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冷冻消融调控癌症–免疫循环的机制及免疫联合治疗策略

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摘要　近年来, 冷冻消融(cryoablation, CRA)作为肿瘤微创治疗技术, 其作用机制已从单纯的局部物理破坏拓展为协同调控癌症–免疫循环(cancer-immune cycle)。研究表明, CRA通过诱导肿瘤细胞多种形式的死亡, 使其释放天然肿瘤特异性抗原及炎症性细胞因子, 激活树突状细胞(dendritic cell, DC)的抗原呈递功能, 增强$CD8^+$T细胞与自然杀伤细胞(natural killer cells, NK)的抗肿瘤活性。但CRA单独应用时全身免疫应答强度有限且持续时间短, 难以有效抑制远端转移病灶。该综述系统解析了CRA调节癌症–免疫循环的多维机制, 包括抗原释放与呈递、T细胞活化、细胞因子释放及远隔效应(abscopal effect, AE), 并据此提出了联合治疗策略优化方向, 为CRA在肿瘤免疫治疗中的精准应用提供了理论依据与转化路径。

关键词　冷冻消融; 癌症–免疫循环; 免疫治疗; 联合治疗

Mechanisms of Cryoablation in Regulating the Cancer–Immune Cycle and Strategies for Immuno–Combination Therapy

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Abstract　In recent years, CRA (cryoablation), a minimally invasive tumor therapy, has extended its mechanism from mere local physical destruction to synergistically regulating the cancer-immune cycle. Studies show CRA induces diverse tumor cell death, releasing native tumor-specific antigens and inflammatory cytokines, activating DC (dendritic cell) antigen presentation, and enhancing the anti-tumor activities of $CD8^+$T cells and NK (natural killer cells). However, CRA alone elicits a weak, short-lived systemic immune response, poorly inhibiting distant tumor metastases. This review systematically analyzes CRA's multidimensional regulation of the cancer-immune cycle, including antigen release/presentation, T cell activation, cytokine release, and AE (abscopal effect). Based on this, it proposes optimized combination strategies, offering theoretical basis and translational pathways for precise CRA application in tumor immunotherapy.

Keywords　cryoablation; cancer-immune cycle; immunotherapy; combination therapy

冷冻消融(cryoablation, CRA)是一种通过极低温(通常使用液氮或氩氦刀)选择性诱导肿瘤细胞死亡的微创消融技术, 其作用机制显著区别于基于高温的热消融技术, 如高强度聚焦超声(high intensity focused ultrasound, HIFU)、射频消融(radiofrequency ablation, RFA)、微波消融(microwave ablation,

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MWA)及热疗(hyperthermia therapy, HT)等[1-2]。CRA的核心优势在于复合杀伤机制: 通过快速冷冻使细胞内形成冰晶从而引发肿瘤细胞渗透性休克, 同步破坏微循环导致肿瘤细胞缺血性坏死, 实现了坏死与凋亡的联合杀伤, 避免了RFA或MWA的热沉效应及HT治疗温度不足(40~45 °C)问题[3-5]。此外, 与传统手术切除相比, CRA具有微创性、周围组织损伤小、失血量少、治疗成本低以及术后并发症少和死亡率低等显著优势[6-7]。

在过去的几十年中, CRA已广泛应用于肝癌、肺癌、前列腺癌、肾癌、食管癌、胃癌、乳腺癌等多种实体肿瘤的临床治疗, 且并发症发生率低, 即使在肝、肺等关键器官靠近大血管的病灶中也显示出相对较低的血管损伤相关并发症风险[8-13]。例如, 对于无法手术的肝细胞癌(hepatocellular carcinoma, HCC)患者,《原发性肝癌诊疗指南》推荐CRA作为重要的替代方案。多中心随机对照试验结果表明, 与RFA相比, CRA组3年局部进展率显著降低(7.7% *vs* 18.2%), 且对肿瘤长径>3 cm或邻近大血管的病灶仍可实现安全治疗[14-15]。在肺癌治疗中, CRA与MWA疗效相当, 中位无进展生存期(median progression-free survival, mPFS)为10~11个月, 对放化疗失败患者的1年生存率可达81.8%[16-17]。对于肾癌和低位直肠癌, CRA可作为手术的替代选择。例如在CRA治疗肾癌中, 其复发率和生存率与肾部分切除术相当; 在低位直肠癌中, CRA可有效避免永久性造口需求(患者无需护理造口), 肛门功能损伤轻微, 仅出现Clavien-Dindo2级的肛门疼痛(可通过止痛药缓解), 且治疗后患者功能状态(KPS评分90分)与治疗前无明显差异[18-21]。此外, CRA 在实体瘤及特殊解剖位置肿瘤治疗中的应用已得到有效验证。具体而言, 在乳腺癌小体积肿瘤(直径≤1.5 cm)的治疗中, 同侧复发率仅为2.06%[22]; 在前列腺癌治疗中, 低风险患者10年无放射治疗(radiation therapy, RT)干预率达51%[23]; 而在特殊解剖位置肿瘤(如中央型肾T1b 肿瘤)的治疗中, 患者3年局部复发率为11.1%[24]。

