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泌乳素-泌乳素受体信号在妇科及女性高发疾病中的情境依赖性作用及转化前景

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摘要: 女性在月经周期、妊娠、哺乳及绝经等不同生理阶段经历显著的内分泌变化, 这不仅关系到正常生殖功能的维持, 也影响多种女性特异性或高发疾病的发生发展。近年来, 人们逐渐认识到泌乳素 (prolactin, PRL) 是一种具有广泛生物学效应的调节因子。除参与泌乳和生殖调控外, PRL还可影响免疫稳态、能量代谢、组织重塑及痛觉感受等过程, 其作用主要由泌乳素受体 (prolactin receptor, PRLR) 介导。由于PRL具有多种分子形式, 可来源于垂体及多种外周组织, 且PRLR的亚型构成和下游信号通路存在差异, 因此该信号系统的生物学效应在不同组织和疾病背景中呈现出明显的情境依赖性。现有证据提示, PRL-PRLR信号异常并非仅表现为血清PRL升高, 还可体现为局部信号增强和特定响应细胞群持续活化。本文从局部炎症维持、组织重塑、神经敏化、免疫耐受失衡及代谢调节等多重病理环节出发, 讨论PRL-PRLR轴在子宫内膜异位症、子宫腺肌症、多囊卵巢综合征、女性易感性疼痛及系统性红斑狼疮中的疾病特异性作用及转化意义, 为理解PRL-PRLR轴参与妇科及女性高发疾病的病理机制提供了新的视角。

关键词: 泌乳素; 泌乳素受体; 妇科疾病; 女性高发疾病

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Context-dependent roles and translational prospects of prolactin-prolactin receptor signaling in gynaecological and female-prevalent diseases

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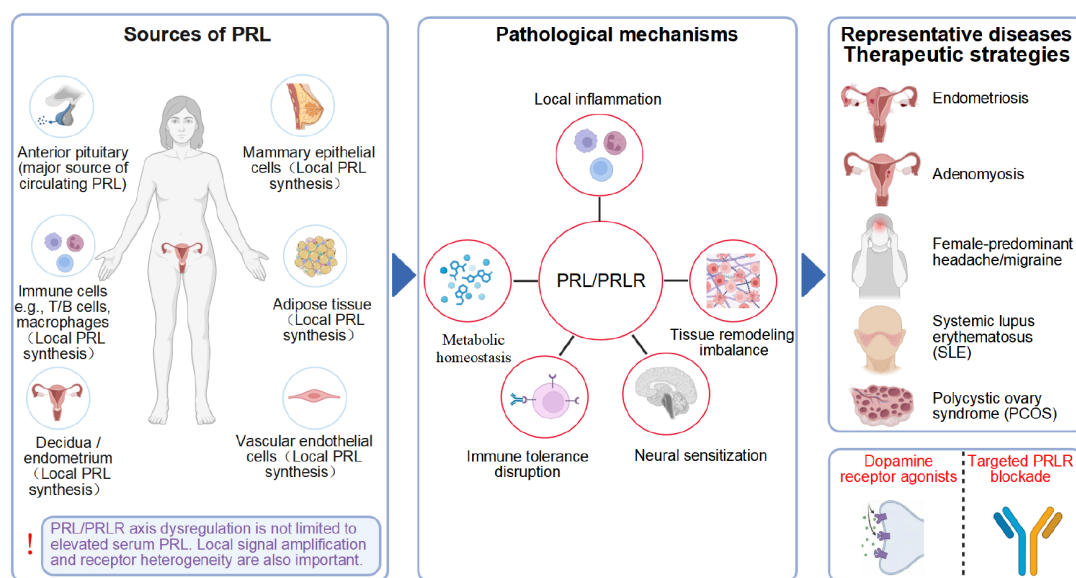
Abstract: Women undergo substantial endocrine changes during the menstrual cycle, pregnancy, lactation and menopause. These physiological changes are essential for reproductive function, but they also influence the onset and progression of a range of female-specific and female-prevalent diseases. Prolactin (PRL), classically defined as a pituitary hormone involved

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in lactation and reproductive regulation, also exerts broad biological effects on immune homeostasis, energy metabolism, tissue remodeling and nociceptive signaling, mainly through the prolactin receptor (PRLR). The actions of PRL-PRLR signaling are highly context dependent. PRL exists in multiple molecular forms and can be produced not only by the anterior pituitary but also by peripheral tissues and cell types, including the endometrium, decidua, immune cells and adipose tissue. Moreover, tissue-specific PRLR isoforms and downstream signaling programmes differ across cell populations, physiological states and disease contexts. As a result, PRL-PRLR dysregulation is not necessarily reflected by elevated circulating PRL levels. Its pathological relevance may also involve local signal amplification, altered PRLR expression or isoform composition, and sustained activation of specific PRL-responsive cell populations. In this review, we discuss the disease-specific roles and translational implications of the PRL-PRLR axis in endometriosis, adenomyosis, polycystic ovary syndrome, female-prevalent pain disorders and systemic lupus erythematosus. We focus on pathological processes that recur across these conditions, including persistent local inflammation, tissue remodeling, neural sensitization, disruption of immune tolerance, and metabolic adaptation. By integrating evidence from reproductive biology, immunology, metabolism and pain research, we highlight PRL-PRLR signaling as a context-dependent immunoendocrine regulatory system rather than a uniform pathogenic driver. Defining how this axis operates in distinct tissue microenvironments, disease stages and responsive cell populations may help refine disease stratification and support the development of targeted therapeutic strategies for gynaecological and female-prevalent diseases.



