

微针递送系统在疫苗中的研究进展

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摘要: 疫苗往往通过肌肉注射或皮下注射等方式给药。虽然这些方式能够有效地将疫苗抗原递送到机体内, 触发免疫反应, 但也存在注射疼痛、操作复杂、运输条件严格以及疫苗自身的免疫原性和稳定性不佳等局限性。随着技术的发展, 皮肤给药成为疫苗给药的新途径。在众多皮肤给药方式中, 微针展现出独特的优势与潜力。本文简述了微针经皮免疫的机制及其优势, 列举了微针的分类, 重点介绍了仿生微针的设计理念、结构优势及制备工艺, 分析了其在疫苗中的应用潜力。同时, 简述了微针在疫苗方面的应用, 包括细菌感染、病毒感染、癌症治疗及当前的临床应用进展, 并从微针疫苗的安全性、稳定性、可接受性等方面总结了微针疫苗的挑战与前景。

关键词: 微针; 经皮免疫; 疫苗; 仿生; 临床研究

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Research progress of microneedle delivery system in vaccine

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Abstract: Vaccines are often administered by intramuscular or subcutaneous injection. Although these methods can effectively deliver vaccine antigens to the body and trigger the immune response. However, there are also some limitations, such as injection pain, complex operation, strict transportation conditions, poor immunogenicity and stability of the vaccine. With the development of technology, skin administration has become another new way to solve the above-mentioned problems of vaccine. Among the many ways of skin administration, microneedles show unique advantages and potential. This paper briefly describes the mechanism of microneedle transdermal immunity and its advantages over traditional injection. This paper briefly describes the mechanism and advantages of transdermal immunity of microneedles, enumerates the classification of microneedles, focuses on the design concept, structural advantages and preparation technology of bionic microneedles, and analyzes its application potential in vaccines. At the same time, this paper briefly describes the application of microneedle in vaccine, including bacterial infection, viral infection, cancer treatment and current clinical application progress. The challenges and prospects of microneedle vaccine are summarized from the aspects of safety, stability and acceptability of microneedle vaccine.

Key words: microneedle; percutaneous immunity; vaccine; bionics; clinical research

大多数疫苗需要使用注射针头和注射器进行肌肉

或静脉注射。这种方法能够有效地将疫苗抗原递送到机体内, 触发免疫反应。但这种方法也存在一些局限性, 包括: 由针刺引起的疼痛和恐惧, 需专业医护人员操作的限制性, 冷链运输引起的高成本以及使用针头后的安全处置等问题。随着技术的发展, 皮肤给药或

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将成为疫苗接种的创新途径,其不仅具有便捷、无痛的潜力,甚至可以减少疫苗的剂量。在皮肤给药的诸多方法中,微针作为一种新兴的递送方法备受关注,它使通过皮肤接种流感疫苗成为可能,并且展示出了独特的递送优势,如无痛感、给药便捷、不产生尖锐医疗废弃物以及宽松的运输条件等。本文将通过皮肤免疫的机制,阐述微针递送疫苗的免疫优势的支撑理论,总结微针疫苗相比于传统注射疫苗的优势,简述微针的分类,介绍微针疫苗的应用及研究进展。

1 微针经皮免疫概述

1.1 经皮免疫原理

皮肤是人体中面积最大的器官,相比于血液、肌肉和脂肪,皮肤具有独特的致密性。同时,皮肤中还含有多种免疫细胞,这些特点为疫苗和免疫疗法的递送提供了便利。因此,皮肤愈加成为免疫递送的新兴目标。另外,皮肤能够作为新兴的免疫递送目标还依靠其较为完备的免疫机能,如图1所示:皮肤中含有多种抗原递呈细胞 (antigen presenting cell, APC),这些细胞能够使其更快、更有效地激活免疫反应。当病原体进入皮肤后,表皮层 (0.05~0.2 mm) 的树突状细胞 (dendritic cell, DC) 或朗格汉斯细胞 (Langerhans cell, LC) 会迅速将其吞入胞内,经过加工后,再递送给初始T细胞,激活初始T细胞成为效应T细胞。随后,效应T细胞通过刺激B细胞在淋巴结中形成生发中心,进而产生浆细胞和记忆B细胞。最后,浆细胞分泌的抗体同其他免疫细胞一起,随血液循环进入机体的各个组织,清除或中和入侵的病原体。

