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评 述
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肿瘤治疗性mRNA疫苗的研发进展

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摘要 近年来, 肿瘤疫苗作为肿瘤免疫疗法的重要组成部分, 已经取得了显著的进展. 肿瘤治疗性mRNA疫苗通过递送肿瘤相关抗原或肿瘤特异性抗原, 激发机体产生特异性免疫反应, 以识别并杀伤肿瘤细胞. 相较于其他类型的肿瘤疫苗, mRNA疫苗因其独特的优势, 在临床试验中展现出良好的治疗效果和巨大的应用潜力. mRNA疫苗的优势在于其快速的开发周期、高度的特异性, 以及能够激发强烈的免疫反应. 它们不整合入宿主基因组, 降低了安全性风险, 同时可以快速应对病原体的变异. 此外, mRNA疫苗的稳定性可以通过特定的修饰来提高, 增强其在体内的持久性和翻译效率, 从而增强疫苗的效果. 目前, 多种个体化mRNA肿瘤疫苗在临床试验中表现出较好的安全性及免疫原性, 显示了其作为肿瘤治疗工具的潜力. 本文总结了肿瘤治疗性mRNA疫苗的构成、优势、稳定性提高方法、作用机制、给药途径、递送系统、局限性和挑战等, 旨在促进肿瘤治疗性mRNA疫苗的发展和应用.

关键词 mRNA疫苗, 递送系统, 给药途径, 作用机制, 肿瘤免疫

肿瘤免疫治疗是癌症治疗的新兴领域, 肿瘤治疗性疫苗作为肿瘤免疫治疗的重要组成部分, 是未来癌症治疗领域最具前景的候选药物[1~3]. 肿瘤治疗性疫苗通过刺激机体针对特异性肿瘤抗原产生适应性免疫, 放大并维持特异性T细胞响应来杀死肿瘤细胞, 从而达到控制肿瘤生长、延长患者生存期的目的[4,5](图1), 同时不同的给药方式会影响治疗效果, 结合不同的递送体系可以实现特异性治疗, 提高治疗效果.

肿瘤治疗性疫苗包括重组蛋白/多肽疫苗、细胞疫苗、DNA/mRNA疫苗、细菌和病毒载体疫苗[6,7]. 其中, mRNA疫苗因其独特的优势而备受关注. mRNA疫苗的核心组成部分是编码肿瘤抗原的mRNA序列, 这些序列通过特定的递送载体进入宿主细胞, 并指导细胞产生相应的肿瘤抗原蛋白, 从而激活免疫系统. 一个典型的mRNA疫苗分子包括5′帽子结构, 5′非翻译区(5′UTR)、开放阅读框(ORF)、3′非翻译区(3′UTR)、以及3′Poly(A)尾部. 这些结构元件共同确保mRNA的稳定性、翻译效率以及免疫原性[8,9]. 基于mRNA的结构, mRNA肿瘤治疗性疫苗主要分为非复制型mRNA疫苗、自扩增mRNA疫苗和反扩增mRNA疫苗. mRNA疫苗用于肿瘤治疗具有许多优势, 首先, 机体对mRNA疫苗的耐受性良好, mRNA肿瘤治疗性疫苗产生的药物不良反应通常是可控且短暂的[10~13]; 其次, 与DNA疫苗相比, mRNA疫苗没有插入宿主基因组引起突变的风险[9,14]; 与细菌或病毒载体疫苗相比, mRNA治疗性疫苗不使用致病性细菌或病毒制剂, 具有非传染性[15];

