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IL-6与结直肠癌治疗及预后相关研究进展

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摘　要

白细胞介素6 (IL-6)作为一种细胞因子，在炎症、免疫、肿瘤发生发展等多个方面发挥重要作用。结直肠癌是全球常见的恶性肿瘤，其发病及死亡均居世界前位。结直肠癌患者血清IL-6水平显著升高，IL-6通过多种途径调控结直肠癌的发生发展，且与患者不良预后相关。传统抗肿瘤治疗以及治疗过程中不良反应及耐药的发生同样与IL-6的息息相关。靶向IL-6或其受体在结直肠癌治疗方面具有极大潜力。本文将对IL-6与结直肠癌治疗及预后相关研究进展进行综述，为寻找新的结直肠癌预后标志物及治疗手段提供新的思路。

关键词

结直肠癌，细胞因子，白细胞介素6

Research Progress on the Relationship between IL-6 and the Treatment and Prognosis of Colorectal Cancer

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Abstract

Interleukin 6 (IL-6), as a cytokine, plays an important role in inflammation, immunity, tumorigenesis and development. Colorectal cancer is a common malignant tumor in the world, and its morbidity and mortality rank first in the world. Serum IL-6 levels in patients with colorectal cancer

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are significantly increased, and IL-6 regulates the occurrence and development of colorectal cancer through various ways, and is associated with poor prognosis of patients. Traditional antitumor therapy and the occurrence of adverse reactions and drug resistance during treatment are also closely related to IL-6. Targeting IL-6 or its receptors has great potential in the treatment of colorectal cancer. This article will review the research progress related to IL-6 and the treatment and prognosis of colorectal cancer, and provide new ideas for the search for new prognostic markers and treatment methods of colorectal cancer.

Keywords

Colorectal Cancer, Cytokines, Interleukin-6

1. 引言

白细胞介素 6 (Interleukin-6, IL-6)是一种细胞因子，参与机体各种反应，在炎症、免疫以及肿瘤增殖、生存、侵袭、转移等多种方面发挥重要作用[1]-[6]。IL-6 作为 STAT3 的激活因子，其在结直肠癌、胃癌等多种恶性肿瘤中显著升高，STAT3 的激活在肿瘤发生发展中发挥重要作用。结直肠癌是全球常见的恶性肿瘤，其发病及死亡人数均高居全球前 3 位[7]，结直肠癌的早期诊断与治疗目前仍面临巨大挑战，常因确诊较晚或出现耐药影响患者生存，IL-6 作为一种多效细胞因子，与结直肠癌的发生发展息息相关，本文将在作用机制、预后、治疗等方面对 IL-6 与结直肠癌相关研究进展进行综述。

2. IL-6-STAT3 通路与结直肠癌

IL-6 是一种小分子糖基化蛋白，大小约 21~28 kDa，可由免疫细胞、基质细胞、肿瘤细胞等多种细胞类型产生，参与机体免疫、炎症、造血、骨代谢、胚胎发育等多种过程，在炎性病变、急性应激反应、衰老、免疫疾病、肿瘤发生发展甚至 2019 冠状病毒病(COVID-19)中起重要作用[1] [2] [3] [4]。IL-6 与其受体结合激活信号通路，调控肿瘤的代谢、凋亡、增殖、血管生成、肿瘤侵袭转移等过程。IL-6 一般通过两种途径激活下游 STAT3，一是通过与肿瘤细胞或免疫细胞膜上的受体(IL-6R)结合激活经典信号通路，二是与组织中可溶性受体(sIL-6R)结合，作用于表达 gp130 的细胞，激活反式信号通路，此通路可更广泛的作用于各类细胞。两种通路最终均诱导 STAT3 基因表达，通过 STAT3 的激活编码出能够驱动肿瘤增殖(cyclin D1)或肿瘤存活(bcl-XL)的蛋白质，并可诱导血管生成因子(vascular endothelial growth factor，VEGF)、基质金属蛋白酶(matrix metalloproteinases, MMPs)、免疫制剂(Interleukin-10, IL-10, transforming growth factor-β, TGF-β)等多种活性物质的表达，在应激反应、造血、血管生成、保护肿瘤细胞免受抗肿瘤治疗诱导的 DNA 损伤、氧化应激、肿瘤凋亡等多种方面发挥作用[4] [8]-[13]。

结直肠癌患者常常表现出细胞因子异常增高，尤其是炎性细胞因子 IL-6 水平的升高。当 IL-6/STAT3 通路被阻断时，结直肠癌的发生率下降，同时肿瘤区域的细胞因子表达减少[14]。肝是结直肠癌最常见的转移部位，这种明显的转移倾向的原因与循环肿瘤细胞、肿瘤微环境、血供等多种因素有关，已有研究证实非恶性细胞释放的 IL-6 能够激活肝细胞 IL-6-STAT3 信号通路，从而改变肝脏免疫和纤维化微环境，从而建立前转移生态位，促进肿瘤肝转移的发生[15]。Chien-Chang Lu 等人在一项体外实验中应用 IL-6 上游基因 TLR8 激动剂(CL075 (3M002))刺激肿瘤细胞使 IL-6 分泌显著减少，能够抑制癌细胞的转移[16]。