Key words: prolactin; prolactin receptor; gynecologic disorders; female-predominant disorders

长期以来,泌乳素(prolactin,PRL)多被视为与泌乳和生殖活动密切相关的垂体激素^[1]。但近年来的研究表明,PRL并非仅由垂体产生,子宫内膜、蜕膜、脂肪组织以及多种免疫细胞等外周组织同样能够合成PRL,并在局部微环境中发挥调节作用。PRL的生物学效应主要依赖泌乳素受体(prolactin receptor,PRLR)。由于PRLR存在多种剪接亚型,且其表达谱随组织类型和生理状态而变化,PRL-PRLR信号在不同器官中的作用呈现出显著异质性。PRL与PRLR结合后,可进一步调节JAK/STAT (Janus kinase/signal transducer and activator of transcription)、MAPK(mitogen-activated protein kinase)、PI3K/Akt(phosphoinositide 3-kinase/protein

kinase B)等信号通路,从而调控细胞增殖、凋亡、代谢以及神经敏化等多种生物学过程^[2]。

值得注意的是,PRL-PRLR轴与多种女性相关疾病或女性高发疾病密切相关。研究显示,除子宫内膜异位症、子宫腺肌症和多囊卵巢综合征(polycystic ovary syndrome,PCOS)等女性特有的妇科疾病外,偏头痛、系统性红斑狼疮(systemic lupus erythematosus,SLE)等多种疾病也表现出明显的女性患病倾向,部分疾病在女性患者中的临床表现亦更为严重^[3]。从临床表型看,这些疾病涉及生殖、神经和免疫等不同生理系统;但从病理过程看,它们在局部炎症持续、组织重塑失衡、神经敏化增强以及免疫耐受破坏等环节中存在一定交叉。现有证据提

示,PRL-PRLR轴可能以疾病特异性和阶段依赖性的方式参与上述共同病理过程,而非在不同疾病中发挥完全相同的致病作用。

值得注意的是,PRL-PRLR信号异常并不总表现为持续性高泌乳素血症。相反,在不少疾病中,更具疾病相关性的异常可能发生在组织局部,例如病灶微环境中PRL的旁分泌/自分泌作用增强、特定细胞群对PRL的敏感性增强,或PRLR亚型构成改变所引起的下游信号重塑。也正因如此,单纯以血清PRL水平评估PRL-PRLR轴的病理意义,往往难以解释其在不同疾病中的复杂作用。

基于此,本文在总结PRL来源与分泌调控、PRLR结构特点及其下游信号通路的基础上,从共同病理机制与疾病特异性两个层面,探讨PRL-PRLR轴在局部炎症、组织重塑、疼痛易感、免疫失衡和代谢重塑等过程中的潜在作用,并结合子宫内异症、子宫腺肌症、多囊卵巢综合征、女性易感性疼痛和系统性红斑狼疮等代表性疾病进行整合分析,以期对相关疾病的机制研究和临床干预提供新的思路。

1 PRL-PRLR轴的生物学基础

1.1 PRL的分子特征及多效性基础

PRL传统上被视为调控泌乳与生殖的经典腺垂体激素,但近年来研究表明,其生物学功能远不止于此。除参与乳腺发育、泌乳和生殖调控外,PRL还可影响代谢稳态、免疫应答、血管生成、组织重塑及神经元兴奋性等多种生物学过程,表现出连接内分泌调控、免疫应答与局部组织反应的多效性特征。

从分子基础看,PRL是由199个氨基酸组成的单链多肽,相对分子质量约23 kDa。PRL的空间构象以4条反向平行的 α 螺旋为核心,并由二硫键维持结构稳定,这一构象特征是其与受体结合并发挥生物学活性的基础^[4]。PRL在体内存在多种形式

(表1),除23 kDa单体外,尚可见二聚体及巨分子PRL等^[5];此外,PRL还可被裂解为约16 kDa的片段,该片段并不主要通过经典PRLR信号发挥作用,而是具有抗血管生成活性^[6]。这些不同分子形式及其功能差异,是PRL产生多样化生物学效应的重要基础之一。

需要强调的是,PRL的生物学效应并非由其循环水平简单决定,而是受到组织微环境、PRLR亚型构成及细胞特异性信号的共同调控。

1.2 PRL的来源特征与分泌调控

PRL生物学效应的多样性,与其来源广泛及分泌调控方式的差异密切相关。循环PRL主要由垂体前叶泌乳素细胞分泌^[7],该细胞群在非妊娠生理状态下占垂体前叶细胞总数的15%~25%,妊娠和哺乳期则显著增多^[8,9]。然而,子宫蜕膜、脂肪组织以及多种免疫细胞等垂体外组织和细胞同样具备合成PRL的能力^[10](图1)。尽管垂体外PRL对循环水平贡献有限,但在局部微环境中可能发挥更直接的调节作用。

垂体与垂体外来源的PRL受不同启动子调控^[11],前者主导经典内分泌功能,后者则更多通过自分泌或旁分泌方式参与局部调节,这样的调控差异使局部PRL变化在一定程度上可以独立于循环PRL水平。因此,在子宫内膜、病灶组织及免疫和神经相关微环境中,PRL的作用并非完全依赖循环水平,局部产生的PRL也可能构成持续的自分泌或旁分泌信号。

