皮肤黑色素瘤药物递送系统研究进展

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摘要: 皮肤黑色素瘤是一种高度侵袭性和致命性的恶性肿瘤, 近年来发病率不断上升。尽管针对皮肤黑色素瘤的各种治疗方法取得了一定成果, 但基于药物的理化性质、复杂的肿瘤微环境和手术部位感染等因素, 使用传统治疗策略实现理想治疗效果仍然是一个巨大挑战。在过去的几十年里, 药物递送系统在癌症治疗方面显示出了巨大的潜能, 纳米颗粒展现了高度可调控的能力, 而水凝胶和微针在药物储存库、伤口敷料和透皮给药方面表现出色。本文介绍了这3种给药系统在皮肤黑色素瘤治疗中的最新研究进展, 根据不同治疗阶段的需求对这些递送系统进行功能定位, 并进一步分析其临床转化前景, 旨在为该领域创新药物开发提供参考。

关键词: 药物递送系统; 透皮给药系统; 皮肤黑色素瘤; 纳米颗粒; 水凝胶; 微针

中图分类号: R943 **文献标识码**: A **文章编号**: 0513-4870(2025)07-2142-16

Advances in drug delivery systems for cutaneous melanoma therapy

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Abstract: Cutaneous melanoma is a highly aggressive and lethal malignant tumor, with an increasing incidence in recent years. Despite the advancements in various treatment approaches for cutaneous melanoma, achieving ideal treatment with conventional treatment strategies remains a big challenge due to factors such as the physicochemical properties of drugs, the complex tumor microenvironment, and surgical site infections. In the last decades, drug delivery systems have shown remarkable potential in the treatment of cancers, the nanoparticles (NPs) exhibit highly tunable capabilities, while hydrogels and microneedles excel in drug reservoirs, wound dressings, and transdermal delivery. This article introduces the latest research progress of these three drug delivery systems in the treatment of cutaneous melanoma, then functionally positions these delivery systems according to the requirements of different treatment stages, and further analyzes their clinical translation prospects, aiming to provide references for innovative drug development in this field.

Key words: drug delivery system; transdermal delivery system; cutaneous melanoma; nanoparticle; hydrogel; microneedle

收稿日期: 2024-11-27; 修回日期: 2025-03-03.

基金项目: 四川省中医药管理局科学技术研究专项2023MS(026).

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DOI: 10.16438/j.0513-4870.2024-1127

黑色素瘤起源于黑色素细胞的异常生长, 由于黑色素细胞分布广泛, 根据原发肿瘤的组织位置可分为皮肤黑色素瘤、葡萄膜黑色素瘤、黏膜黑色素瘤和肢端黑色素瘤, 其中皮肤黑色素瘤占诊断的绝大多数[1-3]。此外, 由于皮肤黑色素瘤高度侵袭性和致死性特点, 转移性皮肤黑色素瘤患者的存活率较低[4-6]。事实上, 相关数据表明, 虽然皮肤黑色素瘤仅占皮肤癌病例的4%, 但它贡献了皮肤癌相关死亡的75%[7]。根据国际癌症研究机构"Cancer Tomorrow"板块预测显示, 到2050年, 全球皮肤黑色素瘤将新增发病599 565例, 新增死亡117 222例[8]。

与其他癌症一样, 皮肤黑色素瘤的临床推荐治疗原则包括手术切除、放疗、化疗、靶向疗法和免疫疗法等。然而, 这些治疗方式存在不同方面的缺陷。当处于III期和IV期病程时, 肿瘤呈现深度浸润和转移特点, 手术只能切除可见肿瘤部分, 残留的肿瘤细胞和组织以及术后炎症的发生增加了肿瘤复发的可能性[9]。作为传统抗肿瘤策略, 化疗与放疗并未为皮肤黑色素瘤的治疗带来显著增益, 而且由于非特异性杀伤, 患者会出现脱发、恶心和呕吐等多种不良反应[10,11]。全基因组序列分析的出现揭示了皮肤黑色素瘤在*BRAF*、*CDKN2A*、*NRAS*和*TP53*等基因的显著突变[12]。在过去的10余年里, 美国食品药品管理局 (Food and Drug Administration, FDA) 批准了一系列用于皮肤黑色素瘤的靶向制剂 [如*BRAF*抑制剂维莫非尼和达拉非尼, 丝裂原活化细胞外信号调节激酶 (mitogen-activated extracellular signal-regulated kinase, MEK) 抑制剂考比替尼和曲美替尼] 和免疫抑制剂 [如程序性细胞死亡蛋白-1 (programmed cell death-1, PD-1) 抑制剂纳武利尤单抗、细胞毒性T淋巴细胞相关抗原-4 (cytotoxic T lymphocyte-associated antigen-4, CTLA-4) 抑制剂伊匹木单抗和淋巴细胞活化基因-3 (lymphocyte activation gene-3, *LAG-3*) 抑制剂瑞拉利单抗][13,14]。尽管免疫疗法在晚期和高危早期黑色素瘤展现了广阔的应用前景, 但先天性/获得性耐药使得只有11%～61%患者对此有反应, 并且由于免疫相关不良事件的存在使得受益人群数量更少[9,15-17]。基于高选择性和低毒副作用的特点, 光热疗法 (photothermal therapy, PTT) 和光动力疗法 (photodynamic therapy, PDT) 的发现为皮肤黑色素瘤的治疗提供了一种微创的物理疗法[18]。然而, 传统光热剂和光敏剂的治疗效果受到能量转换不足、水溶性低、光穿透受限等缺点的限制[19]。

为克服以上治疗方法的劣势, 研究人员基于对肿瘤分子机制的深入研究开发了一系列递送策略, 并在皮肤黑色素瘤治疗中取得一定效果[20]。纳米颗粒因其高度可调控的特点, 可以改善药物溶解性、实现药物靶向递送和可控释放, 在肿瘤治疗中显示出了巨大的应用前景, 并且部分类型已经投入临床使用[21]。然而, 皮肤黑色素瘤的异质性和复杂的肿瘤微环境 (tumor microenvironment, TME) 极大限制了治疗效果[22,23]。水凝胶和微针作为重要的药物递送系统, 不仅可实现药物在靶部位的持续释放, 还能构建多模式协同治疗平台以增强肿瘤治疗效果, 在术后创面恢复和透皮递送方面也展现了极大优势[24,25]。本综述将重点呈现目前用于皮肤黑色素瘤研究的纳米颗粒、水凝胶和微针3种药物递送系统, 分别讨论其具有的特点和设计理念, 并分析各递药体系从实验室到临床的可能性。

