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脉冲电场消融专题 评 述
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脉冲电场消融的生物学效应与胰腺癌治疗中的增敏策略

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摘要 脉冲电场(pulsed electric field, PEF)消融作为一种新兴的非热消融技术, 通过高压电脉冲在细胞膜上造成不可修复的穿孔, 破坏细胞膜完整性, 诱导多种细胞信号模式, 不仅可直接杀伤肿瘤细胞, 还可以诱发潜在的抗肿瘤免疫反应, 进而抑制肿瘤的发展. PEF消融在临床治疗中展现了独特优势, 尤其适合无法手术切除的患者, 但其面临的最大挑战是低场强消融区域的肿瘤复发. 近年来PEF消融与化疗、放疗、免疫和靶向治疗等传统治疗方法联合使用时, 可抑制消融术后肿瘤局部复发与转移, 延长患者的生存期, 为改善患者预后提供了新思路. 本文围绕PEF消融技术的生物效应、细胞死亡方式, 及其在胰腺癌治疗中与其他治疗手段(化疗、放疗、免疫和靶向治疗)的联合应用效果展开综述, 系统总结了近年来有关PEF消融的研究成果, 涵盖临床试验和基础实验的治疗机制、疗效评价、临床挑战及增敏治疗策略, 希望为临床治疗策略优化提供重要理论依据.

关键词 脉冲电场消融, 胰腺癌, 细胞死亡, 联合治疗

脉冲电场(pulsed electric field, PEF)消融是一种新兴介入治疗手段, 其作用原理, 是利用短促的高压电脉冲在细胞膜上造成不可修复的穿孔, 导致胞内环境失衡和细胞死亡, 因此也被称为不可逆电穿孔(irreversible electroporation, IRE)[1]. Yao等人[2~5]首次从细胞与分子水平证实脉冲电场通过不可逆电击穿特异性杀伤肿瘤细胞. 美国Davalos等人[6]于2005年首次提出利用IRE消融肿瘤等病变组织. 近20年来, IRE在胰腺癌、肝癌、肾癌和前列腺癌等实体肿瘤的临床治疗中已显示出独特优势[1,7~11]. 与射频消融、微波消融或冷冻消融等基于热量传递的传统消融手段不同, IRE不依赖热效应杀伤细胞. 因此, 它受消融病灶附近血流散热导致的“热沉效应”的影响较小, 也能减轻对病灶周围血管和健康组织的附带损伤. 此外, IRE可以激活机体的抗肿瘤免疫应答, 与免疫检查点抑制剂联合使用时有较好的疗效[1,6,12,13].

脉冲电场消融的肿瘤杀伤能力与其电场强度和脉冲作用时间相关. 当场强较低或作用时间较短时, 细胞膜孔在去除PEF后可以自行恢复, 细胞也由此存活. 研究显示, 实体肿瘤内异质性的肿瘤微环境(tumor microenvironment, TME)可以扭曲PEF的场强分布, 使得在IRE治疗过程中, 某些区域内的肿瘤细胞仅经受低场强PEF的扰动而存活, 继而导致肿瘤复发[14]. 也有文献报道, IRE术后存活的肿瘤细胞的恶性程度显著增强[15]. IRE术后的肿瘤复发已成为制约患者长期生存的重要临床难题. 本文将围绕PEF处理后的细胞响应机制、死亡模式及相应的联合治疗方案展开系统叙述, 深入解析肿瘤细胞接受PEF处理后的关键生物学过程变化, 旨在为探索与优化PEF治疗的增敏策略提供新思路与理论依据.

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1 脉冲电场消融中常见参数

脉冲电场的场强、脉宽、脉冲重复频率和脉冲波形等参数均对其消融效果有重要影响. PEF消融常见参数如图1所示[16], 目前使用的消融方式根据脉宽和脉冲波形不同, 一般分为微秒PEF(microsecond pulsed electric field, μsPEF)、纳秒PEF(nanosecond pulsed electric field, nsPEF)、毫秒PEF(millisecond pulsed electric field, msPEF)和高频PEF(high-frequency pulsed electric field, H-FIRE). μsPEF是最为常用的消融方式[1], 脉冲宽度70~100 μs, 场强1000~1000 V/cm, 每次消融20~100个脉冲; 主要通过诱导凋亡杀伤细胞, 在电极周围的极高场强区内也可以引起细胞坏死. nsPEF可以穿透细胞膜在细胞器膜上诱导孔道形成, 具有选择性杀伤肿瘤的潜力[17]. 其脉冲宽度10~300 ns, 场强20~150 kV/cm, 每次消融10~100个脉冲. 值得注意的是, nsPEF可根据脉宽进一步细分: 脉冲宽度为100 ns~1 μs的又被称为亚微秒级脉冲(submicrosecond pulsed electric field, sub-μsPEF), 而脉宽低于100 ns的则被归类为nsPEF[18~20]. msPEF一般仅使用单个脉冲, 脉冲宽度1~20 ms, 场强1000~2000 V/cm, 可诱导细胞凋亡或坏死[1]. H-FIRE使用交替正负波形, 激活神经或引起肌肉收缩的程度较轻, 是一种安全性更高的消融方式[21]. 其脉冲宽度1~2 μs, 场强500~4000 V/cm; 每次消融使用50~200个脉冲簇, 每个脉冲簇包含25~300个脉冲. 研究显示, 可以通过优化脉冲电场消融参数改变膜穿孔的尺寸、靶向损伤的细胞内亚结构和胞内信号转导通路, 从而精准调控细胞死亡方式, 为处于不同解剖位置或病理状态的肿瘤提供个性化的治疗方案.

2 脉冲电场的生物学效应

2.1 PEF对肿瘤细胞与正常细胞的差异性杀伤效应

相比于正常细胞, 肿瘤细胞具有更高的电容、膜电导率和膜通透性, 而跨膜电压和电阻抗则更低[22].

