综述

孕酮信号与子宫内膜功能

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摘要 孕酮是女性体内重要的类固醇激素, 在调控子宫内膜功能以及维持妊娠和生殖健康中发挥着关键作用。孕酮受体包括响应较慢的经典受体和响应较快的非经典受体, 这些受体存在多种功能各异的异构体。该综述详细讨论了经典和非经典孕酮受体的分子特性及其作用机制, 总结了这些机制如何影响子宫内膜容受态建立、调控子宫功能及影响胚胎着床过程。此外, 该文还讨论了孕酮信号响应异常所导致的内膜功能障碍, 如子宫内膜异位症的发病机制和临床治疗策略, 为治疗相关生殖障碍提供了新见解。

关键词 孕酮受体; 子宫内膜容受性; 子宫内膜异位症; 生殖健康

Progesterone Signaling and Endometrial Function

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Abstract Progesterone, a vital steroid hormone in women, plays an integral role in regulating endometrial functions and sustaining pregnancy and reproductive health. Its receptors are categorized into two types: classical receptors, which respond slowly, and non-classical receptors, known for their rapid response. Each type possesses distinct functional isoforms. This review delved into the molecular properties and action mechanisms of the both receptor types, elucidating how they modulated endometrial receptivity, uterine function, and embryo implantation. Moreover, this review also discussed endometrial dysfunctions caused by aberrant progesterone signaling responses, such as endometriosis, including its pathogenesis and clinical treatment strategies, and provided new insights into the treatment of related reproductive disorders.

Keywords progesterone receptors; endometrial receptivity; endometriosis; reproductive health

1 孕酮受体及其作用机制

孕酮(progesterone, P4)是一种由胎盘、卵巢和肾上腺合成的类固醇激素, 参与调控女性月经周期以及妊娠建立和维持过程中的一系列关键事件(如排卵、受精、着床、胚胎发育等)[1-2]。P4通过与靶细胞中的孕酮受体(progesterone receptor, PGR)结合, 从而实现

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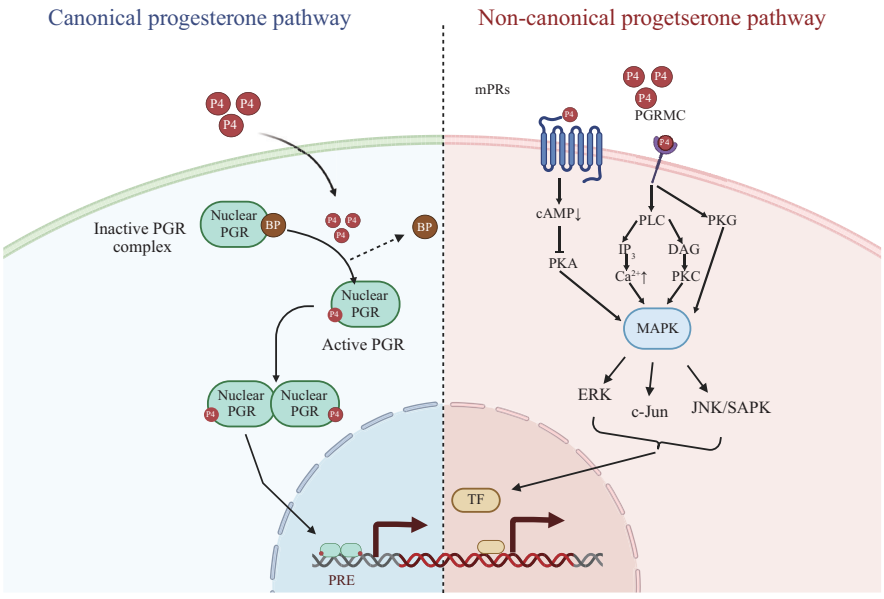
其生理效应。PGR分为两类。一类被称为经典孕酮受体, 也称核孕酮受体, 主要表达于人的卵巢、子宫、输卵管以及胎盘等器官和组织中[3-5]。核孕酮受体与孕酮结合后, 可以调节孕酮响应基因的表达, 并使靶细胞在几小时后出现长期且稳定的细胞反应[6]。另一类是非经典孕酮受体, 因其主要定位在细胞膜上, 故又被称为膜孕酮受体(membrane progesterone receptors, mPRs)[7]。孕酮与非经典孕酮受体的结合会激活多种次级信使和信号转导途径, 从而使靶细胞在几秒钟内迅速产生激素效应[7](图1)。这些非经典孕酮受体已在不同物种的生殖和非生殖器官中被发现[7-8]。经典和非经典孕酮受体调控不同的下游反应, 从而实现不同的生理功能。

1.1 经典孕酮受体及其作用方式

经典孕酮受体有两种主要异构体: PGR-A(94 kDa)和PGR-B(120 kDa)。它们是由同一基因通过两个不同的启动子转录而成的。人类的*PGR*基因位于11号染色体上, 且包含8个外显子[9]。*PGR*转录通常依赖于雌激素, 当17β-雌二醇或相关雌激素与雌激素受体结合时, 后者识别位于*PGR*基因启动子区域的几个雌激素反应元件并诱导*PGR*表达[10]。

PGR的结构包含一个DNA结合域(DNA-binding domain, DBD), 其上游N-端区域包括一个激活功能域[AF1(activation function 1)]和一个抑制结构域(inhibitory domain, ID), 其下游C-端区域为包含了另一个激活功能域(AF2)的配体结合域(ligand-binding domain, LBD)[11]。PGR-A和PGR-B的结构基本相同, 唯一的区别在于PGR-B在蛋白序列的N-端增加了164个氨基酸, 其中包含一个额外的激活功能域(AF3)[12]。除了PGR-A和PGR-B外, 人基因组上还会产生一些由于外显子插入或通过其他可变剪接产生的PGR异构体[6]。例如在人类胎盘中表达的

