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·文献综述·

G蛋白偶联雌激素受体在免疫调节中作用的研究进展

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摘　要　近年来研究发现，G蛋白偶联雌激素受体（GPER）不同于传统的核受体，是第三种独立作用的雌激素受体，它属于七次跨膜的G蛋白偶联受体（GPCR）家族成员。雌激素通过GPER介导G蛋白信号通路活化从而在正常生理及多种异常疾病中扮演重要角色，包括癌症、心血管疾病和炎症性疾病等。GPER表达于多种免疫细胞中，通过增强免疫细胞活性或调节免疫细胞之间的互动从而在免疫反应中发挥作用。同样，GPER还可参与炎症因子相关基因的表达从而抑制炎症反应。近期研究进一步揭示GPER不仅参与正常免疫系统的维持、异常免疫性疾病及炎症性病变，而且在肿瘤免疫调节中或有重要价值。笔者研究团队前期在多种恶性肿瘤中证实GPER介导的下游信号通路及其生物学功能，并发现GPER在乳腺癌和肝癌的肿瘤微环境中可能通过能量代谢重塑调节肿瘤免疫，以及血液肿瘤免疫治疗中靶向GPER有协同抗肿瘤药物的正向作用。综合现有研究发现，GPER可通过多样化的调节方式参与多种癌症的肿瘤免疫过程，包括乳腺癌中GPER通过调节免疫检查点分子的表达影响肿瘤免疫逃逸；肝癌中GPER调节免疫微环境和免疫细胞浸润，增加细胞因子和趋化因子的产生影响肿瘤免疫调节；结直肠癌中GPER增强免疫细胞的抗肿瘤活性和促进免疫细胞的细胞毒杀伤能力；血液肿瘤中GPER影响不同免疫细胞之间的“交叉对话”增强抗肿瘤免疫治疗等。因此，GPER为免疫相关疾病的治疗发展提供了新的途径，尽管目前尚处于探索阶段，但GPER作为新靶点联合免疫检查点抑制剂等药物的研发充满了临床潜力。本文综述当前GPER相关免疫调节作用的研究进展，为相关的基础与临床研究提供参考。

关键词　受体，雌激素；免疫调节；免疫疗法；综述
中图分类号：R457.2

Role of G protein-coupled estrogen receptor in immunomodulation: a review of research progress

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Abstract　In recent years, studies have found that G protein-coupled estrogen receptor (GPER), distinct from traditional nuclear receptors, is a third independent estrogen receptor that belongs to the family of seven-transmembrane G protein-coupled receptors (GPCRs). Estrogen activates G protein signaling pathways through GPER, playing important roles in normal physiology and various pathological conditions, including cancer, cardiovascular diseases, and inflammatory diseases. GPER is expressed in various immune cells and plays a role in immune responses by enhancing immune cell activity or modulating interactions between immune cells. Additionally, GPER can participate in the expression of inflammatory factor-related genes, thereby inhibiting inflammatory responses. Recent studies have further revealed that GPER is not only involved in maintaining normal immune system function, abnormal immune diseases, and inflammatory diseases but also may have important value in tumor immune regulation. The authors' research team has previously confirmed the downstream signaling pathways mediated by GPER and its biological functions in various malignant tumors, and have found that GPER may regulate tumor immunity of breast and liver cancer through energy metabolism remodeling in the tumor microenvironment, and targeting GPER in hematologic tumor immune therapy has a synergistic effect with anti-tumor drugs. Based on existing research findings, GPER participates in tumor immune processes of various cancers in diverse ways. For example, in breast cancer, GPER affects tumor immune escape by regulating the expression of immune checkpoint molecules; in liver cancer, GPER regulates the immune microenvironment and immune cell infiltration, affecting tumor immune regulation by increasing the production of cytokines and chemokines; in colorectal cancer, GPER enhances the anti-tumor activity of immune cells and promotes the cytotoxicity of immune cells; in hematologic tumors, GPER influences the "cross-talk" between different immune cells, enhancing anti-tumor immune therapy, etc. Therefore, GPER provides a new avenue for the development of immune-related diseases treatments. Although it is still in the exploratory stage, the development of GPER as a new target combined with immune checkpoint inhibitors and other drugs is full of clinical potential. This article reviews the current research progress on the immune regulatory effects of GPER, to provide a reference for related basic and clinical research.

