

肿瘤坏死因子- α 与卵巢疾病的研究进展

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摘 要

卵巢疾病, 包括多囊卵巢综合征(PCOS)、卵巢子宫内膜异位症(OEM)、卵巢癌(OC)等, 通过炎症因子介导(如TNF- α)的发病机制影响患者生殖功能与内分泌稳态。TNF- α 作为炎症反应的核心调控因子, 通过激活NF- κ B、MAPK及凋亡信号通路, 在卵巢疾病进程中发挥重要作用。在PCOS的病理进程中, TNF- α 参与并加剧胰岛素抵抗与慢性炎症状态, 进而促进高雄激素血症, 这些因素共同作用, 可能最终对卵巢储备功能(OR)产生不利影响; 而在OEM及OC等疾病进展中, TNF- α 的增加改变了卵巢微环境, 损伤卵泡, 导致卵巢储备功能减退(DOR)。卵巢疾病对女性长期健康及生育力造成损害, 从而显著降低女性的生活质量, 近年来备受关注。基于此, TNF- α 抑制剂及相关该通路的药物可用于治疗卵巢疾病, 但相关药物属于超说明书用药, 目前研究较少; 这类药物长期使用对卵巢储备功能(OR)、生育力及潜在的母婴安全性影响尚不明确。本文将对TNF- α 与卵巢疾病发病机制及目前针对该通路的药物疗效进行综述, 为卵巢疾病临床治疗及卵巢功能保护提供新思路。

关键词

肿瘤坏死因子- α , 多囊卵巢综合征, 卵巢子宫内膜异位症, 卵巢癌, 卵巢储备功能减退, 肿瘤坏死因子- α 抑制剂

Research Progress on Tumor Necrosis Factor- α and Ovarian Diseases

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Abstract

Ovarian diseases, including polycystic ovary syndrome (PCOS), ovarian endometriosis (OEM), and

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ovarian cancer (OC), affect patients' reproductive function and endocrine homeostasis through mechanisms mediated by inflammatory factors such as $\text{TNF-}\alpha$. As a core regulatory factor of the inflammatory response, $\text{TNF-}\alpha$ plays a significant role in the progression of ovarian diseases by activating NF- κ B, MAPK, and apoptotic signaling pathways. In the pathological process of PCOS, $\text{TNF-}\alpha$ is involved in and exacerbates insulin resistance and chronic inflammation, which in turn promotes hyperandrogenemia. These factors collectively may ultimately have an adverse effect on ovarian reserve (OR). In the progression of diseases such as OEM and OC, the increase of $\text{TNF-}\alpha$ alters the ovarian microenvironment, damaging follicles and leading to diminished ovarian reserve (DOR). Ovarian diseases damage long-term health and fertility in women, significantly reducing their quality of life, and have gained considerable attention in recent years. Based on this, $\text{TNF-}\alpha$ inhibitors and medications related to this pathway could be used to treat ovarian diseases; however, these medications fall under off-label use, and there is currently limited research on them. The long-term effects of such drugs on ovarian reserve (OR), fertility, and potential mother-infant safety remain unclear. This article will review the role of $\text{TNF-}\alpha$ in the pathogenesis of ovarian diseases and the efficacy of current medications targeting this pathway, providing new insights for clinical treatment and ovarian function preservation.

Keywords

Tumor Necrosis Factor- α , Polycystic Ovary Syndrome, Ovarian Endometriosis, Ovarian Cancer, Decreased Ovarian Reserve, Tumor Necrosis Factor- α Inhibitors

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1. 引言

肿瘤坏死因子- α (Tumor necrosis factor alpha, $\text{TNF-}\alpha$)是由 157 个氨基酸构成的同型三聚体蛋白, 其主要由活化的巨噬细胞(Macrophage, M)、T 淋巴细胞(T-lymphocyte cell, Tc)以及自然杀伤细胞(Natural killer cell, NKc)所分泌产生[1]。作为一种对多种细胞类型展现多效性的促炎细胞因子, $\text{TNF-}\alpha$ 在炎症的发生和发展过程中发挥着关键作用, 并在多种卵巢疾病的发生机制中具有重要意义。本文选取多囊卵巢综合征(Polycystic ovary syndrome, PCOS)、卵巢子宫内膜异位症(Ovarian Endometriosis, OEM)及卵巢癌(Ovarian Cancer, OC)作为研究对象, 不仅因其在临床与病理机制上均涉及炎症与免疫调节异常, 更因 $\text{TNF-}\alpha$ 作为共同的关键炎症介质, 在这三类疾病的发生、发展中扮演重要角色, 并对可能卵巢功能造成影响。异常表达的 $\text{TNF-}\alpha$ 可通过不同途径促进上述疾病的病理进展, 并最终共同导致卵巢储备功能减退(Diminished Ovarian Reserve, DOR), 影响卵巢功能。因此, 深入研究 $\text{TNF-}\alpha$ 在这些疾病中的作用机制, 不仅有助于理解其共同的病理基础, 也对卵巢功能的保护具有重要理论及潜在临床应用价值。