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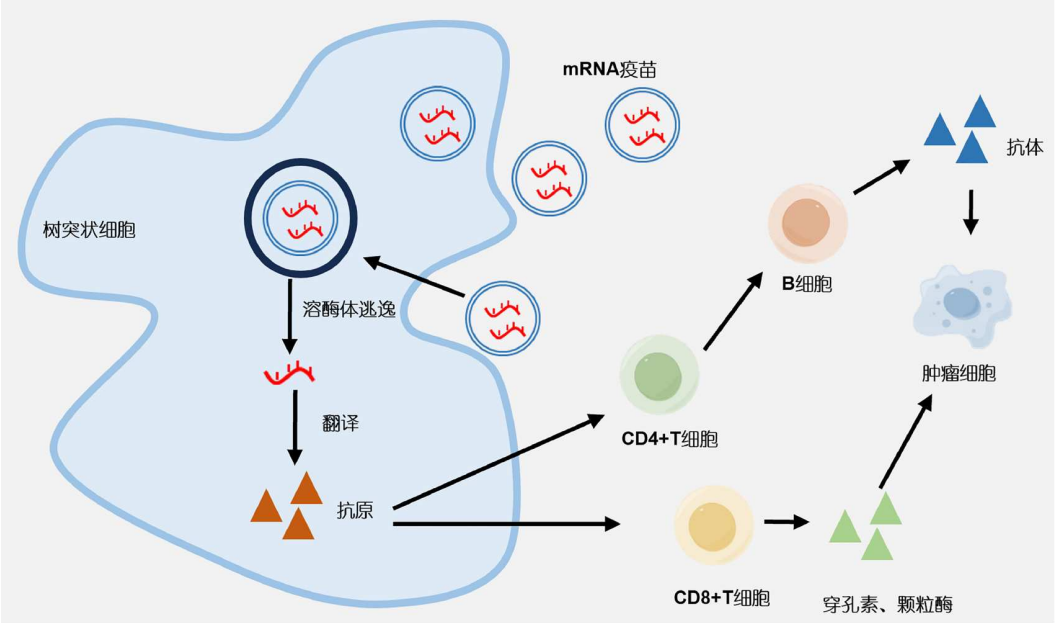

图 1 (网络版彩色)肿瘤治疗性mRNA疫苗的作用机制
Figure 1 (Color online) Mechanism of therapeutic mRNA vaccines for cancer treatment

另外, 相较于直接注射抗原, mRNA疫苗能够使人体持续高效地形成自发性的体液和细胞免疫; 最后, mRNA可通过体外转录技术合成, 生产过程简单快速, 生产成本较低[9,16,17].

保证mRNA的完整性和稳定性是合成有效的肿瘤mRNA治疗性疫苗的关键[18,19]. 从mRNA的结构上讲, mRNA的5′帽子结构是真核生物信使核糖核酸的特征, 有助于核糖体识别和翻译[20~23]. 体外转录技术获得的mRNA具有无帽或异常的帽子结构, 被模式识别受体(pattern recognition receptors, PRRs)识别, 从而刺激I型干扰素产生, 干扰mRNA翻译, 因此体外转录技术获得的mRNA应进行适当封端, 以防被识别为外来抗原[20,24]. mRNA的Poly(A)尾部也影响mRNA的翻译效率和稳定性, Poly(A)尾部能够降低RNA核酸外切酶的活性, 从而有助于提高mRNA的翻译效率和稳定性[25~27]. Poly(A)尾部的长度应控制在100~300个核苷酸, 长度对调控mRNA的翻译和稳定性起着重要作用, Poly(A)尾部的长度与翻译效率成正比[28]. 体外转录技术合成的mRNA可以通过DNA模板合成或使用Poly(A)聚合酶在转录后通过酶促反应添加Poly(A)尾[6,24]. UTR元件是mRNA结构设计的关键部分, 5′UTR对靶蛋白的表达至关重要, 3′UTR影响mRNA的半衰期, 因此, 修饰5′和3′UTR能够有效提高体外转录mRNA翻译效率和半衰期[15,29]. 此外, 通过假尿苷、1-甲基假尿苷和5-甲基胞嘧啶等对mRNA进行适当修饰能够有效提高mRNA的稳定性和翻译效率[30]. 体外转录技术合成的mRNA具有许多siRNA、dsRNA等副产物, 这些副产物能够激活体内PRRs, 阻断mRNA翻译, 并诱导先天性免疫反应, 因此, 需要对体外转录技术合成的mRNA进行纯化以减少免疫刺激[31,32].