Key words　Receptors, Estrogen; Immunomodulation; Immunotherapy; Review

CLC number: R457.2

G 蛋白偶联雌激素受体（G protein-coupled estrogen receptor，GPER）最早发现于 20 世纪 90 年代，不同于传统的核雌激素受体，它主要定位于细胞内质网和线粒体质膜上[1-2]。笔者的前期研究[3-4]发现，GPER 还可定位于细胞核与细胞膜中，提示 GPER 不是一个静止的蛋白分子，可能随着细胞功能状态的不同而在亚细胞器间穿梭。GPER 介导雌激素的快速非基因组效应，甚至间接参与基因组的转录调控[5]，从而作用于下游靶点促进细胞增殖、分化、迁徙和侵袭等行为[6]。随着研究的深入，GPER 参与的信号转导机制被逐步揭露：(1) GPER 介导下游表皮生长因子受体（epidermal growth factor receptor，EGFR）的反式激活[7]，其途径由 Gβγ 亚基介导 Src 相关酪氨酸激酶激活，促进基质金属蛋白酶活化从而反式激活 EGFR，随后快速活化丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）以及磷脂酰肌醇 3 激酶（phosphoinositide 3-kinase，PI3K）活化涉及的蛋白激酶 B 聚集；(2) Gα 亚基还可导致环磷酸腺苷生成和蛋白激酶 A 激活；(3) GPER 还能通过磷脂酶 C 促进内质网的钙离子动员[8]。以上 GPER 介导的下游通路活化在正常免疫系统、免疫性疾病、炎症性

病变与肿瘤免疫调节中发挥重要作用[6, 9-10]，本文笔者将对GPER参与的上述免疫调节作用进行总结。

1 GPER与正常免疫系统

GPER可在各类免疫细胞（如T淋巴细胞、B淋巴细胞、巨噬细胞、中性粒细胞和嗜酸性粒细胞）中表达[11-14]，并涉及多种超敏反应（表1）。研究[15]发现，长期雌激素暴露导致胸腺发育萎缩，GPER特异性激动剂G1激活GPER促进胸腺细胞凋亡。在T淋巴细胞体液免疫过程中，G1激活GPER下游细胞外调节蛋白激酶（extracellular signal regulated kinases，ERK）信号通路促进T细胞上调白介素10（interleukin 10，IL-10）表达[16-17]。在B淋巴细胞的非基因组信号传导中，雌激素通过GPER诱导其活化[18]。在纯化的人外周血嗜酸性粒细胞中，G1可抑制其自发凋亡及代谢活性[12]。此外，中性粒细胞非特异性免疫过程中，G1激活GPER/MAPK信号通路促进人中性粒细胞极化并增强代谢[19]。脱氢表雄酮可通过激活脂多糖诱导巨噬细胞中GPER的表达从而加剧细胞的异常自噬[11]。以上证据提示GPER介导的雌激素效应对调节免疫系统功能具有重要作用，靶向GPER及其下游MAPK/ERK通路在维持免疫系统功能中的作用值得深入探讨。

表1 I~IV型超敏反应中GPER介导的相关免疫细胞、免疫因子功能变化

Table 1 Functional changes of related immune cells and immune factors mediated by GPER in type I-IV hypersensitivity reactions

超敏反应分型	I型	II型	III型	IV型
免疫细胞	嗜酸性粒细胞	巨噬细胞、NK细胞	中性粒细胞	T细胞
免疫因子	IgE	IgG	免疫复合物	效应T细胞
GPER功能	降低IgE[20]	诱导IgG增加[11]	增强中性粒细胞代谢，延长其寿命[19]	诱导胸腺凋亡，增强IL-10[15, 21]