在皮肤中,由于表皮和真皮层的血管分布较小,细胞密集程度较低,疫苗药物在此可以停留更长的时间,因此皮肤递送有利于DC和LC对于免疫信号的检测和提高免疫反应的灵敏度^[1]。许多临床和临床前研究也体现了这一特征,例如,牛痘病毒通过皮肤伤口(或皮肤划痕)传播时,效果显著增强^[2]。美国食品药品监督管理局 (Food and Drug Administration, FDA) 在2022年8月将猴痘疫苗的给药途径从皮下改为皮内^[3]。有数据显示,这种改变使得给药剂量降低为原来的1/5,且同样可以获得所需的免疫反应^[4]。上述优势使得皮肤

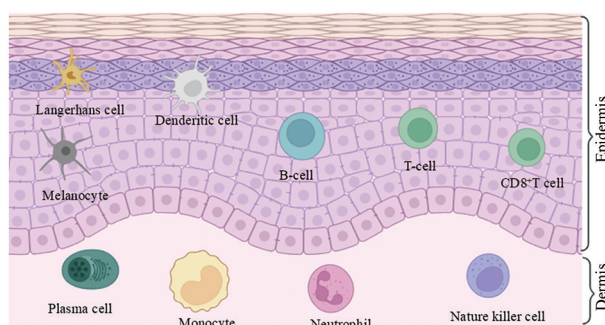


Figure 1 Schematic diagram of percutaneous immunization (drawn using BioRender.com)

递送相关的制剂研究也大放异彩,而微针就是其中颇具前景的给药方式。

1.2 微针经皮免疫技术

2002年 Mikszta 等^[5]使用一种新型微增强阵列打破了皮肤屏障,并首次在体内局部递送疫苗。研究发现,基于此种微增强阵列的外用疫苗比针头注射更具诱导性,这种方式有效地使疫苗直接渗透到真皮层,减少了皮肤刺激,消除了疼痛和不适。2010年第一个可溶性微针成功用于小鼠皮肤中的流感疫苗接种,耐受性良好,且产生了强烈的抗体反应^[6]。随后,在2015年,一种基于可溶性微针的疫苗首次在非人灵长类动物中进行了测试^[7]。随着研究的深入,微针疫苗的应用越来越广泛,涵盖流感疫苗、狂犬病疫苗^[8]、人乳头瘤病毒 (human papilloma virus, HPV) 疫苗^[9]等的递送。目前,研究人员正尝试将微针应用于新型冠状病毒感染 (coronavirus disease 2019, COVID-19) 疫苗的递送^[10]。相信在未来,对于微针疫苗的研究将会日渐深入和全面。

微针 (microneedle, MN) 是一种有规律排列的微小针尖的小片。它的针尖虽小,但具有足够的长度(通常在100~1100 μm之间),能够刺入皮肤而不引起痛感(针尖的长度不足以抵达痛觉神经)。在此方面,微针相比于注射给药具有绝对的优势。同时,微针穿透皮肤的给药方式破除了皮肤这一天然屏障,相较于贴剂,其具有显著的药物吸收优势。微针的其他优势详见表1。

Table 1 Comparison between microneedle and traditional injection in the field of vaccine delivery

Project	Microneedle array	Injection
Drug stability	The stability of the drug can also be maintained at room temperature	Certain conditions (such as low temperature) are needed to maintain drug stability
Targeting	Can reduce the miss effect	It is easy to cause systemic reaction
Patient compliance	It can be vaccinated by itself, and there is almost no pain	Need to be vaccinated by professional trainers, and there is obvious pain
Transportation condition	No need for cold storage	Cold chain transportation is usually required
Medical sharp instrument	No	Yes
Safety problems such as infection caused by accidental stab wounds	Never	Frequently