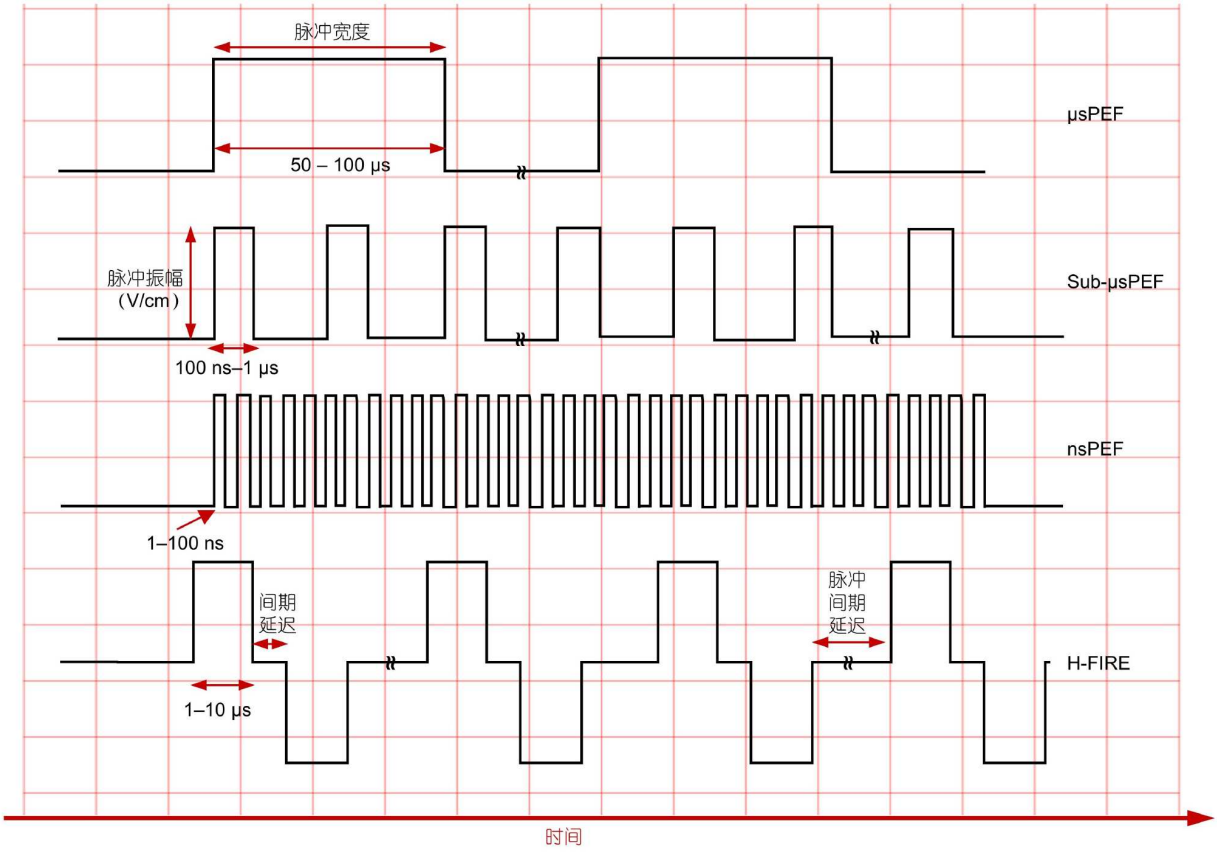


图 1 (网络版彩色)PEF消融常见参数[16]: 微秒PEF(μsPEF)、纳秒PEF(nsPEF)、毫秒PEF(msPEF)和高频PEF(H-FIRE)

Figure 1 (Color online) Typical parameters of PEF ablation[16]: microsecond PEF (μsPEF), nanosecond PEF (nsPEF), millisecond PEF (msPEF), and high-frequency PEF (H-FIRE)

Aslam等人[22]利用混合分析-数值模型比较了PEF对乳腺癌细胞和正常乳腺细胞的差异性影响，发现肿瘤细胞膜电导率更高、跨膜电压更低；在相同脉冲电场作用下，膜孔密度可高出正常细胞一个数量级. 肿瘤细胞膜缺乏脂蛋白和磷脂酰脂肪酸，杨氏模量较低、在PEF作用下更加容易变形. 因此，肿瘤细胞膜在PEF作用下形成孔道的能量壁垒较低，细胞膜中脂质分子也更容易重排形成稳定的亲水孔道、加速孔道的产生和扩张，有利于形成更多孔道. Gudvangen等人[23]发现，处于癌前病变期的食管上皮细胞对PEF的敏感性显著高于正常上皮细胞，而正常上皮细胞的细胞膜结构的稳定性和电穿孔阈值均高于前者. Rao等人[24]报道，nsPEF对B16小鼠黑色素肿瘤细胞的消融能力显著高于L929小鼠成纤维细胞. Ibey等人[25]对比分析了PEF对人T淋巴瘤Jurkat细胞与人正常单核U937细胞的杀伤效应，结果发现，μsPEF对两类细胞的杀伤能力均强于nsPEF，但不具备细胞选择性；而nsPEF对Jurkat肿瘤细胞的杀伤效率显著高于正常U937细胞，表现出良好的靶向杀伤选择性. Gianulis等人[26]在IMR-32神经母细胞瘤、HepG2肝癌、HT-1080纤维肉瘤、HPAF-II胰腺癌细胞和两种正常细胞(BJ皮肤成纤维细胞和MRC-5肺成纤维细胞)中考察了nsPEF的消融效果，发现不同细胞对nsPEF的敏感性差异极大，敏感性从高到低依次为：IMR-32神经母细胞瘤>BJ正常皮肤成纤维细胞>MRC-5正常肺成纤维细胞>肝癌Hep G2>纤维肉瘤HT-1080>胰腺癌HPAF-II. 正常细胞敏感性介于不同肿瘤细胞之间. 该选择性与细胞形态、代谢及膜穿孔程度无关，而与细胞固有生理特性相关；延长脉宽可提高杀伤效率，但会改变选择性谱.