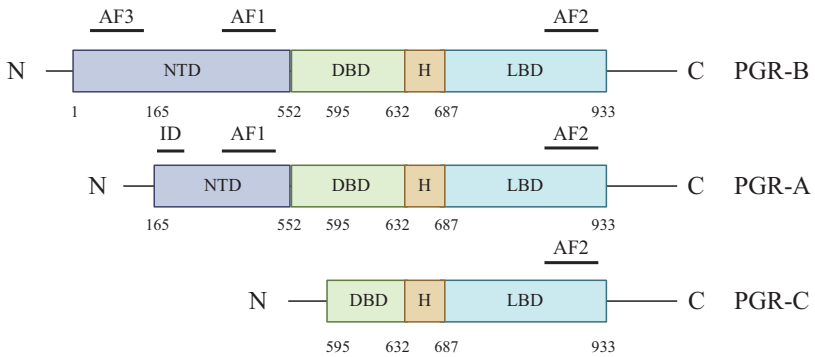


左图描述了经典孕酮信号通路。P4与细胞质中的孕酮受体(PGR)结合后使得后者活化, 具体为PGR释放结合蛋白(binding protein, BP)后进入活化状态, 随后二聚体化进入细胞核, 与DNA上的孕酮反应元件(P4 response element, PRE)结合, 直接调控基因转录, 发挥长期基因激活效应。右图描述了非经典孕酮信号通路。P4与膜孕酮受体(membrane progesterone receptors, mPRs)或孕酮受体膜成分(progesterone receptor membrane component, PGRMC)结合, 激活多种第二信使(如cAMP、IP_3、DAG)和激酶(如PKA、PKC、PKG)的信号级联反应。这些反应最终会激活MAPK信号通路, 从而激活ERK、c-Jun和JNK/SAPK等激酶, 介导更快速的非基因组反应, 并可进一步影响转录因子(transcription factor, TF)活性进而调节基因表达。

The left described the canonical progesterone signaling pathway. After P4 binds to the PGR (progesterone receptor) in the cytoplasm, the latter is activated. Specifically, PGR releases the BP (binding protein) and enters an activated state, then dimerizes and enters the nucleus, binds to the PRE (progesterone response element) on the DNA, directly regulating gene transcription and exerting long-term gene activation effects. The right described the non-canonical progesterone signaling pathway. P4 binds to mPRs (membrane progesterone receptors) or PGRMC (progesterone receptor membrane component), activating a cascade of reactions involving various second messengers (such as cAMP, IP_3, DAG) and kinases (such as PKA, PKC, PKG). These reactions ultimately activate the MAPK signaling pathway, thereby activating kinases such as ERK, c-Jun, and JNK/SAPK, mediating more rapid non-genomic responses, and can further influence the activity of TF (transcription factor) to regulate gene expression.

图1 经典和非经典孕酮信号通路

Fig.1 Canonical and non-canonical progesterone signaling pathways



PGR-B为全长PGR亚型(933个氨基酸), 包含完整的N-端结构域(N-terminal domain, NTD)、DNA结合结构域(DBD)、铰链区(H)和配体结合域(LBD), 以及3个激活功能域(AF1、AF2和AF3)。PGR-A与PGR-B结构相似, 但N-端缺少164个氨基酸, 保留AF1和AF2, 并在NTD区包含一个抑制结构域(ID)。PGR-C是最短的PGR亚型, 缺少整个NTD, 仅包含DBD、H和LBD, 以及AF2。所有PGR亚型共享相同的C-端结构。图中数字表示各结构域的氨基酸位置, 不同方框的颜色代表不同的功能区域。

PGR-B is the full-length PGR isoform (933 amino acids), containing a complete NTD (N-terminal domain), DBD (DNA-binding domain), H (hinge region), and LBD (ligand-binding domain), as well as three activation function domains (AF1, AF2, and AF3). PGR-A has a similar structure to PGR-B but lacks 164 amino acids at the N-terminal domain, retaining AF1 and AF2, and includes an ID (inhibitory domain) in the NTD. PGR-C is the shortest PGR isoform, lacking the entire NTD and only containing the DBD, H, LBD, and AF2. All PGR isoforms share the same C-terminal domain. The numbers in the figure indicate the amino acid positions of each structural domain, and the different colored boxes represent different functional regions.

图2　三种经典孕酮受体的结构示意图

Fig.2　Schematic diagram of the structures of the three classical progesterone receptors

PGR-C(60 kDa), 它的N-端发生截断, 丢失了DBD域的第一个锌指结构, 但其仍可以结合P4。目前对于PGR-C的作用机制并不清楚, 有报道认为它可以与PGR-A和PGR-B形成异二聚体并调节它们的转录活性[13](图2)。

PGR-A和PGR-B可形成同源二聚体(AA或BB)或异源二聚体(AB), 从而产生极其广泛的调控反应[10]。在细胞中, 未结合配体的PGR位于细胞质中, 并与伴侣蛋白结合产生复合体。当P4与PGR的LBD结构域结合时, 受体会发生一系列构象变化, 并从伴侣蛋白中释放, 最终进入细胞核[11]。在细胞核中, PGR二聚体化并结合到目标基因启动子的孕酮反应元件(P4 response element, PRE)上, 并且会进一步招募共调节因子, 这些因子可以是共激活因子或者共抑制因子, 调节目标基因表达(图1, 左图)。而PGR对于这些目的基因的调控也存在一定的PGR异构体特异性。在乳腺癌细胞系中, 有人通过基因芯片确定了337个PGR调控基因, 其中83个只被PGR-A调控, 229个只被PGR-B调控, 剩下的25个可以被二者同时调控, 由此可以看出, PGR-B单独调控的基因数量明显多于PGR-A, 而两种亚型共同调控的基因相对较少[10]。这种PGR异构体特异性调控目的基因的现象, 使得在PGR-A和PGR-B含量相近的情况下, 对靶器官/组织产生不同的生理效应, 从而扩大了孕酮信号的作用范围, 并增强了其特异性。