与多数垂体激素不同,PRL的基础分泌主要受到持续性的抑制性调控。下丘脑多巴胺经垂体门脉系统到达腺垂体,并作用于泌乳素细胞表面的D2型多巴胺受体,从而抑制PRL的合成与释放^[12,13];PRL亦可反向促进多巴胺释放,形成负反馈环路^[14]。此外,雌激素、促甲状腺激素释放激素、血管活性肠肽等因素可促进PRL分泌^[15],其循环水平还受妊娠、哺乳、应激、睡眠节律及月经周期等生理因

表1 PRL的主要分子形式及其生物学特点

Table1 Major molecular forms of PRL and their biological characteristics

异构体	结构	主要作用
16 kDa PRL	由组织蛋白酶D或金属蛋白酶切割单体PRL产生	抗血管生成
23 kDa PRL	单体、非糖基化,受体亲和力高	PRL的主要形式;具有生物学和免疫学活性
25 kDa糖基化PRL	糖基化形式	免疫反应性和生物活性通常低于23 kDa PRL
48~56 kDa大PRL	多为单体PRL的二聚体或高分子聚集形式	生物活性和临床意义不如单体PRL明确
>100 kDa巨分子PRL	泌乳素与免疫球蛋白结合而成	可导致巨泌乳素血症;生物活性非常低

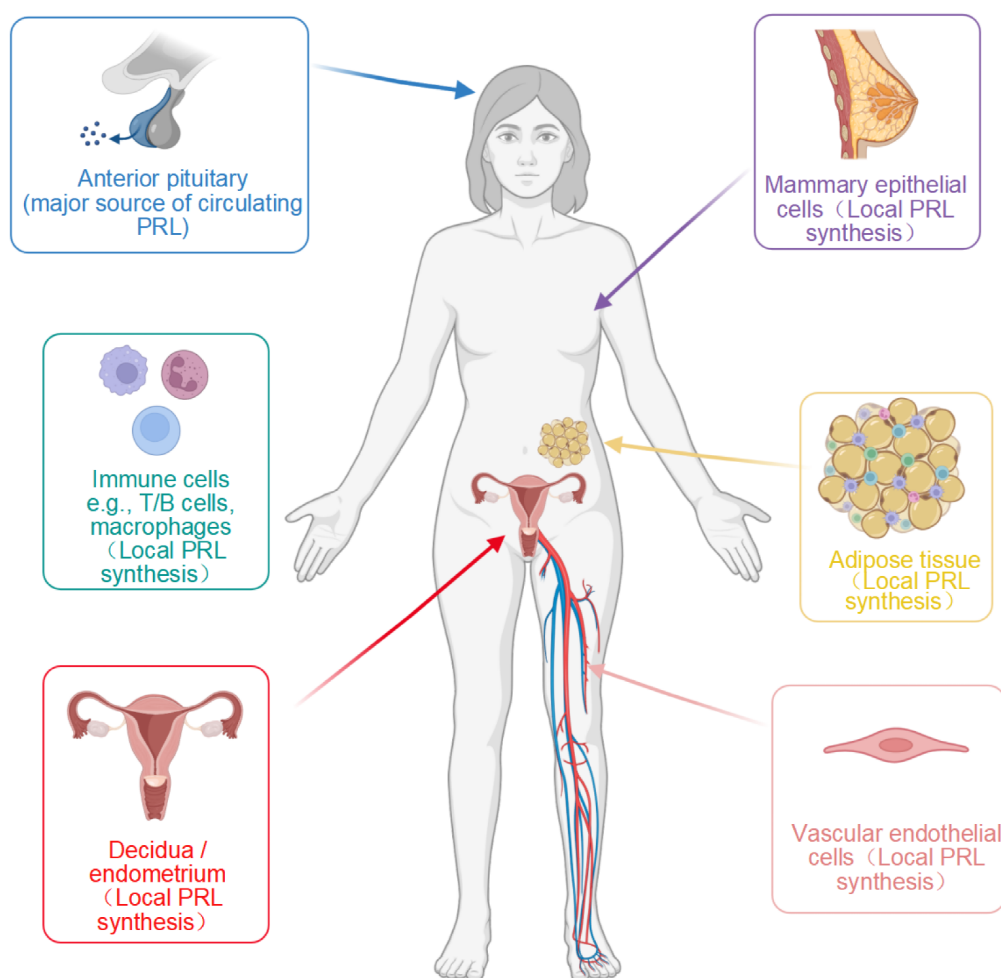


图1 PRL的主要组织来源及局部合成特点

循环PRL主要来源于垂体前叶泌乳素细胞,并作为经典内分泌激素发挥全身作用。除垂体来源外,子宫蜕膜/子宫内膜、免疫细胞、乳腺上皮细胞、脂肪组织及血管内皮细胞等多种外周组织或细胞也可局部合成PRL。外周来源PRL通常通过自分泌或旁分泌方式参与局部微环境调控,其变化可能并不完全反映在血清PRL水平上。(使用BioRender.com制图)

Figure 1 Major tissue sources and local synthesis of PRL

Circulating PRL is mainly produced by lactotroph cells in the anterior pituitary and functions as a classical endocrine hormone with systemic effects. In addition to the pituitary source, multiple peripheral tissues or cell types, including the decidua/endometrium, immune cells, mammary epithelial cells, adipose tissue, and vascular endothelial cells, can also locally synthesize PRL. Peripherally-derived PRL usually participates in local microenvironmental regulation through autocrine or paracrine mechanisms, and its changes may not be fully reflected by serum PRL levels. (Created with BioRender.com)

