Advances in Clinical Medicine 临床医学进展, 2024, 14(3), 206-213
Published Online March 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.143686

Hans汉斯

肿瘤微环境与放疗敏感性的研究进展

美合日班·艾克拜，赵化荣

新疆医科大学第一附属医院肿瘤中心，新疆 乌鲁木齐

收稿日期：2024年2月8日；录用日期：2024年3月2日；发布日期：2024年3月12日

摘　要

放射治疗是许多癌症的主要治疗方式，提供潜在的治疗结果。尽管放射治疗取得了成功，但肿瘤细胞可能对其产生抵抗，从而导致疾病复发。肿瘤微环境的组成部分可能在放疗的成功或失败中起着不可或缺的作用。为此，本综述讲述了微环境中成纤维细胞、免疫细胞、细胞外基质、肿瘤血管以及缺氧微环境对放疗敏感性的影响，以加深我们对肿瘤微环境与放疗敏感性关系的了解，有助于建立一个临床前的理论基础，以支持基质靶向药物与放疗联合使用以增加放射敏感性。

关键词

肿瘤微环境，放射敏感性，放疗抵抗，辐射抵抗

Research Progress on Tumor Microenvironment and Radiotherapy Sensitivity

Meiheriban Aikebai, Huarong Zhao

Department of Oncology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi Xinjiang

Received: Feb. 8th, 2024; accepted: Mar. 2nd, 2024; published: Mar. 12th, 2024

Abstract

Radiotherapy (RT) is a primary treatment modality for a number of cancers, offering potentially curative outcomes. Despite its success, tumour cells can become resistant to RT, leading to disease recurrence. Components of the tumor microenvironment (TME) likely play an integral role in managing RT success or failure. This review describes the effects of cancer-associated fibroblast (CAF), immune cells, extracellular matrix (ECM), tumor

文章引用: 美合日班·艾克拜, 赵化荣. 肿瘤微环境与放疗敏感性的研究进展[J]. 临床医学进展, 2024, 14(3): 206-213.
DOI: 10.12677/acm.2024.143686

blood vessels, and hypoxic microenvironment in the microenvironment on radiotherapy sensitivity, in order to deepen our understanding of the tumor microenvironment and radiotherapy sensitivity, and help establish a preclinical theoretical basis to support the combination of stromal-targeted drugs and radiotherapy to increase radiation sensitivity.

Keywords

Tumor Microenvironment, Radiation Sensitivity, Radiotherapy Resistance, Radiation Resistance

1. 引言

肿瘤微环境(tumor microenvironment, TME)是肿瘤细胞、免疫细胞和癌症相关成纤维细胞(cancer-associated fibroblast, CAFs)相互作用并与细胞外元素相互作用的组合[1]。TME 的组成在癌症的起始、进展和对治疗的反应中起着不可或缺的作用[2]。放疗是一种强大的抗癌疗法，用于治疗高达 50~60%的癌症患者[3] [4]。放疗的目的是靶向攻击高度增殖的癌细胞，同时保留正常组织，但恶性肿瘤细胞与 TME 内其他细胞之间复杂的相互作用非常重要。有报道称[5]，放疗可导致 TME 内基质细胞发生大量变化，进一步促进肿瘤生长、侵袭和耐药。本文对肿瘤微环境与放疗敏感性之间的联系进行综述。

2. 放疗对微环境的影响

放疗在利用恶性肿瘤细胞的 DNA 修复缺陷的同时也会影响肿瘤本身或其边界的基质细胞[6]。研究发现[7] [8] [9]，放疗后促炎通路 NF-κB 上调的同时伴有 IL-1β、IL-6、IL-8、粒细胞－巨噬细胞集落刺激因子(granulocyte-macrophage colony stimulating factor, GM-CSF)和环氧化酶 2 (Cyclooxygenase 2, COX-2)的增加。此外，放疗增强了涉及 RAS 和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)级联的增殖机制的激活，侵袭途径，包括基质金属蛋白、层粘连蛋白 5 和丝素 A；转化生长因子 β (transforming growth factor-β, TGF-β)信号通路，参与肿瘤进展、抵抗和转移[3] [10]。而由于 MAPK 活性的增加，间质的辐射可以增加肿瘤的侵袭性，这增强了肿瘤的迁移能力[11]。而对于免疫系统，放疗既不引起完全的免疫刺激也不引起完全的免疫抑制，放疗可触发部分炎症细胞因子的产生，抗辐射免疫抑制巨噬细胞和 T 细胞群的相对增加。同时癌细胞的免疫原性细胞死亡(immunogenic cell death, ICD)和放射治疗诱导的内皮细胞变化的多因子信号也导致循环免疫细胞的涌入，这些免疫细胞比 TME 固有的免疫细胞更具有免疫刺激作用。除此之外，放疗引起血管损伤，增强肿瘤缺氧，并通过诱导免疫细胞募集的细胞因子、趋化因子的增加引发免疫反应。肿瘤血管通过缺氧诱导因子-1α (hypoxia-inducible factor-1α, HIF-1α)和独立的骨髓源性细胞的招募重建[5]。

