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集落刺激因子联合放疗对抗肿瘤免疫调节的相关研究进展

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摘　要

集落刺激因子(Colony-stimulating factor, CSF)是一种细胞因子，可以预防或治疗化学治疗引起的中性粒细胞减少，主要用于接受化疗或接受高度血液毒性治疗方案的患者。随着现代放射治疗技术和支持治疗的发展，放化疗与集落刺激因子的联合治疗值得被重新评估。放射治疗在体内和体外均可诱导免疫系统介导的抗癌全身效应。这种效果在联合CSF的创新放射治疗模式的临床前和临床试验中得到了加强。到目前为止，放疗与CSF的联合效应尚未与免疫疗法相结合。然而，它可能在引发针对癌细胞的免疫应答中起主要作用，进而诱导远隔效应。本文通过对集落刺激因子、放疗和免疫治疗联合疗法的有效性，以及放疗联合集落刺激因子对抗肿瘤免疫调节方面的最新研究进行综述，进一步评估集落刺激因子与放疗及免疫治疗联用的可行性。

关键词

放射治疗，集落刺激因子，免疫治疗，肿瘤

Research Progress on Colony-Stimulating Factor Combined with Radiotherapy to Fight Tumor Immunomodulation

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Abstract

Colony-stimulating factor (CSF) is a cytokine that can prevent or treat chemotherapy-induced neutropenia, primarily in patients receiving chemotherapy or receiving highly hematotoxic treatment regimens. With the development of modern radiotherapy techniques and supportive care, the combination of chemoradiotherapy and colony-stimulating factor deserves to be re-evaluated. Radiation therapy can induce systemic effects mediated by the immune system against cancer both *in vivo* and *in vitro*. This effect is reinforced in preclinical and clinical trials of an innovative radiotherapy modality in combination with CSF. So far, the combined effect of radiotherapy with CSF has not been combined with immunotherapy. However, it may play a major role in eliciting an immune response against cancer cells, which in turn induces the distancing effect. This article reviews the effectiveness of the combination of colony-stimulating factor, radiotherapy and immunotherapy, as well as the latest research on the immunomodulation of radiotherapy combined with colony-stimulating factor against tumors, and further evaluates the feasibility of combining colony-stimulating factors with radiotherapy and immunotherapy.

Keywords

Radiation Therapy, Colony-Stimulating Factor, Immunotherapy, Tumors

1. 引言

在肿瘤治疗中，随着化疗药物剂量的增加和可用治疗方法的增加，控制癌症患者因化疗引起的中性粒细胞减少症变得越发重要[1] [2]。集落刺激因子(CSF，包括粒细胞集落刺激因子(G-CSF)和粒细胞－巨噬细胞集落刺激因子(GM-CSF))是[3]一种细胞因子，可以预防或治疗化学治疗引起的中性粒细胞减少，主要用于接受化疗或接受高度血液毒性治疗方案的患者[4] [5] [6]。随着现代放射治疗技术和支持治疗的发展，放化疗与集落刺激因子的联合治疗值得被重新评估。放疗和化疗的联合治疗在总体生存率(OS)上的优势已得到明确证明，3 年时绝对获益率达 5.7%，5 年时达 4.5%，现已成为许多恶性肿瘤的标准治疗方法[7]-[12]。然而，高达 51%的患者在治疗过程中经历了 4 级急性血液学毒性反应。因此，在这些患者中使用 CSF 可以带来显著的获益[13]。

最近，如何更好地利用免疫治疗已经成为肿瘤治疗的一个关键问题，尤其是在相关放疗远隔效应的研究中[14] [15]。远隔效应被定义为除了受照射的肿瘤病灶以外，非受照射的病灶也产生了缩小的现象[16]。最近的研究表明，GM-CSF 和放疗的联用对促进远隔效应的发生可能是有效的，这可能是通过上调抗原提呈细胞和调节性 T 细胞(Treg 细胞) [17]。因此，GM-CSF 可能是放射免疫治疗领域的重大突破[18]。

本文旨在通过对集落刺激因子、放疗和免疫治疗联合疗法的有效性，以及放疗联合集落刺激因子对抗肿瘤免疫调节方面的最新研究进行综述，进一步评估集落刺激因子与放疗及免疫治疗联用的可行性。