1 皮肤黑色素瘤的临床治疗药物与递送系统革新

皮肤黑色素瘤是侵袭性很强的一种皮肤恶性肿瘤, 得益于分子生物学机制与肿瘤免疫微环境的深入探索, 其治疗模式已从传统"一刀切"迈入靶向治疗与免疫治疗并行的精准医学时代[26]。基于上述背景, 本研究根据相关权威指南, 系统性地梳理和归纳了当前中国临床实践中皮肤黑色素瘤治疗药物[27,28](表1)。

阐明皮肤黑色素瘤的分子调控机制对皮肤黑色素瘤临床诊疗策略的制定具有重要指导意义。皮肤黑色素瘤的生成和发育涉及多种信号通路的级联调控, 主要包括丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 通路、磷脂酰肌醇3激酶/蛋白激酶B (phosphoinositide 3-kinase/protein kinase B, PI3K/AKT) 通路和细胞周期调节通路[7,13,29,30]。其中, MAPK信号轴通过介导细胞增殖、分化、迁移与凋亡等过程发挥核心作用, 而*c-Kit*、*NF1*、*NRAS*及*BRAF*等关键基因的突变可导致该通路异常激活, 进而驱动肿瘤细胞恶性增殖[31,32]。大约50%的黑色素瘤患者存在*BRAF*的突变, 其中70%～88%为*V600E*突变, 针对该突变的*BRAF*抑制剂联合MEK抑制剂组合策略已成为*BRAF V600*突变患者的一线疗法[33,34]。然而, 该联合疗法在延长患者中位无进展生存期的同时, 发热、光敏性和胃肠道等不良反应发生率也有所增加[35]。

在免疫治疗领域, 基于CTLA-4阻断抗体和PD-1及其配体PD-L1抑制剂的治疗模式彻底改变了转移性黑色素瘤的临床管理[36]。一项为期6.5年的随访研究证实, 相比于单药治疗, 纳武利尤单抗和伊匹木单抗的联合疗法显著提高了不可切除的III/IV期黑色素瘤患者中位无进展生存期[37]。然而, 尽管免疫检查点抑制剂在黑色素瘤治疗中取得显著成功, 其临床应用仍面临双重障碍: 因耐药导致治疗反应率下降, 而免疫相关不良事件的发生迫使部分患者中断治疗[38]。此外, 传统化疗方案虽因靶向性不足及组织穿透效率低下而引发系统性毒

Table 1 Clinical therapeutic drugs for cutaneous melanoma. MEK: Mitogen-activated extracellular signal-regulated kinase; PD-1/PD-L1: Programmed death-1/programmed cell death ligand 1; CTLA-4: Cytotoxic T lymphocyte-associated antigen-4; VEGF-A: Vascular endothelial growth factor-A; IFN: Interferon

Class	Drug	Indication
BRAF inhibitors	Vemurafenib	IIC, IIIA, IIIB and advanced/metastatic with *BRAF V600* mutation
	Dabrafenib	Combination therapy, for III with *BRAF V600* mutation
MEK inhibitors	Trametinib	
	Cobimetinib	Advanced/metastatic with *BRAF V600* mutation
PD-1/PD-L1 inhibitors	Pembrolizumab	IIB, IIC, advanced/metastatic
	Nivolumab	Advanced/metastatic
	Toripalimab	
	Atezolizumab	
	Pucotenlimab	
CTLA-4 inhibitors	Ipilimumab	Advanced/metastatic
VEGF-A inhibitors	Bevacizumab	Advanced/metastatic
Protein kinase inhibitor	Imatinib	Advanced/metastatic with *Kit* mutation
Chemotherapeutic drugs	Fotemustine	Advanced/metastatic
	Paclitaxel	
	Albumin-bound paclitaxel	
	Platinum-based drugs	
	Temozolomide	
	Dacarbazine	
Interferon	IFN-α2b	IIB, IIC and III

性, 但其在转移性黑色素瘤联合治疗中仍显示出协同增益效应。全脑放射治疗是脑转移病灶的一线治疗方法, 但需权衡认知功能损伤等远期并发症风险。

现有治疗方案的局限性凸显了优化递送策略的迫切需求。基于纳米技术等多种生物技术赋能的靶向递送系统可以通过药物靶向性 (配体−受体特异性结合)、局部精准给药 (微针或可注射性水凝胶)、药物的缓控释 (智能响应性体系) 等策略, 有效克服由细胞外基质致密化、血管结构异常及缺氧等多种机制介导的细胞耐药, 减少脱靶效应带来的全身毒性作用, 从而提高患者的依从性[39]。

2 皮肤黑色素瘤药物递送策略

2.1 纳米颗粒

生物药剂学分类系统基于水溶性和渗透性将原料药划分为4种类别, 而多数癌症药物在新化学实体阶段都表现出较差的成药性[40]。纳米颗粒可以通过包封方式, 改善药物的溶解度、渗透性和稳定性, 以提高药物的生物利用度。此外, 它们还可以调节大小、形状、力学性质和电荷状态, 实现靶向给药和响应性释放[41,42]。皮肤黑色素瘤治疗的常用纳米颗粒类型如图1所示, 其相关的临床研究如表2[43-50]所示。

2.1.1 无机纳米颗粒

2.1.1.1 金属纳米颗粒 金纳米颗粒 (gold nanoparticles, AuNPs) 作为一种惰性金属, 具有良好的生物相容性和稳定性, 而局部表面等离子体共振现象存在赋予其光热特性[51,52]。金纳米笼 (gold nanocages, AuNCs) 是一种中空多孔壁结构的AuNPs, 其尺寸紧凑且局部表面等离子体共振可调控, 与金纳米棒相比, 一半质量