综上所述，PEF可凭借肿瘤与正常细胞在膜电学特性、结构稳定性、修复能力和自身的固有特征差异，实现对肿瘤细胞的差异性杀伤；其中nsPEF的细胞选择性更为突出，识别nsPEF易感性差异的机制和细胞标志物，将对nsPEF消融疗法作出关键贡献，为肿瘤精准消融提供了可靠的理论基础.

2.2 脉冲电场的生物化学效应

PEF对细胞膜结构的破坏可以引起活性氧(reactive oxygen species, ROS)水平上升、胞质钙离子浓度上调与腺苷三磷酸(adenosine triphosphate, ATP)耗竭等生物化学变化，进而造成细胞损伤. Breton和Mir[27]发现，PEF本身不直接产生ROS，而是通过细胞膜穿孔促进胞外ROS渗透入细胞膜的核心区域，与膜内的不饱和脂肪酸链接触而生成过氧化脂质. Michel等人[28]认为ROS主要来源于PEF处理时阳极发生的电化学反应；PEF的场强未达到膜穿孔阈值时即能产生ROS. Szlasa等人[29]也报道PEF显著提升了黑色素细胞内的ROS水平，除了电极的电化学反应之外，PEF对线粒体、内质网等的损坏也可以将这些细胞器中的ROS释放到细胞质中，加剧氧化应激反应并引起细胞膜起泡和破裂. Rajagopalan等人[30]发现，ROS水平与PEF处理中投放的总电荷量呈正相关，而与场强没有直接关联. 电极上电化学反应产生的ROS经由PEF诱导的膜孔道进入细胞，进而引起氧化应激响应和脂质过氧化.

PEF可以提升调细胞质内的钙离子浓度，其主要机制源于胞外钙离子的内流和内质网等亚细胞器中储存的钙离子外流. Craviso等人[31]研究发现，nsPEF可激活牛嗜铬细胞上的电压门控钙离子通道，进而引起钙离子内流. 而Hristov等人[32]进一步发现，在HEK293细胞中过表达电压门控钙离子通道能够显著提升细胞对nsPEF的敏感性，使细胞膜通透性、膜电导率及胞质钙离子浓度的上升幅度均明显增强. 此外，Semenov等人[33]研究报道，PEF还可以增加内质网膜的通透性，促使钙离子内流至细胞质中，进一步加剧胞内钙超载.

PEF可以通过抑制ATP合成、加速ATP损耗两种模式导致胞内ATP的耗竭. PEF诱导的钙离子内流导致线粒体内的钙过载，在产生大量ROS的同时也加剧了线粒体的损伤，削弱了其产生ATP的能力；钙离子过载也可以抑制ATP合成酶的活性[33]. 此外，PEF造成的细胞膜穿孔导致胞内ATP泄露；细胞为稳定膜电位、修复膜损伤、清除过量钙离子也会消耗大量ATP，ATP的快速耗竭可能导致细胞死亡[30]. 目前，基于低场强PEF联合钙离子的“钙穿孔”治疗已在临床前研究中显示了良好的抗肿瘤效果和安全性.

2.3 PEF诱导的细胞死亡方式

PEF消融可以诱导多种细胞死亡模式，包括凋亡、坏死、坏死性凋亡和焦亡等不同类型，其电场分布和诱导的细胞死亡方式如图2所示[16]. PEF的脉冲参数、细胞或肿瘤类型、治疗条件等不同因素均对细胞死亡模式有调控作用.

凋亡是PEF消融中最常见的细胞死亡方式[34~36]. PEF消融后的细胞多呈典型的凋亡形态特征，包括核凝聚与碎裂、细胞皱缩并释放凋亡小体等[35,37]. 在信号

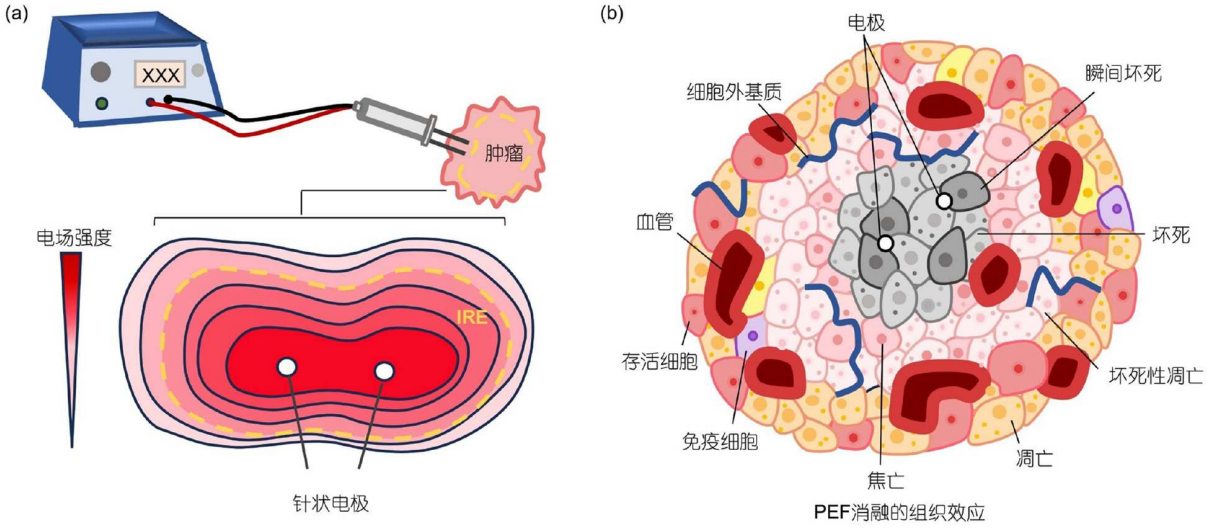


图 2 (网络版彩色)PEF消融电场分布和诱导的细胞死亡方式[16]. (a) PEF消融电场分布; (b) PEF消融诱导的细胞死亡方式

Figure 2 (Color online) Electric field distribution and cell death modes induced by PEF ablation[16]. (a) Electric field distribution of PEF ablation; (b) cell death modes induced by PEF ablation

通路上, PEF消融激活了半胱天冬酶-3(caspase-3)和caspase-7两种凋亡执行阶段的终末剪切酶[38], 并诱导末端脱氧核苷酸转移酶介导的dUTP缺口末端标记末端脱氧核苷酸转移酶介导的dUTP缺口末端标记(terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling, TUNEL)的阳性染色[39]. PEF介导的线粒体损伤同样也参与凋亡调控机制, 包括线粒体膜电位丧失、细胞色素c释放、caspase-9激活、BAX、BAK、BAD等促凋亡蛋白表达上调, 以及B-cell lymphoma-2(Bcl-2)、Bcl-xL、MCL-1等抗凋亡蛋白表达下调[40,41].