素影响^[16-18]。相较之下,垂体外PRL通常不直接受下丘脑多巴胺的经典调控,更多受到局部激素环境、炎症状态及细胞类型等因素影响。因此,在相关疾病中,循环PRL水平变化与局部PRL-PRLR信号异常既可能同步出现,也可能相互分离。

1.3 PRLR亚型构成及信号转导特征

PRL的生物学效应主要通过PRLR介导^[19]。PRLR属I类细胞因子受体超家族,广泛表达于多种

组织,其自身不具有内在酪氨酸激酶活性,主要通过胞内结构域募集并激活JAK2介导信号转导。PRL结合PRLR后诱导受体二聚化,激活JAK2/STAT5经典通路,进而调控下游基因转录^[20,21];此外,PRL-PRLR信号还可调控MAPK、PI3K/Akt等信号通路,参与细胞增殖、分化、代谢重塑及迁移等过程^[22,23]。

PRLR可通过可变剪接形成长型、短型及中间型等多种亚型(表2)。其中,长型PRLR具有较完整的

表2 PRLR主要亚型及其结构、信号转导和功能特征

Table 2 Major PRLR isoforms and their structural, signaling, and functional characteristics

PRLR亚型/形式	结构特点	主要信号转导能力	主要生物学/功能意义
长型PRLR	膜结合型受体;具有胞外配体结合区、单次跨膜区和较完整的胞内结构域	经典信号能力最强;和PRL结合后主要激活JAK2/STAT5,同时可联动MAPK/ERK、PI3K/Akt、Src等通路	通常被视为介导PRL经典生物学效应的主要受体形式,参与细胞增殖、分化、存活、泌乳相关基因表达、免疫和代谢调控
短型PRLR	膜结合型受体;胞外区与长型基本相似,但胞内尾部较短;人短型可由可变剪接产生,如S1a、S1b等	通常不能完整介导长型PRLR样JAK2/STAT5转录信号;S1a/S1b可与长型PRLR形成复合物,并在特定细胞背景下调节或抑制长型PRLR信号	可改变细胞对PRL刺激的反应阈值和信号持续时间;在某些细胞背景中表现为调节/抑制长型PRLR,也可能介导特定快速效应
中间型PRLR	膜结合型受体;由可变剪接产生,胞内区长度和序列介于长型与短型之间	可激活部分PRLR相关信号,但信号模式与长型不同;早期研究提示其STAT转录活性和增殖效应较长型弱或需较高PRL浓度;近期研究显示其与长型共表达时可增强乳腺上皮增殖、锚定非依赖性生长和转化相关表型	可能具有亚型特异性尾部和病理效应,尤其在乳腺上皮/肿瘤背景中受到关注
可溶性PRLR/PRL结合蛋白	缺乏跨膜区和胞内区,主要保留胞外配体结合相关结构;可由可变剪接产生或与受体外切/剪切相关	不直接传递膜受体信号;可通过结合PRL影响其局部可及性、生物利用度或受体激活强度	可能发挥缓冲、转运、拮抗或调节PRL作用的功能;部分研究显示人PRL结合蛋白可拮抗PRL作用并抑制PRL诱导的细胞增殖

胞内信号转导结构域,是介导经典PRL信号的主要亚型;短型PRLR的胞内结构域较短,经典信号转导能力相对有限,但在特定细胞背景下可调节长型PRLR介导的信号效应^[6]。因此,PRL的组织效应不仅取决于激素水平,还受到PRLR亚型构成及表达比例的影响。疾病进展过程中PRLR亚型构成及表达比例的改变,可能成为影响局部PRL响应的重要因素,而这一变化未必与循环PRL水平同步。

综上,PRL-PRLR轴的生物学复杂性源于PRL分子形式、组织来源、分泌调控、PRLR亚型及下游信号网络等多个层面的共同作用。这种多层次调控特征,使PRL-PRLR信号能够在不同组织和病理背景下产生差异化的生物学效应。

2 妇科及女性高发疾病中PRL-PRLR轴参与的共享病理环节

2.1 局部炎症维持与组织微环境重塑

在部分妇科和女性高发疾病中,PRL-PRLR轴的异常并不一定表现为持续性高泌乳素血症,而可能更多表现为局部信号失衡。子宫内膜异位症患者的血清PRL水平在现有研究结果中尚不一致,且循环PRL水平本身难以充分解释疼痛、不孕及病灶形成等复杂表型^[24-28]。现有证据亦不支持异位病灶是循环PRL升高的主要来源,腹腔液PRL升高的结论同样缺乏一致性^[26,29]。正常子宫内膜可在孕酮作用下合成PRL,这一过程独立于垂体调控^[30,31];

体外研究进一步显示,来源于不同亚型子宫内膜异位症病灶的基质细胞同样具备PRL合成能力^[32]。这些结果提示,子宫内膜异位症病灶局部可能存在独立的PRL旁分泌或自分泌调控。