多年的临床治疗结果显示, CRA在诱导肿瘤细胞死亡的方式上具有独特的免疫学优势。相较于HIFU、RFA及MWA等热消融技术, CRA导致的细胞死亡可有效保留天然肿瘤抗原(未变性抗原)的完整性, 从而更高效地促进其原位释放[25-26]。据报道, 前列腺癌患者在接受CRA治疗后, 血清前列腺特异性抗原(prostate-specific antigen, PSA)水平显著升高[27]。近年来, 基础研究进一步揭示, CRA可通过诱导肿瘤细胞死亡并释放肿瘤相关抗原及损伤相关分子模式(damage-associated molecular patterns, DAMPs), 激活树突状细胞(dendritic cell, DC)的抗原呈递功能, 模拟“原位疫苗接种”效应, 进而引发全身性抗肿瘤免疫反应[28-31]。这一免疫学潜力的理论基础是癌症–免疫循环(cancer-immunity cycle)[31-32]。在该过程中, 抗原呈递细胞(antigen-presenting cell, APC)首先捕获并加工抗原, 再通过主要组织相容性复合物I/II类(major histocompatibility complex class I/II, MHC I/II)将其呈递给T细胞, 进而激活初始T细胞。随后, 效应T细胞向肿瘤迁移并浸润肿瘤, 从而识别并杀死远端肿瘤细胞。目前临床研究中的免疫治疗药物, 大多针对癌症–免疫循环中的一个或多个环节研发, 因此, 不同药物联合成为癌症治疗的共识。

与此同时, 近年来有证据显示, CRA对全身抗肿瘤免疫反应无显著贡献, 在B16F10黑色素瘤模型中, 其诱导的全身抗肿瘤免疫反应强度有限, 主要发挥肿瘤减瘤作用[33]。因此, 需考虑如何通过联合治疗提高AE的发生率并增强其效果。本综述将根据CRA的作用机制, 及其联合免疫治疗的最新进展, 从原理和临床应用的角度来阐述CRA诱导的免疫学机制。

1 冷冻消融调节癌症–免疫循环机制

CRA通过物理性破坏肿瘤组织, 触发多重免疫调节机制, 进而影响癌症–免疫循环的动态平衡(图1)。其核心作用包括诱导肿瘤细胞死亡并释放特异性抗原、调控抗原呈递过程、增强效应T细胞功能, 以及产生远隔效应。这些机制的协同作用可能启动或增强抗肿瘤免疫应答, 为后续免疫治疗提供潜在协同效应。然而, CRA也会促进IL-10、TGF-β等抗炎因子的释放并上调PD-1和PD-L1的表达水平, 可快速促进T细胞活性降低及耗竭, 对肿瘤免疫反应存在一定抑制作用。因此, CRA对癌症–免疫循环具有双重调节作用。

1.1 冷冻消融促进肿瘤抗原释放的机制

不同的消融治疗方式对肿瘤细胞的杀伤机制不同。如RT通过高能辐射直接电离DNA, 引发DNA双链断裂(double-strand break, DSB)等致命损伤, 同时使水分子水解产生活性氧(reactive oxygen species, ROS), 间接损伤核酸与蛋白质, 从而使肿瘤细胞因修复能力