3. 微环境对放疗敏感性的影响

3.1. 肿瘤相关成纤维细胞(CAFs)对放疗的影响

CAFs 可以被定义为结缔组织细胞的异质群体，通过分泌特定的分子，包括生长因子、蛋白酶、趋化因子和细胞因子，促进癌症的发展[1] [12] [13]。CAFs 通过诱导干扰素(interferon, IFN)相关的 DNA 损伤抵抗特征，以 stat1 依赖的方式保护乳腺癌细胞，使肿瘤产生放疗抵抗[14]。有研究[15]表明胶质母细胞

瘤的 TME 产生大量的 TGFβ，这是一种多效细胞因子，促进有效的 DNA 损伤反应。当在胶质母细胞瘤模型中抑制 TGFβ 阻止了肿瘤细胞 DNA 修复并增强了放疗疗效。此外，CAFs 可以通过产生一些分泌因子促进放疗后的癌细胞恢复和肿瘤复发。这些分泌因子增加放疗后活性氧(reactive oxygen species, ROS)水平，增强蛋白磷酸酶 2A 活性，抑制雷帕霉素活化的哺乳动物靶点，从而诱导癌细胞自噬，促进癌细胞恢复[16]。

CAFs 分泌因子触发许多下游自分泌和/或旁分泌信号通路，调节治疗反应。CAFs 与癌细胞一起时，高度表达并分泌 C-X-C 基序趋化因子配体 1 (C-X-C motif chemokine ligand 1, CXCL1)，CXCL1 抑制 ROS 清除酶超氧化物歧化酶 1 的表达，导致放疗后 ROS 积累，从而增强 DNA 损伤修复机制，最终产生辐射抗性[17]。研究发现[18] CAFs 可以通过旁分泌网络来丰富癌症干细胞(cancer stem cells, CSCs)，CSCs 与化疗和辐射耐药性有关。在胰腺癌中，胰腺星状细胞(pancreatic stellate cells, PSCs)的存在可以通过增加上皮-间充质转化(epithelial to mesenchymal transition, EMT)表型来诱导 CSC 特征。Hen, W.J.等发现[19]，CAFs 衍生的肝细胞生长因子(hepatocyte growth factor, HGF)、胰岛素样生长因子-2 (Insulin-Like Growth Factor, IGF-2)、碱性成纤维细胞生长因子和抑癌素 M 通过对应受体信号元件和茎干因子以旁分泌方式调节 CSCs 样特征，阻断 IGF-2/IGF-1R/AKT/Nanog 信号可以降低 CSC 的干性，认为这对靶向治疗有潜在的临床应用，可以改善化疗和放射耐药性。CAFs 是 TME 中关键的细胞组成成分，可介导 CSCs 发挥促肿瘤和放疗抵抗作用。Osuka 等研究发现分割放疗可增强 CSCs 中 IGF-1 的分泌及随后 IGF-1R 的上调，IGF-1R 的上调通过诱导 AKT/ERK 生存信号的上调和 FoxO3 的激活发挥双重辐射保护作用，从而产生辐射保护作用[20]。以上研究表明 CAFs 可以通过其 CSC 促进作用触发辐射抗性。

CAFs 在引起放疗抵抗的同时由于放疗而引起的 CAFs 的变化也可以进一步引起放疗抵抗。CAFs 通常不会被射线杀死；由于 p53/p21 反应途径的缺陷，它们具有高度的耐辐射性，和高表达的癌症标志物 Survivin [21]。照射成纤维细胞可促进鳞状细胞癌的侵袭性生长，也可表达高水平的 TGFβ1 [22]。Li 等[23]发现放疗可激活 CAFs 衍生的 CXCL12 作用于肿瘤细胞并下游激活 P38 通路促进 EMT 转化和胰腺癌细胞侵袭。Hellevik 等[24]在研究中表明暴露于 18 Gy 照射的 CAFs 可有效诱导多 DNA 损伤反应病灶;诱导细胞过早衰老；抑制了 CAFs 的增殖、迁移和侵袭能力。这个剂量增加了整合素 α2、β1 和 α5 的表达，显著增加了病灶接触点，并使其重新分布。β1 整合素的增加与放射抗性相关[25]。所有这些例子都表明，放疗诱导的 CAFs 变化可以进一步引起辐射抗性。

3.2. 细胞外基质(Extracellular Matrix, ECM)对放疗的影响

ECM 在调节癌症进展和放疗敏感性方面起着重要作用。ECM 硬度和密度的变化与疾病侵袭性、无进展生存期以及在某些情况下对不同治疗方式的耐药性相关。在 ECM 中有约 300 种调节组织稳态的蛋白质，其中胶原蛋白，弹性蛋白、纤维连接蛋白和层板蛋白等参与控制肿瘤表型[26]。Cordes [27]在研究中发现肿瘤细胞可通过与整合素的相互作用与 ECM 相互作用，从而导致细胞存活、增殖、迁移和侵袭。另有研究发现[28]，β1 整合素通过激活 AKT 信号抑制放疗引起的细胞凋亡，从而控制辐射抗性。抑制 β1 整合素可通过减少增殖和增加凋亡使肿瘤细胞对放疗再敏感。另一组研究人员还发现，β1 整合素介导的粘附通过下游的 fak 相互作用蛋白(p130Cas 和 paxillin)和 PI3K/akt 介导的促生存信号通路赋予放疗抵抗。这些例子表明，肿瘤细胞和肿瘤中 ECM 蛋白之间的接触介导的信号传导有助于抗辐射。