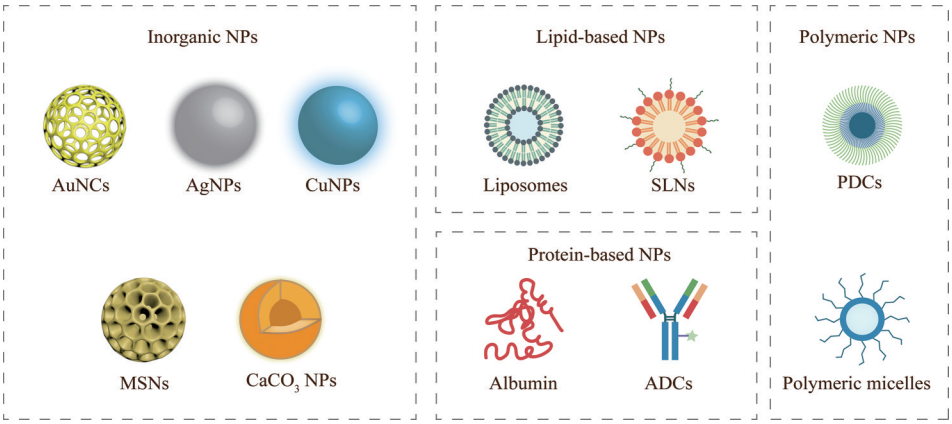


Figure 1 Common nanoparticle carriers for cutaneous melanoma treatment. NPs: Nanoparticles; MSNs: Mesoporous silica nanoparticles; SLNs: Solid lipid nanoparticles; PDCs: Polymer-drug conjugates; ADCs: Antibody drug conjugates

Table 2 Clinical studies on nanoparticle treatments for cutaneous melanoma (ClinicalTrials.gov). IL: Interleukin

Type of NP	Drug	Phase	Condition	NCT	Ref.
Liposomes	Vincristine	I	Completed	NCT00145041	
	Autologous total tumor mRNA	I	Recruiting	NCT05264974	[43]
	Lipovaxin-MM	I	Completed	NCT01052142	[44]
	Cytarabine	I	Terminated	NCT01563614	
	MicroRNA-34	I, II	Withdrawn	NCT02862145	
	IL-2	II	Completed	NCT00004104	
Lipid NPs	mRNA-2752	I	Active, not recruiting	NCT03739931	[45]
Albumin	ABI-007	I	Not yet recruiting	NCT02020707	
	ABI-007	II	Completed	NCT00081042	[46]
	ABI-007	II	Completed	NCT00626405	[47]
	ABI-007	II	Completed	NCT00404235	[48]
	ABI-007	II	Completed	NCT02158520	[49]
Antibody-drug conjugates	MGC018	I	Recruiting	NCT05293496	
	CDX-011	IB, II	Withdrawn	NCT03326258	
	BA3021	I, II	Recruiting	NCT03504488	
	MGC018	I, II	Terminated	NCT03729596	[50]
	CDX-011	II	Terminated	NCT02302339	

的AuNCs即可引起等效温升[53-55]。Zhang等[56]利用AuNCs共载免疫佐剂CpG寡脱氧核苷酸和PD-L1抑制因子JQ1制备成原位疫苗。其中, 光热效应杀灭的肿瘤细胞可以通过释放肿瘤抗原激活树突状细胞(dendritic cells, DCs)以改善TME的免疫抑制。有研究表明, AuNCs的短半衰期和高浓度诱发的细胞毒性等问题限制了光热治疗效果, 而功能化修饰则可以改善这一问题[57]。Zheng等[58]通过叶酸修饰的热敏脂质体赋予AuNCs载体的靶向性和稳定性, 并延长其全身循环时间, 在叶酸的引导下, AuNCs在肿瘤中积累并成功捕捉抗原形成原位重组疫苗实现从头免疫。研究发现, 单独的PDT难以根除实体肿瘤, 而基于AuNCs的PTT/PDT联合疗法不仅可以解决光敏剂水溶性差的问题, 还可提高光疗效果[59]。Xie等[60]使用单磷酰脂质A (monophosphoryl lipid A, MPLA)作为热敏脂质涂层保护装载光敏剂吲哚菁绿(indocyanine green, ICG)的AuNCs用于皮肤黑色素PTT/PDT双重疗法(图2)。制备的MLI-AuNCs纳米颗粒在近红外光(near infrared, NIR)照射下可以产生热和单线态氧($^1O_2$)使肿瘤暴露抗原与MPLA一同诱导DC成熟, 并激活细胞毒性T淋巴细胞(cytotoxic T lymphocytes, CTLs)和释放干扰素-γ (interferon-γ, IFN-γ)从而实现转移/复发/特异性抗肿瘤免疫反应。

除了AuNPs, 银纳米颗粒(silver nanoparticles, AgNPs)也是一种很有前景的金属纳米载体材料[61-64]。例如, Mahadev Patil等[65]通过将有机分子phophoride A加载到AgNPs中, 合成了荧光银纳米颗粒, 并将其用于黑色素瘤的化疗、光热治疗和成像, 显著减轻了肿瘤负担。此外, AgNPs还有望参与抗体–药物偶联物(antibody-drug conjugates, ADCs)创建的PDT主动靶向策略[66]。由于成本低廉, 铜纳米颗粒(copper nanoparticles, CuNPs)作为细胞毒性纳米材料受到了极大的关注[67]。Liu等[68]开发了一种多功能纳米复合材料, 通过在铜基金属有机框架上涂覆多巴胺, 其中铜离子的释放不仅可以抑制细菌生长, 还可以促进细胞迁移和血管生成, 有助于皮肤黑色素瘤术后恢复。

2.1.1.2 非金属纳米颗粒 二氧化硅来源丰富, 由于其优异的生物相容性, 被广泛应用于食品添加剂、制药等行业[69]。其中, 介孔二氧化硅纳米颗粒(mesoporous silica nanoparticles, MSNs)因具有比表面积大、粒径可调、表面修饰可选等结构特点, 在抗癌药物递送载体研究中备受青睐[70,71]。为实现M2型巨噬细胞重编程为M1型并解除免疫抑制, Zhang等[72]开发了一种药物共递送系统, 使用二硫桥接MSNs负载toll样受体7/8激动剂瑞喹莫德(R848), 并通过静电相互作用将抗SIRPα抗体(aSIRPα)吸附到表面, 在B16F10荷瘤小鼠治疗上获得高达92.0%的肿瘤抑制率(图3)。同样以M2型肿瘤相关巨噬细胞为作用靶点, Qiao等[73]成功构建了负载半胱氨酸蛋白酶抑制剂E64的MSNs, 并采用经人工配体修饰的源于手术切除癌细胞的细胞膜进行包覆, 进而实现M2型肿瘤相关巨噬细胞的精准靶向递送。该递药体系可作为个性化治疗平台, 通过协同免疫检查点抑制剂治疗策略, 显著增强术后复发预防效果。

微棒、纳米棒、空心和树突状等特定形态的MSNs具有佐剂性质, 可用于癌症免疫疗法[74]。Nguyen等[75]偶联MSNs和介孔二氧化硅微棒制备了一种可注射双尺度疫苗。在注射后, 介孔二氧化硅微棒形成三维大孔支架, 通过释放粒细胞–巨噬细胞集落刺激因子以