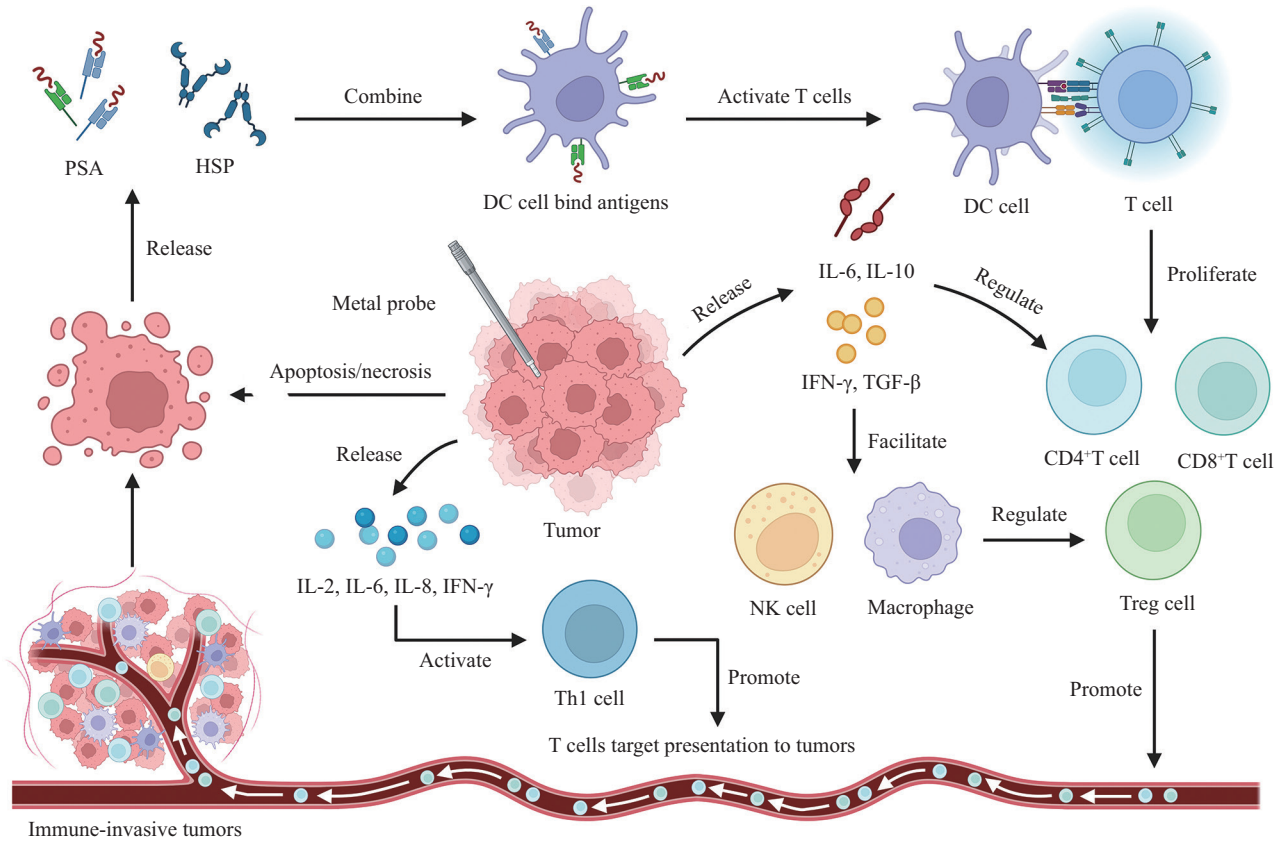

图1 CRA作为一种癌症–免疫循环的调节剂(根据参考文献[28-32]修改)

Fig.1 Cryoablation as a modulator of the cancer-immune cycle (modified from the references [28-32])

低下(尤其分裂期)更易死亡[34-35]; RFA通过离子振荡产热, 高温(>50 °C)直接引发肿瘤细胞蛋白质变性及凝固性坏死[36]; MWA治疗主要依托电磁波的热效应及分子与细胞层面的选择性作用, 导致肿瘤细胞的蛋白质变性、细胞膜破裂, 从而造成肿瘤细胞的凝固性坏死[37-39]; 而HT治疗的核心机制是通过40~45 °C的温度调控实现多层次生物效应, 如肿瘤细胞骨架蛋白与DNA修复酶变性, 会增强DNA损伤, 将细胞周期阻滞于G_1/S期和G_2/M期[40-41], 且在41~43 °C时HT激活线粒体凋亡通路, 导致DNA片段化, 并引发由氧化应激等引起的DNA损伤[42], 从而实现生物效应调控。