在免疫学上,微针能够满足疫苗的防治需要。如图2所示,微针递送的疫苗药物通常含有特定蛋白或多糖抗原以及佐剂,当微针穿透皮肤后将抗原和共刺激信号递送给皮肤中的各种APC,如DC、LC和B细胞,向它们表明该抗原的致病性,引起这些细胞向二级淋巴器官的迁移,随着抗原和共刺激信号被递呈给初始T细胞,免疫反应开始驱动。激活T细胞对感染细胞和病原体的直接攻击和B细胞释放高亲和力抗体中和病原体的机制。由于皮肤的致密细胞层中接收到了传递的抗原和共刺激信号,使得APC与抗原和共刺激信号的接触时间得到了有效的延长。这些均有助于确保药物诱导足够的免疫反应,并且减少全身递送相关的脱靶效应,使微针能够以相同的给药量获得更好的免疫反应和疗效。在一项使用固体微针递送DNA疫苗的研究中发现,与传统注射给药相比,使用微针在皮肤中接种DNA疫苗会诱发更高的体液和细胞免疫反应,并提高保护免疫力^[11]。

2 微针的分类

根据微针的结构和材料,可将其分为四种类型,分别为:固体微针^[12]、涂层微针^[13]、空心微针^[14]、可溶解/可降解微针^[15](多孔微针、可分离微针、冷冻微针、核壳微针、水凝胶微针),以及仿生微针如表2^[16-35]。简单来讲,固体微针是一种先穿透皮肤形成微通道,再涂敷药物于皮肤表面,使药物或疫苗能够到达真皮层的递送方式。S.B.V.J.等^[36]研究发现,固体微针优异的机械性能,为药物的递送提供了值得研究的平台。为了克服固体微针两步给药的不便,研发了涂层微针和空心微针。涂层微针是一种在微针的表层涂敷药液,药物可在穿透皮肤后,迅速于皮肤组织中扩散的微针。Choi等^[37]通过浸渍涂层将第二代天花疫苗负载到针尖,成功在小鼠体内诱导了免疫反应。空心微针是一种针尖内部含空

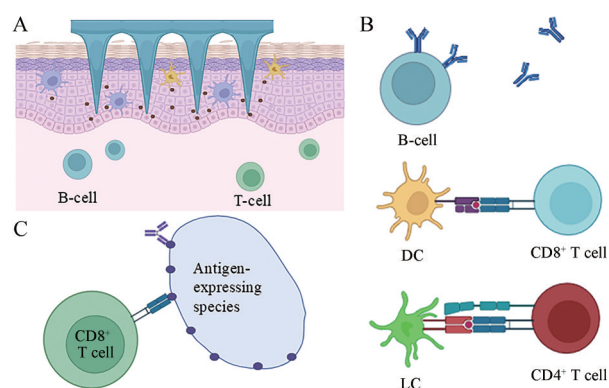


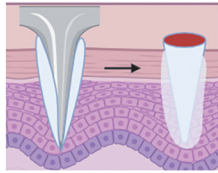
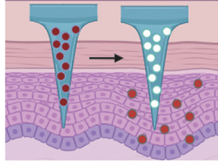
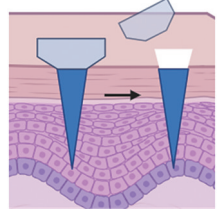
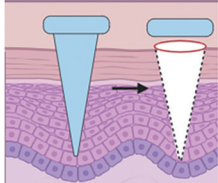
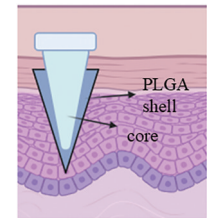
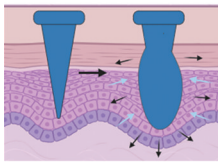
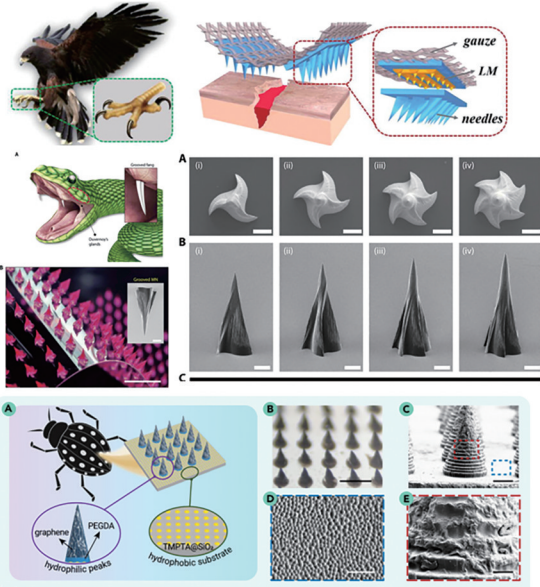
Figure 2 Mechanism of microneedle immunity. A: Microneedle delivers antigens to APC; B: B cells release antibodies, DC cells and LC cells present antigenic information and costimulatory signals to the corresponding initial T cells, activating and triggering the related effector T cells to clear the virus; C: T cells attack pathogens. DC: Dendritic cell; LC: Langerhans cell. (Drawn using BioRender.com)