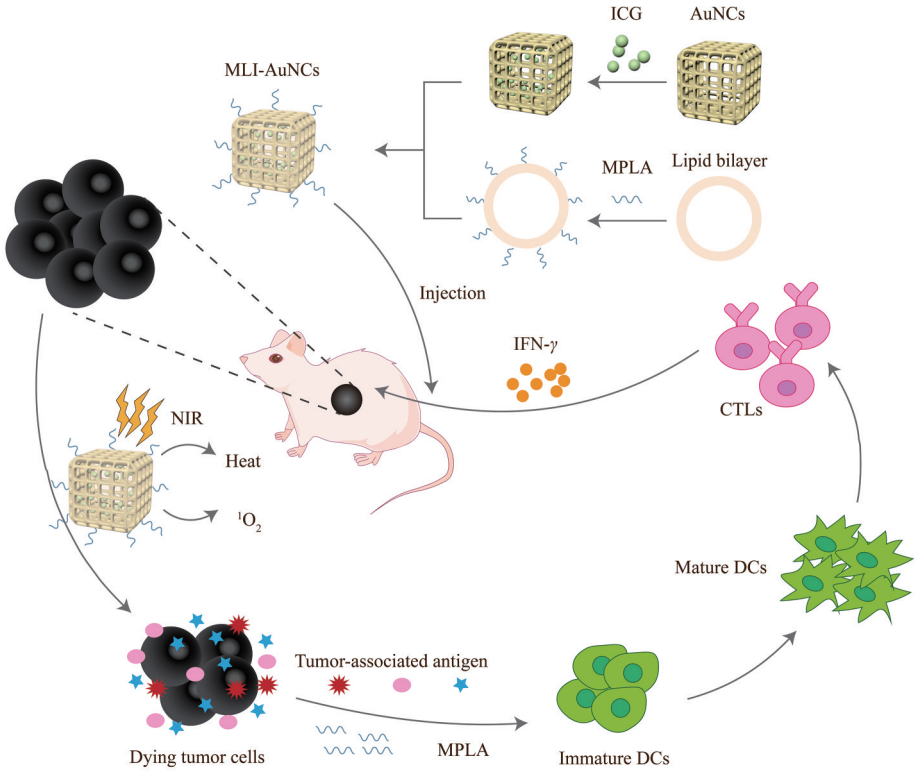


Figure 2 Preparation method and mechanism of MLI-AuNCs[60]. AuNCs: Gold nanocages; ICG: Indocyanine green; MPLA: Monophosphoryl lipid A; MLI-AuNCs: MPLA lipid bilayer-enveloped and ICG-loaded AuNCs; CTLs: Cytotoxic T lymphocytes; IFN-γ: Interferon-γ. Adapted from Ref. 60 with permission. Copyright © 2022 Elsevier

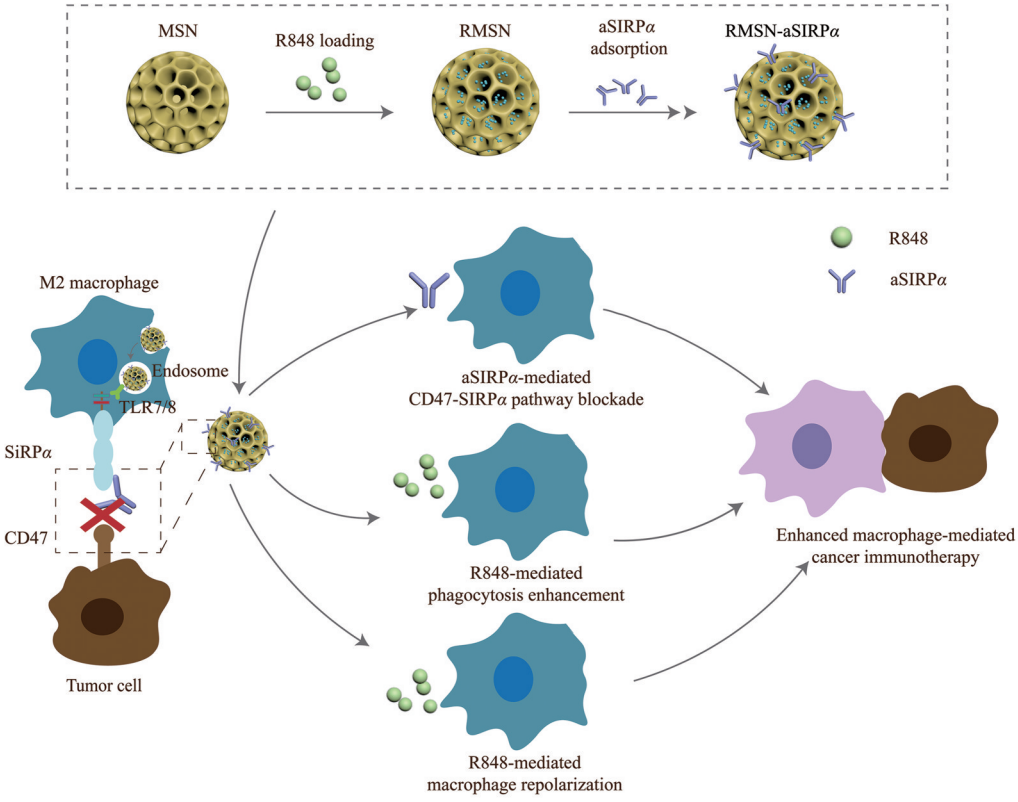


Figure 3 Preparation method and mechanism of RMSN-aSIRPα[72]. RMSN: R848-loading MSN; aSIRPα: Anti-SIRPα antibody; RMSN-aSIRPα: RMSN absorbed with aSIRPα. Adapted from Ref. 72 with permission. Copyright © 2022 Elsevier

募集大量DCs。虽然MSNs展现了优异的药物递送能力, 但蓄积引起的毒性问题仍旧是临床转化路上的巨大挑战[76]。目前临床有关黑色素瘤的二氧化硅纳米颗粒 (NCT02106598) 只局限于诊断阶段, 并且因体积较小规避了蓄积毒性[77]。

基于肿瘤组织的酸性微环境特点, 具有pH响应性和生物可降解的碳酸钙 (calcium carbonate nanoparticles, $CaCO_3$ NPs) 纳米颗粒也可用作药物载体[78]。Yakubova等[79]使用$CaCO_3$ NPs加载光敏剂Ce6和化疗药多柔比星 (doxorubicin, DOX), 与游离药物和单一疗法相比, DOX/Ce6@$CaCO_3$可在肿瘤中持续积累48 h, 显著抑制B16F10荷瘤小鼠肿瘤生长, 并表现高度稳定性。