ECM 还含有肿瘤和基质细胞分泌的可溶性信号分子，其中 TGFβ 和基质金属蛋白(matrix metallo-proteins, MMP)也可引起放疗抵抗。放疗可进一步提高 TGFβ 水平，加速肿瘤进展。TGFβ 中和抗体的抑制已被证实可防止辐射诱导的转移性进展[29]。Chetty 等在研究中发现在放疗前抑制 MMP2 可解除 FoxM1 表达的诱导，降低 p53 和 p21 表达，降低部分 DNA 修复基因，并解除 G2 细胞周期阻滞，导致细胞凋亡

和辐射敏感性增强[30]。因此 ECM 作为肿瘤生长因子和细胞因子的汇集地，有助于肿瘤的放射抵抗，值得在未来的治疗规划中考虑。

3.3. 免疫细胞对放疗的影响

免疫微环境(tumour immune microenvironment, TIME)由 T 细胞、自然杀伤细胞(natural killer, NK)、树突状细胞(dendritic cells, DCs)和肿瘤浸润性髓样细胞(tumour-infiltrating myeloid cells, TIMs)组成，包括肿瘤相关的巨噬细胞(tumour-associated macrophages, TAMs)、髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)和树突状细胞(DCs)，所有这些细胞都通过改变的趋化因子和细胞因子信号被招募到 TME [31]。肿瘤相关巨噬细胞(TAMs)、MDSCs 和 $CD4^+$调节性 T 细胞(treg)已知具有免疫抑制和促肿瘤作用；另一方面，免疫细胞如 $CD8^+$ T 细胞和 NK 细胞具有抗致瘤性[3]。诱导 $CD8^+$ T 细胞耗竭是 TME 中常见的放疗抵抗机制之一。通过靶向 PD-1、T 细胞免疫球蛋白粘蛋白-3 (T cell immunoglobulin mucin 3 polypeptide C terminal, TIM3)或淋巴细胞活化基因-3 (lymphocyte-activation gene 3, LAG3)的表达来调节这些耗竭途径，在肿瘤治疗中已经取得显著效果[32] [33]。此外，有研究表明，辐射激活的巨噬细胞可能通过诱导肿瘤坏死因子-α (tumornecrosis factor-α, TNF-α)的高表达和促进血管生成，引起癌细胞的辐射抵抗，从而促进放疗后肿瘤的复发[34]。研究发现，由于 DNA 损伤诱导激酶 ABL1 在细胞核中与菌落刺激因子(colony-stimulating factor 1, CSF1)基因启动子结合并增强其转录，使用 CSF1 抑制剂阻断巨噬细胞的迁移可使肿瘤放射增敏[17]。除此之外在宫颈癌及乳腺癌的研究中证实，M2 型肿瘤相关巨噬细胞可以引起肿瘤细胞的放疗抵抗[35] [36]。这些研究表明促肿瘤免疫细胞可以调节许多癌症的辐射抗性，然而放疗后的免疫内环境的变化也能引起辐射抵抗。

放疗的成功依赖于免疫激活的抗原特异性，通过将放疗与免疫检查点阻断疗法结合，可以增强免疫激活的抗原特异性[37] [38] [39]。其中 PD-1 受体(PD-L1)/PD-1 轴在放疗和免疫调节方面的研究是最深入的。在 TME 中，PD-1 在 T 细胞膜表面的高表达提示 T 细胞的衰竭，导致 T 细胞介导的适应性免疫反应无效另外，放疗后肿瘤细胞表面 PDL1 的上调也参与了肿瘤放疗抵抗。相关研究证实，阻断 PD-L1/PD-1 轴联合放疗可以有效地缓解肿瘤放疗后的远端效应，这进一步证实了免疫治疗与放疗相联合的治疗策略在 肿瘤治疗中具有广泛的应用前景[40] [41] [42] [43] [44]。根据剂量、给药方法和放疗方案的不同，在临床前研究和临床观察中获得了不同的免疫反应[45]。根据剂量的不同，电离辐射可以招募和激活各种类型的免疫细胞[46]。T 淋巴细胞对辐射的敏感性取决于它们的活化状态——静息(非活化)的淋巴细胞比活化的淋巴细胞更容易受到红外的影响[47]。Treg 比其他人类 T 细胞更能抵抗辐射[48]。另一方面，B 淋巴细胞表现出较高的辐射敏感性，在辐射后呈现抗原和产生抗体的能力降低[49]。巨噬细胞比单核细胞更能抵抗射线[50]。这些发现表明，宿主的免疫状态是预测辐射敏感性的一个主要因素。