此外, 紧邻电极区域的细胞在高强度PEF作用下, 也可能发生坏死或坏死性凋亡. López-Alonso等人[42]利用PEF消融猪肝脏时, 观察到肝细胞出现细胞膜破裂; 但是核膜在消融后3 d内保持完整, 之后才逐渐破裂, 直至术后7 d才完全解体; 也没有形成凋亡小体. 这些现象提示肝细胞更可能发生了坏死性凋亡. Zhang等人[43]和Lv等人[44]报道PEF上调了受体相互作用激酶-3 (receptor-interacting kinase 3, RIP3)与混合谱系激酶域样蛋白(mixed lineage kinase domain-like, MLKL), 提示出现坏死性凋亡. Gibot等人[45]在高浓度钙离子存在下进行PEF消融, 细胞经受大量钙离子内流后发生肿胀、破裂和裂解死亡. 在形态变化上主要表现为坏死, 但也有部分细胞呈现凋亡特征. Wasson等人[46]也发现钙离子能够增强PEF的消融效果, 同时上调真核翻译起始因子5B(eukaryotic translation initiation factor 5B, EIF5B)与60S核糖体亚基的mRNA转录, 下调NADPH氧化酶1/4(NADPH oxidase 1/4, NOX1/4), 提示坏死性凋亡通路被激活.

发生细胞焦亡(pyroptosis)时, 含热蛋白结构域NOD样受体(NOD-like receptor pyrin domain-containing, NLRP)炎症小体可激活caspase-1, 活化的caspase-1特异性剪切焦亡关键蛋白GSDMD(gasdermin D)并促使其功能结构域转位至细胞膜. 由此形成的非选择性离子孔道引发细胞膜通透化, 最终产生细胞膜破裂、膜表面气泡样突起及焦亡小体生成的典型形态学特征[47]. 前述Zhang等人[43]和Lv等人[44]的研究中也观察到, PEF消融处理的肝组织中存在caspase-1和GSDMD诱导的焦亡. Ringel-Scaia等人[21]发现, PEF消融可在乳腺癌细胞中激活NLRP炎性小体与caspase-1, 并同时诱导坏死与焦亡两种细胞死亡模式. 在此过程中, ROS、ATP以及高迁移率族蛋白B1(high mobility group box1, HMGB1)等损伤相关分子模式(damage-associated molecular patterns, DAMP)随之被释放, 进而推动肿瘤微环境向促炎表型转化.

2.4 PEF与铁死亡和自噬的关系

铁死亡是一种铁元素依赖的、由脂质过氧化诱导的免疫原性细胞死亡方式, 受铁离子催化的芬顿反应和脂氧合酶的驱动. Wiczew等人[48]通过分子动力学模拟和自由能计算, 证实PEF产生的ROS可以引起细胞膜

内的脂质过氧化, 进而使细胞膜在PEF撤除后仍长时间保持高通透性. Nikolova等人[49]报道, PEF联合拓扑异构酶1抑制剂SN38可以提升细胞内的超氧化物和过氧化氢水平、耗竭谷胱甘肽(glutathione, GSH), 最终通过凋亡和铁死亡双重途径介导细胞死亡. Li等人[50]基于铁基纳米颗粒诱导胰腺癌细胞铁过载, 同时利用蛋白水解靶向嵌合体(proteolysis targeting chimera, PROTAC)分子靶向降解铁储存蛋白FTH1, 协同诱导PEF消融后强烈的脂质过氧化的发生, 从而诱导铁死亡克服胰腺癌细胞PEF消融后残存癌细胞的治疗抵抗.

自噬是细胞内质量控制与能量稳态的核心调控机制, 通过自噬-溶酶体途径降解受损细胞器和异常积聚的大分子[51]. 产生的氨基酸、脂肪酸等小分子物质回流至代谢池, 为蛋白质合成、ATP生成提供原料; 以此在营养匮乏、氧化应激等不利条件下维持细胞稳态和正常生理活动. Zhao等人[52]和Ye等人[53]发现μsPEF消融诱导胰腺癌细胞内HMGB1释放, 作用于晚期糖基化终产物受体(receptor for advanced glycation end products, RAGE)和Toll样受体4(Toll-like receptor 4, TLR4)而诱导自噬, 有利于细胞在PEF消融后的存活. Ullery等人[54]探究了nsPEF对自噬的调控作用, 发现亚毒性剂量nsPEF上调p62、Beclin、ATG5-ATG12复合物、LC3B-II等自噬相关靶点的基因和蛋白表达, 激活自噬; 而毒性剂量nsPEF则显著抑制了自噬. 由此可见, 自噬可能是细胞应对PEF消融损伤的补偿性修复机制. 当损伤程度超出修复能力时, 细胞由自噬修复转向凋亡. Condello等人[55]使用PEF和丝裂霉素C处理鳞癌细胞, 发现PEF可以通过提升细胞膜通透性促进细胞摄取丝裂霉素C, 并下调HMGB1、Beclin1、LC3和p62等自噬相关蛋白, 从而阻断自噬介导的细胞存活通路. 同时, 线粒体释放的细胞色素C激活了内源性凋亡机制, 实现了“自噬抑制”到“凋亡激活”的表型转换.