2 GPER与免疫性疾病

GPER对免疫性疾病的影响逐渐受到重视[20]。G1激活GPER降低支气管气道高反应及减轻过敏性肺炎，在保护气道上皮屏障完整性的同时，G1还降低血清IgE抗体水平与炎症细胞积累，从而改善小鼠急性哮喘的症状[21-22]，提示GPER特异性活化对抑制免疫因子及降低炎症细胞起着重要作用。此外，雌激素还通过减轻胃肠道炎症反应和增强胃黏膜保护屏障改善克罗恩病（Crohn's disease，CD）的临床症状[23-24]。GPER特异性活化介导核因子κB（nuclear factor κB，NF-κB）信号降低促炎细胞因子[如肿瘤坏死因子α（tumor necrosis factor α，TNF-α）、IL-6等]的产生，以及microRNA（如miR-145、miR-148-5p和miR-592）的表达从而降低CD小鼠病死率[25]。以上数据提示GPER介导的免疫调节作用参与免疫性疾病发生发展，并与临床严重程度及预后密切关系。

3 GPER与炎症性病变

GPER激活可抑制炎症性疾病[26]，参与NF-κB信号抑制TNF-α和IL-6的表达[27]。在化疗诱发的肠黏膜炎小鼠中，G1激活GPER/ERK途径抑制肠黏膜炎相关DNA损伤达到预防和减轻化疗诱发的肠黏膜炎症[28]。G1还可增强调节性T细胞反应，降低IL-4、IL-5和IL-13从而缓解小鼠鼻炎症状[29]。同时，在患有系统性红斑狼疮的小鼠血清中，GPER可降低血清IgG产生的促炎细胞因子TNF-α和IL-8的表达，从而减轻皮肤炎症反应[30-31]。与上述相符的是，GPER降低NF-κB磷酸化水平从而减轻牙周炎并刺激骨保护素分泌减少骨质流失[32]。综上，GPER在炎症性病变中可通过多种作用抑制促炎因子从而减轻炎症反应，但相关研究中细胞类型及整体炎症环境差异较大，仍需更多的研究进一步阐述其具体作用机制。

4 GPER与肿瘤免疫调节

GPER在多种恶性肿瘤中广泛表达，具有较好的肿瘤诊断、预后及临床治疗价值[33]。目前有关雌激素/GPER信号对恶性肿瘤免疫调节相关研究集中于女性生殖系统肿瘤、消化系统肿瘤、体表肿瘤与血液系统肿瘤[34]（图1）。因此，围绕上述肿