3.4. 乏氧微环境对放疗敏感性的影响

缺氧是肿瘤生长的一个关键调节因子，在放疗抵抗中起着至关重要的作用[3]。细胞对电离辐射的反应强烈依赖氧的存在，而缺氧导致高达 3 倍的辐射抗性[51]。其相关机制的研究有很多，最易接受的是固氧假说，辐射诱导靶细胞基因组 DNA 内部或附近的电离，产生各种自由基，导致 DNA 链断裂。氧是细胞中电子亲和性最强的分子，与自由基反应极快，使损伤永久。在没有氧气的情况下，DNA 自由基被含有巯基的化合物还原，从而修复 DNA 到其原始形态。从某种意义上说，氧气可以“固定”或使辐射损伤永久，这被称为氧固定假说[52]。缺氧诱导因子(HIF-1)是介导缺氧反应的最典型的转录因子，它由一个诱导 α 亚基和一个构成表达的 β 亚基组成[53]。活性氧(ROS)是辐射的效应分子，通常在肿瘤细胞和肿瘤环境中上调，有助于辐射诱导的 DNA 损伤和癌细胞死亡。HIF-1 可以增强糖酵解、丝氨酸合成途径和磷

酸戊糖途径的活性，进而增加抗氧化剂的生成，从而缓冲辐射诱导的 ROS，引起辐射抗性。缺氧本身会增加 ROS 的产生，进而触发反馈循环，刺激新陈代谢，有利于产生抗氧化剂，激活自噬，加速清除细胞 ROS 产物，使细胞癌症耐辐射。此外，缺氧维持了干细胞的“静止”状态，保持了它们增殖和分化的潜力，从而保护它们免受放射治疗[54]。

3.5. 肿瘤血管与放疗

了解放疗对肿瘤血管功能的影响，对放疗效果的最大化具有重要意义。新生的血管通常缺乏基膜和周细胞，使它们比健康组织周围的血管更通透、更渗漏，对辐射更敏感。内皮细胞的快速增殖使其对放疗敏感[3]。血管对放疗的敏感性与其形态有关——毛细血管和小的、未成熟的血管极其敏感，而大的、成熟的血管对放疗的抵抗力更强[5]。Smolarczyk 等的研究发信，照射后，肿瘤中会分泌大量促生存细胞因子。细胞因子抑制内皮细胞凋亡，防止血管损伤，削弱抗癌辐射效应[55]。放射治疗引起的肿瘤血管系统的变化仍然取决于总剂量和部分大小，以及肿瘤本身的类型、位置和阶段[56]。在最近的一项剂量增加研究中，2、4 或 8 Gy 剂量的单次给药被证明以剂量依赖性的方式损害肿瘤血管，延长了患高级别胶质瘤肿瘤的小鼠的生存时间。这也与其促进了 $CD8^+$ T 细胞的增加和 m2 样 TAMs 的减少有关[57]。高辐射剂量(>20 Gy)还可导致胰腺肿瘤中短暂的内皮功能障碍、血小板白细胞粘附和缺氧诱导因子-1α (HIF-1α)表达增加[58]。前文提到 HIF-1 是介导缺氧反应的最典型的转录因子，参与缺氧引起的放疗抵抗过程。

4. 总结与展望

在肿瘤生命周期的每一步，这些恶性肿瘤细胞和它所在的环境有着紧密的联系。它们之间高度动态的相互作用控制着肿瘤的起始、进展、侵袭、转移和耐药。肿瘤微环境是非常多样的，我们目前对不同细胞类型的知识仍然缺乏。随着连续的治疗，肿瘤和微环境中的细胞变得更耐药，我们在这里综述了肿瘤微环境是如何促进癌症辐射抵抗的，为的是能够有助于根除癌症，防止治疗耐药和肿瘤复发。尽管最近有许多发现，该领域仍有许多有待解决的问题，如 CAF 多样性如何影响放射抗性，肿瘤间质如何随着不同的照射剂量和分级方案而变化。未来对这些机制的发现可用于研发新的基质靶向药物与放疗联合使用以增加放射敏感性。

参考文献

[1] Kalluri, R. (2016) The Biology and Function of Fibroblasts in Cancer. *Nature Reviews Cancer*, **1**6, 582-598. https://doi.org/10.1038/nrc.2016.73

[2] Krisnawan Varintra, E., Stanley Jennifer, A., Schwarz Julie, K. and DeNardo David, G. (2020) Tumor Microenvironment as a Regulator of Radiation Therapy: New Insights into Stromal-Mediated Radioresistance. *Cancers*, **12**, Article 2916. https://doi.org/10.3390/cancers12102916

[3] Barker, H.E., Paget, J.T.E., Khan, A.A. and Harrington, K.J. (2015) The Tumourmicroenvironment after Radiotherapy: Mechanisms of Resistance and Recurrence. *Nature Reviews Cancer*, **15**, 409-425. https://doi.org/10.1038/nrc3958