3 脉冲电场消融在胰腺癌治疗中的增敏策略

临床实践中, 部分肿瘤组织由于微环境异质性、纤维化或耐药性等因素, 对PEF消融治疗的响应不佳, 导致消融范围受限、肿瘤残留和术后肿瘤复发, 严重制约了该技术的应用推广. 为突破该瓶颈, PEF消融增敏策略的研发与优化逐渐成为近年来肿瘤介入治疗领域内的新热点. 通过联合化疗药物、免疫佐剂或物理干预等不同策略, 可有效降低肿瘤细胞对PEF消融的耐受阈值, 在强化消融效应的同时重塑肿瘤免疫微环境, 进而实现局部精准消融与全身抗肿瘤免疫应答激活的协同增效. 如图3所示, 此部分将围绕PEF消融在胰腺癌中的应用, 梳理PEF消融在胰腺癌治疗中增敏策略实例, 为PEF消融治疗胰腺癌的临床应用和优化提供理论参考.

3.1 PEF消融联合化疗

PEF消融在直接杀伤肿瘤细胞的同时, 也可以打破药物递送屏障, 让化疗药物更高效地穿透肿瘤组织、被癌细胞高效摄取. PEF消融联合化疗不仅能提升化疗药物的细胞毒性, 也可以通过降低肿瘤间质阻力、调控凋亡信号等机制减轻肿瘤的化疗耐药, 同时降低化疗对正常组织的损伤. Tasu等人[56]评估了17例不可切除局部晚期胰腺癌(locally advanced pancreatic cancer, LAPC)患者在新辅助化疗后接受PEF消融的疗效, 患者中位生存期(overall survival, OS)达21.2月. 值得注意的是, 该方案治疗后可将患者成功转化为可手术切除病例, 且在35%的患者中实现了R0/R1切除, OS达31.1月. 因此, PEF消融联合新辅助化疗用于胰腺癌治疗具有良好潜力. Zeng等人[57]回顾性比较了20例接受PEF消融联合化疗与18例仅接受化疗的IV期胰腺癌患者. 发现联合治疗组患者的中位OS和无进展生存期(progression-free survival, PFS)分别是(14.00±3.73、6.00±1.68月)均显著优于化疗组(10.00±1.51、5.00±0.40月). 联合治疗组术后2周的疼痛评分显著低于术前, 治疗相关的不良反应也可以经对症治疗后好转. Belfiore等[58]在20例LAPC患者中评估了经皮PEF消融术联合吉西他滨/奥沙利铂新辅助化疗的安全性和疗效. 术后6个月90%的患者实现局部疾病控制, 3例患者成功实现肿瘤降期并接受了R0手术切除. 只有2例患者中发生了疾病快速进展出现腹膜转移, 并在术后3~4个月时死亡, 其余18例患者在9.1个月的随访期内未出现肿瘤进展或复发. 由此可见, PEF消融联合化疗的疗效较好, 安全性也可控.

近年来, 亦有PEF联合化疗临床前相关研究. Bhutiani等人[59]在胰腺癌细胞和小鼠胰腺癌原位肿瘤模型中评估了PEF消融联合吉西他滨或FOLFIRINOX化疗方案的功效. 在细胞水平, 联合方案显著上调了caspases-3的mRNA和蛋白表达, 下调了抗凋亡蛋白Bcl-2的水平. 此外, 紧密连接蛋白Claudin-1表达下调破坏了细胞间的黏附连接, 细胞集落形成能力随之降低. 联合

