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IL-6/STAT3信号通路在非小细胞肺癌发生和治疗中的进展

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摘 要

IL-6/STAT3通路是非小细胞肺癌发展的关键途径之一，可通过参与癌细胞的抗凋亡、增殖及肿瘤血管生成等多种恶性表型促进肿瘤发展。此外，临床研究表明，IL-6/STAT3信号通路与非小细胞肺癌的化疗、靶向及放疗耐药相关，针对IL-6/STAT3信号通路的靶向药物对非小细胞肺癌的治疗有益，有望成为治疗非小细胞肺癌的有效药物。深入了解IL-6/STAT3信号通路与非小细胞肺癌的关系有助于阐明非小细胞肺癌发病机制，并为其治疗提供新方向。本文就该通路在非小细胞肺癌发展及治疗中的最新进展作一综述。

关键词

恶性肿瘤，非小细胞肺癌，白介素-6，IL-6/STAT3信号通路

Progress of IL-6/STAT3 Signaling Pathway in the Development and Treatment of Non-Small Cell Lung Cancer

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Abstract

The IL-6/STAT3 pathway is one of the key pathways in the development of non-small cell lung

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cancer (NSCLC), which can promote the development of tumor by participating in various malignant phenotypes such as anti-apoptosis, proliferation and tumor angiogenesis. In addition, clinical studies have shown that IL-6/STAT3 signaling pathway is associated with chemotherapy, targeting and radiotherapy resistance of NSCLC. Targeted drugs targeting IL-6/STAT3 signaling pathway are beneficial for the treatment of NSCLC and are expected to be effective drugs for the treatment of NSCLC. A deeper understanding of the relationship between IL-6/STAT3 signaling pathway and NSCLC will help clarify the pathogenesis of NSCLC and provide a new direction for its treatment. This article reviews the latest progress of this pathway in the development and treatment of non-small cell lung cancer.

Keywords

Malignant Tumor, Non-Small Cell Lung Cancer, IL-6, IL-6/STAT3 Signaling Pathway

1. 引言

肺癌(lung cancer, LC)是威胁人们生命安全和健康最大的恶性肿瘤之一，在全球[1]，肺癌的发病率占恶性肿瘤总发病例数的 11.6%，病死率占恶性肿瘤病死例数的 18.4%，发病率和病死率均居首位[2]。在我国，肺癌也是发病率和死亡率较高的恶性肿瘤，第 3 次国人死亡原因调查显示，肺癌病死率为 22.7%，位居首位[3] [4]。在组织学上，肺癌分为非小细胞肺癌(non-small cell lung carcinoma, NSCLC)和小细胞肺癌(small cell lung carcinoma, SCLC)，其中 NSCLC 占肺癌的 85%。在过去 20 年中，NSCLC 尽管在手术、放疗、化疗和靶向治疗等治疗选择方面取得了进展，但由于大多数患者在诊断时存在局部晚期或广泛转移，所以 NSCLC 的总生存率和治愈率仍然较低，5 年生存率约为 15% [5]。因此，有必要进一步研究肺癌的生物学和恶性增殖机制，以加强对 NSCLC 进展的了解，提高生存率。

白介素-6 (interleukin-6, IL-6)是一种多功能的细胞因子，可介导免疫和炎症反应，IL-6 信号通路通过 IL-6 受体、gp130 和 Janus 蛋白酪氨酸激酶(Janus protein tyrosine kinase, JAK)发挥作用。信号转导和转录激活因子 3 (Signal transducers and activators of transcription 3, STAT3)是 JAK 激酶家族中的成员之一，是增殖、存活、分化、凋亡、免疫功能和血管生成等多种细胞过程的关键调节因子[6]。临床研究表明，STAT3 在 22%~65%的 NSCLC 中持续激活[7]，并且 STAT3 活性与肿瘤进展、预后不良和患者生存期短相关[8]。因此，确定 IL-6/STAT3 信号通路是否以及如何参与肺癌的发生发展具有重要意义。本文就 IL-6/STAT3 信号通路在介导肺癌中的发展及其在肺癌治疗中的研究进展进行阐述。