1.2　经典孕酮受体的表达调控

在体内, *PGR*的表达受到多种机制(包括雌激素信号、*PGR*基因多态性、表观遗传学、转录因子以及PGR异构体之间的相互调节等[14])的调控。

早在上世纪70年代, 就有人发现雌激素对孕酮受体的表达发挥调控作用[15]。雌激素的作用通过两个受体ERα和ERβ来实现。这些受体被雌激素激活后可以与靶基因启动子的雌激素响应元件(estrogen response element, ERE)结合进而发挥功能[16]。在人类的*PGR*基因上不存在这种具有回文结构的ERE。但有趣的是, 有人发现人类*PGR-A*基因启动子上有一个半回文结构的ERE, 而*PGR-B*中却没有这个位点[17]。另外, *PGR-A*基因的启动子还包含2个Sp1位点, 这些位点紧邻半回文结构的ERE, 也可以激活*PGR-A*启动子来增加PGR-A的表达量[18]。尽管*PGR-B*启动子上不包含ERE, 但它也包含2个Sp1位点, 并且可以通过ERα与Sp1互作进而被雌激素激活[19]。

基因多态性包括单核苷酸多态性(single nucleotide polymorphisms, SNPs)、限制性片段长度多态性(restriction fragment length polymorphisms, RFLPs)和重复序列多态性(repeated sequence polymorphisms)。近年来, 许多研究表明*PGR*基因的SNPs与女性生殖

系统疾病有关, 其中最广为研究的是PROGINS和+331 G/A多态性[20-21]。PROGINS多态性包括VII号内含子中由306个碱基组成的Alu元件的重复、V号外显子中的沉默点突变(H770H)和IV号外显子中的单个氨基酸改变(V660L)[20-22]。Alu元件存在于ERE/Sp1位点中, 作为增强子, 它可以增强细胞对雌激素信号的响应, 并进一步增加*PGR*的转录水平[22]。相比之下, V660L和H770H对*PGR*转录和表达没有特别显著的影响。PROGINS被报道会增加子宫内膜异位症、子宫内膜癌、乳腺癌和卵巢癌的风险[23-26]。另一个被广泛研究的是+331 G/A多态性, G到A的改变可以增强转录因子GATA5对*PGR-B*的转录激活, 从而增加*PGR-B*的表达量, 进而打破PGR-A/PGR-B的平衡, 影响PGR的效应[20,27]。其他一些*PGR*基因多态性(如+44 C/T和Q886Q)研究得较少, 其具体影响机制仍需进一步探究[28]。

表观遗传学修饰, 如DNA甲基化, 在调控*PGR*基因表达方面也发挥关键作用。DNA甲基化由DNA甲基转移酶(DNA methyltransferase, DNMT)催化, 主要发生在基因启动子附近的CpG岛, 在胞嘧啶的第5个碳原子上添加甲基基团[29]。*PGR*基因的启动子和I号外显子区域都含有丰富的CpG岛, 其甲基化与*PGR*表达抑制密切相关[30]。此外, 转录因子PU.1可以通过靶向Notch信号结合到小鼠*PGR*的I号外显子区域并招募DNMT3b, 使得该区域高度甲基化而导致*PGR*沉默[31]。

一些转录因子也可调节PGR的表达。比如HOXA5(homeobox A5)可以通过结合到*PGR*基因3′端启动子区域来正向调节PGR表达[32]。C/EBPβ(CCAAT/enhancer binding protein beta)可以结合到*PGR*基因的II号内含子上来调节其表达[33]。RNPC1α(RNA-binding region-containing protein 1 alpha)通过直接结合到*PGR* 3′-UTR区来增强其mRNA的稳定性, 从而调控其表达[34]。

另外, PGR的异构体也可以通过彼此之间的分子互作而调节各自的功能。PGR-A可以通过其抑制结构域(ID)来抑制PGR-B的作用, 这种方式可以用来减弱高浓度P4对目标细胞的效应[35]。因此, 这个过程也被认为是调节卵巢周期中P4效应的基础: 当黄体细胞分泌的P4水平较高时, P4会诱导靶细胞中更高的*PGR-A*表达, 这会抑制*PGR-B*的转录, 从而减弱P4的效应; 相反, 这些细胞中较低的P4水平可能抑制*PGR-A*的表达, 促进*PGR-B*的表达, 并随后增强P4的作用[6]。