2. $\text{TNF-}\alpha$ 信号通路

$\text{TNF-}\alpha$ 以可溶型(Soluble $\text{TNF-}\alpha$, s $\text{TNF-}\alpha$)及跨膜型(Transmembrane $\text{TNF-}\alpha$, tm $\text{TNF-}\alpha$)存在, 其中 s $\text{TNF-}\alpha$ 由 tm $\text{TNF-}\alpha$ 经过 $\text{TNF-}\alpha$ -转化酶($\text{TNF-}\alpha$ -converting enzyme, TACE)酶切释放[2]。其功能主要通过肿瘤坏死因子受体 1 (Tumor necrosis factor receptor 1, TNFR1)和肿瘤坏死因子受体 2 (Tumor necrosis factor receptor 2, TNFR2)两种受体介导。

TNFR1 广泛表达于所有组织, 与 $\text{TNF-}\alpha$ 结合后迅速招募 TNFR1 死亡结构域招募蛋白(TNFR1-

associated death domain, TRADD)、受体相互作用蛋白激酶 1 (Receptor-interacting serine/threonine-protein kinase 1, RIPK1)、细胞凋亡抑制蛋白 1/2 (Cellular inhibitor of apoptosis protein 1/2, cIAP1/2)及线性泛素链组装复合体(Linear ubiquitin chain assembly complex, LUBAC)形成复合体 I (Complex I) [3]-[5]。

复合体 I 通过两条核心通路触发炎症[5] [6]: (1) LUBAC 介导的线性泛素化激活核因子 κ B (Nuclear factor- κ B, NF- κ B)信号通路, 诱导包含白细胞介素-6 (Interleukin-6, IL-6)在内的促炎因子和 FLICE 样抑制蛋白(FLICE-like inhibitory protein, FLIP)等抗凋亡蛋白表达; (2) 转化生长因子- β 激活激酶 1 (Transforming growth factor- β -activated kinase 1, TAK1)-TAK1 结合蛋白(TAK1-binding protein, TAB)复合体通过丝裂原活化蛋白激酶(Mitogen-activated protein kinases, MAPKs)通路(如 c-Jun 氨基末端激酶, JNK; p38 丝裂原活化蛋白激酶, p38)进一步放大炎症信号。

当复合体 I 的促生存调控失效, RIPK1 解离并形成胞质复合体 II (Complex II), 触发三类死亡程序[6]: (1) 凋亡(Apoptosis): 半胱氨酸 - 天冬氨酸蛋白酶-8 (Caspase-8)激活下游效应 Caspase-3/7, 其活性受 FLIP 抑制; (2) 坏死性凋亡(Necroptosis): RIPK1-RIPK3-混合系激酶区域样蛋白(Mixed lineage kinase region-like protein, MLKL)磷酸化 MLKL, 导致细胞膜破裂并释放损伤相关分子模式(Damage-associated molecular patterns, DAMPs); (3) 焦亡(Pyroptosis): Caspase-8 切割 Gasdermin D/E 形成膜孔, 释放白细胞介素-1 β (Interleukin-1 beta, IL-1 β)等促炎介质。

TNFR2 的表达仅限于免疫细胞和少数非免疫细胞, 包括内皮细胞、心肌细胞和神经胶质细胞[7]。其通过非经典 NF- κ B 通路与 TNFR1 协同调控炎症微环境[6]。例如[7], tmTNF- α 对 TNFR 2 的激活导致 TRAF 2-cIAP 1/2 复合物的胞浆池耗尽, 进而拮抗 TNFR 1 介导的细胞死亡信号, 引起轻度炎症和细胞保护。