[4] Weichselbaum, R.R., Liang, H., Deng, L. and Fu, Y.X. (2017) Radiotherapy and Immunotherapy: A Beneficial Liaison? *Nature Reviews Clinical Oncology*, **14**, 365-379. https://doi.org/10.1038/nrclinonc.2016.211

[5] Byrne, N.M., Tambe, P. and Coulter, J.A. (2021) Radiation Response in the Tumour Microenvironment: Predictive Biomarkers and Future Perspectives. *Journal of Personalized Medicine*, **11**, Article 53. https://doi.org/10.3390/jpm11010053

[6] Leroi, N., Lallemand, F., Coucke, P., Noel, A. and Martinive, P. (2016) Impacts of Ionizing Radiation on the Differentcompartments of the Tumor Microenvironment. *Frontiers in Pharmacology*, **7**, Article 78. https://doi.org/10.3389/fphar.2016.00078

[7] Jin, X., Ding, D., Yan, Y., *et al*. (2019) Phosphorylated RB Promotescancer Immunity by Inhibiting NF-κB Activation and PD-L1 Expression. *Molecular Cell*, **73**, 22-35.E6. https://doi.org/10.1016/j.molcel.2018.10.034

[8] Hou, Y., Liang, H., Rao, E., *et al*. (2018) Non-Canonical NF-κB Antagonizes STING Sensor-Mediated DNA Sensing

in Radiotherapy. *Immunity*, **49**, 490-503.E4. https://doi.org/10.1016/j.immuni.2018.07.008

[9] Kim, J.Y., Jeon, S., Yoo, Y.J., *et al*. (2019) The Hsp27-Mediated IkBαNFκB Signaling Axis Promotes Radiation-Induced Lung Fibrosis. *Clinical Cancer Research*, **25**, 5364-5375. https://doi.org/10.1158/1078-0432.CCR-18-3900

[10] Turley, S.J., Cremasco, V. and Astarita, J.L. (2015) Immunological Hallmarks of Stromal Cells in the Tumourmicroenvironment. *Nature Reviews Immunology*, **15**, 669-682. https://doi.org/10.1038/nri3902

[11] Bouquet, F., Pal, A., Pilones, K., *et al*. (2011) TGFβ1 Inhibition Increases the Radiosensitivity of Breast Cancer Cells *in Vitro* and Promotes Tumor Control by Radiation *in Vivo*. *Clinical Cancer Research*, **17**, 6754-6765. https://doi.org/10.1158/1078-0432.CCR-11-0544

[12] Morgan, A., Griffin, M., Kameni, L., Wan, D.C., Longaker, M.T. and Norton, J.A. (2023) Medical Biology of Cancer-Associated Fibroblasts in Pancreatic Cancer. *Biology*, **12**, Article 1044. https://doi.org/10.3390/biology12081044

[13] Chen, J., Zhu, H., Yin, Y., Jia, S. and Luo, X. (2022) Colorectal Cancer: Metabolic Interactions Reshape the Tumor Microenvironment. *Biochimica et Biophysica Acta* (*BBA*)—*Reviews on Cancer*, **1877**, Article ID: 188797. https://doi.org/10.1016/j.bbcan.2022.188797

[14] Boelens, M.C., Wu, T.J., Nabet, B.Y., Xu, B., Qiu, Y., Yoon, T., Azzam, D.J., Twyman-Saint Victor, C., Wiemann, B.Z., Ishwaran, H., *et al*. (2014) Exosome Transfer from Stromal to Breast Cancer Cells Regulates Therapyresistance Pathways. *Cell*, **159**, 499-513. https://doi.org/10.1016/j.cell.2014.09.051

[15] Agosti, E., Panciani, P.P., Zeppieri, M., De Maria, L., Pasqualetti, F., Tel, A., Zanin, L., Fontanella, M.M. and Ius, T. (2023) Tumor Microenvironment and Glioblastoma Cell Interplay as Promoters of Therapeutic Resistance. *Biology*, **12**, Article 736. https://doi.org/10.3390/biology12050736

[16] Wang, Y., Gan, G., Wang, B., Wu, J., Cao, Y., Zhu, D., Xu, Y., Wang, X., Han, H., Li, X., *et al*. (2017) Cancer-Associated Fibroblasts Promote Irradiated Cancer Cell Recovery through Autophagy. *eBioMedicine*, **17**, 45-56. https://doi.org/10.1016/j.ebiom.2017.02.019

[17] Zhang, H., Yue, J., Jiang, Z., Zhou, R., Xie, R., Xu, Y. and Wu, S. (2017) CAF-Secreted CXCL1 Conferred Radioresistanceby Regulating DNA Damage Response in a ROS-Dependent Manner in Esophageal Squamous Cell Carcinoma. *Cell Death & Disease*, **8**, e2790. https://doi.org/10.1038/cddis.2017.180