2. G-CSF 与 GM-CSF：定义与区别

虽然 G-CSF 和 GM-CSF 都可以刺激中性粒细胞的产生，但在刺激其他髓系细胞时，它们的作用是不

同的，因此，他们有不同的适应症。G-CSF 受体几乎只在中性粒细胞和单核细胞上表达。它被 G-CSF 激活，参与粒系祖细胞的成熟和增殖[19]。G-CSF 可特异性地提高中性粒细胞的活性，并增强其吞噬作用和抗体依赖的细胞毒性，同时对嗜酸性粒细胞或嗜碱性粒细胞没有显著影响。

GM-CSF 是由巨噬细胞、T 细胞、肥大细胞、自然杀伤细胞、内皮细胞和成纤维细胞分泌的一种细胞因子。与 G-CSF 专门促进中性粒细胞增殖和成熟不同，GM-CSF 还驱动许多类型的髓系细胞的增殖，如巨噬细胞、嗜酸性粒细胞、单核细胞和树突状细胞等[20]。此外，它还强化了中性粒细胞、嗜酸性粒细胞和巨噬细胞的抗菌和抗肿瘤功能(粘附、趋化和吞噬活性)。更重要的是，GM-CSF 在几个临床前研究中被发现能够通过已知的信号通路(PI3K-Akt，ERK1/2，JAK2/STAT5，NF-κB)参与免疫系统的调节[21] [22]，以及对成熟的髓系细胞，如粒细胞、巨噬细胞和嗜酸性粒细胞的活性的调节。因此，GM-CSF 被认为既是生长/分化因子，也是免疫调节剂[23]。

最后，G-CSF 和 GM-CSF 对中性粒细胞的影响亦不相同：G-CSF 促进肿瘤坏死因子受体和 IL-1 受体拮抗剂蛋白的释放，而 GM-CSF 促进花生四烯酸的代谢，诱导 B4-亮三烯的释放，促进 IL-1 的产生[23] [24] [25]。

3. 放疗－集落刺激因子与抗肿瘤免疫

大量基于动物或人类肿瘤细胞的临床前研究证明，放射治疗能够增强抗肿瘤特异性免疫反应[26]。其中涉及的机制主要有调节性 T 细胞的增加[27]，对细胞毒性 T 淋巴细胞的刺激[28]，促免疫原性细胞因子的 I 类主要组织相容性复合体(MHC-I)的上调[29]和肿瘤抗原的释放[30]，这种抗肿瘤特异性免疫反应被认为是触发辐射介导的远隔效应的基础。进一步的研究表明，放射治疗对肿瘤微环境和患者免疫系统的影响与远隔效应密切相关。辐射导致肿瘤细胞死亡，进而导致肿瘤抗原的释放。辐射也渗透到血管内皮细胞，这刺激了抗原提呈细胞的激活。然后，基于 NK 细胞的直接细胞毒作用和 CD8+ T 细胞的特异性克隆扩增，也会产生抗肿瘤免疫反应，其中 CD8+ T 细胞更是单次大剂量(10GY)放射治疗的主要疗效影响因素[31] [32]。

3.1. G-CSFs

在一个临床前小鼠模型中，研究者发现了将放疗和 G-CSF 结合的潜在可能。首先，他们证明了受到辐射的肿瘤会吸引抗肿瘤的中性粒细胞。有趣的是，通过辐射激活的中性粒细胞具有特殊的特性，例如产生活性氧(ROS)的能力很高，这是辐射增敏的关键元素。研究者们随后观察到，肿瘤经照射后内源性的 G-CSF 浓度(即由肿瘤微环境产生的 G-CSF)增加，并推测它参与了肿瘤的局部控制。最后，他们证明外源性 G-CSF 联合放射治疗具有比单纯放射治疗更好的抗肿瘤效果。这一方面是由于激活的中性粒细胞增加了局部 ROS 的产生，另一方面则是对细胞毒性 T 细胞的激活作用[15]。总之，G-CSF 和放疗的结合上调了抗肿瘤免疫反应。