类似的局部PRL信号异常也见于子宫腺肌症。现有机制模型多将子宫内膜与肌层之间的交接区(junctional zone,JZ)视为病变形成的关键区域。JZ受损后,内膜源性细胞可进入肌层,并在持续的“损伤-修复”循环中伴随血管新生、平滑肌增殖和细胞外基质重构,最终推动病灶形成和子宫壁重塑^[33-35]。从分子层面看,子宫腺肌症与子宫内膜异位症具有局部雌激素生成增强、孕激素反应减弱、慢性炎症和基质重构异常等共性^[36]。这些特征提示,PRL-PRLR轴在此类疾病中的作用并不局限于病灶形成后的被动响应,而可能参与局部炎症维持、组织重塑及病灶扩展等关键过程。尤其在子宫腺肌症中,PRL转基因小鼠可自发形成腺肌症样病变,提示PRL信号增强在特定背景下可能具有较强的致病驱动作用;而在子宫内膜异位症中,现有证据则更支持PRL参与病灶局部微环境中病理表现的维持与放大。因此,PRL-PRLR轴在不同疾病中的作用阶段和病理贡献可能存在差异。

2.2 神经敏化与女性疼痛易感

神经敏化是理解女性慢性疼痛易感性的重要病理环节,而PRL-PRLR信号在痛觉调控中表现出明确的性别特异性。PRLR在背根神经节和三叉神经

节的伤害感受神经元中表达丰富^[37],可通过调节离子通道活性增强神经元兴奋性,促进外周痛觉敏化^[38-40]。尽管雌雄感觉神经元中均可检测到PRLR转录本,但其蛋白表达与功能性信号响应受到雌激素调控,从而使PRL诱导的神经元兴奋和痛觉敏化呈现明显的雌性优势^[38,41]。

动物研究进一步支持这一性别差异。PRL作用于硬脑膜或三叉系统后,可在雌性动物中更显著地诱导偏头痛样行为,增强三叉神经元兴奋性并促进降钙素基因相关肽(calcitonin gene-related peptide, CGRP)释放,而雄性动物的反应相对较弱^[42]。在炎症痛、术后痛及阿片类药物诱导的痛觉敏化模型中,PRL相关促痛效应同样表现出一定的雌性优势^[43-45]。临床研究也发现,部分偏头痛患者,尤其是在慢性或发作期状态下,可出现血清PRL水平升高^[46-48];垂体泌乳素瘤患者头痛及偏头痛风险亦明显升高,而经多巴胺受体激动剂治疗降低PRL水平后,部分患者的头痛频率和强度可随之改善。

值得注意的是,子宫内膜异位症、子宫腺肌症等疾病中的PRL异常不仅常伴盆腔疼痛,亦与偏头痛等慢性疼痛性疾病存在较高的共病现象^[49]。结合PRL-PRLR轴在感觉神经敏化中的作用,这提示该信号可能参与不同疼痛表型之间的共同调控。因此,PRL-PRLR轴介导的促痛效应可能并非局限于单一疾病,而是女性多种慢性疼痛状态中值得关注的共同调节机制。

2.3 免疫耐受破坏与炎症放大

除参与局部炎症微环境调控外,PRL-PRLR轴还可影响免疫细胞活化及免疫耐受维持。子宫内膜异位症病灶周围常可见巨噬细胞、T细胞、B细胞和肥大细胞等免疫细胞聚集,这些细胞不仅参与炎症反应,也能够表达PRLR,部分细胞还可合成PRL^[50,51]。因此,PRL-PRLR轴可能参与局部炎症网络的活化,影响细胞因子释放、组织修复及纤维化进程。

相较于局部炎症性疾病,SLE为观察PRL-PRLR轴参与系统性免疫失衡提供了更直接的证据。荟萃分析显示,SLE患者血清PRL水平整体高于健康对照,且与疾病活动度及器官损伤累积呈正相关^[52-55]。更重要的是,SLE中的PRL并非完全源于垂体,T细胞、B细胞及树突状细胞等免疫细胞亦可合成PRL,以自分泌或旁分泌方式作用于表达

PRLR的免疫细胞^[56,57]。在B细胞中,PRL可干扰免疫耐受建立,促进自身反应性克隆存活及自身抗体生成^[58-61];在T细胞中,PRL可增强T细胞活化,推动其向Th1/Th17型偏移,同时抑制Treg细胞功能^[62-66];此外,PRL还可促进树突状细胞成熟及促炎因子分泌,增强抗原呈递效率及干扰素信号活化^[67]。

因此,PRL-PRLR轴可能并非SLE发生的单一始动因素,却可在遗传易感基础上持续削弱免疫耐受阈值,并放大自身免疫反应。换言之,在自身免疫背景下,PRL更像促炎反应的“增敏器”,使本已失衡的免疫网络进一步向持续激活方向偏移。

2.4 代谢适应与表型分层

与前述疾病不同,目前尚缺乏证据支持PRL是PCOS发生发展的直接驱动因素,其临床意义可能更多体现为与代谢状态及不同表型之间的关联。PCOS是育龄女性最常见的生殖-代谢综合征,以排卵障碍、高雄激素血症及卵巢多囊样形态为核心特征,常伴肥胖、胰岛素抵抗及脂代谢异常^[68-71]。由于高泌乳素血症同样可致月经紊乱与排卵障碍,PRL检测被长期用于鉴别诊断PCOS^[72]。然而,现有研究对于PCOS患者PRL水平的变化并未得出一致结论^[73-77]。

近年来,PRL逐渐被认识到同时具有生殖和代谢调节作用。其受体PRLR广泛分布于胰腺、肝脏、脂肪组织及下丘脑等代谢器官,而PRL的代谢效应具有明显的浓度和生理状态依赖性^[78-80]。有学者提出“稳态功能性一过性催乳素血症”(homeostatic functionally increased transient prolactinemia,简称HomeoFIT-PRL)概念,认为正常范围内偏高或轻度升高的PRL可能代表机体面对代谢负荷时的适应性反应,而PRL过低或显著升高则更常与代谢失衡相关^[79-81]。在PCOS人群中,PRL偏低者更易合并腹型肥胖、胰岛素抵抗及血脂异常,而PRL处于中高正常范围者的代谢表型相对更稳定^[74,75,82]。