2.1.2 脂质纳米颗粒

2.1.2.1 脂质体 脂质纳米颗粒 (lipid nanoparticles, LNPs) 是由聚乙二醇 (polyethylene glycol, PEG) 和其他脂质成分构成的脂质递送载体[80]。脂质体是最早出现的LNPs, 由单个/多个磷脂双分子层组成的囊泡结构组成, 具有生物膜类似的性质, 其尺寸可调、易于修饰, 可搭载疏水性和亲水性药物[81-83]。为解决塞来昔布水溶性差问题和大量口服导致的心血管不良反应, Jahani等[84]制备了DC疫苗和gp100肽修饰的塞来昔布脂质体用于B16F10黑色素瘤的预防和治疗。脂质体膜的存在增加了药物在肿瘤部位的有效积累, 而gp100肽作为黑色素瘤抗原进一步提高DC疗法的效力, 这种联合治疗模式显著改善肿瘤治疗效果。PEG修饰是常见的改善脂质体团聚、增加稳定性和延长血液循环时间的方法[85,86]。Fu等[87]使用DSPE-PEG_{2000}-PEP脂质体装载免疫原性细胞死亡诱导剂奥沙利铂并吸附CD39抑制剂多氧钨酸钠。该递药系统可有效地隐藏多氧钨酸钠的系统毒性, 并对原位、肺转移和术后复发黑色素瘤产生了优异的化学免疫协同治疗效果。

目前国内上市脂质体癌症治疗药物已经有10余种, 是一种非常有前景的成果转化剂型。MicroRNA-34 (miR-34) 是一种肿瘤抑制因子, 在大多数肿瘤细胞中呈现下调趋势[88]。基于临床前数据的研究, Cuciniello等[89]开发了miR-34脂质体并在I期临床试验 (NCT02862145) 探究在晚期/转移性皮肤黑色素瘤治疗中的安全和有效性。然而, 因其严重的免疫介导反应研究被迫终止。Patel等[45]开发了一种基于mRNA的新型治疗剂mRNA-2752 (NCT03739931), 截至2019年, 临床试验数据证明了其安全性, 而抗肿瘤效果还在进一步探究。而另一项基于肿瘤衍生的mRNA疫苗 (NCT05264974) 还在进行患者招募, 有望用于辅助抗PD-1抗体早期黑色素瘤复发[43]。

2.1.2.2 固体脂质纳米颗粒 固体脂质纳米颗粒 (solid lipid nanoparticles, SLNs) 也是一种经典的脂质纳米颗粒, 自1991年推出以来多用于疏水性药物的包埋[90]。SLNs可以增加药物稳定性、实现药物的持续释放, 特别是其通过网状内皮系统吸收以避免口服导致的首过代谢的特点,被广泛开发用于亲水性药物的递送[91]。Dattani等[92]比较了纳米胶束、脂质体和SLNs作为紫杉醇递送载体用于黑色素瘤治疗的能力。结果显示, 相比于纳米胶束、脂质体, SLNs表现出了更加缓慢的释放速率, 24 h释放药物不到50%, 并且具有更强的稳定性和更优秀的抗肿瘤能力。为增加黑色素瘤放射疗法的效果, Meng等[93]使用B16F10细胞膜包裹搭载了5-氨基乙酰丙酸甲酯和去铁胺的SLNs。在瘤内注射后, 因为B16F10细胞膜与肿瘤之间的特异性结合作用以及SLNs的缓释能力, 实现了药物在靶部位的长期滞留和缓释。

2.1.3 蛋白质纳米颗粒

2.1.3.1 白蛋白 白蛋白是最丰富的血浆蛋白, 其在生理条件下表现为强负电荷状态并且表面存在的羧基和氨基等官能团为其与配体结合提供条件[94,95]。目前有多项临床试验 (NCT00081042、NCT00626405、NCT00404235和NCT02158520) 研究紫杉醇白蛋白药物 (ABI-007) 独立或联合治疗黑色素瘤, 其中位无进展生存期和中位总生存期都有所增加[96]。

2.1.3.2 抗体–偶联药物 抗体–偶联药物 (antibody drug conjugates, ADC) 由单克隆抗体和细胞毒性药物通过连接头结合而成, 具有高效靶向性和杀伤性[97,98]。CDX-011和MGC018都在黑色素治疗中展现出希望, 2021 ASCO年会上生物制药公司MacroGenics公布的I期剂量递增临床试验 (NCT03729596) 结果表明MGC018可控的安全性和临床活性, 然而该项试验终止于II期临床[50]。不过, 最近该公司又针对MGC018开启了新一项临床试验 (NCT05293496), 将MGC018和MGD019联合给药, 用于恶性黑色素瘤等多种晚期、不可切除实体瘤。

2.1.4 聚合物纳米颗粒

聚合物纳米颗粒由天然聚合物和/或合成聚合物构建而成, 包括聚合物–药物偶联物 (polymer-drug conjugates, PDCs) 和聚合物胶束 (polymer micelles) 等[99-101]。

2.1.4.1 聚合物–药物偶联物 相比于ADC药物, PDC药物的研发则提供了更多可能[102]。药物被接到线性、支链和刷状聚合物的主链或侧官能团上, 通过提高全身稳定性、减少毒副作用和改变药代动力学, 从而达到高效的肿瘤抑制能力[103,104]。PEG是最常见的聚合物,

此外, 聚 (α,*L*-谷氨酸) [poly(α-)*L*-glutamic acid, PGA] 和 *N*-(2-羟丙基)-甲基丙烯酰胺共聚物等合成聚合物也已经引入临床和临床前研究[102,105,106]。例如, Pisarevsky 等[107]利用 PGA 偶联改良 *BRAF* 抑制剂达拉非尼和 MEK 抑制剂司美替尼用于治疗原发性黑色素瘤小鼠。其中, PGA 作为高分子骨架改善了药物溶解度和提高稳定性。鉴于 PEG 等偶联物体积大且实体肿瘤渗透性差的特点, 研究人员开发了一种半衰期长达 51 h 的 IFN−聚 (*N*-氧化物) 偶联物用于黑色素瘤的治疗[108]。这种偶联物具有长循环性, 在肿瘤环境的缺氧和酸性条件下呈现正电状态, 通过吸附带负电荷的肿瘤细胞促进药物的快速吸收, 从而发挥更有效的抗癌作用。