TNF- α 信号稳态由三大检查点调控[6]: (1) IKK 检查点: 在复合体 I 中, IKK α/β 与 TBK1/IKK ϵ 通过磷酸化 RIPK1 的 S25 位点抑制其激酶活性, 阻断 RIPK1 依赖性凋亡及坏死性凋亡信号的传递[8]-[10]; (2) NF- κ B 检查点: 转录上调 FLIP, 与 Caspase-8 竞争性结合复合体 IIa, 抑制其激活并维持细胞存活[11] [12]; (3) Caspase-8 检查点: 活化的 Caspase-8 通过切割 RIPK1 不可逆终止其促凋亡功能, 并抑制 RIPK1-RIPK3-MLKL 坏死性凋亡复合体的组装[13] [14]。三大检查点通过时空特异性调控 RIPK1 活性, 共同维持炎症与细胞死亡的动态平衡。

综上所述, TNF- α 通过促炎基因激活和死亡依赖性 DAMPs 释放双重途径驱动炎症。抑制 TNF- α 产生可减弱炎症反应, 而促进 TNF- α 的分泌可介导细胞死亡。临床上对于 TNF- α 的抑制或促进视疾病而定。

3. TNF- α 与卵巢疾病

3.1. TNF- α 与 PCOS

PCOS 是妇科常见的生殖、内分泌、代谢性疾病, 以排卵障碍、高雄激素血症及卵巢多囊样改变为特征, 临床表现为月经不规律、多毛、痤疮、肥胖及胰岛素抵抗(Insulin resistance, IR)。全球育龄期女性中 PCOS 的发病率约为 15% [15]。

PCOS 患者存在慢性低度炎症[16]。TNF- α 作为炎症反应的核心因子, 其水平升高在 PCOS 中受到多种因素驱动: ① 高水平的雄激素可激活 NF- κ B 信号通路, 促使脂肪细胞分泌 TNF- α [17]; ② 肠道菌群失调导致体内脂多糖增加, 同样可激活 NF- κ B 通路, 促进炎症及 TNF- α 产生[18] [19]。升高的 TNF- α 通过以下机制参与 PCOS 病理进程: ① 与高水平的活性氧(Reactive oxygen species, ROS)共同作用, 激活 NF- κ B 通路, 形成正反馈循环, 进一步释放 TNF- α 并加剧氧化应激和炎症反应[20] [21]; ② 激活 c-Jun 氨基末端激酶 1 (C-Jun N-terminal kinase 1, JNK-1)致胰岛素受体底物-1 (Insulin receptor substrate-1, IRS-1)丝氨酸磷酸化[18]、通过 NF- κ B p65 通路下调葡萄糖转运蛋白 4 (Glucose transporter 4, GLUT-4)表达[22] 以及抑制脂联素活性[23], 共同介导 IR, 加重 PCOS 代谢异常。动物模型研究表明, 百令胶囊(Cordyceps

sinensis extract)可下调卵巢 NF- κ B p65 表达,显著降低 PCOS 模型小鼠血清 TNF- α 水平,并改善肠道菌群失调和炎症[24]。临床随机对照试验发现,具有抗氧化特性的物质如油酰乙醇酰胺(Oleylethanolamide, OEA) [25]和鞣花酸[26]能显著降低 PCOS 患者血清 TNF- α 水平,改善氧化应激状态。更直接的,一项针对 PCOS 不孕妇女促排卵的回顾性分析发现,使用 TNF- α 抑制剂组相较于对照组,所需促性腺激素用量更少、达到触发时间更短,且优质胚胎率和临床妊娠率均显著更高[27]。

综上所述, TNF- α 介导的慢性炎症是 PCOS 发生发展的重要环节。研究发现, PCOS 患者出现早发性卵巢功能不全(premature ovarian insufficiency, POI),即 40 岁之前发生的 DOR 的风险增高[28],但具体机制尚未明确, TNF- α 可能在此过程发挥重要作用。因此,靶向干预 TNF- α 信号通路一如抑制其产生、阻断其活性或使用特异性抑制剂一有望成为治疗 PCOS 的新策略,尤其在改善炎症状态、代谢异常、卵巢储备功能(Ovarian Reserve, OR)及生殖结局方面具有潜在价值。

3.2. TNF- α 与 OEM

子宫内位症(Endometriosis, EM)是指子宫内膜的腺体和间质出现在子宫内膜以外的部位,引起疼痛、不孕、结节或包块等临床表现[29]。卵巢子宫内位症(Ovarian Endometriosis, OEM)是一种特殊的 EM,其慢性炎症微环境可导致卵巢功能进行性损伤,并加速 DOR 的发生。全球约 2%~10%的育龄期女性患有 EM,而在不孕女性中其患病率高达 50% [30]。