因此,PRL在PCOS中的临床意义目前更多体现在与代谢表型的关联及患者分层上,其是否作为直接致病因素参与PCOS的发生发展,仍有待进一步研究。这说明PRL-PRLR轴在女性高发疾病中的作用方向存在显著异质性:在同一疾病的不同亚群中或在不同疾病背景下,该轴可能扮演促病、伴随或代偿性调节等不同角色,其具体作用取决于遗传背景、

代谢状态及信号异常发生的具体环节。

3 代表性疾病中的研究证据

3.1 子宫内膜异位症与子宫腺肌症

子宫内膜异位症和子宫腺肌症虽属不同疾病,但二者均提示PRL-PRLR轴的病理意义不能仅由循环PRL水平解释,局部信号异常可能具有更重要的作用;两种疾病的病理过程也都涉及慢性炎症、异常组织重塑和病灶的持续存在。

在子宫内膜异位症中,单纯以血清PRL水平难以充分解释病灶形成、疼痛或不孕等复杂表型,且现有研究关于其血清PRL变化的结论并不一致^[24,25,83]。相较之下,局部PRL系统可能更值得关注。正常子宫内膜在孕酮作用下可由间质细胞合成并分泌PRL,其调控方式不同于垂体来源PRL,且与血清PRL浓度并不直接对应^[30,31]。进一步的体外研究显示,来源于腹膜型、卵巢型及深部浸润型内异症病灶的基质细胞同样具有合成和分泌PRL的能力^[32],提示异位病灶内可能存在独立的PRL自分泌/旁分泌调节机制,并参与病灶的维持与进展。

与此同时,关于PRLR在异位病灶中的表达,现有研究结果并不完全一致。有研究提示其在基质和血管周围区域表达增强,但也有报告显示其表达降低或呈周期性波动^[84]。这些差异可能与月经周期、病灶类型、激素暴露及检测方法有关。总体来看,现有证据提示子宫内膜异位症中的PRL-PRLR异常可能更多发生于病灶局部,并与炎症维持、组织修复及疼痛敏化有关。

在子宫腺肌症中,PRL-PRLR轴与病灶维持的关联更为直接。动物实验表明,垂体移植或药物诱导的高PRL状态可在小鼠子宫中引发类似腺肌症的病理改变;而在关键阶段抑制PRL分泌,则可减轻病变程度^[85-88]。临床观察亦提示,部分子宫腺肌症患者血清PRL升高,小样本研究显示阴道给予溴隐亭可缓解疼痛、减少月经量^[89-91]。本课题组前期研究发现,PRLR不仅高表达于特定上皮细胞亚群,也富集于部分成纤维细胞,提示该通路可能同时参与上皮扩增、间质重塑及局部炎症调控^[92]。动物模型中PRL升高可诱导腺肌样表型,以及靶向PRLR的单克隆抗体HMI-115可改善病理改变,说明PRL-PRLR轴很可能是推动子宫腺肌症进展的重要信号通路。

3.2 女性易感性疼痛与偏头痛

女性慢性疼痛,尤其是偏头痛,不仅表现出明显的女性患病倾向,其背后还可能存在着痛觉调控机制的性别差异。PRL-PRLR轴已成为解释痛觉调控性别差异的重要候选机制之一。现有证据从多个层面支持其参与女性疼痛易感:在动物模型中,PRL可选择性诱导雌性伤害感受神经元敏化;在临床研究中,部分偏头痛患者常伴随PRL水平升高,而纠正高泌乳素状态后头痛症状可得到改善^[37,39-42,44,45,48,93-96]。

这些发现为理解女性偏头痛、炎症痛、术后痛及妇科疾病相关共病性疼痛提供了一个共同的机制框架。内分泌波动、PRL水平变化以及局部PRLR表达或信号响应增强,均可能通过提高神经元兴奋性、促进神经肽释放而放大痛觉输入,并与CGRP等痛觉相关介质形成协同放大效应^[95,96]。因此,女性慢性疼痛的干预除直接针对痛觉通路外,还应进一步关注内分泌信号与神经敏化之间的交互作用。

3.3 多囊卵巢综合征与系统性红斑狼疮

PCOS和SLE分别提示了PRL-PRLR轴在代谢调节和免疫失衡中的两种不同作用模式。对于PCOS,PRL的临床价值更多体现于代谢状态评估和患者分层,而非作为独立的致病指标;对于SLE而言,PRL-PRLR轴异常则更倾向于参与免疫耐受破坏及炎症放大。尽管二者临床表型和病理基础截然不同,但均提示PRL-PRLR轴异常不能仅以循环PRL水平高低加以判断,其生物学意义仍需结合组织背景、疾病阶段及下游信号响应模式综合判断。

从临床转化角度看,这种差异提示相关评估和干预策略应建立在疾病特异性分层基础之上。对于PCOS,PRL更适合作为代谢表型评估的参考指标;而在SLE中,PRL则可能兼具疾病活动度评估和治疗干预的潜在价值。