1 肿瘤治疗性mRNA的作用机制

当mRNA疫苗在给药部位附近被抗原呈递细胞(antigen presenting cell, APC)内吞, 内体化的mRNA转运到细胞质核糖体中进行翻译, 翻译产生的相关抗原蛋白随后进行如泛素化等翻译后修饰. 蛋白酶体复合物将抗原蛋白降解成为小片段, 通过主要组织相容性复合物(major histocompatibility complex, MHC) Ⅰ类分子进行两种类型的抗原呈递: (1) 部分小片段肽通过抗原处理相关转运蛋白转运到糙面内质网上, 由MHC Ⅰ类分子呈递到细胞表面, 活化的$CD8^+$ T细胞识别到相关抗原后, 分泌穿孔素、颗粒酶等分子诱导肿瘤细胞凋亡[33]. (2) 分泌的抗原可被细胞摄取, 随后被降解, 并由MHC II类分子呈递给辅助性T细胞. 辅助性T细胞可以激活B细胞产生中和抗体, 并通过炎症因子激活吞噬细胞, 最终清除肿瘤细胞[34].

在肿瘤抗原的选择上，肿瘤治疗性mRNA疫苗的抗原通常包括肿瘤相关抗原(tumor-associated antigens, TAAs)(表1)和肿瘤特异性抗原(tumor-specific antigens, TSAs)(表2)[32,35]. TAAs通常在肿瘤细胞中过表达, 肿瘤特异性和免疫原性较弱. 肿瘤相关自身抗原是目前最常采用的肿瘤抗原，但哺乳动物对单一的TAAs具有较高的免疫耐受性，因此目前通常采用多种TAAs联合应用的方法[6,36]. TSAs是来源于肿瘤细胞突变的肿瘤新抗原, 正常组织不表达, 具有较高的肿瘤特异性和免疫原性, 但机体耐受性较弱[37]. 通过癌症患者肿瘤细胞内独特的突变特征可设计出个性化定制的肿瘤疫苗，目前临床上已经开发了多种编码TSAs的个性化疫苗，但由于TSAs的特殊性，个性化肿瘤疫苗的成本较大，这极大限制了基于TSAs肿瘤疫苗的开发和应用[38,39].

2 肿瘤治疗性mRNA疫苗的给药途径

不同的给药途径会影响mRNA肿瘤治疗性疫苗的免疫效力及刺激响应区域，目前mRNA肿瘤治疗性疫苗的给药途径主要包括静脉注射、肌内注射、皮下注射、经鼻给药、皮下注射等[9](表3).

2.1 静脉注射

静脉注射(intravenous injection)是目前治疗性mRNA肿瘤疫苗临床试验中较常采用的给药方式. 静脉给药能使疫苗达到多个淋巴器官，高效诱导对肿瘤细胞的免疫反应[40~42]. 通过静脉注射mRNA疫苗BNT111能有效诱导黑色素瘤患者体内$CD4^+$ T细胞和$CD8^+$ T细胞免疫应答[43], 但可能会导致全身性的副作用, 如脾损伤和淋巴细胞耗竭.

2.2 肌内注射

肌内注射(intramuscular injection)是将疫苗直接注射到肌肉组织中, 操作方便、副作用小且耐受性好, 是一种广泛使用且可行的注射方式, 但是剂量有限, 容易引起局部疼痛，红肿. 目前批准上市的SARS-CoV-2 mRNA疫苗采用的是肌内注射[44~46]. Chen等人[47]报道了通过肌内注射基于iso-A11B5C1脂质的疫苗能够显著减缓B16F10黑色素瘤的生长且肿瘤组织表现出显著

表 1 TAA联用疫苗

Table 1 TAA combination vaccines

疫苗名称	针对肿瘤类型	抗原	研发公司
CV9201	非小细胞肺癌	NY-ESO-1、MAGE-C1/C2 5T4	德国CureVac
CV9202	非小细胞肺癌	MAGE-A3、MAGE-C1、MAGE-C2、5T4、Survivin和MUC-1	德国CureVac
BNT111	黑色素瘤	NY-ESO-1、MAGE-A3、酪氨酸酶和TPTE	德国BioNtech

表 2 代表性TSA疫苗

Table 2 TSA-based vaccines

疫苗名称	针对肿瘤类型	抗原	研发公司
mRNA-5671	广谱实体瘤	G12D、G12V、G13D、G12C	美国Moderna
mRNA-4157	黑色素瘤	34种病患特异性新抗原	美国Moderna
BNT122	胰腺导管腺癌	20种病患特异性MHC I类和II类限制新抗原	德国BioNtech
CV9103	前列腺癌	PSA、PSCA、PAP、PSMA	德国CureVac