相较于上述消融手段, CRA通过低温介导的多层次分子通路协同诱导肿瘤细胞死亡(图2), 包括低温形成冰晶对细胞膜的机械损伤、细胞损伤应激导致的坏死和凋亡、冷冻导致肿瘤血液供应中断等。在直接细胞杀伤方面, 该技术通过焦耳–汤姆逊效应实现的超低温(–196~–140 °C)可诱导肿瘤组织细胞内、外冰晶形成, 不仅通过机械损伤直接破坏细胞膜及细胞器, 还因细胞外高渗透压引发细胞脱水破裂[43-44]。在这一过程中, 物理性冰晶损伤直接破坏细胞膜完整性, 激活线粒体凋亡通路(BAX/BCL-2失衡→细胞色素C释放→caspase-9/3级联活化)与坏死性凋亡通路(RIPK1/RIPK3-MLKL磷酸化介导膜破裂); 继发性生化应激则通过释放ATP、HMGB1等危险信号激活NLRP3炎症小体(依赖TLR4/MyD88通路), 促进IL-1β成熟及炎性微环境形成; 同时, 缺氧诱导的HIF-1α信号上调促凋亡因子BNIP3表达, 并加剧血管渗漏。

此外, 低温可损伤肿瘤微血管内皮, 导致血小板聚集形成血栓, 引发组织缺血[45-46]。当温度降低时, 组织中的细胞外液冻结, 细胞外冰的形成增加了细胞外的渗透压, 导致了液体从细胞内渗透到细胞外, 同时, 在这种高渗环境中细胞内pH值和内容物的变化会导致细胞损伤。而后解冻阶段的血流恢复(再灌注)导致氧化应激反应增强, 进一步加剧组织损伤[47-48]。最终结果表现为: 中心区肿瘤细胞发生凝固性坏死; 边缘区肿瘤细胞则主要因线粒体损伤等因素发生延迟性凋亡[2,46]。例如, WEN等[49]在T739小鼠LA795肺腺癌

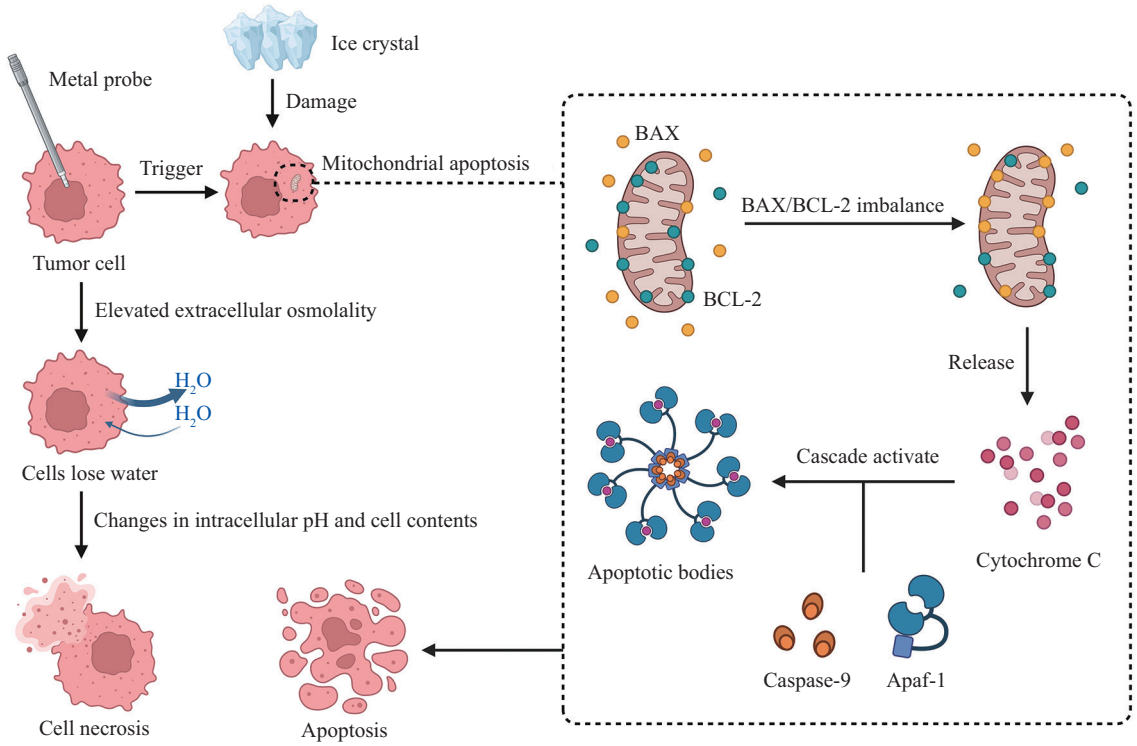

图2　CRA促进肿瘤特异性抗原的释放(根据参考文献[43-49]修改)