一项研究发现，IL-6-STAT3 的新效应因子 NEK9 可以直接影响细胞运动和 RhoA(一种调节细胞运动，细胞分裂和基因转录的蛋白)的激活，从而促进肿瘤转移[17]。另外，来源于间充质干细胞的 IL-6 通过 IL-6/STAT3 途径促进上皮间充质转化(EMT)，最终导致结直肠癌的发生和转移[18]。癌症相关成纤维细胞(CAFS)也可以通过 IL-6/STAT3 通路诱导肠上皮细胞的增殖扩增，其诱导的磷酸化 STAT3 会导致结直肠癌的进展，并与结直肠癌患者生存期呈负相关[19]。由此可见，IL-6/STAT3 通路在多种肿瘤相关基质细胞中的激活共同促进了有利于肿瘤发展的微环境形成，或许从源头抑制相关细胞的激活或阻断 STAT3 相关通路能够成为抑制肿瘤转移的关键。

3. IL-6 与结直肠癌患者预后的关系

IL-6 在正常结直肠组织及结直肠癌组织中均有表达，但无论是癌组织还是患者血清中的 IL-6 水平均显著高于健康人群。IL-6 水平与 TNM 分期、组织分化程度相关[20] [21]。多项研究显示血清 IL-6 水平的升高能够预示患者复发风险增加，高水平 IL-6 预示着较差的预后，并与肿瘤坏死和全身炎症反应密切相关，当联合癌胚抗原(CEA)与 IL-6 共同分析时，IL-6 的预测作用则更加显著[22] [23] [24] [25]。相对特殊的是，IL-6 作为一种炎性细胞因子，能够同时反映机体炎症水平，Chang PH 等人对血清 CRP 水平低(CRP < 5 ml/L)的患者单独分析时，IL-6 水平对 PFSR (无进展生存期率)的预测性反而更加显著，或许与当患者机体处于高水平炎症状态而血清 CRP 水平偏低时，血清 IL-6 水平则能够反映出患者的高炎症状态，并与肿瘤进展相关[13]。在一项对 393 名接受一线治疗的转移性结直肠癌患者研究中发现接受治疗前血清 IL-6 水平及 CRP 水平可以作为晚期患者的独立预后不良因素，值得注意的是，在 BRAF 突变患者中，IL-6 的预测作用尤为显著，而在 RAS 突变患者中并没有这种现象，研究者推测这种差异与 IL-6 和 BRAF、RAS 突变激活致癌机制的方式差异相关[25]。一项韩国多中心老年转移实体瘤患者的研究中，同样也发现化疗前血清 IL-6 和 CRP 水平可能有助于评估老年患者的早期死亡风险[26]。综上所述，IL-6 能够显示结直肠癌患者的预后水平，联合一种或多种生物标志物与 IL-6 共同检测能够为 IL-6 的预后作用提供更高的敏感度或特异性。

4. IL-6 水平与抗肿瘤治疗的关系

目前结直肠癌的主流治疗模式有手术治疗、放射治疗、化学治疗、靶向及免疫治疗等，探索治疗手段与 IL-6 的关系或许能为后续研究带来新的启发。有研究显示化疗后大部分患者血清 IL-6 水平会出现显著降低，并在排除炎症因素后仍证实 IL-6 是化疗耐药的基质驱动因素[27]。化疗耐药是临床上常见的严重影响肿瘤患者生存预后的因素，研究发现 IL-6 通过 STAT3 途径抑制肿瘤抑制因子 miR-204-5p 介导化疗耐药，而靶向 IL-6 治疗则可以阻断这一过程[28]。值得一提的是，最新的研究证实 IL-6 还可通过 JAK2-BECN1 途径参与细胞自噬并诱导耐药发生[2]。

在靶向、免疫治疗方面，有研究显示 IL-6-STAT3 轴在曲妥珠单抗、贝伐珠单抗等靶向治疗以及抗 PD-1/PD-L1 免疫治疗过程中发挥作用并参与耐药发生[29] [30] [31] [32]。令人欣喜的是，靶向 IL-6 治疗后能够恢复肿瘤细胞对药物的敏感性、增加治疗疗效[33] [34] [35]，且有利于控制免疫相关不良反应[36]。由此可见，检测血清 IL-6 水平或 IL-6 相关标志物可提示免疫治疗疗效，而靶向 IL-6 治疗或许是克服抗肿瘤药物耐药、改善患者生存的一种新思路。然而值得注意的是，在西妥昔单抗的类似研究中，因药物作用机制不同，产生了截然相反的结果，西妥昔单抗为 IL-6 依赖性抗肿瘤药物，在结肠癌小鼠模型研究中，敲除 IL-6 后西妥昔单抗的抗肿瘤效果显著降低[37]，靶向 IL-6 也未能恢复耐药细胞的药物敏感性[38]，因此在应用靶向 IL-6 药物治疗时，应考虑联合的药物作用机制中是否有 IL-6 参与。