表 3 不同mRNA肿瘤治疗性疫苗给药途径对比表

Table 3 Comparison of different mRNA therapeutic vaccine delivery routes for tumor

给药途径	生物利用度	免疫应答强度	安全性	可能的副作用
静脉注射	高	强	较高	静脉炎、全身反应
肌内注射	中	中	高	局部疼痛、红肿
经鼻给药	中	中	高	鼻腔刺激、吸入风险
瘤内注射	高	强	中	注射部位感染、局部反应
皮下注射	中	中	中	局部肿胀、疼痛、过敏反应

的CD8$^+$ T细胞浸润.

2.3 经鼻给药

经鼻给药(intranasal administration)属于非侵入性给药，可以将mRNA疫苗有效地递送到外周淋巴结的抗原呈递细胞，但受限于鼻腔体积，给药剂量较小，容易刺激鼻腔[48~50]. Mai等人[51]设计了一种经鼻给药的阳离子脂质体/鱼精蛋白复合物LPC，该疫苗在体内经鼻给药后显示出强烈的细胞免疫反应并能够明显减缓小鼠肿瘤生长.

2.4 瘤内注射

瘤内注射(intratumoral injection)mRNA疫苗可以快速激活免疫细胞并最大限度地减少药物脱靶，但瘤内给药有效性受到肿瘤大小和位置的限制，还容易产生局部强烈的免疫反应[52~54]. Deng等人[55]设计并优化了编码OX40L的mRNA疫苗，该疫苗通过瘤内注射给药后能够显著抑制肿瘤生长，提高小鼠存活率并增加疫苗给药组小鼠体内的CD4$^+$ T细胞和CD8$^+$ T细胞水平.

2.5 皮下注射

皮下注射(subcutaneous injection)mRNA疫苗易被局部区域的抗原呈递细胞处理，同时容易实现大剂量给药，但皮下给药往往会引起较大的局部注射部位反应[24,56,57].

3 肿瘤治疗性mRNA疫苗的递送系统

由于mRNA分子量比较大且带有负电荷，游离的mRNA无法穿过同样带有负电荷的磷脂双分子层膜，进入细胞比较困难[58]. 在体内，游离的mRNA容易被机体先天性免疫系统识别吞噬，且很难实现溶酶体逃逸，体内广泛存在的核酸酶容易将mRNA降解，因此需要合适的递送载体，能将mRNA完整高效地递送到体内，并能根据实际需求应用于多种场景[34,59]. 目前，针对肿瘤治疗性mRNA疫苗已经开发出多种创新型的递送系统，如基于脂质的递送、基于聚合物的递送、基于树突状细胞的递送等，能够有效提高mRNA的递送效率和稳定性[33,34](图2).

3.1 基于脂质的递送系统

脂质纳米颗粒是目前最成熟的mRNA递送体系，批准上市的治疗新冠病毒mRNA疫苗使用脂质纳米颗粒(lipid nanoparticles, LNPs)作为递送载体[60~62]. 一般来说，脂质纳米颗粒由四种主要组分构成：阳离子或可电离脂质、辅助性中性脂质、胆固醇和聚乙二醇(polyethylene glycol, PEG)化脂质. 其中，阳离子或可电离脂质是LNPs的主要成分，通过静电相互作用吸附mRNA，促进封装，有利于mRNA疫苗完成溶酶体逃逸，同时能提高mRNA转染效率[63]. 常用的阳离子脂质如DOTAP、DOTMA等. 常见的可电离脂质如SM-102、Dlin-MC3-DMA、ALC-0315等[34,64]. 辅助性中性脂质如DOPE、DSPC等有助于提高脂质纳米颗粒的稳定性，促进核酸封装[65,66]. 胆固醇嵌入磷脂分子中，可以调节LNPs磷脂双分子层膜的流动性，稳定纳米材料，减少药物渗漏[67]. 聚乙二醇化脂质如ALC-0159、PEG-DMG是LNPs的重要组成部分，PEG在脂质体纳米颗粒表面，通过大分子空间位阻减少LNPs的聚集，同时降低脂质体和血浆蛋白的相互吸附，延长脂质体在体内的循环时间，另一方面，可根据需求将脂质体通过PEG进行改造，达到提高生物相容性和稳定性等目的[68].