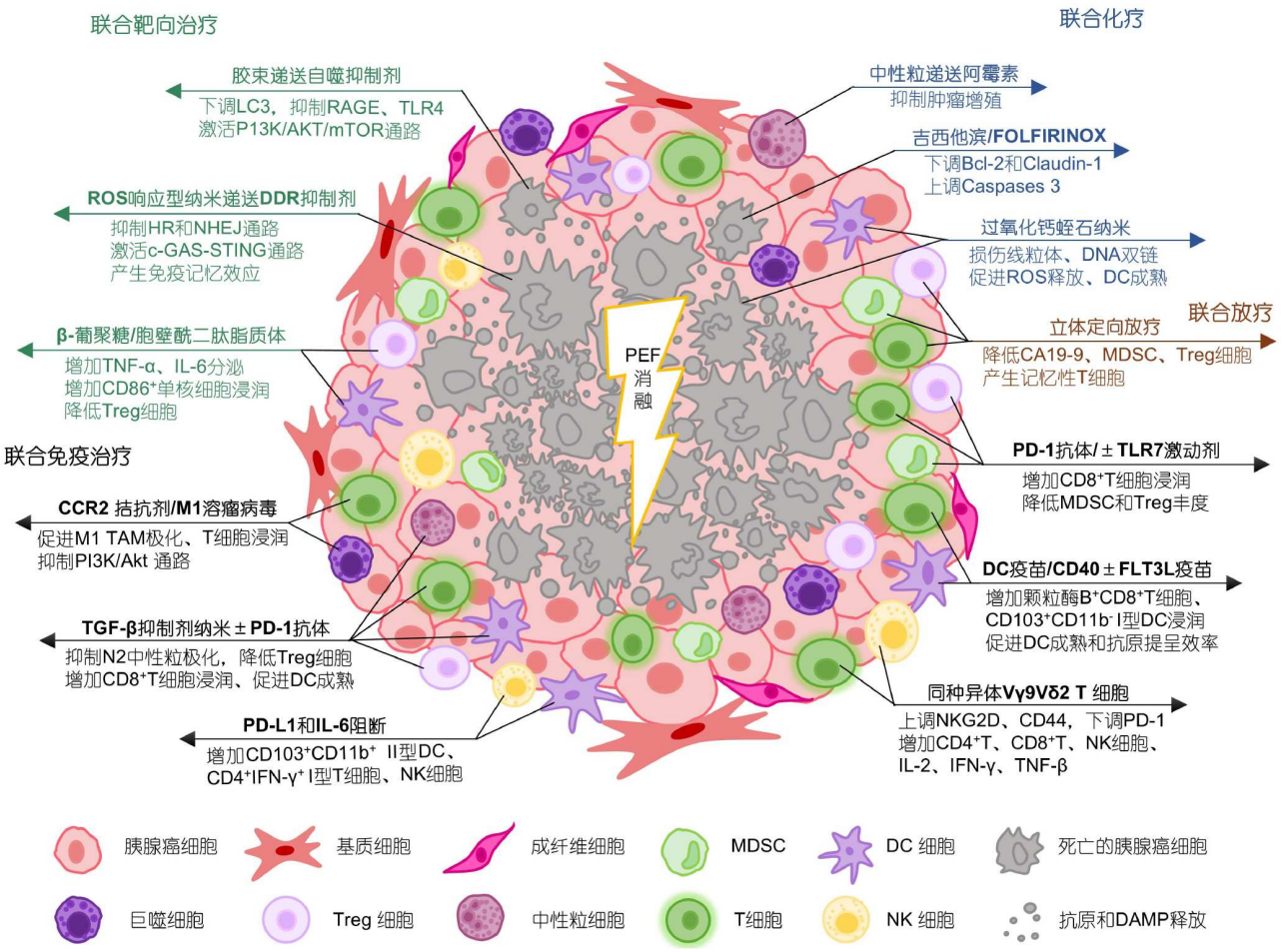


图 3 (网络版彩色)胰腺癌PEF消融联合治疗的策略与机制
Figure 3 (Color online) Strategies and mechanisms of combination therapy with PEF ablation in pancreatic cancer

方案显著延长了荷瘤小鼠的生存期. 近年来, 关于新型化疗方案的探索已有报道. Huang等人[60]开发了基于活体中性粒细胞的阿霉素递送平台NP@NE. PEF消融后的急性炎症反应快速招募大量中性粒细胞浸润肿瘤. NP@NE在这种趋化作用下可在PEF消融后的胰腺肿瘤模型中有效蓄积, 显著抑制肿瘤生长. Li等人[61]开发了负载过氧化钙的蛭石纳米片(VMT/CaO_2 NS)用于辅助PEF消融. PEF有利于VMT/CaO_2 NS被细胞摄取; 纳米片中的$Fe^{2+/}Fe^{3+}$随后通过芬顿反应催化生成大量ROS, 损伤线粒体和DNA双链, 从而与PEF消融的损伤效应叠加而实现对肿瘤细胞的双重杀伤. 此外, 纳米片释放的钙离子促进了树突状细胞(dendritic cells, DC)的成熟和抗原提呈效率的提升, 诱导了细胞毒性T细胞应答和长期免疫记忆效应, 建立了持久的抗肿瘤免疫响应, 降低了肿瘤复发风险.

3.2 PEF消融联合放疗

立体定向放疗(stereotactic body radiotherapy, SBRT)是一种新型放疗模式, 可将辐射剂量聚焦于肿瘤靶区, 降低正常组织中的剂量摄取和辐射相关毒性[62]. Geboers等人[63]在LAPC患者中比较了PEF消融与SBRT诱导的全身免疫应答特征. 两种疗法均成功诱导了抗肿瘤免疫应答, 其中PEF消融显著降低了调节性T细胞(regulatory T cells, Treg)、髓系来源抑制性细胞(myeloid-derived suppressive cells, MDSC)等免疫抑制细胞亚群的丰度, 并激活了T细胞; SBRT微弱下调了Treg, 对MDSC无显著影响, 但产生了持久的记忆性T细胞响应. Hong等人[64]在7例寡转移性胰腺癌患者中考察了PEF消融联合放疗的效果, 其中6例患者在胰腺癌原发灶处接受PEF消融, 同时在寡转移灶处接受手术

切除或放疗. 患者中位OS约16个月, 2例患者的无病生存时间达16~41个月. Jiang等人[65]在1例LAPC患者中分析了PEF消融联合术中放疗的疗效. 该患者的肿瘤侵犯肝动脉、肠系膜上动脉和脾动脉等血管, 并伴随腹腔干周围淋巴结转移, 单纯PEF消融难以完全杀灭肿瘤. PEF消融联合术中放疗后, 患者CA19-9水平显著降低, 未出现手术并发症, 癌痛完全缓解, 生活质量显著改善. 该患者在联合治疗后47个月因肿瘤局部复发伴可疑腹膜转移导致肠梗阻而死亡, 但是其生存期仍远超LAPC接受标准治疗方案的中位OS, 展现了该方案的潜力.

3.3 PEF消融联合免疫治疗

胰腺癌的肿瘤微环境具有高度的免疫抑制性, 对单纯免疫治疗的响应有限[66]. 而PEF消融可以激活机体的抗肿瘤免疫应答. 肿瘤细胞膜被PEF消融破坏后释放的HMGB1、钙网蛋白等DAMP分子激活DC细胞等抗原呈递细胞, 提升肿瘤抗原提呈效率. PEF消融也可以重塑肿瘤免疫微环境, 将免疫"冷肿瘤"转化为"热肿瘤", 增强效应T细胞的功能, 克服胰腺癌对免疫治疗的抵抗[67,68]. Zhao等人[52]在小鼠胰腺癌模型中考察了PEF消融联合程序性死亡受体-1(programmed death-1, PD1)单抗的疗效. 发现联合方案增强了$CD8^+$细胞毒性T细胞的肿瘤浸润, 降低了Treg和MDSC的瘤内丰度, 显著延长了小鼠生存期并诱导长期抗肿瘤免疫记忆. Narayanan等人[69]在PEF消融联合PD-1单抗的基础上, 进一步联用TLR7激动剂, 通过强化免疫原性细胞死亡与逆转免疫抑制微环境, 在小鼠胰腺癌模型中同样取得了显著的抗肿瘤疗效. Lin等人[70]在62例LAPC患者中, 探究了PEF消融联合异体Vγ9Vδ2 T细胞的临床抗肿瘤疗效. 结果显示, 联合治疗后患者外周血中$CD4^+$ T细胞、$CD8^+$ T细胞及自然杀伤(natural killer, NK)细胞数量显著增加, 白介素-2(interleukin-2, IL-2)、干扰素-γ(Interferon-γ, IFN-γ)、肿瘤坏死因子-β(tumor necrosis factor-β, TNF-β)等促炎细胞因子水平升高, 同时Vγ9Vδ2 T细胞表面NKG2D和CD44表达上调、PD-1表达下调. 临床观察表明, 患者肿瘤体积明显缩小, OS延长近3个月, 提示该联合方案可作为改善LAPC患者预后的潜在策略.