瘤的免疫调节机制总结，能更好地理解 GPER 对恶性肿瘤发生发展的内在机制及其影响肿瘤免疫治疗敏感性的潜在临床意义。

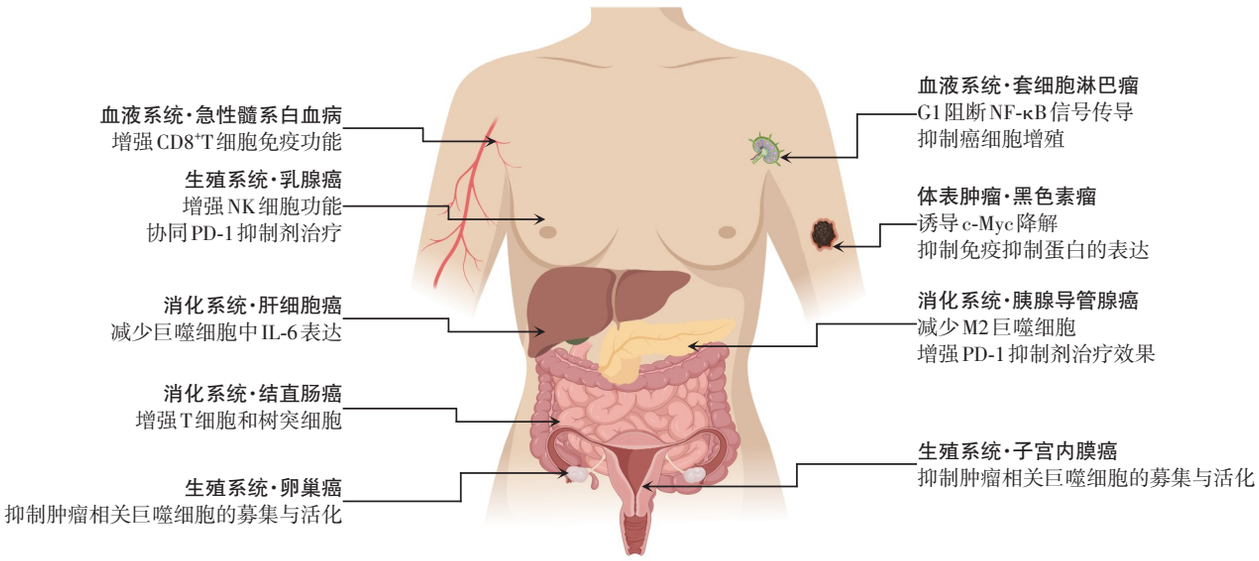

图 1　GPER 在多种肿瘤免疫调节中的功能

Figure 1　GPER functions in immunomodulation of multiple tumors

4.1　GPER 与女性生殖系统肿瘤

长期雌激素暴露会增加女性生殖系统肿瘤（如乳腺癌、子宫内膜癌及卵巢癌等）的发生风险[35]。作为一种新型雌激素受体，GPER 在促进以上肿瘤的基因转录、增殖和细胞迁移变化过程中发挥着重要作用[36]。他莫昔芬（tamoxifen，TAM）耐药对雌激素受体 α（ERα）阳性乳腺癌患者临床治疗提出严峻挑战，GPER 介导乳腺癌相关成纤维细胞中高迁移率族蛋白 B1 的分泌以保护肿瘤细胞免受 TAM 诱导的细胞凋亡[37]；GPER 激活同时促进缺氧诱导因子-1α 上调癌细胞的有氧糖酵解，从而影响 TAM 敏感性[38]。而 TAM 耐药可抑制免疫细胞的激活并降低免疫检查点分子的表达[39]，提示在 ERα 阳性乳腺癌中 GPER 可能通过 TAM 耐药作用实现肿瘤的免疫逃逸。而在三阴性乳腺癌中，G1 则活化 GPER 介导 NK 细胞的杀伤力增加，并协同提高程序性死亡受体 1 抑制剂的免疫治疗敏感性[40]。

在卵巢癌与子宫内膜癌中亦发现 GPER 过表达与患者较差的生存期有关[41-42]，且 GPER 活化下游 PI3K/Akt[43] 和 MAPK/ERK[44] 通路来实现癌细胞的增殖和转移。肿瘤相关巨噬细胞在子宫内膜癌[45] 与卵巢癌[46] 中发挥着促进肿瘤免疫逃逸及化疗抵抗，在肿瘤微环境中 GPER 抑制肿瘤相关巨噬细胞的募集与活化促进子宫内膜癌与卵巢癌的抗肿瘤免疫效果[47]。因此，有理由推测 GPER 诱导的肿瘤微环境改变可能促进女性生殖系统肿瘤的免疫逃逸，联合靶向 GPER 信号有望提高免疫治疗疗效。

4.2　GPER 与消化系统肿瘤

胰腺癌细胞外基质中聚集着大量 M2 型巨噬细胞和中性粒细胞，它们与活化的星状细胞共同刺激下促进缺氧环境并改变肿瘤细胞代谢，从而达到免疫抑制效果[48]。有趣的是，在胰腺导管腺癌小鼠模型中，TAM 显著降低 M2 型巨噬细胞比例[47]，且接受 G1 与 PD-1 抑制剂联合治疗较单药免疫治疗显著延长小鼠生存期[49]。此外，白杨素还可激活 GPER 增强对胰腺癌细胞生长抑制效应，明显降低肿瘤增殖能力及细胞增殖指数（Ki-67）的表达[6]。以上数据提示靶向活化 GPER 与微环境成分间的“交叉对话”可能参与胰腺癌免疫调控及增敏免疫疗效，有望成为较好的临床分子靶标。

男性肝细胞癌的发病率和病死率均显著高于女性，同时在正常肝细胞中雌激素受体表达具有性别差异[50]。团队前期研究[10]发现肝细胞癌组织与正常组织中 GPER 表达具有显著差异，而 GPER 阳性表达与肝细胞癌患者较好的预后密切相关。在小鼠模型中发现 GPER 敲除显著加速肿瘤细胞的发生，GPER 降低原始单核细胞和巨噬细胞中炎症因子（如 IL-6 和 TNF-α）的表达从而抑制肝细胞癌的