目前，许多肿瘤治疗性mRNA疫苗的研究主要采用脂质纳米颗粒作为递送系统. 目前还没有上市的治疗肿瘤的mRNA疫苗，基于脂质体纳米颗粒的肿瘤疫苗mRNA-4157目前进入临床三期研究(NCT03897881)，该研究以完全切除皮肤黑色素瘤且复发风险高的受试者作为对象，旨在比较mRNA-4157与帕博利珠单抗(pembrolizumab)联合或单药治疗在肿瘤患者术后辅助治疗中对无复发生存率(recurrence free survival, RFS)的影响. mRNA-4157是一款个性化的肿瘤疫苗，可编码多达34种肿瘤新抗原，疫苗的前期临床结果表明，与单药治疗相比，联合治疗的无复发生存期更长[69]. 以脂质为递送系统的肿瘤治疗性mRNA疫苗在三阴性乳腺癌、黑色素瘤、肺癌等肿瘤的研究也有许多进展，如Liu等人[70]基于脂质合成LCP纳米颗粒来递送编码肿瘤相关抗原1型跨膜黏蛋白(mucins 1, MUC1)的mRNA，该mRNA疫苗能够有效诱导针对三阴性乳腺癌的抗原特异性免疫反应，并和抗细胞毒性T淋巴细胞相关蛋白4 (cytotoxic T-lymphocyte-associated protein 4, CTLA-4)的单克隆抗体联合治疗可显著增强疫苗的免疫反应，抑制肿瘤生长. Chen等人[71]设计了一种基于脂质纳米颗粒的淋巴结靶向mRNA疫苗113-O12B，该疫苗的靶向递送可引发强大的CD8$^+$ T细胞响应，治疗小鼠黑色素瘤效果明显. Ma等人[72]开发了一种mPLA/mRNA (mLPR)肿瘤疫苗，鼻腔给药后，mLPR疫苗刺激树突状

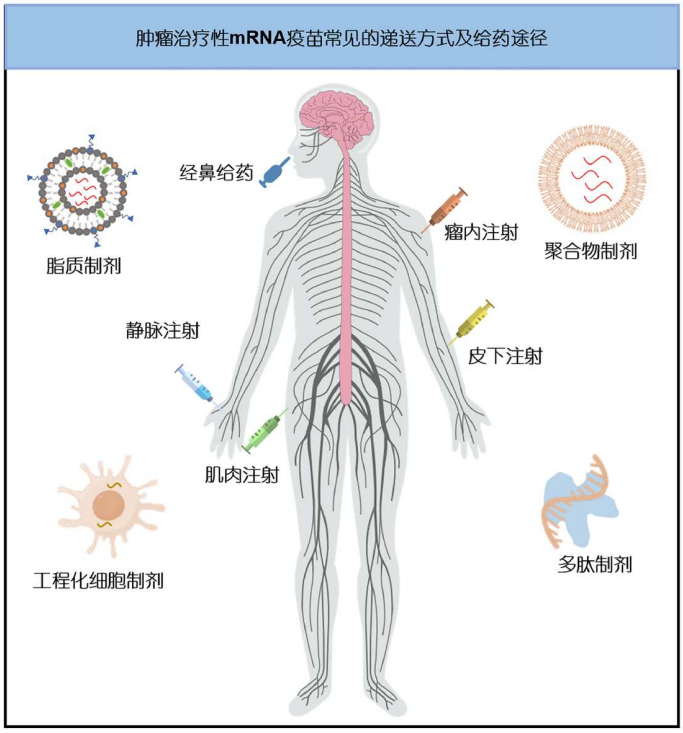

图 2 (网络版彩色)肿瘤治疗性mRNA疫苗常见的递送方式及给药途径
Figure 2 (Color online) Delivery methods and administration routes of therapeutic mRNA vaccines for cancer treatment

细胞成熟, 进而通过激活IFN-γ等细胞因子分泌和自然杀伤细胞介导的抗体依赖性细胞毒性(antibody-dependent cell-mediated cytotoxicity, ADCC)来抑制肿瘤发展并减少骨转移.