4 干预前景:从广泛抑制到精准调控

从干预策略看,围绕PRL-PRLR轴的治疗探索大致可分为两类:一类是通过多巴胺D2受体激动剂抑制垂体PRL分泌,从而降低循环PRL水平;另一类是直接靶向PRLR或PRL-PRLR信号,以期更精准地阻断局部病灶或特定细胞群中的异常信号转导。

4.1 降低PRL水平的多巴胺能干预及其局限性

多巴胺D2受体激动剂是目前较为成熟的PRL相

关于干预手段。其通过抑制垂体PRL分泌,在部分子宫腺肌症和子宫内膜异位症患者中可减轻疼痛、缩小病灶^[97-99];在高泌乳素血症相关PCOS中,可改善月经周期、雄激素水平及妊娠结局^[100-103];在SLE中,临床研究亦提示在常规免疫抑制基础上联合溴隐亭,可进一步降低疾病活动度,并改善部分免疫学及肾脏相关指标^[52,104]。

但多巴胺能干预也存在明显局限。其疗效并不总能完全归因于PRL水平下降,因为它可同时作用于中枢和外周多巴胺能通路;此外,胃肠道、心血管及神经系统相关不良反应亦限制了患者的长期使用^[105-107]。尤其对于以局部PRL-PRLR信号异常为主而无明显系统性高泌乳素血症的疾病状态,单纯降低循环PRL水平的作用可能受到限制。

4.2 PRL-PRLR信号阻断的转化前景

相比单纯降低循环PRL,直接阻断PRLR属于更具靶点特异性的干预策略,可在受体水平抑制PRL介导的信号转导。

在子宫内膜异位症治疗中,PRLR单克隆抗体HMI-115已显示出良好的疗效和转化前景^[108]。该抗体通过结合并阻断PRLR,抑制PRL介导的下游信号转导。已发表的多中心、随机、双盲、安慰剂对照Ⅱ期研究显示,HMI-115可改善中重度子宫内膜异位症相关疼痛。治疗12周后,HMI-115每2周给药组(240 mg)痛经数字评定量表(numerical rating scale,NRS)评分较基线下降约41.6%,非经期盆腔痛评分下降约50%;疗效在随访期仍呈持续趋势。安全性方面,HMI-115总体耐受性良好,未观察到治疗相关严重不良事件或典型低雌激素/围绝经期样不良反应,治疗期间患者月经周期、骨密度及主要性激素水平未见明显异常。目前,HMI-115已进入针对中重度子宫内膜异位症相关疼痛的Ⅲ期临床试验阶段。

在子宫腺肌症中,本课题组前期研究表明,HMI-115在小鼠模型中可显著改善病理表现^[92],提示PRLR阻断不仅可能缓解症状,更有望干预病灶活动。对于女性易感性疼痛,近年来开发的PRL中和抗体及PRLR阻断抗体在临床前研究中同样表现出明确的镇痛作用,可减轻应激相关、炎症性及偏头痛样疼痛^[93,95,109]。这些结果共同提示,阻断PRLR可能为女性相关疾病提供一种不同于传统激素抑制疗法的非激素型干预策略。

为便于比较不同干预策略的作用机制、适应证及临床研究进展,表3、4汇总了目前代表性的PRL-PRLR相关药物及临床或转化研究。

5 讨论与展望

综合上述证据,PRL-PRLR轴在不同妇科及女性高发疾病中的病理作用虽具有明显异质性,但其参与方式具有若干共性。首先,PRL的生物学功能已远超传统的泌乳调控范畴,兼具内分泌、免疫调节与局部组织调控功能。其异常并不必然表现为持续性高泌乳素血症,还可体现为局部PRL信号增强、PRLR表达或亚型构成改变以及特定细胞亚群对PRL的响应增强。其次,PRL-PRLR轴在不同疾病中的作用阶段和病理贡献并不一致:在子宫内膜异位症中,现有证据更多支持其参与病灶局部炎症维持、微环境重塑及疼痛敏化;在子宫腺肌症中,动物研究提示PRL信号增强可能具有更直接的致病作用;在女性易感性疼痛中,PRL-PRLR轴促进感觉神经元敏化并增强伤害性信号传递;在SLE中,则可能削弱免疫耐受并放大自身免疫反应;而在PCOS中,PRL的临床意义更多体现于代谢状态关联和患者分层,其是否作为直接致病因素仍有待进一步研究。

当前本领域仍面临若干关键问题。其一,现有临床研究对PRL的评估仍主要依赖血清浓度测定,而PRL存在多种分子形式,其水平又受到昼夜节律、月经周期、应激状态及药物暴露等多种因素影响,从而增加了不同研究间结果比较和重复验证的难度。其二,在部分疾病中,具有关键病理意义的可能并非单纯的循环PRL水平,而是局部组织来源的PRL及其微环境效应,但目前对局部PRL合成、释放及作用范围的认识仍十分有限。其三,PRLR具有多种亚型,其在不同细胞类型及疾病阶段中的表达差异可能显著影响疾病表型及治疗反应,但相关证据仍较有限。其四,现有研究虽已提示多巴胺受体激动剂和PRLR靶向抗体具有转化潜力,但获益患者人群、最佳干预时机,以及长期治疗对生殖功能和内分泌稳态的影响,仍需要进一步研究。

结合本课题组先前对子宫腺肌症的研究,PRL-PRLR异常并非存在于所有细胞,而是集中于特定上皮细胞亚群和部分成纤维细胞^[92]。这一发现提示,未来研究不宜仅停留于PRL水平是否有变化或