2.1.4.2 聚合物胶束 由两亲性嵌段共聚物制成的聚合物胶束广泛用于输送疏水治疗药物, 并且可以根据尺寸、载药能力和亲疏水特性的不同要求进行定制[109]。Tokarska 等[110]合成了直径约为 25 nm 的 mPEG-b-PLGA 胶束, 用于共递送疏水性光敏剂 IR-768 和抗肿瘤抗生素柔红霉素。利用细胞内吞作用, 这些胶束可以靶向递送到线粒体, 促进 PDT 中单线态氧的产生, 同时实现比游离药物更有效的药物积累。与线性两亲共聚物相比, 树突状聚合物具有优越的单分散性, 其致密的结构可以防止反向胶束化从而提高胶束稳定性[111]。Thuy 等[112]将低代树枝状大分子 PAMAM G2−组氨酸−精氨酸与胆固醇结合制备聚合物胶束, 然后辅以维生素 E 聚乙二醇丁二酸酯修饰以提高胶束稳定性。这些树突状聚合物胶束成功地包裹了细胞毒性药物姜黄素和紫杉醇, 有效地抑制了黑色素瘤细胞的生长, 并显示出抗菌活性。此外, 还可以设计还原反应性聚合物胶束, 通过靶向肿瘤细胞的相对还原环境来增强抗肿瘤功效[113]。

3 水凝胶

水凝胶是由天然和/或合成单体或聚合材料衍生的亲水性均聚物或共聚物形成的三维网络[114,115]。目前, 中国上市的水凝胶主要用于伤口止血和疤痕修复, 在 COVID-19 流行期间也被用于手部消毒。为了适应皮肤黑色素瘤的结构特点, 促进各种治疗手段的联合应用, 研究人员开发了具有不同给药途径、材料类型、溶胀度和扩散性能的水凝胶[116,117]。基于是否和手术切除相结合, 将水凝胶分为非创面治疗和创面治疗 (图 4)。

3.1 非创面治疗

3.1.1 口服水凝胶

口服给药是最简单方便和应用最广泛的给药方法, 但胃肠道的多重屏障阻碍了药物的吸收[118]。高艳锋课题组[119]利用镜像噬菌体展示技术, 开发了第一个靶向 PD-1/PD-L1 通路的抗蛋白水解 D 肽拮抗剂 ^{D}PPA-1。

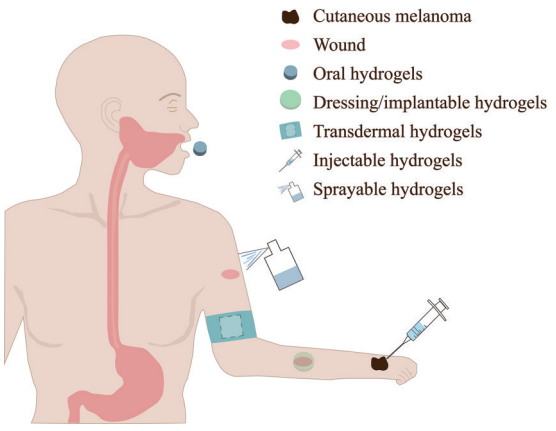


Figure 4 Treatment modalities of hydrogels for cutaneous melanoma

基于课题组研究基础, Li 等[120]优化构象得到 OPBP-1 阻断肽, 并开发了 *N*,*N*,*N*-三甲基壳聚糖水凝胶用于增加 OPBP-1 的肠道渗透性和稳定性。结果表明, 与 OPBP-1 溶液相比, 负载 OPBP-1 的 TMC 水凝胶的口服生物利用度提高了 5.4 倍, 并具有较好的抗肿瘤活性。

3.1.2 可注射水凝胶

基于溶胶−凝胶相变和原位交联的可注射水凝胶显著提高了水凝胶给药的方便性和灵活性[121]。这些水凝胶可以携带多种治疗药物, 从而减少与单一治疗相关的耐药性性状, 并且由于其优异的适应性, 可以作为药物储存库在靶部位缓慢持续释放载荷[122]。例如, Rothe 等[123]开发了一种二茂铁修饰的可注射活性氧 (reactive oxygen species, ROS) 响应性水凝胶用于黑色素瘤化疗药物的程序化释放。亲水性的多柔比星通过简单扩散机制从水凝胶中迅速释放, 紫杉醇因与二茂铁的疏水相互作用嵌入水凝胶网络, 在 TME 中 ROS 将 Fe^{2+} 氧化成亲水性更强的 Fe^{3+} 从而削弱疏水作用以实现紫杉醇的缓慢且可控性释放。

基于聚合物的稳定性和机械强度, 研究人员利用聚氨酯接枝的糊精刷状共聚物和凝胶剂甲基纤维素开发了刷状聚合物注射水凝胶, 用于递送糖皮质激素药物地塞米松以治疗小鼠 B16F10 细胞诱导的黑色素瘤[124]。刷状聚合物实现了亲疏水性的平衡, 水凝胶体系中药物的受控释放不仅增强了药代动力学, 延长了治疗时间, 而且保护了重要器官免受损害。

3.1.3 透皮水凝胶

免手术经皮给药模式保证了患者良好的依从性, 并且可以通过调控暴露时间来确定药物治疗持续时间, 而皮肤黑色素瘤的特殊发病位置则为透皮递药提供了可能[125]。Ni 等[126]报道了一种泊洛沙姆和壳聚糖热敏透皮水凝胶用于装载紫杉醇线粒体靶向树突状脂

肽脂质体, 该脂质体还加载了表面活性剂Tween 80和脱氧胆酸钠以增加皮肤渗透。结果表明, 制备的透皮水凝胶体系不仅能根据黑色素瘤的大小和形状实现个性化治疗, 其缓释特性还可减少给药次数, 从而提升患者依从性。

3.2 创面治疗

3.2.1 伤口敷料

皮肤黑色素瘤切除手术产生的伤口创面存在继发感染的可能, 伤口敷料可以覆盖伤口表面并作为保护屏障促进伤口的修复并抑制肿瘤再生[127]。多种类型伤口敷料已获开发, 而水凝胶凭借其优异的亲水性、生物相容性和载药能力, 成为最具前景的候选材料[128,129]。一项研究发现, 从大鲵 (*Andrias davidianus*, SSAD) 皮肤分泌物中提取的仿生黏合剂不仅具有很强的黏附性, 而且可以缩短皮肤伤口愈合所需的时间, 同时促进伤口再生和血管生成[126,130]。基于该研究基础, Liu等[131]开发了一种DOX-SSAD水凝胶敷料同时用于伤口愈合和抗肿瘤治疗。在荷瘤伤口愈合试验中, DOX-SSAD水凝胶治疗的皮肤黑色素瘤切除小鼠显示出100%的存活率, 并且保持无瘤状态。