3.2 基于聚合物的递送系统

聚合物作为核酸递送平台具有巨大的应用前景, 与基于脂质的递送系统相比, 聚合物递送载体稳定性及可控性更好, 可以延长疫苗体内循环时间、实现组织或细胞靶向[30,73]. 常见的聚合物递送载体包括聚乙烯亚胺(polyethyleneimine, PEI)、聚酯(polyesters)、聚氨基酸(poly-amino acids)和壳聚糖(chitosan)等糖类[74~76]. 其中, 聚乙烯亚胺应用较为广泛, PEI具有良好的"质子海绵效应", 可以高效促进溶酶体逃逸, 同时, PEI还可以激活树突状细胞、促进细胞因子产生[77]. Li等人[78]合成了递送mRNA的材料氟接枝聚乙烯亚胺材料(F-PEI), F-PEI能够促进核酸递送并激活TLR4介导的信号通路. F-PEI和编码肿瘤相关抗原的mRNA自组装形成纳米疫苗, 能刺激树突状细胞成熟进而呈递抗原, 引起抗肿瘤免疫反应. Yin等人[79]研究了一种注射用水凝胶, 由氧化石墨烯和PEI构成, 包裹编码卵清蛋白mRNA和佐剂R848, 皮下注射至少30天后形成纳米疫苗, 该疫苗可靶向淋巴结, 刺激$CD8^+$ T细胞生成, 杀伤肿瘤细胞.

3.3 基于树突状细胞的递送系统

树突状细胞(dendritic cells, DCs)能够通过多种机制摄取和呈递肿瘤相关抗原(TAAs), 从而引发肿瘤特异性免疫反应. 此外, 树突状细胞还可以在淋巴和非淋巴组织之中迁移、调节细胞因子和炎症趋化因子等, 在维持系统和持久的抗肿瘤反应中发挥着重要作用[80,81]. 树突状细胞作为最有效的抗原呈递细胞, 一直是肿瘤治疗性疫苗的开发重点, 这种疫苗疗法通常通过从外周血中分离出单核细胞或造血干细胞/祖细胞, 用重组细胞因子诱导成熟, 并负载各种TAAs, 最后将成熟的DC疫苗回输到患者体内发挥作用[82~85]. 2010年4月, 美国FDA批准治疗转移性去势抵抗性前列腺癌的肿瘤疫苗Sipuleucel-T (provenge; dendreon)上市[86]. Sipuleucel-T的活性成分包括自体外周血APCs和重组人源PAP-GM-CSF[87,88]. 虽然基于树突状细胞的肿瘤

mRNA治疗性疫苗应用前景良好，但与基于脂质等的mRNA疫苗相比，树突状细胞的来源及体外培养激活等操作既繁琐又费时耗力[89].

3.4 其他

阳离子肽鱼精蛋白在mRNA递送领域受到广泛研究，主要通过静电相互作用实现对mRNA的包封，从而有效避免其被核酸酶降解. 此外，鱼精蛋白-mRNA复合物还可作为一种佐剂，引发Th-1型免疫反应[15,90,91]. 阳离子细胞穿透肽(cationic cell-penetrating peptides, CPPs)在mRNA疫苗研究中也显示了不错的疗效. Udhayakumar等人[92]报道了一种递送mRNA的阳离子穿透肽，形成的纳米复合物促进mRNA内体逃逸，进而在DC细胞内表达，且具有pH依赖性的膜破坏特性.

