在植入侧的PDZ表达停止, *p21* mRNA在此区域表达上调, 说明p21通过抑制CyclinD3/CDK4活性使细胞周期停滞在G_1期, 从而抑制蜕膜细胞增殖, 使细胞转向分化[26]。*p57* mRNA的表达在时空上与蜕膜细胞脱离细胞周期一致, 并且p57在蜕膜过程中的上调是因为失去了Hoxa10的抑制作用[35]。p27是在CKI家族中与p57同源性最多的成员, 在睾丸、子宫、阴道等器官中, p27能够修复$p57^{-/-}$小鼠的发育缺陷[36-37]。总之, p21、p57和p27与Cyclin/CDK共同作用, 精准地调控核内复制周期, 使子宫内膜细胞的蜕膜化和多倍体化顺利进行。

目前, 临床上对于CKI的研究也越来越多, 细胞周期的抑制与胚胎发育异常、细胞的衰老和凋亡以及子宫内膜无法自发蜕膜等都有关系。研究发现, p57表达水平在分泌期上调, 对人子宫内膜蜕膜细胞分化和恶性细胞的生长抑制具有重要作用[38], 这为该疾病的治疗提供更多的线索。另外, 在糖尿病患者的胎盘上PCNA、CyclinD3的表达水平极显著提高, 而p27、p57的表达水平降低, 因此推测糖尿病患

表1 细胞周期调节因子在小鼠子宫蜕膜化中的表达情况和功能

Table 1 Expression and function of the cell cycle regulators in mice uterine decidization

	在小鼠蜕膜区的表达特点 Expression characteristics in decidual area	在小鼠子宫蜕膜化中的功能 Function in the mice uterine decidua	在细胞周期中的作用 Function in cell cycle
CyclinD3	The expression level increased with endometrial decidual process gradually, with the specificity of space-time and cell.	CyclinD3 can promote uterine stromal cell proliferation during perimplantation period that is the main regulator of uterine decidual cells polyploidization.	CyclinD3 is required for G_0-G_1 transition.
CyclinE	Expression of *CyclinE* mRNA reached a peak in pregnancy D5, then decreased with the process of decidualization.	CyclinE can promote uterine stromal cell proliferation during window period of uterus, and play a role in embryo implantation process, but it is not the only determining factor.	CyclinE is required for G_1-S transition and cell cycle reenter.
CyclinG	CyclinG1 mainly expressed in SDZ, while CyclinG2 mainly expressed in PDZ.	CyclinG1 can inhibit uterine stromal cell proliferation, while CyclinG2 can promote decidual cell differentiation and apoptosis.	CyclinG1 is associated with G_2-M stagnation, while cyclinG2 is associated with G_1-S stagnation.
CDK4	There is a disparate and overlapping expression of CDK4 and Cyclin D3 at the site of implantation, and CDK4 can only be expressed in the mesometrial pole when pregnancy D8.	CDK4 can promote uterine stromal cell proliferation.	CDK4 can promote the cell to enter S phase.
CDK6	There is a disparate and overlapping expression of CDK6 and Cyclin D3 at the site of implantation, and CDK6 can only be expressed in the antimesometrial pole when pregnancy D8.	CDK6 can promote decidual cell differentiation and polyploidization.	CDK6 can promote cell to enter S phase.
p21	p21 expression level was up-regulated with decidual cells out of the cell cycle, and the expression of *p21* mRNA with concomitant down-regulation of CyclinD3 /CDK4.	p21 can inhibit uterine stromal cell proliferation and promote its differentiation and apoptosis.	p21 can inhibit cell G_1-S transition.
p57	p57 expression level was up-regulated with decidual cells out of the cell cycle, and the reason may be down-regulation of HOXA10.	p57 can inhibit uterine stromal cell proliferation and promote its differentiation and apoptosis.	p57 can inhibit cell G_1-S transition.

者胎盘异常情况可能与细胞增殖和细胞周期停滞机制有关[39-40]。利用CKIs(p21, p27)的抑制作用使癌细胞衰老凋亡的思路, 为今后治疗癌症疾病提供可行依据[34]。但对于利用CKI作为抗肿瘤和癌症的药品还需要更多的理论支持。

表1介绍了上述细胞周期调节因子在小鼠围着床期子宫中的表达情况和功能。

5 Hoxa10和HBEGF与细胞调控因子

Hoxa10是转录因子同源框基因(homeobox, HOX)家族的一个成员, 通过和DNA结合来激活或抑制目的基因, 对于决定细胞的定向分化与增殖非常重要。母体*Hoxa10*基因的正常表达对胚胎着床、胚胎发育和维持妊娠是必需的。Hoxa10能够调控Cyclin/CDK和CKI, 并在蜕膜多倍性过程中相互作用, 使基质细胞增殖和分化为最佳状态的蜕膜细胞。若这种调控出现偏差, 就会使蜕膜反应缺陷。肝素结合性表皮生长因子(heparin-binding EGF-like growth factor, HBEGF)是表皮生长因子(epidermal growth factor, EGF)家族的一员, 是蜕膜细胞多倍性过程的调节者之一, 也是胚胎信号最早的“指示器”[41]。HBEGF可以增加基质细胞的DNA合成量和双核细胞的数量, 但细胞却不发生分裂, 而细胞的双核化能够作为小鼠子宫基质细胞中多倍性发生的标志。HBEGF的这种作用是通过对CyclinD3的上调来介导的, CyclinD3的缺失可导致HBEGF对基质细胞