表3 靶向PRL分泌调控的药物及其相关临床研究

Table3 Drugs targeting PRL secretion and related clinical studies

药物	类别	作用机制	适应证	临床试验或研究编号	状态/结果概述
Cabergoline (卡麦角林)	多巴胺D2受体激动剂	抑制垂体PRL分泌	PRLR阳性转移性乳腺癌	NCT01730729	小样本临床Ⅱ期/先导研究,评估在PRLR阳性转移性乳腺癌中的临床获益
			子宫内异位症相关慢性盆腔痛	NCT03928288	临床Ⅱ期,作为add-on,与安慰剂比较,用于已接受标准激素治疗但仍有疼痛的内异症患者
			PCOS合并PRL升高或高泌乳素血症相关表型	已发表回顾性队列研究 ^[110]	可降低PRL和部分雄激素水平,并改善月经规律;不宜泛化为所有PCOS患者
Bromocriptine (溴隐亭)	多巴胺D2受体激动剂	抑制垂体PRL分泌	子宫腺肌症	NCT01821001	阴道给药治疗腺肌症的先导研究,可改善月经出血、疼痛及影像学/子宫结合带相关指标
				IRCT20230407057838N1	比较阴道给药溴隐亭与地诺孕素的疗效,溴隐亭在3、6个月时出血评分更低,地诺孕素在3个月时疼痛改善更明显
			系统性红斑狼疮常规治疗基础上的辅助治疗	已发表临床研究;包括双盲、随机、安慰剂对照研究 ^[52]	小样本研究提示可降低SLE疾病活动度
Quinagolide (诺果宁)	非麦角类D2受体激动剂	抑制垂体PRL分泌	系统性红斑狼疮辅助治疗探索	已发表小样本前瞻性/开放标签研究 ^[52]	小样本研究提示可降低SLE疾病活动度;证据有限
			子宫内异位症相关疼痛	NCT03692403	临床Ⅱ期,评估3种剂量药物相较安慰剂对中重度内异症相关疼痛的影响
			子宫内异位症囊肿、深部浸润型子宫内异位症和(或)子宫腺肌症病灶	NCT03749109	临床Ⅱ期,MRI评估病灶大小;主要终点未达到,与安慰剂相比病灶缩小无显著差异

表4 靶向PRLR信号的药物及其相关临床研究

Table 4 Therapeutic agents targeting PRLR signaling and related clinical studies

药物	类别	作用机制	适应证	临床试验或研究编号	状态/结果概述
HMI-115	全人源抗PRLR单抗	阻断PRLR信号	子宫内异位症相关疼痛	NCT05101317	临床Ⅱ期结果已于2025年发表
HMI-115	全人源抗PRLR单抗	阻断PRLR信号	子宫内异位症相关疼痛	NCT07318688	已注册/正在招募的临床Ⅲ期研究
HMI-115	全人源抗PRLR单抗	阻断PRLR信号	雄激素性脱发	NCT06118866	临床Ⅱ期试验已注册
LFA102	人源化抗PRLR单克隆抗体	结合PRLR并抑制PRL-PRLR信号	PRLR阳性转移性乳腺癌和转移性去势抵抗性前列腺癌	NCT01338831	临床Ⅰ期安全性和耐受性尚可,但因在测试剂量下未观察到明确的单药抗肿瘤活性而终止
Prolanta	PRLR拮抗剂;重组PRL类似物/拮抗剂	拮抗PRLR	复发或持续性上皮性卵巢癌、原发性腹膜癌、输卵管癌	NCT02534922	已注册的临床Ⅰ期,后续未明确
ABBV-176	抗体偶联药物(ADC)	PRLR靶向ADC;利用PRLR表达进行细胞毒性药物递送	PRLR表达的晚期实体瘤	NCT03145909	临床Ⅰ期已评估安全性、药代动力学和初步活性;出现显著毒性,未观察到客观缓解,开发结果不理想/研究终止

PRLR表达是否异常的现象描述,而应进一步明确PRL信号的关键响应细胞、参与炎症与组织重塑过程的主要效应细胞群及下游信号通路,并阐明这些异常与临床症状、病灶类型和治疗反应之间的关联。结合单细胞转录组、空间组学、类器官模型及

体内外功能干预实验,有望从细胞谱系、空间定位和因果关系等层面更精准地解析PRL-PRLR轴的致病环节。

在转化层面,未来可从两个方向推进探索。一方面,应建立更严格的分层研究框架,在控制月经周

期、应激状态、药物影响及合并症等混杂因素的基础上,区分循环PRL异常与局部PRL-PRLR信号失衡,并探索可用于患者筛选的生物标志物。另一方面,治疗策略可从单纯降低循环PRL逐步拓展至针对PRLR及其下游信号的靶向干预。尤其在子宫腺肌症、子宫内膜异位症和女性易感性疼痛等疾病中,PRLR阻断已显示出较好的临床前景,未来若能进一步明确适用人群、最佳干预窗口及长期安全性,有望为女性相关疾病提供新颖的治疗策略。

总体而言,PRL-PRLR轴为理解妇科及女性高发疾病提供了一个连接内分泌调控、免疫反应、神经敏化及局部组织微环境的整合视角。明确不同疾病背景下PRL-PRLR轴的实际病理贡献,识别具有决定性作用的响应细胞和信号环节,并在此基础上实现疾病和人群特异性的靶向干预,将是本领域值得进一步关注的研究方向。

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