[18] Al-Assar, O., Demiciorglu, F., Lunardi, S., Gaspar-Carvalho, M.M., McKenna, W.G., Muschel, R.M. and Brunner, T.B. (2014) Contextual Regulation of Pancreatic Cancer Stem Cell Phenotype and Radioresistance Bypancreatic Stellate Cells. *Radiotherapy & Oncology*, **111**, 243-251. https://doi.org/10.1016/j.radonc.2014.03.014

[19] Hen, W.J., Ho, C.C., Chang, Y.L., Chen, H.Y., Lin, C.A., Ling, T.Y., Yu, S.L., Yuan, S.S., Louisa Chen, Y.J., Lin, C.Y., *et al*. (2014) Cancer-Associated Fibroblasts Regulate the Plasticity of Lung Cancer Stemness via Paracrinesignalling. *Nature Communications*, **5**, Article No. 3472. https://doi.org/10.1038/ncomms4472

[20] Osuka, S., Sampetrean, O., Shimizu, T., Saga, I., Onishi, N., Sugihara, E., Okubo, J., Fujita, S., Takano, S., Matsumura, A., *et al*. (2013) IGF1 Receptor Signaling Regulates Adaptive Radioprotection in Glioma Stem Cells. *Stem Cells*, **31**, 627-640. https://doi.org/10.1002/stem.1328

[21] Hawsawi, N.M., Ghebeh, H., Hendrayani, S.F., Tulbah, A., Al-Eid, M., Al-Tweigeri, T., Ajarim, D., Alaiya, A., Dermime, S. and Aboussekhra, A. (2008) Breast Carcinoma-Associated Fibroblasts and Their Counterparts Displayneoplastic-Specific Changes. *Cancer Research*, **68**, 2717-2725. https://doi.org/10.1158/0008-5472.CAN-08-0192

[22] Sahai, E., Astsaturov, I., Cukierman, E., *et al*. (2020) A Framework for Advancing Our Understanding of Cancer-Associated Fibroblasts. *Nature Reviews Cancer*, **20**, 174-186. https://doi.org/10.1038/s41568-019-0238-1

[23] Li, D., Qu, C., Ning, Z., Wang, H., Zang, K., Zhuang, L., Chen, L., Wang, P. and Meng, Z. (2016) Radiation Promotesepithelial-to-Mesenchymal Transition and Invasion of Pancreatic Cancer Cell by Activating Carcinoma-Associated-fibroblasts. *American Journal of Cancer Research*, **6**, 2192-2206.

[24] Hellevik, T., Pettersen, I., Berg, V., Winberg, J.O., Moe, B.T., Bartnes, K., Paulssen, R.H., Busund, L.T., Bremnes, R., Chalmers, A., *et al*. (2012) Cancer-Associated Fibroblasts from Human NSCLC Survive Ablative Doses Ofradiation But Their Invasive Capacity Is Reduced. *Radiation Oncology*, **7**, Article No. 59. https://doi.org/10.1186/1748-717X-7-59

[25] Mantoni, T.S., Lunardi, S., Al-Assar, O., Masamune, A. and Brunner, T.B. (2011) Pancreatic Stellate Cells Radioprotectpancreatic Cancer Cells through β1-Integrin Signaling. *Cancer Research*, **71**, 3453-3458. https://doi.org/10.1158/0008-5472.CAN-10-1633

[26] Gilkes, D.M., Semenza, G.L. and Wirtz, D. (2014) Hypoxia and the Extracellular Matrix: Drivers of Tumour Metastasis. *Nature Reviews Cancer*, **14**, 430-439. https://doi.org/10.1038/nrc3726

[27] Cordes, N. (2006) Integrin-Mediated Cell-Matrix Interactions for Prosurvival and Antiapoptotic Signaling Aftergenotoxic Injury. *Cancer Letters*, **242**, 11-19. https://doi.org/10.1016/j.canlet.2005.12.004

[28] Cordes, N., Seidler, J., Durzok, R., Geinitz, H. and Brakebusch, C. (2006) B1-Integrin-Mediated Signaling Essential-

lyContributes to Cell Survival after Radiation-Induced Genotoxic Injury. *Oncogene*, **25**, 1378-1390. https://doi.org/10.1038/sj.onc.1209164

[29] Biswas, S., Freeman, M.L., Arteaga, C.L., Biswas, S., Guix, M., Rinehart, C., Dugger, T.C., Chytil, A., Moses, H.L., Freeman, M.L., *et al*. (2007) Inhibition of TGF β with Neutralizing Antibodies Preventsradiation-Induced Acceleration of Metastatic Cancer Progression Find the Latest Version: Inhibition of TGF-β with Neutralizing Antibodies Prevents Radiation-Induced Acceleration of Metastatic. *Journal of Clinical Investigation*, **117**, 1305-1313. https://doi.org/10.1172/JCI30740