卡拉胶是来源于海洋红藻的天然硫酸化多糖, 具有良好的黏弹性、生物相容性、抗氧化能力、抗菌性和抗肿瘤效果[132]。Chen等[133]采用卡拉胶作为还原剂和稳定剂制备了卡拉胶封端的金银纳米颗粒, 并将其载入到温敏水凝胶敷料, 用于黑色素瘤术后PTT治疗。该水凝胶体系可有效止血、防止肿瘤复发以及促进术后伤口愈合。透明质酸作为细胞外基质的主要成分, 凭借其多功能化学基团的存在可与其他生物材料协同组装, 从而构建理想的生物功能化平台用于药物负载[134]。例如, Zhao等[135]利用巯基明胶和多巴胺修饰的透明质酸, 制备了一种负载DOX纳米胶束的交联水凝胶支架, 用于皮肤黑色素瘤的术后治疗。药物随着支架的降解而缓慢释放, 降低了术后黑色素瘤的复发率和游离DOX对毛囊组织的损伤。

3.2.2 可喷雾水凝胶

由于混合效率高、喷雾区域调节良好和便携性, 可喷雾水凝胶非常适用于伤口管理[136]。Ye等[137]利用聚乙烯醇乙酰乙酸酯和壳聚糖制备了一种原位喷雾纳米疫苗用于装载高尔基体-PD-*l1*$^{-/-}$外泌体杂交膜包被纳米颗粒和αPD-L1抗体以抑制肿瘤术后复发。该凝胶喷雾在室温混合后即可喷洒到靶部位, 并在含水条件下保持黏附性超过2 h。

4 微针

微针由长为100～1 000 μm的微型针头组成, 穿透皮肤角质层即可将生物活性分子施用到表皮或真皮浅层[138,139]。与传统注射针头相比, 微针被认为是皮下注射和透皮贴片的混合体, 因为它们不需要额外的机械设备, 并可通过控制插入深度实现无痛给药[140-143]。这使得微针成为理想的自我局部给药系统。近年来, 微针介导的黑色素瘤治疗引起了越来越多的关注, 大量研究证实了这些方法的有效性[144-146]。

4.1 微针器械

微针器械包括固体微针 (图5A) 和中空微针 (图5B)。固体微针通常由金属和硅作为制备材料, 特别是不锈钢微针, 易于成型且机械强度高, 已经获得了FDA的批准[147,148]。固体微针不仅可以通过“戳”和“贴”的方式使药物从微通道进入皮肤达到治疗效果, 还可以作为电极阵列直接发挥作用。例如, Pan等[149]制备了一种固体微针阵列集成叉指电极用于电刺激疗法, 当含100个高约600 μm针头的微针阵列刺入后施加1 V正弦波和100 kHz进行电刺激。体内实验表明, 与非微针电极产生的电刺激相比, 该方法产生了强大的免疫性细胞死亡来激活全身免疫反应, 显著抑制了皮肤黑色素瘤的生长。此外, 固体微针和中空微针可以与可穿戴设备集成制备无创的黑色素瘤筛查系统作为采集器用于生物分析便于开展下一步治疗[150,151]。

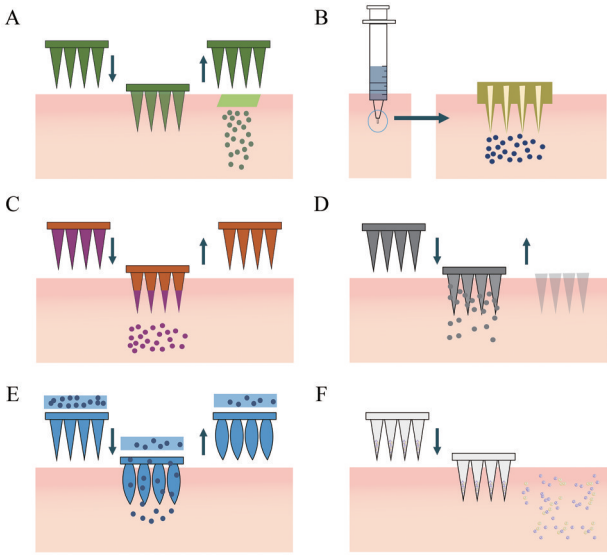


Figure 5 Schematic classification of microneedle based on their drug delivery characteristics. A: Solid microneedle; B: Hollow microneedle; C: Coated microneedle; D: Dissolving microneedle; E: Hydrogel microneedle; F: Cryomicroneedle

4.2 涂层微针

在保留固体微针机械力度基础上, 涂层微针增加了自身载药功能[152] (图5C)。为实现亲水性卡铂和疏水性伏立诺他协同给药治疗多药耐药黑色素瘤, Li等[153]制备了一种聚乙烯亚胺和聚丙烯酸组成的“海绵状”涂

层微针, 通过毛细管效应, 两种亲疏水不同的药物可以在微针表面均匀吸附, 30 min内即可释放大多数药物, 抗肿瘤疗效达到75.6%。不过, 涂层微针的较小表面积限制了载药量, 同时因为药物通常直接暴露在微针表面, 可能导致药物在刺入皮肤前就已经流失[154,155]。

4.3 可溶性微针

为了解决上述难题, 研究人员开发了可溶性微针(图5D)。可溶性微针具有制备简单、药物装载灵活和一步应用的特点, 只用刺入皮肤, 载药微针即可在皮肤中迅速/可控溶解, 从而释放治疗药物, 因此在研究中占据主要地位[155-157]。可溶性微针制备材料广泛, 包括水溶性材料, 如羟丙基甲基纤维素、羧甲基纤维素、羟丙基纤维素、透明质酸、葡聚糖和海藻酸钠; 以及生物可降解聚合物材料, 如聚乙烯吡咯烷酮、聚乙烯醇和聚乳酸[156,158]。

Demartis等[159]开发了一种负载孟加拉红的转移体用于选择性损伤癌细胞, 并进一步设计了一种3层溶解微针阵列来实现转移体的深度递送。结果表明, 微针阵列不仅显著增加了皮肤中孟加拉红的沉积, 而且保持了转移体的结构特征。皮肤黑色素瘤具有不规则的图案和不平坦的表面, 传统的圆锥形或金字塔形可能导致微针插入不完全。Joo等[160]利用3D打印技术设计了一种自锁可溶微针贴片, 皮肤黏附性能实验表明, 与其他形状微针贴片相比, 自锁微针贴片在30°和60°的曲面上具有更强的黏附性, 这可以进一步提高微针在溶解过程中给药的准确性。