2. IL-6/STAT3 信号通路

IL-6 于 1986 年首次被成功克隆，作为一种多效细胞因子，在免疫调节、造血、炎症和肿瘤发生方面具有重要作用[9]，通过与受体结合形成复合物激活下游信号通路而发挥效应。IL-6 受体系统由 2 种跨膜蛋白组成：一种负责信号转导，相对分子质量为 130000 的非配基结合链糖蛋白 130 (gpl30，也称 CD130 或 IL-6R0)；另一种是可与 IL-6 直接结合，相对分子质量为 80000 的配基结合链糖蛋白 80 (gp80，也称 CD126 或 IL-6Rα)。其中 IL-6Rα 可分为膜结合型(mIL-6R)和可溶型(sIL-6R) 2 种，研究认为 mIL-6R 是触发 IL-6 信号传导的最主要途径[10]。IL-6 信号传导途径分为经典信号通路和反式信号通路。在经典信号

传导途径中，胞外 IL-6 与膜上的 IL-6R 结合形成复合物，诱导 gp130 聚集并与之结合，形成了由 2 个 IL-6，2 个 IL-6R 及 2 个 gp130 分子构成的异六聚体，随后复合体激活 JAK，后者通过激活 STAT3 形成二聚体进入细胞核调控靶基因转录[11]。IL-6 的反式信号传导途径与经典信号传导途径基本相同，不同之处在于反式信号通路中与 IL-6 结合的受体是可溶性 IL-6R (sIL-6R)而非 mIL-6R [12]。sIL-6R 由 mIL-6R 的有限蛋白水解或 IL-6R mRNA 可变剪切产生[13] [14]。经典信号通路与反式信号通路表达范围并不相同[15]。mIL-6R 主要表达于中性粒细胞、单核细胞、活化的 B 细胞、$CD4^+$ T 细胞和肝细胞，因此 IL-6 经典信号途径表达的范围有限[16]，而 IL-6 与血清中 sIL-6R 形成的复合物，可以作用于所有表达 gp130 的细胞，因此反式信号通路扩大了 IL-6/STAT3 信号通路的作用范围[17]。在功能上，IL-6 经典信号通路主要诱导急性期反应，具有抗炎作用，与之相反，反式信号传导与促炎反应有关[18]。目前认为，IL-6 对肿瘤的刺激主要由 IL-6 反式信号途径介导[19]。

3. 非小细胞肺癌组织中 IL-6 的表达

IL-6 是 NSCLC 中关键的促肿瘤细胞因子，对肺癌细胞的生长有多种调控作用，在 NSCLC 细胞增殖、侵袭、迁移、血管形成中 IL-6 均发挥促进作用，而对某些肺癌细胞有生产抑制作用，这种调控作用与肺癌细胞的自身特异性和宿主体内环境有关。有研究提示 NSCLC 患者血清中的 IL-6 水平较健康对照组明显升高，肿瘤组织中 IL-6 表达水平与总生存率相关，IL-6 是 NSCLC 患者预后不良的指标[20] [21] [22]。此外，Qihua Gu [23]等的研究显示，IL-6 水平升高与疾病进展风险增加相关，而其他炎性细胞因子与重度肺癌患者的疾病进展无关[24]，据报道，IL-6 还通过核因子 κB (nuclear factor kappa-B, NF-κB)蛋白上调 TIM-4，从而促进非小细胞肺癌的转移[25]。