1.3 非经典孕酮受体及其作用方式

非经典孕酮受体是指一些定位于细胞膜上、对P4有高亲和力的蛋白, 这些受体与G蛋白偶联受体和单次跨膜的受体在结构上很相似[36], 因此, 它们普遍具有酪氨酸激酶活性, 并依赖于激活的MAPK途径发挥功能[37]。目前发现的非经典孕酮受体主要有两类, mPRs和孕酮受体膜组分(progesterone receptor membrane component, PGRMC)[38](图1, 右图)。

mPRs, 又称孕酮和脂联素Q受体, 包括膜孕酮受体α、β、γ、δ和ε(也可分别称为PAQR7、PAQR8、PAQR5、PAQR6和PAQR9)。mPRs基因可以编码多个含有330~377个残基(分子量约为40 kDa)的肽段, 这些肽段形成了多个跨膜区域[39-40]。尽管研究表明mPRs蛋白在脊椎动物细胞的质膜上表达, 但它们也常常存在于细胞内的核周区域, 即内质网所在的位置[41]。mPRs在膜上的拓扑结构仍存在相当多的争议。最初的分析表明, mPRs具有7个跨膜区域, 并且其N-端位于细胞外, 而C-端位于细胞内, 这与G蛋白偶联受体相似[42]。而后来的研究结果显示, mPRs蛋白的N-端部分实际上位于细胞内部[43]。通过同源建模和X射线晶体研究, mPRs与孕酮分子结合的口袋结构域也得到解析[44-45]。研究者们发现, mPRs由7个跨膜结构域和1个能够容纳游离脂肪酸的内部腔室组成[44]。此外, 在7个跨膜结构域的细胞内表面附近含有一个锌结合位点[44]。通过模型预测, mPRs的结合口袋上的第206位谷氨酰胺与孕酮之间会形成一个关键的氢键[45]。通过突变分析证实, 将该位置的谷氨酰胺替换为不能提供氢键的丙氨酸会导致其孕酮结合能力的丧失[45]。另外, 不同的mPRs对孕酮及其类似物的结合也存在差异。mPRα对脊椎动物中的主要孕酮均表现出高亲和力和高结合特异性[46]。而在其他天然类固醇中, 只有21-羟基孕酮和睾酮对人类mPRα显示出较强的结合能力, 它们之间的相对亲和力约为孕酮的20%[42]。而作为主要神经mPR亚型的mPRδ, 在人类大脑中广泛表达, 其与一些神经类固醇表现出较强的结合能力, 而mPRα和mPRβ与该类固醇的结合能力约为mPRδ的5%[42]。

第二类非经典孕酮受体为PGRMC家族蛋白, 该家族均为单跨膜蛋白, 主要代表分子是孕酮受体膜组分1(PGRMC1)、孕酮受体膜组分2(PGRMC2)、neudecin和neuferricin[38]。它们在结构上都存在一

个非共价的血红素结合结构域[47]。在这4个组分中，PGRMC1和PGRMC2研究较多，而另外两种的研究非常局限，因此本文主要讨论PGRMC1和PGRMC2。PGRMC1存在于多个细胞器或亚细胞结构，比如内质网、线粒体、细胞核、纺锤体甚至自噬体上[48-50]。在线粒体中，它可以与细胞色素P450发生互作，参与类固醇的合成和代谢、细胞内吞作用等多个生物学过程[51]。另外，如上所述，PGRMC1也可以与血红素互作，并进一步与表皮生长因子受体(epidermal growth factor receptor, EGFR)结合而参与子宫间质细胞蜕膜化过程[52-54]。血红素和P4可能共同占据PGRMC1的配体结合位点，但是它们的结合似乎并不相互排斥[47]。晶体学研究显示，PGRMC1通过两个突出的血红素分子的堆叠及相互作用形成稳定的二聚体。PGRMC1的血红素结合能力和二聚化对其与EGFR的结合来说是必需的[55]。

PGRMC1也可以与多种其他蛋白质(包括PGRMC2[56]、mPRα[57]、雌激素受体α[57]等)相互作用，这些作用都可以进一步调节胆固醇代谢[58]。此外，有丝分裂和减数分裂中的着丝粒和纺锤体上的PGRMC1均可以参与调控细胞周期中微管蛋白的稳定性[59]。自噬体中的PGRMC1可以与LC3B-II和UVRAG这两种自噬的关键蛋白结合[49]。有人认为PGRMC1在多种细胞器中的定位可能与其发生的类泛素化或磷酸化等蛋白翻译后修饰有关[60]。PELUSO等[56]推测，PGRMC1、PGRMC2和GTP酶激活蛋白结合蛋白2三者之间的相互作用可能与P4抑制细胞进入细胞周期的能力有关。

PGRMC2与PGRMC1的结构和性质非常相似，它也可以与多种蛋白质(包括细胞色素P450[48]、铁螯合酶[61]和mPRα[62])相互作用。另外，PGRMC2同样可以作为细胞内血红素伴侣蛋白，在血红素运输途径中发挥重要作用。类似于PGRMC1，PGRMC2也位于有丝分裂纺锤体上，并且可以使细胞进入细胞周期G_1期[56]。另外，PGRMC2也在猕猴子宫内膜上皮细胞的细胞质和核膜中表达，并与核孔蛋白ALADDIN相互作用，调节有丝分裂纺锤体的组装[50,63]。另外，有趣的是，PGRMC和mPRs家族成员之间可能也存在相互作用。原位邻近连接实验(*in situ* proximity ligation assays, PLAs)表明，PGRMC1、PGRMC2和mPRα在细胞质中可以形成复合物，其中PGRMC1可以作为适配蛋白，将mPRα转运到细胞表面，形成膜孕酮受体蛋白复合物，使孕酮信号可以抑制细胞周期[57,62]。