心空腔以储存药物的微针,其在穿透皮肤后,储存在空心部分的药物释放进入皮肤组织引起药效。Van der Maaden等^[38]研究了空心微针在递送灭活脊髓灰质炎病毒(inactivated poliovirus, IPV)疫苗在大鼠中的免疫效果。结果表明,通过空心微针递送的疫苗触发了与皮下注射针头相当的免疫反应。但这两种方式的微针的载药量受到很大限制。基于此,研究人员又一次升级了微针的设计,提出了可溶性微针的理念。这是一种采用生物可降解聚合物或碳水化合物等材料在组织中的降解或溶胀,释放药物引起药效的微针,包含多孔微针、可分离微针、冷冻微针、核壳微针、水凝胶微针等多种类型。在一项亚单位疫苗递送装置的研究中,报道了可溶性微针在亚单位疫苗的纳米递送平台的技术优势,不但能够成功诱导免疫反应,还具有冷链之外的稳定性^[39]。

Table 2 Microneedle classification table (drawn using BioRender.com). Adapted from Ref. 33 and 35 with permission. Copyright © 2025 Elsevier B.V.

Microneedle type	Illustration	Material	Ref.
Solid		Silicon, stainless steel, titanium and other metals	[16,17]
Hollow		Silicon, stainless steel, polymer	[18,19]

Continued

Microneedle type	Illustration	Material	Ref.
Coated		Silicon, glass, polymer	[20,21]
Soluble/degradable Porous		Polymers such as poly (lactic-co-glycolic acid) (PLGA), Methacrylate Gelatin (GelMA), Cellulose Acetate (CA), etc.	[22-24]
Separable		Polymers, such as hyaluronic acid (HA), chitosan, poly (lactide) (PLA), polymer poly-N-isopropylacrylamide (PNIPAM), etc.	[25-27]
Frozen		Water or water medium	[28]
Core-shell		Polymers, such as formylated gelatin (GelMA), poly (lactic acid-propylene glycol-lactic acid) dimethacrylate (PGLADMA), polyvinyl alcohol (PVA), etc.	[29,30]
Hydrogel		Graft polymers, such as hyaluronic acid grafted with polyhydroxy fatty acid ester (PHAs) nanoparticles (R-PHA NPs)	[31,32]
Biomimetic		2-Hydroxy-2-methylpropanone (HMPP), polyethylene glycol diacrylate (PEGDA), polyethylene glycol diacrylate (PEGDA), silica nanoparticles, graphene aerogel-hydrogel	[33-35]

仿生微针 (biomimetic microneedle, BMN), 是一门为了解决或改善微针在实际应用中遇到的问题, 利用仿生思维设计和制备微针的技术。仿生微针的优势通常得益于其在自然启发下设计的独特结构, 受鹰爪启发设计的仿生微针贴片, 通过黏附并固定伤口以促进伤口愈合^[33]; 受后牙蛇毒牙的启发, 制造的带有开口凹槽的微针, 可在几秒内迅速完成给药, 实现疫苗的快速有效递送^[34]; 受沙漠甲虫背部整体疏水而表面凸起亲水的结构的启发, 制备的离散亲水性微针, 可用于肿瘤的活检^[35]。上述例子均体现了仿生技术在提高微针组织黏附力、调节给药速度等方面提供的创造性的解决思路。