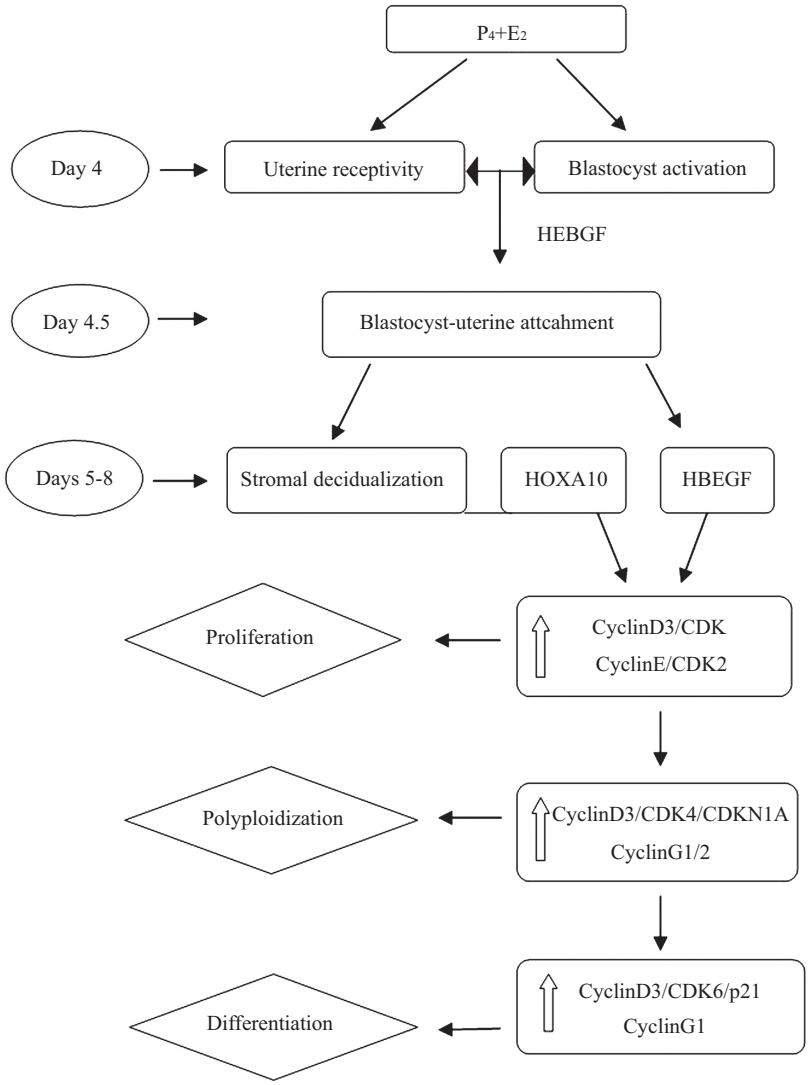

图2 HBEGF、Hoxa10、CyclinD3、CyclinE和CyclinGs在胚胎着床不同时期作用模式图(根据参考文献[8]修改)

Fig.2 The scheme depicting potential roles of HBEGF, Hoxa10, CyclinD3, CyclinE and CyclinGs at various stages of implantation (modified from reference [8])

多倍性的诱导作用受阻[8]。此外, HBGEF可能有助于子宫内膜基质细胞在着床部位的定向调整和非定向迁移[42]。总之, *Hoxa10*和*HBGEF*作为这些细胞周期调控因子的上游基因, 对细胞周期调控的重要性是显而易见的。目前对于Hoxa10和HBGEF的研究已经很多, 但对于真正的临床应用还需要更多的理论依据支持。

图2是Hoxa10、HBEGF、CyclinE、CyclinD3、CyclinG1和CyclinG2在不同阶段的相互关系示意图。图中, Hoxa10和HBEGF是两条相对独立并且平行的信号通路, 能够调控其下游的CyclinD、CyclinE、CyclinG, 使这些正负调控因子达到一种平衡, 从而完成子宫内膜细胞的增殖、分化和多倍体化。

6 结语

目前, 对哺乳动物蜕膜和多倍体化的研究在生理学、遗传学、生态学等多方面展开, 随着研究的深入, 细胞发生多倍体化的生理功能越来越受到重视。细胞的多倍性在肝脏细胞、心肌细胞、巨核细胞和滋养层巨细胞等都有其特殊的意义, 但对蜕膜细胞多倍体化的生理功能和意义研究较少。最近研究表明, 多倍体化可能与动物性别决定基因有关[43]。子宫蜕膜细胞多倍体化是非常复杂的过程, 需要G_1-S期相关的Cyclin/CDK改变正常作用模式, 使得自身活性周期性发生波动, 从而使细胞周期不断重复完成G_1-S期, 而G_2-M期相关的Cyclin/CDK受到阻滞, 并且在负调控因子的作用下, 促进子宫蜕膜细胞分化和诱导其凋亡。CKI调控细胞周期停滞, 使细胞转向分化和多倍体化。这种正、负调节因子的协调作用正是蜕膜细胞多倍体化的关键。细胞周期调控因子在蜕膜和多倍体化过程中的研究已有一定的进展, 但仍有很多的分子机制和信号通路尚不完全清楚, 其上下游的调控也有待研究。

女性随着月经周期子宫内膜循环更新, 自发蜕膜反应是生殖成功必不可少的一步。干预细胞周期调控, 可能为反复性流产、反复植入失败以及移植后早期流产、胎盘异常等症状提供新的解释和理论依据。蜕膜细胞的多倍性的研究可能有助于肿瘤或癌症的预防和治疗, 特别是细胞周期抑制因子调控细胞分化和凋亡的研究近几年一直被广泛关注。今后干预细胞周期调控因子的药物可能在生殖、产科领域得到广泛应用。

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