mPRs和PGRMCs通过结合细胞外的P4，并将信号转导至细胞内而发挥孕酮效应。P4与mPRs结合可以激活MAPK通路，并进一步改变转录因子的磷酸化状态。mPRs的激活可以抑制腺苷酸环化酶活性，降低cAMP浓度，进而影响PKA功能，最终使得MAPK通路激活[64](图1，右图)。此外，mPRs介导的抑制性G蛋白信号可以调节经典孕酮受体的活化，从而增加PGR-B的转录活性。而当PGR-A与PGR-B比例增加时，这一效果会减弱[64]。PGRMC介导的孕酮信号转导过程也依赖第二信使通路来激活MAPK通路，进而激活下游转录因子。例如，在颗粒细胞中，PGRMC1结合血红素并与*SERPINE1* mRNA结合蛋白1(*SERPINE1* mRNA binding protein 1, SERBP1)在质膜上形成复合物，从而激活第二信使通路，这会增强P4相关的抗凋亡效应[65]。在女性怀孕期间，P4在子宫内膜T细胞中与PGRMC1和mPRs结合，通过促进细胞内肌醇三磷酸(inositol trisphosphate, IP_3)生成，进一步动员细胞内Ca^{2+}，从而激活MAPK通路，同时生成的DAG也可以通过调节PKC而激活MAPK通路。MAPK会进一步激活ERK、c-Jun和JNK/SAPK等激酶，最终调节NF-κB、活化蛋白1(activator protein 1, AP-1)和活化T细胞核因子(nuclear factor of activated T-cells, NFAT)等转录因子的磷酸化[66-67](图1，右图)，这些因子与促炎基因表达以及T细胞的激活和增殖有关，有助于构建母胚界面的免疫环境，推动容受态建立过程。

不管是mPRs还是PGRMCs，均可以表达在多种脊椎动物(包括人类)的生殖器官/组织/细胞(子宫内膜、子宫肌层、卵巢、精子、颗粒细胞)以及包括血液、肠道和大脑在内的非生殖组织中[7,46]。与经典孕酮受体相比，非经典孕酮受体与P4的结合能力较差[68]。

2 孕酮效应与子宫内膜容受态建立

人类的月经周期主要分为两个阶段：增殖期(或称为卵泡期)和分泌期(或称为黄体期)[69-70]。在增殖期结束时，黄体生成素(luteinizing hormone, LH)水平达到最高，卵巢排卵，孕酮水平开始升高，子宫进入分泌期。如果没有实现妊娠，黄体就会发生溶解并导致体内孕酮水平下降，这会诱发子宫内膜炎症、细胞死亡和细胞外基质降解，从而导致子宫内膜功能层脱落，最终引起月经来潮[71](图3)。如果发生妊

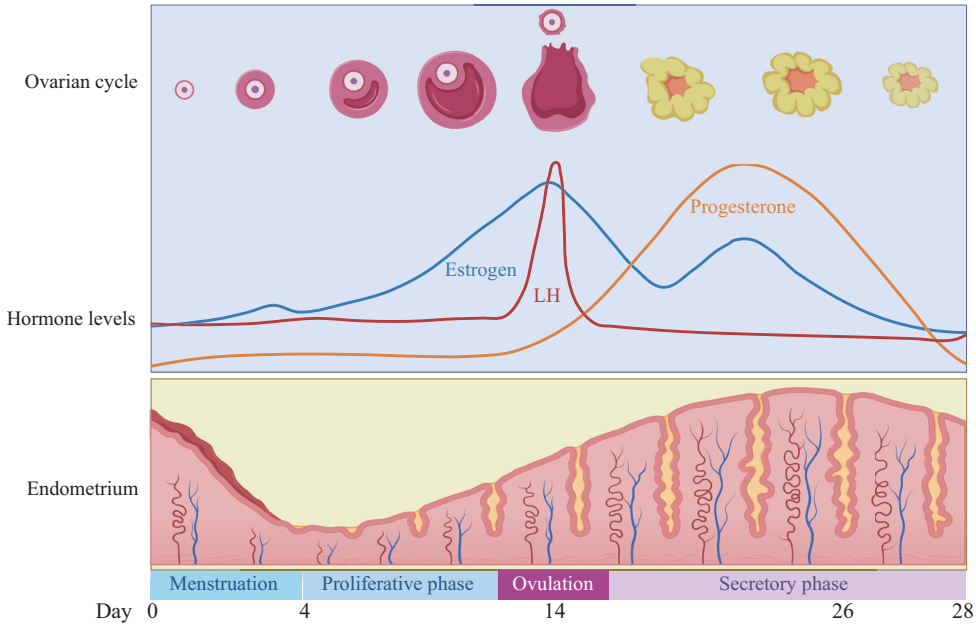
娠, 孕酮水平则能得以维持并进一步促进子宫内膜间质细胞蜕膜化过程[72]。另外有证据表明, 仅通过雌激素/孕酮治疗就足以支持绝经后妇女在胚胎移植后维持正常的妊娠[73]。上述内容说明, 孕酮是子宫内膜建立容受态的基础。

在人类子宫中, 孕酮的效应通过经典和非经典孕酮受体实现。其中在子宫内膜的上皮和间质细胞、子宫肌层的平滑肌细胞[74-75]中均可检测到经典和非经典孕酮受体的表达。子宫中经典和非经典孕酮受体的表达在整个月经周期中显著波动, 这些受体通过调节各类内膜细胞状态, 最终建立子宫内膜容受态并促进妊娠过程的发生[76-78]。