4 进展与展望

近年来，肿瘤治疗性mRNA疫苗在抗原选择、给药途径、递送系统等方面都得到了快速的优化和实质性进展，但仍存在许多问题和挑战[1,30]. 尽管采用TSAs能很大程度地提高mRNA疫苗的免疫原性，但由于肿瘤免疫微环境的复杂性、基因变异的随机性和个体之间的异质性，识别有效的肿瘤特异性突变仍很困难，且大规模生产安全稳定的个性化mRNA疫苗仍有技术壁垒[4,93~95]. 目前肿瘤治疗性mRNA疫苗需要多次给药来加大疫苗效力从而诱导肿瘤免疫反应，这对治疗早期癌症患者较为有效，但晚期癌症患者体内免疫微环境被高度抑制，单一mRNA疫苗治疗效果可能不尽如人意，目前更加关注肿瘤治疗性mRNA疫苗和传统治疗方法如化疗、放疗和其他免疫疗法的联合治疗(图3). mRNA-4157和帕博利珠单抗联合治疗与单用帕博利珠单抗治疗相比，联合用药的患者疾病复发风险显著降低[69,96]. Fotin-Mleczek等人[97]将mRNA疫苗和放疗结合，表现出强大的抗肿瘤协同作用，联合治疗显著增加了小鼠肿瘤的$CD4^+$ T细胞、$CD8^+$ T细胞和NKT细胞浸润. Liu等人[70]构建了编码肿瘤抗原MUC1的mRNA疫苗，并和抗CTLA-4单克隆抗体联用，结果表明，与单药治疗相比，联合疗法可以显著增强抗肿瘤免疫应答. Sahin等人[43]报道BNT111疫苗Ⅱ期临床实验数据，结果表明，治疗晚期黑色素瘤的肿瘤mRNA疫苗BNT111和抗PD-1抗体西普丽珠单抗联用显示出良好的抗肿瘤反应和安全性. Awad等人[98]将个性化肿瘤新抗原mRNA疫苗NEO-PV-01与晚期非鳞状非小细胞肺癌(non-small cell lung cancer, NSCLC)一线治疗药物培美曲塞、卡铂和帕博利珠单抗联用，38名治疗患者没有出现与治疗相关的严重不良反应事件，且接种疫苗后观察到抗原特异性的T细胞反应，证实了其在NSCLC中具有较好的安全性和治疗效果.

肿瘤治疗性mRNA疫苗作为一种新兴的治疗手段，近年来在癌症治疗领域取得了显著进展. 这些疫苗通过利用mRNA分子编码肿瘤特异性抗原，激发机体的

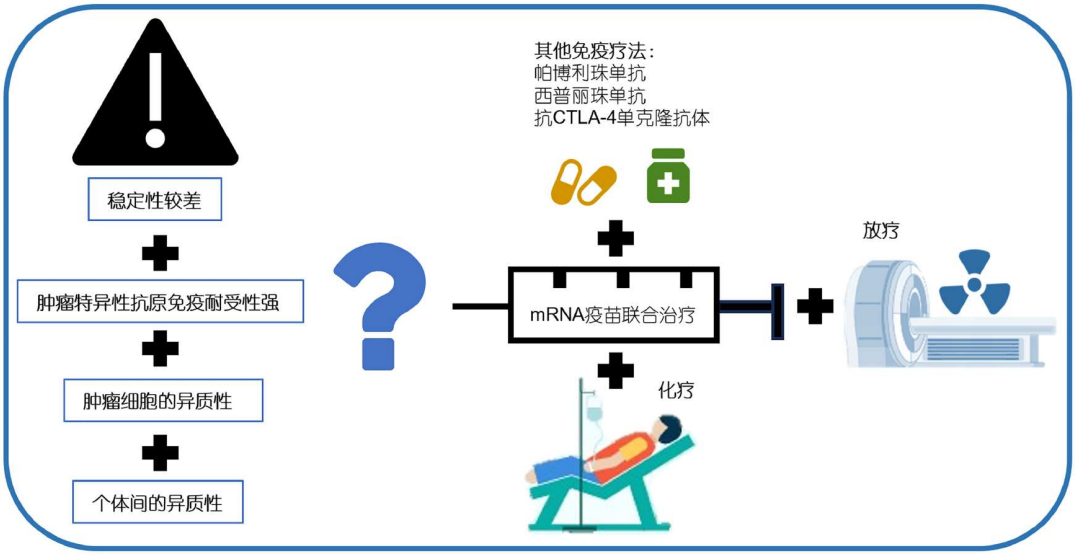

图 3 (网络版彩色)肿瘤治疗性mRNA疫苗的挑战及联合治疗策略
Figure 3 (Color online) Challenges and combination therapy strategies of therapeutic mRNA vaccines for cancer treatment