围绕PEF对DC细胞的激活作用, 近年来开发了一系列增强DC细胞的联合治疗策略. Yang等人[71]报道PEF消融联合DC疫苗的疗效增强了颗粒酶B^+CD8^+活化T细胞的肿瘤浸润. Liu等人[72]制备了负载FMS样酪氨酸激酶3配体(FMS-like tyrosine kinase 3 ligand, FLT3L)和CD40配体(CD40 ligand, CD40L)的水凝胶CD40L@CaCO3/FLT3L/Cas9@lip/@HAMA微球疫苗. 该微球首先利用FLT3L促进肿瘤驻留$CD103^+CD11b^-$ I型常规树突状细胞(cDC1)的招募与增殖, 并通过CD40L诱导其成熟, 增强其向肿瘤引流淋巴结的迁移能力和抗原交叉提呈能力. Wu等人[73]研究证实, 通过双重阻断IL-6和程序性死亡受体配体-1(programmed death-ligand 1, PD-L1), 可有效增强$CD11b^+CD103^+$ II型常规树突状细胞的抗原呈递与免疫激活功能, 显著提供$CD4^+$ T细胞中分泌IFN-γ^+ I型辅助性T细胞的比例, 并增强NK细胞的抗肿瘤免疫活性, 从而增强整体抗肿瘤免疫应答. Shankara Narayanan等人[74]将PEF消融与瘤内注射CD40激动性抗体联用, 通过激活DC细胞有效增强了抗肿瘤免疫应答. 以上联合方案与PEF消融联用时, 均在胰腺癌小鼠模型中表现出良好的治疗效果.

除了上述细胞外, 针对其他先天免疫细胞的调控策略也有报道. Peng等人[75]发现PEF消融后肿瘤相关中性粒细胞(tumor-associated neutrophils, TAN)在胰腺肿瘤内大量聚集, 并被转化生长因子-β(transforming growth factor-β, TGF-β)极化成免疫抑制性N2表型, 促进肿瘤的进展. 将TGF-β抑制剂负载到谷胱甘肽响应的介孔二氧化硅纳米颗粒, 有效阻止了TAN向N2表型的极化, 并增强了PEF消融联合PD-1单抗的疗效. Xu等人[76]发现PEF消融后可诱导趋化因子受体2^+(C–C chemokine receptor 2^+, $CCR2^+$)肿瘤相关巨噬细胞(tumor-associated macrophages, TAM)浸润, 进而形成免疫抑制性肿瘤微环境. 基于该机制, 研究团队构建了巨噬细胞衍生的蛋白脂体囊泡, 并共载CCR2拮抗剂PF-4136309和吉西他滨. 该递送系统可显著降低瘤内$CCR2^+$ TAM的丰度, 促进TAM由免疫抑制型M2表型向免疫激活型M1表型极化, 将免疫抑制型TME转化为免疫激活型, 最终有效抑制PEF消融后的肿瘤复发与肝转移. Woeste等人[77]利用β-葡聚糖可诱导训练免疫记忆, 进而强化二次刺激下细胞免疫应答的特性, 考察了PEF消融联合β-葡聚糖的治疗效果. 研究显示, 小鼠$CD11b^+$骨髓细胞与β-葡聚糖共孵育后, 再经PEF消融处理的肿瘤细胞条件培养基进行刺激, 可显著促进肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)和IL-6的分泌, 同时增强免疫细胞对肿瘤细胞的吞噬和杀伤能力. 值得注意的是, 5例III期胰腺癌患者经PEF消融联合口服β-葡聚糖治疗3

个月后, 外周血CD86$^+$单核细胞丰度上升34.8%, Treg丰度下降20.1%; 其中4例患者CD86$^+$单核细胞的TNF-α分泌升高, 呈现训练免疫表型[77]. 因此, 口服β-葡聚糖可靶向诱导训练免疫记忆, 安全性高、患者依从性好, 为胰腺癌患者提供了新的免疫治疗方向. Wu等人[78]发现胰腺癌的进展会重塑脾脏免疫, 导致髓系细胞比例升高, B细胞和T细胞减少. 这些髓系细胞易向肿瘤迁移并加重免疫抑制. 由此以脾脏髓系细胞作为靶点, 开发了靶向递送免疫调节剂胞壁酰二肽的脂质体纳米剂型. 该剂型高效富集于脾脏并与髓系细胞相互作用, 通过表观遗传调控和代谢重编程维持髓系细胞的抗肿瘤活性. 与PEF消融和PD-L1抗体联用时, 该剂型抑制小鼠胰腺癌模型的复发和转移, 且具有良好的生物相容性良好. 此外, Sun等人[79]探索了PEF消融与M1溶瘤病毒的联合治疗效果. FEF消融通过ROS抑制PI3K/Akt信号、诱导癌细胞凋亡, 并促进M1病毒感染, 协同增强肿瘤杀伤效果. 联合方案也激活T细胞免疫, 在小鼠模型中显著长生存期.