2.1 经典孕酮受体与子宫内膜容受态建立

在子宫内膜增殖期, 较长的雌激素暴露会诱导子宫细胞中经典孕酮受体的表达。在随后的分泌期, 孕酮水平升高进而抑制ER表达, 这会进一步增强孕酮的响应性。经典孕酮受体的表达因子宫内膜细胞类型而异, 并体现出一定的时空特异性。在子宫内膜的上皮中, *PGR-A*和*PGR-B*在胚胎植入前均有表达。此时, PGR-A对*PGR-B*表达的抑制作用会促进上皮增殖和增强炎性反应[79]。在植入过程中, *PGR-A*水平下降, 而*PGR-B*水平保持不变, 该过程会调控子宫腺体的发育过程[79]。而在间质细胞中, PGR-A在整个黄体期均作为主要的孕酮受体, 参与蜕膜化过程[74]。当然, *PGR-A*的过表达也与子宫的增大以及子宫内膜增生相关[80]。因此, 需要准确调节PGR-A/PGR-B表达比例, 以确保子宫内膜上皮和间质对孕酮的正确响应, 进而建立完整的子宫内膜容受态。

在临床上, 一些不孕症患者的子宫内膜上皮的*PGR-A*和*PGR-B*表达水平均低于正常病人[81]。此外, 有研究表明反复植入失败不仅与子宫内膜中较低的经典孕酮受体表达有关, 还与经典孕酮受体基因多态性有关[82]。特别是, *PGR*基因多态性PROGINS会



本图全面展示了女性28天月经周期中卵巢、激素水平和子宫内膜的协同变化。上部展示卵巢周期, 卵泡从原始卵泡发展到成熟卵泡, 经历排卵和黄体形成及退化。中部曲线图描绘了3种关键激素(雌激素、LH和孕酮)水平的动态变化, 其中雌激素和LH在排卵前达到峰值, 而孕酮在分泌期显著升高。下部展示子宫内膜的周期性变化, 从月经期的脱落, 经增殖期的逐渐增厚, 到分泌期的最大厚度。图中标注了月经周期的4个主要阶段: 月经期(0~4天)、增殖期(4~14天)、排卵(约第14天)和分泌期(14~28天)。

The image illustrates the dynamic changes in the ovary, hormone levels, and endometrium during a woman's menstrual cycle. The upper part shows the ovarian cycle, with follicles developing from primordial follicles to mature follicles, undergoing ovulation, and the formation and degeneration of the corpus luteum. The middle line graph depicts the dynamic changes in the levels of three key hormones (estrogen, LH, and progesterone), with estrogen and LH reaching peak levels before ovulation, while progesterone significantly increases during the secretory phase. The lower part demonstrates the cyclic changes in the endometrium, from shedding during the menstrual phase, gradual thickening during the proliferative phase, to the maximum thickness in the secretory phase. At the bottom, we also label the four main stages of the menstrual cycle: menstrual phase (days 0-4), proliferative phase (days 4-14), ovulation (around day 14), and secretory phase (days 14-28).

图3 女性月经周期中子宫内膜状态及激素水平变化模式图

Fig.3 Schematic diagram of endometrial status and hormone levels changing during the female menstrual cycle

导致IV号外显子中的氨基酸发生替换，进而使*PGR*表达水平升高，同时*PGR*稳定性也有所提升，这种变体的存在会导致几种子宫内膜容受态标记的减少甚至消失[83]。

经典孕酮受体介导的孕酮信号的调控在小鼠中已经有了很好的阐述。与人类相较，小鼠子宫在容受态建立过程中具有相似的雌孕激素变化模式和更清晰的内膜容受性研究基础，是目前非常经济且有效的研究子宫内膜容受态建立的动物模型。在小鼠体内，通过使用组织重建技术和子宫特异性*PGR*敲除实验，有人发现无论是间质还是上皮中，*PGR*的表达对于子宫内膜容受态建立都是必需的，且它可以对抗子宫中的雌激素效应[84]。在体外实验中发现转录因子叉头盒蛋白O1(forkhead box protein O1, Foxo1)能够与子宫内膜间质细胞中的PGR相互作用，调节细胞增殖和上皮样分化相关的靶基因表达，并进一步调控蜕膜化过程[85]。而在小鼠胚胎的植入期，*Foxo1*在腔上皮和腺上皮中的表达量显著增加[86]。在子宫*Foxo1*特异性敲除的小鼠种植窗口期的腔上皮中，PGR会过度表达并导致孕酮信号的异常增强。而在正常情况下，上皮PGR的持续表达也会抑制子宫上皮细胞中*Foxo1*的表达[87]。这些结果表明，PGR介导的孕酮信号的强度对于容受态建立至关重要，而*Foxo1*可以与PGR相互抑制彼此的表达，这对于维持早期妊娠的子宫中适当的孕酮效应具有关键作用。

经典孕酮受体介导的孕酮信号通过激活下游基因表达发挥生物学功能。有研究表明PGR能够直接与印度刺猬信号分子(Indian hedgehog signaling molecule, *IHH*)的启动子区域结合，从而促进细胞的增殖[88]。鸡卵清白蛋白上游启动子转录因子2 (chicken ovalbumin upstream promoter transcription factor II, *COUP-TFII*, 亦称*Nr2f2*)，是IHH信号下游的一个靶基因，在小鼠怀孕第五天时，*Nr2f2*主要在子宫上皮下方的间质细胞中表达[89]。子宫中敲除*Nr2f2*后，胚胎无法着床[89]。孕酮信号诱导的另一个转录因子HAND2在子宫间质细胞中表达，对于调节子宫容受态和胚胎着床至关重要。缺少*Hand2*的子宫表现为上皮细胞雌激素信号的过度激活和上皮的过度增殖，这些表型是通过FGF信号通路的上调实现的[90]。这表明孕酮信号可以调节间质细胞中*Hand2*的表达，并通过FGF信号通路来抑制上皮细胞的增殖。另外，FKBP52也是一种必需的孕酮诱导分子，同时也是调控孕酮受体活性所必需的分子[91-92]。*Fkbp52*基因敲除小鼠因子宫对孕酮的反应受损而导致胚胎无法着床。*Fkbp52*缺失还导致了子宫对氧化应激的敏感性增加，并减少了特异性抗氧化酶——过氧化物酶6的表达水平[93]。然而，这种不育状况可以通过抗氧化剂的注射来逆转，因此，在正常情况下，*Fkbp52*对于胚胎着床可能并非是绝对必需的[93]。这些结果说明经典孕酮受体可以通过调控多个下游基因和信号通路，精细地调节子宫内膜的功能状态，为胚胎着床创造合适的环境。