EM 存在慢性炎症状态,活化的免疫细胞(如巨噬细胞)释放包括 TNF- α 在内的细胞因子和趋化因子,导致炎症及内皮损伤[31]。在 OEM 中,这种炎症微环境尤为突出。OEM 缺乏包膜,仅被基质和单层柱状上皮细胞包围,其内产生的 TNF- α 在内的促炎因子和 ROS 易扩散到邻近卵巢皮质和卵泡微环境中,直接造成卵泡损伤[32],导致 DOR。回顾性研究[33]发现 OEM 患者囊内液、腹腔液、血浆中 TNF- α 浓度依次递减,且与 EM 分期(III/IV 期)无关,提示 TNF- α 主要在局部微环境发挥促炎作用。体外研究[34]证实,应用 NF- κ B 抑制剂和 MAPKs 抑制剂可阻断 TNF- α 诱导的 OEM 基质细胞 IL-6 表达,减轻炎症。前瞻性研究[35]发现患者卵泡液 TNF- α 升高使得颗粒细胞(Granulosa Cells, GCs) IKK β 、I κ B α 磷酸化增强,激活 NF- κ B 通路,显著抑制人端粒酶逆转录酶(human telomerase reverse transcriptase, hTERT)蛋白表达及端粒酶活性(Telomerase Activity, TA)。TA 降低与获卵数及成熟卵数减少显著相关,从功能层面揭示了 TNF- α 通过抑制 GCs 端粒酶功能影响卵母细胞成熟,进而加速 DOR 的具体通路。

OR 是一种衡量剩余卵母细胞数量和质量的指标[36]。DOR 是指卵母细胞数量减少和(或)质量下降,伴随生育力下降,并表现为抗苗勒管激素(Antimüllerian Hormone, AMH)水平降低、窦卵泡(Antral Follicle Count, AFC)减少及基础卵泡刺激素(Base Follicle Stimulating Hormone, bFSH)水平升高[37]。在 DOR 发生过程中, TNF- α 介导的炎症微环境紊乱同样扮演了关键角色。研究表明患者血清及卵泡液中的 TNF- α 水平显著升高。西班牙的一项横断面研究发现 DOR 患者与对照组相比血清 TNF- α 有显著差异[38]。Huang [39]等人通过检测 46 例 DOR 和 56 例正常卵巢储备(Normal Ovarian Reserve, NOR)患者卵泡液(Follicular Fluid, FF)炎症指标,发现 DOR 组 TNF- α 浓度显著高于 NOR 组。Li [40]等人的研究通过检测 DOR 组(42 例)和 NOR 组(73 例)的 FF 中 TNF- α 浓度,得到了类似的结果。这提示 TNF- α 参与卵母细胞微环境失衡。Jiao [41]等人研究进一步揭示血清 TNF- α 水平与卵泡刺激素(Follicle Stimulating Hormone, FSH)呈显著正相关; TNF- α 协同 IFN- γ 直接诱导颗粒细胞凋亡,抑制增殖,并通过下调芳香化酶 CYP19A1 显著减少雌激素合成; TNF- α 使 p65 磷酸化增加,激活 NF- κ B 通路抑制结缔组织生长因子(Connective Tissue Growth Factor, CTGF)表达,介导颗粒细胞功能障碍。这些研究结果表明, TNF- α 水平的升高通过直接损害颗粒细胞功能(促进凋亡、抑制增殖与雌激素合成)和破坏卵泡微环境,共同加速卵巢功能衰退。

综上, OEM 病灶来源的 TNF- α 通过介导慢性炎症及激活 NF- κ B 信号通路,不仅直接造成局部卵泡

损伤,还可引起颗粒细胞端粒酶活性下降和功能障碍,共同促进 DOR 的发生与发展。靶向干预 TNF- α 或其下游 NF- κ B 信号通路可能成为缓解卵巢炎症微环境、延缓 DOR 进展的潜在策略,但其临床应用价值仍需前瞻性干预研究进一步验证。

3.3. TNF- α 与 OC

2020 年全球数据显示[42], OC 发病率在妇科肿瘤居第三位;死亡病例位列第二。在我国, OC 发病率在妇科生殖肿瘤位列第三位,严重威胁女性的生命健康。其病理分型多样,其中最常见的是上皮性肿瘤(Epithelial Ovarian Cancer, EOC),约占 OC 的 80%。值得注意的是, OC 本身可能导致卵巢组织损伤和功能衰退,进而引发或加速 DOR,严重影响患者的生育结局及长期内分泌健康。