4. IL-6/STAT3 信号通路促进肺癌发展

IL-6 对肺癌具有抑制和促进双重作用，与肺癌细胞的自身特异性和宿主体内环境有关，二者均涉及其激活 STAT3 的能力。

IL-6 通过维持肺内环境稳定和以 STAT3 依赖方式诱导肿瘤细胞杀伤来抑制肺癌发生。矛盾的是，IL-6 也通过 STAT3 依赖机制促进肺癌的生长。在这种情况下，IL-6 激活 STAT3，在肺癌细胞中诱导细胞周期蛋白 D1，从而促进癌症增殖[26]。Jing [27]等的研究发现 IL-6/STAT3 信号通过协调转移前生态位的形成和免疫抑制特性促进肺转移。Li [28]等人研究表明，持续激活 STAT3 可诱导 STAT3 转基因小鼠发生肺肿瘤。受体酪氨酸激酶，如(EGFR 和 MET)、细胞因子受体(如 IL-6 受体)和非受体激酶(如 Src)激活 STAT3，可调节某些 NSCLC 细胞的存活途径[29]。Zimmer [30]等人认为 STAT3 活性独立于 EGFR 突变，有助于 NSCLC 的致癌潜力。Looyenga [31]等人证明，STAT3 在人类 NSCLC 样本和多种 NSCLC 细胞系中被组成性激活，与激活 KRAS、EGFR 和 PDGFR 突变或 MET 扩增无关。而 Greulich [32]等人报道，STAT3 被各种 EGFR 突变激活，包括外显子 19 框架内缺失或外显子 21 L858R 点突变，并可能参与成纤维细胞和人类肺癌细胞中这些突变的致癌效应[32]。Jiang [33]等人通过免疫组化染色显示，发现 STAT3 或 pSTAT3 高表达是 NSCLC 患者预后不良的有力预测因素。Zhao [34]等人报道，与 pJAK2 低表达的 NSCLC 患者相比，接受手术的 pJAK2 高表达的 NSCLC 患者的总体生存率明显更低。他们还发现，pJAK2 和 pSTAT3 高表达的 NSCLC 样本中的微血管密度(MVD)较高，而 MVD 高的患者生存率较低。这些数据表明，高 pSTAT3 表达是 NSCLC 患者预后不良的有力预测因子。人类 NSCLC 常表现为结缔组织增生，其特征是存在肿瘤相关成纤维细胞(CAFs) [35]。在实体瘤中，CAF 介导癌细胞增殖、血管生成、侵袭、转移和耐药性[36]。从人类肺癌组织中分离的 CAF 分泌白细胞介素-6 (IL-6)，其刺激人类肺癌细胞中的 STAT3 信号，以促进肺癌的转移[37]。Bo Jing [27]等的研究表明，IL-6/STAT3 信号诱导的免疫抑制对肺

转移至关重要，研究发现 IL-6/STAT3 信号通过协调转移前生态位的形成和免疫抑制特性促进肺转移。

microRNA (miRNAs)是一类单链非编码 RNA，由 19-25 个核苷酸组成，通过与靶基因的 3'非翻译区(3'UTR)相互作用，作为基因表达的负调节因子[38]。miRNAs 的异常表达在包括肺癌在内的不同疾病中均有报道，它们可能作为癌基因或肿瘤抑制因子[39]。据报道，MiR-17-92 [40]、MiR-21 [41]和 MiR-221/MiR-222 [42]可促进肺肿瘤的发生，而 let-7 [43]、MiR-126 [44]、MiR-16 [45]、MiR-340 [46]、MiR-145 [47]和 MiR-373 [48]可作为肿瘤抑制因子。Yan Yang [49]等的研究表明 miR-218 通过负性调节 STAT3 信号通路来调节肺癌细胞表型。研究表明，miR-218 在 EGFR 野生型细胞中通过 IL-6R 和 JAK3 负调控 STAT3 信号，在 EGFR 突变细胞中通过 IL-6R、JAK3 和 EGFR 负调控 STAT3 信号。miR-218 的过表达通过靶向 STAT3 信号降低体内肿瘤生长。

5. IL-6/STAT3 信号通路抑制剂在肺癌治疗中的临床研究

多项研究显示，对 STAT3 的抑制抑制了癌细胞的生长，并增强了多种癌症对抗癌药物的敏感性，且与肿瘤治疗的耐药性相关，作为一种选择性激活的途径在治疗获得性耐药中发挥重要作用。因此，STAT3 被认为是抗肿瘤治疗的潜在靶点。

据报道，STAT3 与肿瘤发生和化疗耐药性有关[7]。虽然 STAT 的激活在正常细胞中受到严格控制，但恶性肿瘤中酪氨酸激酶的持续激活会导致 STAT 的结构性激活，尤其是 STAT3 和 STAT5 [50] [51] [52]。STAT 激活后，调节癌症进展过程的基因表达将发生变化，包括不受控制的增殖、抗凋亡、持续的血管生成和逃避免疫监视[51] [52] [53] [54]。几份报告[55]-[61]显示，对 STAT3 的抑制抑制了癌细胞的生长，并增强了多种癌症对抗癌药物的敏感性。研究[62] [63]显示，在 NSCLC 细胞中，STAT3 mRNA 的过度表达与顺铂耐药性有关。通过 siRNA 沉默 STAT3 可使耐药细胞对紫杉醇、阿霉素和顺铂等细胞毒性药物更敏感[64] [65] [66]。