放射治疗方面，IL-6 已被报道在部分放射治疗中参与放疗抵抗[39]。研究发现 IL-6 可作为线粒体转

录终止因子(MTERFD1)的效应因子增强结直肠癌的放疗抵抗作用，而 MTERFD1 或许可称为放疗有效性的潜在标志物[40]。在一项研究中发现 IL-6 通过诱导糖酵解并减少线粒体损伤诱导产生放疗抵抗[41]。值得注意的是在一项研究中，阻断 IL-6 相关通路会加重放射治疗相关肠道损伤的发生[42]。目前尚无更多相关研究进一步探索结直肠癌中 IL-6 的抗辐射机制。

手术及其他治疗方面，有研究显示血清 IL-6 水平在结直肠癌根治术后显著下降，但不会恢复至正常，而术后早期 IL-6 升高是术后发生并发症的独立预后因素[43] [44]。手术和术后并发症所产生的 IL-6 或许会促进肿瘤发展，在某研究中预防性应用甲基强的松龙后可以显著降低根治术后患者血清 IL-6 水平，从而抑制肿瘤生长和转移[45]。IL-6 作为一种炎性因子，其水平也与抗肿瘤治疗中疲劳严重程度、生活质量减低程度呈正相关。由此可见，加用抗炎治疗或对 IL-6 靶向治疗或许更能为患者带来更大获益[46]。另外，辅助治疗中也显示，IL-6 等炎症相关细胞因子可随益生菌的补充所减少，同时也预示着患者更好的预后[47]。

由此可见，IL-6 在治疗抵抗、耐药以及不良反应中均发挥重要作用，我们猜测抗肿瘤过程或许在多种途径中促进 IL-6 分泌，并通过诱导炎症发生、免疫抑制或辐射抵抗，最终导致耐药及肿瘤进展。

5. 靶向 IL-6 及其受体与抗肿瘤治疗

目前靶向 IL-6/IL-6R 的单克隆抗体已在临床研究中显示出良好效果，尤其在自身免疫性疾病中发挥出显著的疗效。抗 IL-6/IL-6r 单克隆抗体(siltuximab、tocilizumab)目前已获批应用于多中心 Castleman 氏病(MCD)以及类风湿性关节炎[48] [49]，并在器官移植中发挥重要的抗炎作用[50] [51]。在肿瘤领域，如前文所述，靶向 IL-6/IL-6R 治疗在肿瘤传统治疗过程中具有增加疗效、抵抗耐药等作用。但在既往的随机试验中并未发现该类靶向药对结直肠癌(NCT00841191：35 例结直肠癌/84 例实体瘤患者) (NCT02119676：175 例结直肠癌患者)的疗效[52] [53]。疗效的缺乏或许与其他细胞因子敏感型细胞触发了类似 IL-6 相关信号通路相关。尽管如此，在靶向治疗过程中能够观察到 CRP 水平的显著降低以及其他抗 IL-6 治疗相关的生物活性存在。最新的结肠癌小鼠模型研究中，IL-6R 抗体通过抑制 STAT3 途径抑制肿瘤细胞的生长及侵袭[54]。

另外需要我们关注的是，合成长肽疫苗(Synthetic longpeptide, SLP)作为一类肿瘤疫苗，是抗肿瘤免疫治疗的新型手段。然而在免疫疫苗诱导肿瘤破坏过程中，IL-6 相关通路对巨噬细胞功能至关重要，阻断 IL-6 及其受体会严重降低肿瘤疫苗疗效[55]，而靶向 STAT3，小鼠结直肠癌发生减少，且肿瘤区的细胞因子分泌减少[14]。

IL-6 及其相关通路的功能多样性使其疗效具有不确定性，但依据目前的研究及成果来看，靶向 IL-6 及其受体在抗肿瘤治疗、抑制肿瘤转移甚至克服肿瘤耐药等方面十分值得期待，尽管目前仍然缺乏具有权威的前瞻性研究结果证实其疗效，抗 IL-6/IL-6R 抗体仍是一种非常具有前景的结直肠癌靶向药物。

6. 总结和展望

综上所述，可以明确 IL-6 是结直肠癌发生发展以及治疗过程中发挥重要作用的细胞因子，血清 IL-6 水平能够反应结直肠癌预后及治疗效果，并指导临床医生进行诊疗决策。靶向 IL-6/IL-6R 治疗结直肠癌方面，尽管在初步临床研究中未见确切疗效，但在化疗、免疫、靶向治疗、放疗乃至手术等治疗过程中均有 IL-6 的参与，靶向 IL-6 治疗与传统治疗手段的联合应用仍值得期待。

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