免疫系统识别并攻击肿瘤细胞. 尽管许多研究仍处于临床试验阶段, 但初步结果表明, mRNA疫苗在提高患者生存率和生活质量方面具有巨大潜力. mRNA疫苗的优势在于其设计和生产的灵活性, 能够快速响应肿瘤抗原的变化, 以及其非整合性, 降低了插入突变的风险. 此外, mRNA疫苗能够诱导强烈的免疫反应, 包括激活T细胞和产生特异性抗体. 这些特性使得mRNA疫苗成为癌症治疗中一个有前景的研究方向. 然而, mRNA疫苗的研究和应用也面临一些挑战, 包括如何提高mRNA的稳定性和递送效率, 以及如何克服机体可能产生的免疫耐受. 为了解决这些问题, 研究人员正在探索多种策略, 如优化mRNA序列、开发新型递送系统, 以及结合其他治疗方法(如免疫检查点抑制剂)来增强疫苗的效果. 随着技术的不断进步和临床试验的深入, mRNA疫苗有望在癌症治疗中发挥更加重要的作用. 预计mRNA疫苗将不仅限于治疗性应用, 还可能扩展到预防性疫苗的开发, 为癌症患者提供更多的治疗选择和更好的治疗效果. 此外, mRNA疫苗的研究也可能推动其他领域, 如传染性疾病和遗传性疾病的治疗, 开启医学治疗的新篇章.

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Summary for “肿瘤治疗性mRNA疫苗的研发进展”

Advances in the development of therapeutic mRNA vaccines for cancer therapy

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In recent years, therapeutic mRNA vaccines for tumors have emerged as a pivotal component of cancer immunotherapy. These vaccines stimulate specific immune responses against tumor-associated or tumor-specific antigens, leveraging the immune system in the body to target and eliminate cancer cells. Composed of mRNA-encoding tumor antigens and delivery vehicles, mRNA vaccines undergo structural modifications to enhance stability and transfection efficiency. Compared to other types of cancer vaccines, mRNA vaccines offer unique advantages. The mRNA vaccines exhibit excellent tolerability *in vivo*, with adverse reactions typically manageable and short-lived. Compared with DNA vaccines, mRNA vaccines do not pose risks of genomic integration and mutations. Moreover, mRNA vaccines avoid the use of pathogenic bacteria or viruses as carriers, ensuring non-infectious profiles. Furthermore, mRNA vaccines can induce sustained and robust humoral and cellular immune responses more effectively than direct antigen injection. The production process of mRNA vaccines is straightforward and cost-effective due to *in vitro* transcription technology. Herein, this review outlines the mechanism of action of therapeutic mRNA vaccines for cancer therapy. Upon administration, mRNA vaccines are internalized by antigen-presenting cells near the injection site. The internalized mRNA is transported to the cytoplasm and ribosomes for translation. This work discusses the commonly targeted antigens in mRNA vaccines, including tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs). TAAs are often overexpressed in tumor cells but possess weaker immunogenicity, which are commonly used in combination to overcome immune tolerance in mammals. TSAs, derived from tumor cell mutations, are highly tumor-specific and immunogenic but elicit weaker tolerance in body. Personalized vaccines targeting unique mutations in cancer patients have been developed clinically, although their cost remains a significant limitation. The review also covers various administration routes for mRNA vaccines, including intravenous, intramuscular, subcutaneous, nasal, and epicutaneous injections. Importantly, delivery systems play a crucial role in mRNA vaccine efficacy due to the molecule’s large size and negative charge, which hinder cellular uptake, including lipid-based, polymer-based, dendritic cell-based, and other common carriers, each tailored for specific applications and scenarios. Additionally, lipid nanoparticles (LNP) are currently the most advanced delivery system, employed in approved COVID-19 mRNA vaccines. Finally, this review summarizes current limitations and future challenges facing therapeutic mRNA vaccines for cancer. Addressing these challenges is essential for advancing the development and application of mRNA vaccines in oncology. This comprehensive review not only provides insights into the evolving landscape of therapeutic mRNA vaccines for cancer therapy, but also highlights the mechanisms, advantages, challenges, and potential for cancer combination therapy.

mRNA vaccine, delivery system, administration route, mechanism of action, tumor immunotherapy

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