3.4 PEF消融联合靶向治疗

PEF消融与靶向治疗的联合应用, 也是突破胰腺癌治疗瓶颈的重要探索方向. PEF消融可快速、精准地杀伤局部实体瘤组织, 降低肿瘤负荷; 而靶向治疗则通过精准阻断肿瘤细胞关键驱动通路, 抑制肿瘤细胞增殖、侵袭及血管新生, 从而减少局部复发与远处转移风险. Long等人[80]研究表明, PEF消融后残留的胰腺癌细胞会发生DNA双链断裂, 并激活同源重组(homologous recombination, HR)和非同源末端连接(nonhomologous end joining, NHEJ)两种DNA损伤修复(DNA damage repair, DDR)通路, 进而促进肿瘤术后复发. 基于此, 该团队构建了ROS响应型高分子胶束, 共载HR和NHEJ通路抑制剂. 该纳米制剂可有效抑制PEF消融后残留癌细胞的DDR过度激活, 同时通过cGAS-STING通路强效激活适应性抗肿瘤免疫应答, 在胰腺癌模型中成功诱导抗肿瘤免疫记忆, 显著降低复发风险. Ye等人[53]基于PEF消融后HMGB1介导肿瘤自噬水平上调和细胞存活的现象, 制备了共装载RAGE和TLR4的生物可降解纳米胶束. 该剂型通过激活P13K/AKT/mTOR信号抑制自噬, 联合PEF消融时显著增加肿瘤凋亡, 阻滞细胞周期, 进而延长胰腺癌小鼠模型的生存.

4 总结与展望

PEF消融作为一种新兴的非热消融技术, 通过高压脉冲精准破坏肿瘤细胞膜完整性, 在实现局部肿瘤高效控制的同时, 能最大程度保护周围血管、胰管等重要组织结构. 《中国胰腺癌诊疗指南(2022年版)》已将PEF消融列为胰腺癌的推荐治疗手段之一. PEF消融引起的细胞死亡机制复杂多样, 主要包括凋亡、坏死、坏死性凋亡和焦亡等类型, 其发生与电场参数、细胞及组织类型、治疗条件密切相关. 由于肿瘤内部电场强度分布不均匀, 癌细胞在低场强刺激后得以存活, 进而引发肿瘤复发, 这是临床上PEF消融面临的最大挑战. 在胰腺癌治疗中将其与化疗、放疗、免疫和靶向治疗传统手段有机联合, 不仅能提升药物的肿瘤渗透性、增强肿瘤细胞对放疗的敏感性; 还可增强药物递送效率, 有效激活抗肿瘤免疫应答, 实现药物对PEF消融肿瘤的精准调控, 协同抑制肿瘤转移与复发, 显著延长胰腺癌的生存期. 该联合策略在保护周围血管、胰管等重要组织结构方面的优势, 可良好适配胰腺癌的解剖特点, 安全性与耐受性良好.

尽管PEF消融的临床应用已取得显著进展, 但仍面临部分挑战, 电场分布不均导致的局部消融不彻底、治疗相关不良反应, 以及个体化治疗方案的缺乏, 均限制了其治疗效果. 未来需进一步明确不同电场参数对细胞死亡通路的调控, 完善联合治疗的策略, 结合对患者免疫状态的深入解析以构建个体化治疗策略, PEF消融有望成为癌症多维度精准治疗体系中的关键核心技术.

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Summary for “脉冲电场消融的生物学效应与胰腺癌治疗中的增敏策略”

Pulsed electric field ablation: biological effects and sensitization strategies in pancreatic cancer therapy

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As an emerging minimally invasive and non-thermal ablation technology, pulsed electric field (PEF) ablation has gradually become a promising local therapeutic modality for the clinical management of solid tumors, exhibiting unique advantages in clinical treatment over conventional thermal ablation approaches such as radiofrequency ablation and microwave ablation. It is particularly amenable to patients with locally advanced and unresectable pancreatic tumors that are adjacent to vital blood vessels, bile ducts, and nerve tissues, who are not eligible for traditional surgical treatment. Different from conventional thermal therapies that rely on heat conduction to kill tumor tissues, PEF ablation exerts therapeutic effects mainly by delivering transient high-voltage electric pulses to induce irreversible electroporation at tumor cell membranes. The generated electric pulses create irreversible and unrecoverable nanoscale pores on the lipid bilayer of cell membranes, disrupt the stability and integrity of membrane structure, and further trigger a cascade of intracellular biochemical responses and trigger diverse cellular signaling pathways.

Upon PEF intervention, a series of significant intracellular alterations occur, including the massive accumulation of reactive oxygen species (ROS), sustained intracellular calcium overload, adenosine triphosphate (ATP) depletion, and mitochondrial dysfunction. These biochemical disturbances further initiate multiple programmed cell death modalities, including apoptosis, necrosis, necroptosis, and pyroptosis, thereby achieving direct elimination of tumor cells. Meanwhile, PEF ablation can effectively release a large number of damage-associated molecular patterns (DAMP), which activate antigen-presenting cells, remodel the tumor immune microenvironment, convert immunologically “cold tumors” into “hot tumors”, and trigger underlying anti-tumor immune responses to suppress tumor proliferation, invasion, and distant metastasis.

The main clinical challenge of PEF ablation is tumor recurrence in the areas with low electric field intensity, which limits its further clinical application. In recent years, the combination of PEF ablation with conventional treatment strategies, including chemotherapy, radiotherapy, immunotherapy, and targeted therapy, has been demonstrated to inhibit local tumor recurrence and distant metastasis after ablation, as well as prolong the overall survival of cancer patients. This review focuses on the biological effects and cell death modes of PEF ablation, highlighting its synergistic efficacy with conventional therapies (chemotherapy, radiotherapy, immunotherapy, and targeted therapy) in the treatment of pancreatic cancer, and provides evidence for clinical translation and optimization. A comprehensive review of contemporary research on PEF ablation was performed, systematically summarizing recent research progress, including those on therapeutic mechanism and efficacy evaluation, clinical challenges, and sensitization strategies in both preclinical and basic experimental studies. Particular emphasis was given to the application value of combined PEF ablation in pancreatic cancer, aiming to provide a critical theoretical basis for the optimization of clinical therapeutic regimens and promote the clinical translation of PEF ablation technology.

pulsed electric field ablation, pancreatic cancer, cell death, combined therapy

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