2.2 非经典孕酮受体与子宫内膜容受态建立

非经典孕酮受体在人类、恒河猴和小鼠的子宫中均有表达[94-96]。其中大多数受体的表达会随月经周期波动。

在人类中，膜孕酮受体mPRγ的转录本在增殖期表达上调，在分泌期会逐渐减少，而mPRα则在分泌期明显高表达，并且高表达的时间点与排卵后孕酮水平升高的时间点相一致[76,97]。而有些受体的表达并不受月经周期影响，如mPRβ，其在人类子宫内膜中相对于mPRα更为丰富，但在月经周期中并没有显著变化[98]。另外有研究显示，反复种植失败(recurrent implantation failure, RIF)患者在月经周期第10~14天时，其子宫内膜*mPRβ*基因表达量明显减少[99]。上述研究说明，mPRs可能会参与子宫内膜容受态建立过程。

同时，孕酮受体膜组分家族中的PGRMC1和PGRMC2在月经周期中也表现出相反的表达模式，通过微阵列分析发现，与增殖期相比，*PGRMC1*在分泌期的表达减少，这种表达模式也在恒河猴中被观察到，而*PGRMC2*在月经周期的分泌期表达最为丰富[100-102]，这种表达模式的差异可能与其特定的功能有关。PGRMC1可以促进细胞增殖，因此在增殖期负责子宫内膜的增厚和发育[103]。有研究表明，*Pgrmc1*敲除会导致雌性小鼠生育能力下降[104]。而在分泌期，PGRMC1在间质细胞中的过表达会抑制蜕膜化，并造成内膜容受性缺陷[76]。同时，PGRMC1的异常下调也会损害子宫的容受性及囊胚的植入[105]。因此，PGRMC1水平的相对平衡对于子宫内膜容受态的建立是必要的。另外，有趣的是，在人类的内膜蜕膜化过程中，PGRMC1可以从细胞质移动到细胞核中[76]。这与经典孕酮

受体不同, 后者已知在胚胎植入时在子宫内膜间质细胞中表达缺失[106]。这种有趣的核定位暗示了PGRMC1可能会调节一组与经典孕酮受体目标基因不同的特定基因的表达, 使增殖状态的间质细胞转变为终末分化的蜕膜细胞, 进而调节子宫内膜功能。EGFR对于维持间质细胞蜕膜化至关重要, 而其表达被认为与PGRMC1相关, 且PGRMC1可以通过其血红素域与EGFR相互作用, 来调节其功能[52-54]。PGRMC2的主要功能是抑制细胞增殖, 因此其主要表达在子宫内膜分泌期。*Pgrmc2*的敲除在雌性小鼠中引起的生殖表型比*Pgrmc1*敲除更为严重。有人使用pulldown和质谱实验分析发现, 蜕膜化期间子宫内膜间质细胞中PGRMC2可以与多种蛋白质结合, 这些蛋白质涉及翻译、ATP生成、蛋白质成熟、葡萄糖运输和氧化应激保护等[77]。PGRMC2与这些蛋白的结合表明, 它可能在蜕膜化过程中作为支架蛋白发挥作用。*Pgrmc2*敲除会导致小鼠出现过早的子宫衰老, 这不同于正常生理蜕膜化过程中发生的衰老[107-108], 并且敲除小鼠的胚胎植入过程也会受到影响[102,104]。这些结果说明, PGRMC2对于维持子宫的蜕膜化过程, 建立完整的内膜的容受态也具有调控作用。

3 孕酮信号响应异常与子宫内膜异位症

孕酮信号对子宫内膜状态的正确调节对于女性生殖系统健康至关重要, 如果子宫对于孕酮信号不敏感或抵抗, 会导致子宫间质和腺体细胞异常增殖并进入子宫腔外生长, 进而导致子宫内膜异位症, 最终使胚胎着床失败。子宫内膜异位症影响了10%~15%的育龄女性[109], 这种对孕酮信号不敏感的特点与孕酮受体异构体的表达变化有关[110-111]。

3.1 孕酮受体表达异常与子宫内膜异位症

据报道, 在子宫内膜异位症患者的子宫间质细胞中, PGR-A高表达, 而PGR-B几乎无法检测到[112], 同时这种现象也出现在这些患者的正常位置的子宫内膜组织中[113]。此外, 患者的孕酮效应基因表达水平低[114], 这说明子宫内膜异位症的病因之一是子宫内膜无法对孕酮信号产生反应, 表现为孕酮抵抗。经典孕酮受体的表达失调在孕酮抵抗过程中起关键作用。子宫内膜蜕膜化过程需要有连续的孕酮信号调控, 这依赖于孕酮受体的正常表达。而经典孕酮受体的表达受到雌激素、ERβ/ERα比例以及孕酮水平的影响。在患有子宫内膜异位症的女性中, 孕酮诱导的蜕膜化减少被认为与子宫内膜的孕酮抵抗相关[115]。除了经典孕酮受体的整体表达水平外, 孕酮受体异构体的表达比例也会影响子宫内膜功能。已有报道认为PGR-A/PGR-B表达比例异常升高, 会导致孕酮信号的丢失, 进而使得孕酮效应基因表达异常[115]。此外, 有一些研究调查了经典孕酮受体基因多态性与子宫内膜异位症之间的关联, 结果显示, 经典孕酮受体的基因多态性与欧洲人群中子宫内膜异位症有关, 但在巴西人群中的调查结果则显示二者无关[43]。因此, 目前经典孕酮受体的基因多态性尚且不能解释子宫内膜异位症的孕酮抵抗。