在制备工艺方面, 由于仿生微针大多具有独特的结构, 因此在传统制备工艺中, 溶剂铸造法几乎是其制造的最优途径。这一方法通常包含 3 个步骤: 首先, 运用光刻等打印技术制备阳模; 然后, 利用翻模工艺形成阴模 (通常为聚二甲基硅氧烷材料); 最后, 采用离心或抽真空手段注塑阴模, 复刻出具有独特结构的仿生微针。随着科技的发展, 一些新兴的技术也应用到了微针的制备工艺中, 为仿生微针的制备开创了思路。如磁流变绘图光刻技术^[40]、3D 打印技术 (立体光刻^[41]、数字光投影^[42]、连续液相界面固化技术^[43]、和双光子聚合技术^[44]等), 以及铁磁流体配置成型技术^[45]等。这些技术为仿生微针的结构和相应功能的实现提供了有力的支撑。

基于上述新颖的设计理念和灵活的制备工艺, 仿生微针在针对性目标和个性化方案的疫苗应用中拥有巨大潜能。如其优异的几何形状有助于更好地穿透皮肤, 或更强的黏附组织。同时, 材料与结构相结合的仿生设计, 甚至能实现调节药物释放的目的。由于一些生物相容性较高的材料, 如透明质酸、胶原蛋白、壳聚糖等, 在体内具有无毒且低免疫排斥的特性。因此, 当这些材料用于仿生微针时, 在体内的缓慢降解可以实现长效释放药物的目的, 有助于维持长期的免疫保护, 并提高药物安全性。虽然目前仿生微针应用于疫苗中的实例或研究还相对较少, 但相信在未来的研究中, 仿生设计将会在微针疫苗的设计中得到广泛应用, 为解决微针疫苗的应用需求提供新的思路。

3 微针疫苗的应用

许多类型的病原体通过真皮和黏膜入侵并感染人体, 如割口处的破伤风梭菌引起的破伤风, 或蚊虫叮咬引起的疟疾。而微针恰恰也是以类似的方式递送疫苗药物的。微针凭借足够的机械强度, 刺入皮肤, 帮助药物通过坚韧的角质层, 并最大限度地提高药物与 LC 和 DC 的接触, 提高靶向性, 由此得以用更少的给药量得

到相同的治疗效果。Caudill 等^[46]研究中, 通过递送递减剂量的含 OVA 和佐剂的疫苗比较微针和传统递送方式 (I.D、S.C 和 I.M.) 引起免疫反应的高低时, 发现即使在低于最高剂量 12 倍的情况下, 微针也能在小鼠血清中激发出最高的 OVA 特异性 IgG 滴度。当比较药物在器官中的分布时, 与相同剂量的其他递送途径相比, 微针给药减少了药物在非免疫器官中的积累。另有研究^[47-49]发现, 与非靶向途径相比, 针对免疫细胞的抗原和佐剂的特异性递送方式 (如淋巴结注射或鼻腔递送), 可以改善抗原特异性疾病的预后。而微针, 恰恰可以提供这样一个有利的递送平台。

3.1 病毒感染 在呼吸道传染病中, 流感是一种传播性很强的病毒。尽管人们通过接种疫苗、隔离感染源、阻断传播途径等手段尽力预防流感病毒的感染, 但全球每年仍有数以千万计的人员死于流感。由于流感和许多病毒的高突变频率, 疫苗的致病序列可能会在几年后产生较大的差异, 因此, 一些疫苗需一段时间 (甚至 1 年之内) 后重新设计以匹配流行毒株新的致病序列。此时, 研发无痛、便捷且等效的微针便具有重要意义。在一项关于微针的储存稳定性研究中, 基于海藻糖/支链淀粉的微针即使在 37 °C 高温环境中储存 4 周, 仍能保持良好的机械性能和药物活性^[50]。有数据表明, 微针已经成为流感疫苗 I 期临床试验的主题^[51,52]。一项 I 期临床试验对微针疫苗的安全性和患者接受程度进行了较为全面的评估。结果显示, 微针有可能改进疫苗的热稳定性, 并且在诱导与肌肉注射相当的免疫反应的情况下, 提供比注射给药更安全、更易接受、更便于使用和更低成本的递送方式^[52], 微针疫苗在季节性流感和替代其他疫苗的接种方面有巨大潜力。