Fig.2　Cryoablation promotes the release of tumor-specific antigens (modified from the references [43-49])

皮下移植瘤的CRA模型中, 观察到促凋亡蛋白BAX的表达水平显著上调, 这为边缘区肿瘤细胞凋亡的发生提供了实验证据。

1.2　冷冻消融对肿瘤抗原呈递的影响

尽管目前普遍认为CRA对免疫系统的激活能力较弱, 但一项研究显示, 进行CRA后的小鼠肺癌模型瘤周灌洗液中IL-1β、IL-2、IL-6、IL-12β、IFN-γ、TNF-α水平显著升高, 表明CRA可能通过释放炎症信号激活免疫细胞[50]。虽然没有直接的证据显示CRA激活DC, 但研究表明, CRA使肿瘤细胞释放的肿瘤抗原与DAMPs可激活TLR信号通路[51-53], 而TLR激动剂(如CpG、咪喹莫特)通过激活TLR信号通路促进DC成熟及共刺激分子(co-stimulatory molecule, Co-SM)如CD80/CD86表达, 进而提升抗原呈递效率[54-55], 故CRA可通过激活TLR信号通路提升抗原呈递效率。此外, 小鼠MT901乳腺癌模型CRA治疗结果显示, 单纯手术切除后小鼠的肿瘤复发率为86%, 而CRA后小鼠的肿瘤复发率仅为16%[56]。这表明, CRA通过引起肿瘤细胞坏死并释放大量肿瘤特异性抗原, 进而引发抗肿瘤免疫反应。同样, CRA后前列腺癌患者的血清PSA水平升高[27], 这些新抗原的释放将导致危险信号分子的增加, 并启动抗肿瘤免疫反应。

目前, 关于CRA导致细胞死亡后, 免疫系统发生变化的继发机制尚未明确, 部分研究认为这种变化继发于机械力诱导的细胞坏死, 也有研究认为其继发于混合谱系激酶结构域样蛋白(mixed lineage kinase domain-like protein, MLKL)和RIP激酶磷酸化介导的坏死, 或者继发于血栓形成和其他血管相关因素或上述因素的组合。研究显示, CRA可诱导细胞死亡, 且细胞内容物保持相对完整, 进而使细胞释放出DNA、RNA及热休克蛋白(heat shock protein, HSP)[57]。例如, 黑色素瘤经CRA治疗后HSP70水平升高[58]。释放的肿瘤抗原与HSP70/90复合物结合后, 通过CD91受体提高DC抗原呈递效率, 同时, 局部微环境中IL-6/IFN-γ等细胞因子通过JAK-STAT通路募集并激活$CD8^+$T细胞与自然杀伤细胞(natural killer cells, NK), 最终形成“原位疫苗”效应, 实现抗肿瘤免疫的级联放大[59]。

1.3　冷冻消融对T细胞激活的影响

许多研究指出, CRA激活的特异性淋巴细胞主要是$CD4^+$和$CD8^+$T淋巴细胞[60-61]。在CRA与RFA的对比研究中, 尽管两者都可以诱导抗原特异性$CD8^+$T淋巴细胞反应, 但CRA可以诱导更强的抗原特异性$CD4^+$T细胞反应, 因此CRA在诱导抗肿瘤免

疫靶向性方面的能力更强[62]。一项针对22例肾细胞癌患者的临床研究发现, CRA后免疫相关基因, 如颗粒酶A(granzyme A, *GZMA*)、整合素αX亚基(integrin alpha X subunit, *CD11c*)等基因的转录水平显著升高, 且T细胞受体β(T cell receptor β chain, TCR-β)谱系分析表明, CRA可引起肿瘤组织中某些T细胞克隆的扩增, 也印证了这一免疫刺激过程[63]。此外, 除了肿瘤消退、肺转移减少以及全身$CD4^+$和$CD8^+$T细胞增加外, CRA还促进NK细胞的增加[64-65], 同时, 对HCC和其他癌症的研究发现, CRA治疗不仅促进$CD4^+$和$CD8^+$T细胞的增加, 还导致调节性T细胞(regulatory T cell, Tregs)的减少[66-67]。