有研究表明，在骨髓抑制条件下，G-CSF 可以促进亚致死剂量照射后胸腺细胞的再生和外周 T 细胞的扩增，有助于更快、更有效的 T 细胞免疫重建[33]。

然而，Cui 等人的研究指出放射诱导的 G-CSF 通过触发非小细胞肺癌细胞上皮－间充质细胞转化(EMT)，促进 NSCLC 的迁移和侵袭，辐射诱导的 G-CSF 可被 G-CSFR 识别，并转导其胞内信号 JAK/STAT3 (Janus 激酶/信号转导和转录激活子)，从而触发 NSCLC 的 EMT 程序[34]。

3.2. GM-CSFs

GM-CSF 可以作为促炎因子和免疫调节因子在免疫系统中发挥重要作用[21]。然而，它在肿瘤中的作用是有争议的。一方面，已有大量实验证据表明，GM-CSF 可能有促肿瘤作用，例如在胶质母细胞瘤、

小细胞癌、皮肤癌、脑膜瘤、结肠癌、头颈癌和肺癌等多种癌症中都发现了 GM-CSF 及其受体的异常表达[20]。另一方面，基于产生 GM-CSF 的工程 T 淋巴细胞(siPuleucel-T)的抗癌疫苗被证实可有效提高前列腺癌患者的存活率[35] [36]。因此，GM-CSF 的表达可能具有双重作用，在某些情况下，它对抗肿瘤免疫既有抑制作用[37]，也有刺激作用[21]。有研究表明，GM-CSF 和放疗的联用对促进远隔效应的发生可能是有效的，这可能是通过上调抗原提呈细胞和调节性 T 细胞(Treg 细胞) [17]。GM-CSF 和放射治疗的结合已成为放射免疫治疗领域的重大突破[18]。

Chen 等人开展的一项临床前研究表明，GM-CSF 能和接受 γ 照射的肿瘤细胞释放的细胞因子相结合，从而促进巨噬细胞向 I 型分化的极化，并改善其抗原提呈功能[38]。

一项病例报告表明，GM-CSF 与放射治疗或化疗联合应用可能会诱导远隔效应，该位接受化疗的进展性转移性胰腺癌患者在最初阶段接受了姑息性放疗(45Gy25fr)，从放射治疗第二周开始到治疗结束，每天同时使用 GM-CSF 治疗，患者在放疗后 1 个月和 3 个月出现了远隔效应[39]。这一有趣的结果也驱动了相关临床试验的开展。GM-CSF 和放射治疗的组合首先在基于 GVAX 疫苗的临床试验中进行了测试。放射治疗被用以灭活肿瘤细胞，通过一系列设计使中立化的肿瘤细胞产生 GM-CSF，最终注射到患者体内。其目的是启动一种特异性的抗肿瘤免疫反应，并通过 GM-CSF 的产生而使其局部增强[40]，现已在前列腺癌和胰腺癌患者中得到了令人振奋的结果[41]。

Gold 等人进行了一项“概念证明”临床试验，以探索放疗诱导的远隔效应[42]。41 名至少有三个可测量转移病灶的癌症患者接受了两个转移灶的放射治疗，进行两个序贯放射疗程(35Gy/10 次)。同时允许进行化疗，但剂量较小，以避免不能耐受辐射毒性。GM-CSF 于放疗第 8 天至第 22 天同步进行。同时评估了对非放射转移的影响，以证明联合放射治疗和 GM-CSF 触发的免疫反应的存在。最终共有 11 名患者(26.8%)出现了远隔效应，表明放射治疗和 GM-CSF 相结合可以在转移性实体肿瘤中引起远隔反应。

Liu 等人对 30 名转移性胸部恶性肿瘤患者开展了一项研究显示，GM-CSF 联合放疗可增加远隔效应的发生率，对除食道癌外的胸部恶性肿瘤患者有一定的益处[43]。

Jiang 等人对复发性的晚期脑胶质瘤患者开展了一项单臂 I 期临床试验[44]，患者接受放射治疗联合 GM-CSF 治疗，30 例接受治疗的患者中，CR：1 例(3.3%)，PR：5 例(16.7%)，SD：9 例(30.0%)，PD：15 例(50.0%)，ORR 为 20.0%。整个队列的中位数 PFS 为 88 天，中位数 OS 为 362 天。遗憾的是，这与过往的挽救性疗法[45]相比并无显著优势。值得注意的是，在 3 名患者(10.0%)身上观察到了远隔效应。