[30] Chetty, C., Bhoopathi, P., Rao, J.S. and Lakka, S.S. (2009) Inhibition of Matrix Metalloproteinase-2 Enhancesradiosensitivity by Abrogating Radiation-Induced FoxM1-Mediated G2/M Arrest in A549 Lung Cancer Cells. *International Journal of Cancer*, **124**, 2468-2477. https://doi.org/10.1002/ijc.24209

[31] Binnewies, M., Roberts, E.W., Kersten, K., Chan, V., Fearon, D.F., Merad, M., Coussens, L.M., Gabrilovich, D.I., Ostrand-Rosenberg, S., Hedrick, C.C., *et al*. (2018) Understanding the Tumor Immune Microenvironment (TIME) for Effective Therapy. *Nature Medicine*, **24**, 541-550. https://doi.org/10.1038/s41591-018-0014-x

[32] He, X., Feng, Z., Ma, J., *et al*. (2020) Bispecific and Split CAR T Cells Targeting CD13 and TIM3 Eradicate Acute Myeloid Leukemia. *Blood*, **135**, 713-723. https://doi.org/10.1182/blood.2019002779

[33] Daassi, D., Mahoney, K.M. and Freeman, G.J. (2020) The Importance of Exosomal PDL1 in Tumour Immune Evasion. *Nature Reviews Immunology*, **20**, 209-215. https://doi.org/10.1038/s41577-019-0264-y

[34] Meng, Y., *et al*. (2010) Blockade of Tumor Necrosis Factor α Signaling in Tumor-Associated Macrophages as a Radiosensitizing Strategy. *Cancer Research*, **70**, 1534-1543. https://doi.org/10.1158/0008-5472.CAN-09-2995

[35] 王珍, 茅芯慧, 章恒, 等. STAT3 诱导巨噬细胞 M2 型极化促进宫颈癌细胞的放疗抵抗及机制研究[J]. 现代肿瘤医学, 2022, 30(15): 2710-2715.

[36] Rahal, O.M., Wolfe, A.R., Mandal, P.K., Larson, R., Tin, S., Jimenez, C., Zhang, D., Horton, J., Reuben, J.M., McMurray, J.S. and Woodward, W.A. (2018) Blocking Interleukin (IL)4- and IL13-Mediated Phosphorylation of STAT6 (Tyr641) Decreases M2 Polarization of Macrophages and Protects against Macrophage-Mediated Radioresistance of Inflammatory Breast Cancer. *International Journal of Radiation Oncology, Biology, Physics*, **100**, 1034-1043. https://doi.org/10.1016/j.ijrobp.2017.11.043

[37] Formenti, S.C., Rudqvist, N.P., Golden, E., Cooper, B., Wennerberg, E., Lhuillier, C., Vanpouille-Box, C., Friedman, K., Ferrari De Andrade, L., Wucherpfennig, K.W., *et al*. (2018) Radiotherapy Induces Responses of Lungcancer to CTLA-4 Blockade. *Nature Medicine*, **24**, 1845-1851. https://doi.org/10.1038/s41591-018-0232-2

[38] Sharabi, A.B., Nirschl, C.J., Kochel, C.M., Nirschl, T.R., Francica, B.J., Velarde, E., Deweese, T.L. and Drake, C.G. (2015) Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses Via-cross-Presentation of Tumor Antigen. *Cancer Immunology Research*, **3**, 345-355. https://doi.org/10.1158/2326-6066.CIR-14-0196

[39] Yoshimoto, Y., Suzuki, Y., Mimura, K., Ando, K., Oike, T., Sato, H., Okonogi, N., Maruyama, T., Izawa, S., Noda, S.E., *et al*. (2014) Radiotherapy-Induced Anti-Tumor Immunity Contributes to the Therapeutic Efficacy of Irradiation and Can Be Augmented by CTLA-4 Blockade in A Mouse Model. *PLOS ONE*, **9**, e92572. https://doi.org/10.1371/journal.pone.0092572

[40] Wang, Y., Liu, Z.G., Yuan, H., *et al*. (2019) The Reciprocity between Radiotherapy and Cancer Immunotherapy. *Clinical Cancer Research*, **25**, 1709-1717. https://doi.org/10.1158/1078-0432.CCR-18-2581

[41] Rodríguez-Ruiz, M.E., Vanpouille-Box, C., Melero, I., *et al*. (2018) Immunological Mechanisms Responsible for Radiation-Induced Abscopal Effect. *Trends in Immunology*, **39**, 644-655. https://doi.org/10.1016/j.it.2018.06.001

[42] Edner, N.M., Carlesso, G., Rush, J.S., *et al*. (2020) Targeting Co-Stimulatory Molecules in Autoimmune Disease. *Nature Reviews Drug Discovery*, **19**, 860-883. https://doi.org/10.1038/s41573-020-0081-9

[43] Rodriguez-Ruiz, M.E., Rodriguez, I., Leaman, O., *et al*. (2019) Immune Mechanisms Mediating Abscopal Effects in Radioimmunotherapy. *Pharmacology & Therapeutics*, **196**, 195-203. https://doi.org/10.1016/j.pharmthera.2018.12.002