可溶性微针是一种实现多种联合疗法以及响应性释放的优异载体。例如, 可溶性微针可以局部递送光敏剂黑磷量子点和化疗药物DOX, 通过PDT、PTT和化疗实现三重抗癌效果, 同时最大限度地减少对周围健康组织的损伤[161]。多种疗法联合应用可增强抗肿瘤作用, 而刺激响应性微针可促进和控制有效载荷的释放, 减少全身不良反应[139,162]。步文博课题组[163]于2016年首次提出化学动力学疗法 (chemodynamic therapy, CDT)。由于CDT依靠芬顿反应发挥作用, 而不依靠氧气和激光且具有效率高、特异性高、不良反应小等优点, 在癌症领域得到广泛研究[164]。然而, H_2O_2不足和谷胱甘肽的积累阻碍了芬顿反应。为此, Yu等[165]提出了一种H_2O_2增强谷胱甘肽消耗策略用以增强CDT, 并利用聚乙烯吡咯烷酮微针进行透皮给药。该治疗策略在裸鼠A375黑色素瘤模型得到验证, 载药微针成功递送药物至靶部位, 并对浅表性肿瘤的表现出良好的治疗作用。

4.4 水凝胶微针和冷冻微针

水凝胶微针被认为是可溶性微针的一种亚型, 它结合了水凝胶的膨胀性和微针的微创特点[166] (图5E)。Dosta团队[167]将含有伯胺的改性透明质酸聚合物与含有琥珀酰酰官能团的8-臂氨聚乙二醇交联, 并加载免疫调节剂制备成水凝胶微针平台。该微针平台用于同时递送免疫激活剂和收集间质皮肤液以监测治疗反应, 在原位黑色素瘤癌症模型中得到了验证。这种基于水凝胶微针的诊疗平台为皮肤黑色素瘤患者的管理策略提供了一种新思路。

癌症的细胞疗法已经在临床治疗中获得明显收益, 为保持细胞活力和功能, 研究人员推出了冷冻微针技术[168,169] (图5F)。Chang等[170]利用逐步低温微加工的方法, 开发了一种装有卵清蛋白脉冲树突状细胞的冷冻微针。与皮下注射和静脉注射相比, 冷冻微针接种引起更高的抗原特异性免疫反应, 并显著延缓肿瘤生长。

5 总结与展望

化疗、免疫治疗、PDT、PTT和CDT等多种疗法都被用于抑制肿瘤生长、降低肿瘤复发率、减少转移可能和延长患者生存期。然而, 由于非靶向给药、严重的不良反应及复杂的TME等因素, 这些治疗未能达到预期的疗效[171]。为满足保护载荷、提高药物装载量、增加药物在靶部位的积累和延长治疗时间等目的, 多种药物载体被相继开发出来, 并展现不同的递送特点[172]。

由无机物、脂质、蛋白质、聚合物等材料制成的纳米颗粒可以通过包封或静电吸附的方式装载药物并以被动或主动靶向肿瘤细胞发挥抗肿瘤作用。增强的通透性和滞留效应是纳米颗粒被动靶向的基础, 纳米颗粒可以通过其大小和形状进行调节[173]。然而研究表明, 由于皮肤黑色素瘤的异质性和复杂的TME, 纳米颗粒的被动靶向并不理想[174-176]。相比之下, 基于外源性/内源性响应性的主动靶向方法显然具有更大的优势, 例如上文提到的金属纳米颗粒的光热效应和$CaCO_3$ NPs的pH响应释放。

黑色素瘤切除术后的伤口面临感染和复发的问题, 水凝胶敷料不仅可以作为伤口敷料止血, 防止伤口感染, 还可以携带治疗药物以防止肿瘤复发[177]。由于水凝胶的亲水性, 疏水药物的包封和释放具有挑战性, 并且可能破坏水凝胶的结构[178]。将纳米颗粒封装到水凝胶中制备成纳米复合水凝胶可能具有更大的优势, 因为它保留了纳米颗粒的载药和高度可调控性质, 同时增加了水凝胶的保护和控制药物释放能力, 并且纳米颗粒还可改善水凝胶的黏附性、机械性等物理性能[179,180]。

由于皮肤黑色素瘤常发生在皮肤表面, 经皮给药是一种理想的治疗方法。然而, 经皮给药必须通过角

质层的天然屏障, 这对药物的分子质量和亲脂性提出了要求[181,182]。透皮水凝胶的渗透性能有限, 并且常需要渗透增强剂的支持[183]。基于可溶微针的透皮给药系统是一种有效的替代方法, 因为它们创建了穿透角质层的给药通道, 显著提高了给药效率, 并且无残留医疗废物[184,185]。与水凝胶类似, 可溶性微针也可以装载纳米颗粒, 通过增强靶部位的药物富集作用, 提高抗肿瘤效果[186]。然而, 由于尺寸限制, 微针的载药量通常不超过 1 mg, 并且在反复多次给药后残留的基质可能会诱发安全问题[187,188]。水凝胶微针规避了上述问题, 其插入皮肤后溶胀不溶解, 药物可从设计的储存库中通过多孔水性微导管进入皮肤[189]。不过, 水凝胶微针的制备仍然面临着挑战, 首先需要选择合适的材料来保证机械强度, 其次是储存库中药物释放不完全, 因此需要进一步探索其药代动力学[190,191]。

联合疗法在皮肤黑色素瘤手术替代疗法和术后防止伤口感染和复发展现了显著的疗效, 而药物递送系统可以为治疗剂提供保护、改善药物理化性质、调控药物动力学、减少脱靶效应和增加患者依从性。纳米颗粒是一类高度可调控的药物载体, 可以进行结构修饰以改善负载药物的理化性质。水凝胶是一种以缓释方式递送大剂量药物的有利方法, 特别适合于肿瘤术后创面止血、预防感染和肿瘤复发, 而微针则是透皮递送的优选策略。由于皮肤黑色素瘤的不同阶段需要不同的药物配方和治疗模式, 更好地了解 3 种常见递送系统的特性将有助于开发更适合未来黑色素瘤治疗的药物产品。

作者贡献: 雷知钰负责撰写及修改论文; 赵雅、房玉姗、师健友负责提供修改意见; 肖雯婧、呼永河负责指导论文撰写、修改论文并定稿。

利益冲突: 本文所有作者声明不存在利益冲突关系。

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