然而, 一项结直肠癌研究中的CRA治疗结果表明, CRA治疗后肿瘤组织中的PD-L1表达水平和特定$CD8^+$和$CD4^+$T淋巴细胞中的PD-1分子表达水平增加, 对T细胞活性产生抑制作用[68]。因此, CRA治疗可联合免疫检查点抑制剂(immune checkpoint inhibitors, ICIs; 如抗PD-1、抗PD-L1、抗CTLA-4抗体), 通过阻断免疫抑制信号增强T细胞活性, 进一步增强CRA的治疗效果。

1.4 冷冻消融对细胞因子释放的影响

CRA通过快速冷冻–复温循环直接破坏肿瘤组织, 导致肿瘤细胞中抗原和DAMPs大量释放, 进而促进肿瘤组织中细胞因子的产生。虽然, 目前尚无明确研究显示CRA处理后细胞因子的来源, 但是这些具有免疫促进和免疫抑制作用的细胞因子在肿瘤治疗与耐药方面发挥着重要作用。研究显示CRA处理Lewis肺癌后, 肿瘤组织中释放大量IL-2和IFN-γ[61]。这些细胞因子都是促进T细胞和NK细胞增殖的关键因素, IL-2通过自分泌和旁分泌与IL-2受体结合, 激活STAT5、MAPK和mTORC1信号, 刺激T细胞存活与扩增, $CD4^+$T细胞产生的IL-2还增强$CD8^+$T细胞毒性; IFN-γ则通过激活JAK-STAT信号, 从而增强$CD8^+$T细胞和NK细胞活性[69-70]。

同时, CRA后IFN-γ水平升高, 表明Th1型免疫应答的上调与抗体依赖性细胞介导的细胞毒性(antibody dependent cellular cytotoxicity, ADCC)应答相关[71]。值得注意的是, 在热消融后促炎细胞因子IL-1β、IL-6和IL-8水平均有不同程度的升高[72-73], 这些细胞因子的增加同样有助于特异性T细胞活化和Th1反应。然而研究表明, 正常小鼠的肝脏进行CRA后, 上述炎症和细胞损伤的标志物水平显著升高, 增幅超过其他消融方式, 且在超过20%的肝脏消融案例中, IL-6、IL-10和TNF-α的释放可能会诱导全身炎症反应, 进而产生全身性不良效应[74]。因此, 在肝脏肿瘤治疗时为避免此类全身炎症风险, 更适合采用热消融替代CRA[75]。

然而, CRA不仅诱导促炎因子水平升高, 也促进抗炎因子水平提高。在结肠癌小鼠模型中发现, 与RFA相比, CRA促进了更广泛的细胞因子分泌, 而这些细胞因子中存在抗炎因子如IL-10[76], 在小鼠前列腺癌模型中也证实CRA作用后的肿瘤组织会释放IL-10、TGF-β等抗炎因子, 这些因子可促进Tregs扩增, 进而抑制效应T细胞的功能[77-78]。

多项研究证实CRA能增强免疫反应, 但其持续时间较短, 约为4周。研究表明, 特定T细胞在CRA后2至4周具有抗肿瘤细胞溶解的作用[79-80]。因此, 深入探讨CRA的联合治疗策略, 将有助于更好地提升CRA治疗的抗肿瘤免疫效应。