[44] Grapin, M., Richard, C., Limagne, E., *et al*. (2019) Optimized Fractionated Radiotherapy with Anti-PD-L1 and Anti-TIGIT: A Promising New Combination. *Journal for ImmunoTherapy of Cancer*, **7**, 160. https://doi.org/10.1186/s40425-019-0634-9

[45] Soukup, K. and Wang, X. (2015) Radiation Meets Immunotherapy—A Perfect Match in the Era of Combination Therapy? *International Journal of Radiation Biology*, **91**, 299-305. https://doi.org/10.3109/09553002.2014.995383

[46] Frey, B., Rückert, M., Deloch, L., Rühle, P.F., Derer, A., Fietkau, R. and Gaipl, U.S. (2017) Immunomodulation Byionizing Radiation-Impact for Design of Radio-Immunotherapies and for Treatment of Inflammatory Diseases. *Immunological Reviews*, **280**, 231-248. https://doi.org/10.1111/imr.12572

[47] Manda, K., Glasow, A., Paape, D. and Hildebrandt, G. (2012) Effects of Ionizing Radiation on the Immune System

with Special Emphasis on the Interaction of Dendritic and T Cells. *Frontiers in Oncology*, **2**, Article 102. https://doi.org/10.3389/fonc.2012.00102

[48] Falcke, S.E., Rühle, P.F., Deloch, L., Fietkau, R., Frey, B. and Gaipl, U.S. (2018) Clinically Relevant Radiation Exposure Differentially Impacts Forms of Cell Death in Human Cells of the Innate and Adaptive Immune System. *International Journal of Molecular Sciences*, **19**, Article 3574. https://doi.org/10.3390/ijms19113574

[49] McKelvey, K.J., Hudson, A.L., Back, M., Eade, T. and Diakos, C.I. (2018) Radiation, Inflammation and the Immune-response in Cancer. *Mammalian Genome*, **29**, 843-865. https://doi.org/10.1007/s00335-018-9777-0

[50] Rubner, Y., Wunderlich, R., Rühle, P.F., Kulzer, L., Werthmöller, N., Frey, B., Weiss, E.M., Keilholz, L., Fietkau, R. and Gaipl, U.S. (2012) How Does Ionizing Irradiation Contribute to the Induction of Anti-Tumor Immunity? *Frontiers in Oncology*, **2**, Article 75. https://doi.org/10.3389/fonc.2012.00075

[51] Hall, E.J. and Giaccia, A.J. (2012) Radiobiology for the Radiologist. Lippincott Williams & Wilkins: Philadelphia.

[52] Brown, J.M. and Wilson, W.R. (2004) Exploiting Tumour Hypoxia in Cancer Treatment. *Nature Reviews Cancer*, **4**, 437-447. https://doi.org/10.1038/nrc1367

[53] Movafagh, S., Crook, S. and Vo, K. (2015) Regulation of Hypoxia-Inducible Factor-1a by Reactive Oxygen Species: Newdevelopments in an Old Debate. *Journal of Cellular Biochemistry*, **116**, 696-703. https://doi.org/10.1002/jcb.25074

[54] Wang, H., Jiang, H., Van De Gucht, M. and De Ridder, M. (2019) Hypoxic Radioresistance: Can ROS Be the Key to Overcome It? *Cancers*, **11**, Article 112. https://doi.org/10.3390/cancers11010112

[55] Smolarczyk, R., Cichon, T., Pilny, E., Jarosz-Biej, M., Poczkaj, A., Kułach, N. and Szala, S. (2018) Combination of Anti-Vascular Agent-DMXAA and HIF-1α Inhibitor-Digoxin Inhibits the Growth of Melanoma Tumors. *Scientific Reports*, **8**, Article No. 7355. https://doi.org/10.1038/s41598-018-25688-y

[56] Park, H.J., Griffin, R.J., Hui, S., Levitt, S.H. and Song, C.W. (2012) Radiation-Induced Vascular Damage in Tumors: Implications of Vascular Damage in Ablative Hypofractionated Radiotherapy (SBRT and SRS). *Radiation Research*, **177**, 311-327. https://doi.org/10.1667/RR2773.1

[57] Riva, M., Wouters, R., Nittner, D., Ceuster, J., Sterpin, E., Giovannoni, R., Himmelreich, U., Gsell, W., Van Ranst, M. and Coosemans, A. (2020) Radiation Dose-Escalation and Dose-Fractionation Modulate the Immune Microenvironment, Cancer Stem Cells and Vasculaturein Experimental High-Grade Gliomas. *Journal of Neurosurgical Sciences*, **67**, 55-65.

[58] Maeda, A., Chen, Y., Bu, J., Mujcic, H., Wouters, B.G. and DaCosta, R.S. (2017) *In Vivo* Imaging Reveals Significant Tumor Vascular Dysfunction and Increased Tumor Hypoxia-Inducible Factor-1α Expression Induced by High Single-Dose Irradiation in a Pancreatic Tumor Model. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **97**, 184-194. https://doi.org/10.1016/j.ijrobp.2016.09.005