4. 放疗、集落刺激因子与免疫疗法的结合

尽管放疗和 CSFs 联合诱导的免疫反应可能具有可观的抗肿瘤作用，但肿瘤细胞的免疫逃逸机制比 CSFs 上调的抗肿瘤机制复杂得多。虽然 CSFs 有助于启动适应性免疫反应，但其他癌症机制可能会阻止下游免疫反应[46]。最近有研究发现了经常被癌细胞抑制的免疫检查点，特别是 CTLA4 和 PD-1/PD-L1。它们的激活破坏了抗癌免疫反应的发展。因此，克服这些障碍可能需要组合使用 CTLA-4 抗体[47]和 PD-1/PDL-1 抗体[48]，阻止癌症免疫逃逸。

在一项 II 期临床试验中，ipilimumab 与 GM-CSF 的结合显著提高了 III/IV 期黑色素瘤患者的存活率，并降低了 ipilimumab 的毒性[49]。

在一项针对难治性和转移性头颈部鳞状细胞癌患者的一期临床试验中[50]，15 名患者接受了 cymplimab 加放射治疗、环磷酰胺和 GM-CSF 联合治疗，其中部分缓解 1 例(6.7%)，疾病控制率 40.0%；5 例 SD，7 例 PD，2 例不能评价，中位无进展生存期为 1.8 个月。然而，其疗效相较于抗 PD-1 抑制剂单一疗法并无明显优势。

在最近的一例病例报告中[51]，一名 PD-L1 表达阴性，经放化疗和靶向治疗后肿瘤进展的晚期食管

鳞癌患者，在接受了 3 周期 PD-1 抑制剂联合 GM-CSF 和立体定向全身放射治疗(SBRT)的三联治疗后，其照射部位和远端未照射部位的肿瘤发生显著消退。其机制可能与抗 PD-1 免疫治疗的放射增敏作用有关。据此，研究团队进一步开展了一项 PD-1 抑制剂联合放疗和 GM-CSF 治疗转移性实体瘤的单臂 II 期研究[52]，该项研究纳入了 54 名处于晚期或转移阶段的实体瘤患者，患者接受了至少两个周期的 PraG 方案治疗(在放疗结束后 1 周内静脉滴注 PD-1 抑制剂 1 次，然后每天皮下注射 GM-CSF 200 mg，连续 2 周)。结果显示 ORR 达 16.7%，疾病控制率达 46.3%，证明了 PD-1 抑制剂联合放疗和 GM-CSF 有望成为化疗耐药实体瘤患者的挽救性治疗方案。PRaG 方案的显著疗效可能归因于放疗引发的局部和系统免疫，PD-1 抑制剂和 GM-CSF 进一步增强了局部和系统免疫。

He 等人报告了 1 例复发的晚期甲状腺 Hürthle 细胞癌患者[53]，其 PD-L1 表达阳性，在手术、放射治疗和靶向治疗后肿瘤进展。令人振奋的是，在经过 2 周期 PD-1 抑制剂联合 GM-CSF 和立体定向全身照射(SBRT)治疗后，患者肺部和右侧肾上腺多发结节均较前明显缩小。这种 PD-1 抑制剂联合 GM-CSF 和放疗的三联治疗也被应用在转移性血管周围上皮样细胞瘤[54]和转移性结肠癌[55]中，并取得了可观的疗效。

最近 Ni 等人开展了一项将 PD-1 抑制剂、放疗和 GM-CSF 三联疗法应用于晚期非小细胞肺癌患者的多中心、单臂、II 期试验[56]，其安全性得到了验证，并且还在继续招募受试者，其有效性有待后续的进一步研究。

5. 结论

随着现代放射治疗技术和支持治疗的发展，放化疗与 CSFs 的联合治疗正在被重新评估。放射治疗在体内和体外均可诱导免疫系统介导的抗癌全身效应，它可能在引发针对癌细胞的免疫应答中起重要作用，进而诱导远隔效应。这种效果在联合 CSFs 的创新放射治疗模式的临床前和临床试验中得到了加强。值得注意的是，CSFs 在部分研究中表现出对抗肿瘤免疫调节的两面性。目前，放疗、CSFs 与免疫治疗的联合疗法的相关临床试验更多仍处于招募与试验阶段，当前已发表的文献资料更多为个案病例报告。因此，仍需要更多的相关研究，以明确放疗、CSFs 与免疫治疗的联合疗法的有效性与临床应用价值。

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