1.5 冷冻消融的抗肿瘤远隔效应

CRA通过诱导肿瘤细胞发生免疫原性死亡, 使其释放肿瘤抗原和DAMPs, 激活全身性抗肿瘤免疫反应, 从而产生AE。近年来的临床研究表明, CRA联合治疗诱导的AE明显优于单纯CRA治疗。在针对非小细胞肺癌患者及肺癌细胞同种移植小鼠模型开展的研究中, 对比“CRA+PD-1阻断”与“单纯CRA”两种方案发现, 联合治疗较单独治疗对肿瘤生长的抑制更显著, 6例患者中4例达到部分缓解(总缓解率为66.7%), 且小鼠生存期延长; 同时, CRA后患者循环$CD8^+$T细胞亚群及IFN-α等促炎细胞因子水平显著增加, 肿瘤微环境中$CD8^+$T细胞浸润增多, CRA在增强抗肿瘤效应的同时安全性良好, 未增加免疫相关不良反应[81]。另一项针对III~IV期非小细胞肺癌患者的研究显示, CRA经支气管镜治疗后, 患者系统性炎症指标dNLR显著降低, $CD8^+$效应记忆T细胞被激活, IL-17A、IFN-γ等促炎因子水平升高, 提示Th17通路参与全身免疫应答, 且肿瘤周围淋巴细胞浸润持续6~11周, 证实了局部–全身免疫存在协同作用[82]。尽管CRA在现有临床试验中展现出积极结果, 但当前研究多为II期以下或回顾性分析, 其AE的持久性仍需大规模III期试验验证。需要注意的是, 单独CRA的AE相对较弱, 而联合治疗策略(如与免疫检查点抑制剂、靶向药联用)能够有效促进AE, 这也是未来研究的重点方向。此外, CRA技术本身的创

新(如超低温氮气冷冻、脉冲场联合等), 也将进一步提升AE的强度。

2 冷冻消融联合免疫治疗药物的研究

目前临床中已有CRA与RT、化疗、激素以及免疫治疗联合的报道, 并且显示出了积极的治疗效果。其中, CRA联合免疫治疗的协同效应尤为引人关注, 本文将重点概述CRA联合肿瘤免疫治疗药物的研究进展。

2.1 冷冻消融联合免疫检查点抑制剂的研究

多项研究证实, CRA与ICIs联合应用具有协同抗肿瘤效应。动物实验显示, CRA联合抗CTLA-4抗体可抑制前列腺癌模型远处转移灶生长[83]。临床研究中, 在非小细胞肺癌患者中发现, CRA联合PD-1抑制剂可使循环$CD8^+$T细胞IFN-γ分泌水平提升1.8倍, 而加用表观遗传调节剂后IFN-γ分泌水平进一步提高至2.5倍[81]。同时, 乳腺癌患者经CRA联用伊匹木单抗治疗后, 外周血$Ki67^+$及$ICOS^+$T细胞比例显著升高(P=0.05)[84]; 晚期黑色素瘤肝转移患者经CRA联用帕博利珠单抗治疗后, 客观缓解率达26.7%, mPFS为4个月, 优于单药治疗[85]; 另有宫颈癌病例显示, 联合治疗后远处转移灶完全缓解, 且该缓解状态维持了7个月[86]。

以上研究结果共同表明, CRA与ICIs联合应用在多种实体瘤中均展现出显著的协同抗肿瘤效应。同时, CRA与ICIs的联合应用可作为增强AE的有效策略, 为临床优化肿瘤免疫治疗策略、提升肿瘤全身免疫应答效应、抑制远处转移提供了重要的临床干预方向。

2.2 冷冻消融联合细胞过继疗法的研究

CRA与细胞过继免疫治疗(adoptive cell transfer therapy, ACT)的联合策略通过协同增强抗肿瘤免疫应答展现其应用潜力。CRA使肿瘤细胞释放的肿瘤抗原可被DC捕获并呈递至T细胞, 激活抗肿瘤免疫反应。然而, 部分肿瘤中的DC数量不足以充分呈递肿瘤抗原。临床前研究显示, 对小鼠肿瘤进行CRA预处理后, 向瘤内注射经芽孢杆菌Calmette-Guerin细胞壁骨架(bacille Calmette-Guérin cell wall skeleton, BCG-CWS)处理的DC, 能够增加DC对肿瘤抗原的摄取, 进而诱导肿瘤特异性$CD8^+$CTL的抗肿瘤作用[87]。临床研究证明, DC疫苗联合CRA可改善肿瘤微环境中$CD8^+$T细胞浸润情况, 并延长黑色素瘤患者的无复发生存期(recurrence-free survival, RFS)[88]。在NK细胞疗法方面, CRA通过诱导炎症微环境增强同种异体NK细胞活性, 在非小细胞肺癌、HCC患者中, CRA与NK细胞疗法联合治疗较单纯CRA治疗能够显著提高临床缓解率[89-90]。此外, 细胞因子诱导杀伤细胞(cytokine-induced killer cell, CIK)与CRA的协同作用也已在非小细胞肺癌及转移性肝癌等实体瘤中得到证实[91-92]。