其次，有研究[67] [68]表明，STAT3 的上调直接赋予耐药表型，例如抗紫外线辐射诱导的细胞凋亡。

You [69]等人表明，电离辐射诱导 JAK2 和 STAT3 的磷酸化，并且发现高水平的 STAT3 在耐辐射 NSCLC 细胞的细胞核中积累。他们同时发现，氯硝柳胺是一种有效的 STAT3 抑制剂，通过阻断 STAT3 的磷酸化和核转位来破坏 STAT3 转录活性，单独或与放疗联合使用可克服异种移植模型中的辐射抗性。Sun [70]等人报道，JAK2 的小分子抑制剂(TG101209)能够在体外抑制生存素，降低 pSTAT3，并使肺癌细胞对辐射敏感。

STAT3 与肿瘤靶向耐药性有关。Looyenga [31]等人证明，舒尼替尼或环唑替尼等酪氨酸激酶抑制剂(tyrosine kinase inhibitor, TKI)对 STAT3 活性没有影响。他们还展示了鲁索利替尼(一种 JAK1/2 选择性抑制剂)对 NSCLC 细胞系的治疗，该抑制剂在骨髓纤维化患者的 I/II 期研究中显示了有希望的结果，在软琼脂和异种移植试验中抑制了细胞生长。Jin 等研究[71]表明，抑制 STAT3 是克服磷脂酰肌醇 3-激酶(Phosphatidylinositol 3-kinase, PI3K)和哺乳动物雷帕霉素靶标(Mammalian target of rapamycin, mTOR)双重抑制剂耐药性的有效策略。这表明持续的 STAT3 可能导致对靶向治疗的主要耐药性。Q. Zheng 等[6]研究表明，STAT3 抑制剂 W2014-S 破坏了 NSCLC 细胞系中 STAT3 的二聚化，并选择性地抑制了异常的 STAT3 信号。W2014-S 在小鼠模型中强烈抑制 STAT3 异常激活的肺癌细胞的增殖、存活、迁移和侵袭，并抑制人 NSCLC 细胞异种移植物的生长。W2014-S 在体外对吉非替尼和厄洛替尼显著致敏耐药，并在体内增强吉非替尼在 TKI 耐药肺癌异种移植物中的抗肿瘤作用。研究[33] [72] [73] [74] [75]表明，将 W2014-S 等 STAT3 抑制剂与吉非替尼联合使用可能是克服 NSCLC 患者 EGFR-TKIs 获得性耐药性的一种有希望的策略。此外，具有 EGFR-TKIs 获得性耐药的癌症患者在一定程度上有高水平的磷酸化 STAT3。虽然 STAT3 可以作为 EGFR 的下游，但在 EGFR-TKIs 耐药性中 STAT3 的激活可能与 EGFR 无关[7] [76] [77] [78]。

这些证据表明，靶向 STAT3 可能为克服肺癌中 EGFR-TKI 获得性耐药提供了一种新策略。尽管已经做出了大量努力来开发特异性和有效的 STAT3 抑制剂，但已报道的抑制剂仍然面临多种挑战，例如特异性低、结合亲和力弱、口服生物利用度低、溶解性差、结构不稳定、潜在的严重毒性，尤其是，临床上尚没有一种 STAT3 抑制剂被批准用于肺癌治疗[71]。

6. 小结

人体内的细胞因子是一个复杂的网络系统，在肺癌的发生发展中起着重要作用。IL-6、STAT3 和 P-STAT3 的异常表达可通过影响肺癌细胞的增殖、侵袭、迁移、凋亡等促进肿瘤的进展。通过 IL-6 单克隆抗体、GP130 抑制剂、STAT3 沉默和靶向 miRNAs 阻断该信号通路，已在抗肺癌治疗中取得初步成功。未来这一方向的深入研究将有助于肺癌的靶向治疗，为开发新的靶向药物提供新思路，并通过靶向干预结合其他药物提高临床治疗效果。

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