EOC 中 TNF- α mRNA 过表达,约为正常卵巢组织的 1000 倍[43]。高水平的 TNF- α 可能通过以下机制参与 EOC 疾病进展,并同样可能加速 DOR 的进程:① 通过自分泌及旁分泌结合自身或旁肿瘤细胞表面的 TNFR1 受体,激活 NF- κ B 等信号通路,直接刺激肿瘤细胞增殖[44];② 刺激肿瘤细胞分泌 IL-6 等促炎因子,重塑肿瘤免疫微环境(Tumor Immune Microenvironment, TIME),间接影响卵巢功能[45];③ 通过内皮细胞中 p38 MAPK 和 SAPK/JNK 通路诱导 Ephrin A1 表达促进血管生成,改变局部血供及微环境[46];④ 通过 TNF- α -转化生长因子- α (transforming growth factor- α , TGF α)-表皮生长因子受体(epidermal growth factor receptor, EGFR)促进 OvCA 的腹膜转移[47];⑤刺激肿瘤细胞和基质细胞分泌 MMPs,降解细胞外基质,促进腹腔播散;⑥ 诱导调节性 T 细胞(Treg)扩增或抑制树突细胞成熟,削弱免疫监视[48];⑦ 诱导炎症组织产生诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)和足够一氧化氮(nitric oxide, NO)导致 DNA 损伤并抑制 DNA 修复蛋白[49]。这些机制不仅促进 EOC 进展,其介导的持续炎症状态及卵巢微环境破坏也可能共同加速 DOR 的发生。

基于以上机制,研究者们针对性探索了一些治疗方法。Brown E R 等人[50]发现 TNF- α 拮抗剂英夫利昔单抗(infliximab)在治疗晚期癌症有一定的疗效。随后 Charles K A [51]等人的研究在使用 infliximab 治疗晚期 OC 患者中发现治疗后 1 h 及 24 h 后的血清及腹水 TNF- α 浓度显著下降。另有研究发现,拮抗性 TNFR2 抗体通过稳定受体反向二聚体,阻断 NF- κ B 通路,双重抑制卵巢癌细胞增殖及肿瘤相关 Treg 扩增,且对肿瘤微环境 Treg 具特异性杀伤作用[48],其可能通过同时抑制 Treg 活性和诱导癌细胞死亡,成为卵巢癌患者的潜在疗法[52]。

4. 总结与展望

TNF- α 作为关键的促炎因子,在多种卵巢疾病的病理生理进程中扮演核心角色。在 PCOS 中, TNF- α 不仅直接关联 IR,还加剧氧化应激,参与高雄激素血症(Hyperandrogenemia, HA)形成,并与肠道菌群失调相互作用,共同推动疾病发展。在 OEM 的发病中,高浓度 TNF- α 通过激活 NF- κ B 信号通路抑制端粒酶活性,损害卵母细胞质量及卵泡发育。而在 OC 中,在肿瘤微环境中, TNF- α 可能通过激活 NF- κ B 等通路促进肿瘤细胞增殖、侵袭、转移。升高的 TNF- α 水平通过介导炎症反应,参与卵母细胞微环境失衡、抑制颗粒细胞功能并损害卵母细胞质量,加速了 DOR。

基于其核心炎症调控作用,靶向 TNF- α 通路已成为潜在的治疗策略,尤其在 EM 和 EOC 中已有初步探索,但在 PCOS 和 DOR 治疗中仍处于起始阶段。目前制约其临床转化的关键问题包括:疾病异质性(如 PCOS 表型、OC 分子分型)对疗效的影响、长期用药安全性以及不同人群中的风险-获益评估。未来可建立基于 TNF- α 及其下游效应分子(如 IL-6)的生物标志物组合,用于卵巢疾病风险分层及 TNF- α 抑制剂疗效预测;设计针对特定亚群(如炎症表型 PCOS 或深部浸润型 EM)的多中心随机对照试验,明确试验关键终点(如排卵恢复、病灶缩小或 OR 指标改善),并系统评估感染风险与生育结局;深入探索 TNF- α 通

路与血管生成、代谢重编程等关键病理过程的串扰(Crosstalk), 评估联合靶向治疗(如 TNF- α 抑制剂联合抗血管生成药物或胰岛素增敏剂)的协同潜力及临床应用前景。通过机制深化与临床转化并举的策略, 有望为实现 TNF- α 靶向疗法的精准应用提供可靠依据, 并改善卵巢疾病患者的生殖与长期健康结局。

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