除了经典的孕酮受体信号外, 有证据表明PGRMCs也参与子宫内膜异位症。有人发现在严重的子宫内膜异位症女性的分泌期, *Pgrmc1*和*Pgrmc2*表达下调[97]。而在经过雌二醇和孕酮处理的猕猴子宫的分泌期, *Pgrmc2*表达上调, 但在患有子宫内膜异位症的猕猴中, *Pgrmc2*的表达量却急剧下降, 这表明PGRMC2可能参与孕酮抵抗[116]。尽管如此, PGRMCs导致子宫内膜异位症的分子机制尚未被阐明。

3.2 孕酮抵抗与子宫内膜异位症

在临床上, 由于存在孕酮抵抗, 天然孕酮治疗在子宫内膜异位症中的效果是有限的, 甚至有一部分患者完全无反应[117]。作为合成型孕酮, 地诺孕酮(dienogest)对于缓解子宫内膜异位症患者病情颇有成效[118]。地诺孕酮可以直接增加子宫内膜细胞中的*PGR-B*/*PGR-A*的RNA比例来增强子宫内膜异位症患者的孕酮反应[118], 并下调IL-6和IL-8等促炎细胞因子的表达[119], 此外, 地诺孕酮对子宫内膜细胞中的芳香化酶表达具有直接的抑制作用[120]。这些效果使得地诺孕酮在缓解子宫内膜异位症导致的盆腔疼痛方面显著优于安慰剂[121]。一些高效孕酮, 如醋酸甲羟孕酮, 在减轻轻中度子宫内膜异位症患者的疼痛方面, 具有显著疗效[122]。另外, 左炔诺孕酮宫内系统(levonorgestrel intrauterine system, LNG-IUS)的疗效也已得到证实, 与安慰剂相比, 约88%的患者的中度至重度的痛经得到缓解[123]。患者接受LNG-IUS治疗6个月后, 除了ERα和PGR-A的表达量减少外, 细胞增殖指数也降低了, 同时慢性盆腔疼痛的症状也得到了改善[124-125]。另外一些非激素药物也是未来用于治疗子宫内膜异位症的良好候选药物, 比如芬瑞替尼, 作为一种低毒性维甲酸类药物,

主要用来增强细胞内的维甲酸信号。子宫内膜异位症病灶暴露于芬瑞替尼后，包括*STRA6*在内的参与维甲酸吸收和作用的基因表达量均增加[126]。此外，对异种移植人类子宫内膜异位症组织的小鼠进行为期两周的芬瑞替尼治疗后，子宫内膜异位症病灶的体积有所减少[127]。另外一些抗炎药物有可能使炎症症状态下的孕酮抵抗正常化以达到缓解和治疗的目的。例如，他汀类药物已被证实能够减少IL-1β等促炎因子的表达，同时还能抑制血管生成因子的作用，进一步减缓子宫内膜异位症病灶的形成[128]。

4 总结与展望

孕酮及其受体在维持女性生殖健康中扮演着核心角色，通过两大类受体——经典孕酮受体和非经典孕酮受体——实现其多样化的生理作用。经典孕酮受体主要通过基因组途径调控目标基因表达，而非经典受体如膜孕酮受体和孕酮受体膜组分则主要通过快速的非基因组途径激活细胞内信号通路。

孕酮信号在建立和维持子宫内膜容受态方面发挥着关键作用，其作用机制复杂而精细。一方面，经典和非经典孕酮受体的时空特异性表达以及精确调控对于建立完整的子宫内膜容受态至关重要。这些受体的协同作用确保了子宫内膜对孕酮的正常响应。此外，随着单细胞测序技术和空间组学的发展，研究孕酮受体在子宫内膜不同位置及不同细胞类型中的异质性表达及其生理意义成为可能，有助于深入理解孕酮信号在组织微环境中的精细调控机制。另一方面，孕酮信号响应异常，如子宫孕酮抵抗或拮抗，与子宫内膜异位症密切相关。这种异常主要由经典和非经典孕酮受体的表达失调引起，导致子宫内膜无法对孕酮信号产生正常效应，进而影响子宫内膜的结构和功能。针对孕酮抵抗，临床上采用多种治疗策略，试图从不同角度干预子宫内膜异位症的发病过程，恢复机体正常的孕酮信号响应。未来研究可以进一步深入探索孕酮受体的异构体在不同病理状态下的角色，并结合组织工程和类器官模型等新技术，为开发个体化医疗和精准治疗策略提供重要依据，加深我们对孕酮在人类生殖健康中作用的全面理解。

本文综述了孕酮及其受体在女性生殖健康中的关键作用，重点阐述了经典和非经典孕酮受体在调控子宫内膜功能和建立容受态过程中的重要性。同时我们也阐述了孕酮信号响应异常与子宫内膜异位症的关联，并介绍了当前的临床治疗策略。此外，文章还指出了未来研究方向，包括探索孕酮受体在不同病理状态下的作用、发展个体化医疗方法，以及利用新技术进行深入研究，为改善女性生殖健康提供了重要的理论基础和实践指导。

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