综上, CRA与DC、NK细胞及CIK等细胞过继疗法的联合策略, 通过协同优化抗原呈递、增强效应细胞活性等机制在临床前及临床研究中均展现出了显著的抗肿瘤潜力, 为实体瘤免疫治疗提供了多元且可行的新路径。

2.3 其他

近年来, CRA与多种策略联合应用被证实可以双重调控固有免疫与适应性免疫, 进而增强治疗效果。临床前研究表明, CRA联用TLR7激动剂咪喹莫特后小鼠存活率达90%[55]。同时, 在非小细胞肺癌小鼠模型中, CRA联合mRNA疫苗可使肺转移灶数量减少68%, 且$CD8^+$T细胞记忆性应答持续超12周[93]。此外, 优化设计的肽疫苗与CRA联用可诱导胰腺癌模型中抗原特异性细胞毒性T淋巴细胞(cytotoxic T lymphocyte, CTL)比例从3%提升至18%[94]。粒细胞–巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor, GM-CSF)与CRA联合应用通过调控抗原呈递细胞功能与肿瘤微环境产生免疫协同效应, 具有良好的应用潜力。针对CRA诱导肿瘤细胞释放的HSP(如HSP70)和肿瘤抗原, GM-CSF可促进DC对上述物质的摄取, 并极化巨噬细胞为促炎型(M1型)。在一项针对IV期黑色素瘤患者的研究中发现, CRA联合GM-CSF治疗可使黑色素瘤患者外周血中HSP70特异性CTL比例升高, 且未观察到剂量限制性毒性, 这证实了CRA在该类患者中应用的安全性及免疫激活效应[58]。

综上, 尽管越来越多的临床试验、病例报告和实验研究表明, CRA单独使用时AE发生率较低, 但其能有效地使肿瘤细胞释放肿瘤抗原, 作为强效的内源性疫苗产生平台联合一定的免疫治疗展现出强大的应用前景。然而, DC作为癌症疫苗的主要靶细胞, 其数量和成熟度也是影响癌症疫苗效果的关键因素[95]。因此, CRA联合治疗的同时需探索创新方法以促进DC等免疫细胞的浸润与肿瘤特异性免疫

系统的激活。

3 结论

CRA作为一种肿瘤微创治疗技术, 其抗肿瘤机制已从单纯的局部杀伤拓展为系统性的免疫调控, 揭示了其作为“原位疫苗”的潜在价值。然而, CRA单独应用时存在显著瓶颈: 免疫激活强度不足且持续时间有限(约4周), 难以有效克服肿瘤免疫逃逸[79-80]。这与多重因素相关, 如CRA后PD-1和PD-L1的表达上调, 使其构成的信号轴活性增强, 可快速诱导T细胞耗竭[62], 局部IL-10、TGF-β等免疫抑制因子持续存在阻碍效应细胞长期存活[76-78]; 同时, 不同肿瘤类型对CRA的免疫应答存在异质性, 如前列腺癌中PSA释放引发的全身免疫反应强度远低于黑色素瘤, 提示肿瘤抗原免疫原性及微环境特征对疗效的关键影响[27,58]。

鉴于单一CRA难以突破肿瘤免疫逃逸的多重屏障, 联合治疗成为增强其疗效的重要方向。免疫检查点抑制剂可通过阻断PD-1/PD-L1等抑制性信号, 逆转T细胞耗竭, 延长免疫激活窗口[81-83]; 细胞过继疗法(如NK细胞、CIK细胞)可直接靶向免疫抑制微环境, 清除残留肿瘤细胞[89-92]; 佐剂(如TLR激动剂、GM-CSF)能提高抗原呈递效率, 促进记忆性T细胞形成[58-59]。

然而, 由于CRA技术的免疫激活机制尚未被完全阐明, 联合方案与用药时序的设计仍是关键挑战, 过早干预可能引发过度炎症反应, 而滞后治疗则会错失免疫激活峰值期。未来, 需深入解析CRA后效应T细胞的分化轨迹及肿瘤特异性抗原表位的呈递效率, 并基于“抗原释放–呈递–效应细胞激活”的动态时序, 设计多靶点联合策略, 同时关注联合方案的用药时序以避免过度炎症或错失免疫激活峰值期, 为CRA在肿瘤免疫治疗中的精准应用提供更坚实的理论支撑与更完善的转化路径。

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