发生发展[51]，这些研究为肝细胞癌免疫调节机制提供了新的思路。

雌激素信号在结直肠癌的发展中具有保护性作用[52]，但GPER介导的雌激素效应在结直肠癌进展中的作用存在一定争议[53]。研究[54]发现，GPER高表达于结直肠癌中，并通过Wnt/β-catenin信号通路促进癌细胞的增殖和侵袭。而另一项研究[55]表示，GPER通过ERK信号通路持续抑制NF-κB的磷酸化和转录活性抑制结直肠癌的增殖。在肿瘤微环境中，结直肠癌主要通过高水平的调节性T细胞抑制免疫反应，而GPER可增强免疫细胞（如T细胞和树突细胞）促进抗肿瘤免疫能力[56]，提示GPER可能通过上述免疫途径影响结直肠癌的免疫反应，该机制仍需要进一步的研究证实。

4.3 GPER与体表肿瘤

黑色素瘤中男性患病风险更高且预后更差，雌激素可激活GPER促进黑色素瘤发展[57]。GPER诱导原癌基因转录因子蛋白c-Myc的降解，并抑制包括细胞程序性死亡-配体1（programmed cell death 1 ligand 1，PD-L1）在内的免疫抑制蛋白的表达，PD-L1抑制剂联合G1治疗不仅缩小肿瘤，且显著提高黑素瘤小鼠存活率[58]。LNS8801是一种口服的高选择性小分子GPER激动剂，通过上调p53和p21抑制黑色素瘤细胞增殖和促进细胞凋亡，并增强免疫识别[59]。令人惊喜的是，LNS8801已进入黑色素瘤IB期临床研究阶段[60]，也是目前唯一探讨靶向GPER联合免疫治疗的实体瘤研究。这些数据有望在未来进一步揭示GPER激动剂联合免疫治疗的临床应用前景。

4.4 GPER与血液系统肿瘤

急性T淋巴细胞白血病中，G1在M期阻止细胞周期进程从而抑制细胞增殖并诱导细胞凋亡，并通过影响Ca^{2+}浓度调节线粒体能量代谢，这一过程可被GPER特异性拮抗剂G36所阻断[9]。GPER在急性髓系白血病中有更高的表达，GPER活化增强白血病细胞焦亡和$CD8^{+}$T细胞免疫功能协同药物维奈托特的抗肿瘤作用[61]，并且LNS8801能够抑制人急性髓系白血病细胞在体外模型中得到验证[62]。笔者团队前期研究[63]还发现，GPER在套细胞淋巴瘤的免疫治疗中具有正向作用，G1通过阻断NF-κB信号传导抑制肿瘤细胞增殖，并在小鼠体内证实G1的抗肿瘤作用。因此，GPER活化可增强白血病和淋巴瘤等血液疾病的抗肿瘤免疫反应，使用GPER相关特异性药物联合免疫治疗可能更好地改善血液系统肿瘤的疗效。

5 总结与展望

新型雌激素受体GPER在免疫调节中发挥重要作用，并参与各种免疫疾病、炎症反应和肿瘤免疫。关于自身免疫性疾病、过敏性疾病和炎症性肠病等，GPER激活影响免疫细胞功能、细胞因子的产生和免疫细胞介导的炎症反应，将有助于这些疾病的发生发展。GPER调节肿瘤免疫反应的新兴作用，以及靶向GPER增强免疫治疗的方法有望改变癌症治疗。同时，GPER还表达于多种肿瘤免疫微环境中，增强免疫细胞（包括T细胞、NK细胞）和炎症因子在肿瘤微环境中的浸润和免疫活性。综上，越来越多的证据表明GPER在肿瘤免疫反应中影响肿瘤生长、侵袭和抗肿瘤免疫应答，靶向GPER可能增强抗肿瘤免疫治疗的疗效。然而，仍然需要更多的研究探讨GPER在不同疾病中的具体免疫调节机制，并将这些发现转化为有效的临床治疗方法。

利益冲突：所有作者均声明不存在利益冲突。

作者贡献声明：曾小强负责文献选题、文献资料解读分析和文章初稿撰写；周菁负责文献检索和内容审阅；黄晏骁撰写了特定章节或段落；徐佳伟参与文献选题，协助编辑和修订综述；徐家乐负责收集和整理综述所需的图表、图像和数据；余腾骅负责文献总体选题和设计、文献稿件最终审阅定稿，对学术问题进行解答，并最终同意论文发表。

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