在非呼吸道病毒感染的领域, 微针也有丰富的研究进展。一项关于埃博拉病毒 (Ebola virus, EBOV) 的微针疫苗研究中显示, 将 EBV 糖蛋白 (glycoprotein, GP) 抗原与聚磷腈 (polyphosphazenes, PCPP) 相结合制备的可溶性埃博拉病毒糖蛋白微针疫苗, 在小鼠皮内诱导了与肌肉注射相当的针对 EBOV-GP 的强烈、持久的免疫反应。此外, 接种微针的小鼠可以完全免受小鼠适应 EBV 的致命攻击, 并且没有与埃博拉病毒感染相关的组织学损伤^[53]。

3.2 细菌/寄生虫感染 在全球范围内, 由细菌或寄生虫引起的感染, 如疟疾、鼠疫、河盲症、象皮肿等疾病, 每年同样会造成数百万人患病和丧命。由于细菌或寄生虫的致病机制与病毒的相似性, 因此, 临床上同样可以采用将带有佐剂的抗原递送至富含免疫细胞的生态位, 激活效应细胞的识别与清除, 来预防和治疗疾病。

研究发现,使用装载恶性疟原虫蛋白P47的可溶解微针接种小鼠时,发现小鼠体内的共刺激标志物的高表达与注射疫苗引起的免疫效果相当,展示了微针递送在简化给药方面的巨大潜力^[54]。值得注意的是,微针还能激活针对细菌和寄生虫感染的体液免疫。在一项关于利什曼病微针疫苗的研究中,报告了装载抗原和佐剂的可溶解微针诱导了小鼠对多诺瓦尼乳杆菌感染产生了高水平的保护性免疫,报告显示在微针给药后,小鼠体内IgG的滴度显著升高,提示B细胞大量参与到了免疫反应中,即微针可引起体液免疫的发生^[55]。

在公共卫生方面,用微针接种疫苗可能具有更多现实意义。如前所述,由于细菌的细胞壁大多为多糖成分,而B细胞是与多糖抗原免疫有关的关键免疫细胞,因此微针递送多糖抗原可能具有相比于皮下注射具有更突出的体液免疫优势^[56]。另外,婴儿和老年人以及免疫抑制治疗患者的免疫系统的功能相对较低,对多糖抗原的反应不佳^[57],并且由于行动不便等问题,对自我接种的需求更高,而微针这种便捷、简化的给药方式将显著提高此类患者的顺应性。

3.3 癌症 随着分子生物学和免疫学的进步,疫苗在癌症的预防和治疗中大放异彩,为传统的癌症治疗增添了新的选择。例如,人类乳头瘤病毒(human papilloma virus, HPV)疫苗、乙型肝炎病毒(hepatitis B virus, HBV)疫苗为相关的宫颈癌、肝癌的预防和控制作出了突出贡献。作为新兴的递送系统,微针在癌症疫苗中展现出的潜能也备受关注。

从预防性疫苗角度,一方面,微针递送癌症疫苗具有基于皮内给药的显著优势,如相比于肌肉注射更强烈的免疫反应。一项活肿瘤细胞疫苗研究中,用冷冻微针制备的疫苗与皮下注射相比,在接种部位募集了更多的树突状细胞,并增加CD⁺T细胞在肿瘤中的浸润^[57]。另一方面,在降低疫苗成本和改善接种顺应性上,微针有助于提高疫苗接种的普及性。一项溶解性HPV疫苗微针的研究发现,Q β -HPV聚合物微针不仅具有更高的效价强度,还展现出了室温下长达5个月的稳定储存和便捷的接种方式,为发展中国家广泛地接种疫苗提供了可能^[58]。

在治疗性疫苗角度,微针能将核酸疫苗药物直接递送到皮肤中的APC细胞,增强免疫反应,实现肿瘤深处的传递信号,并且有助于利用微针的几何形状进行电穿孔,种种优势均利于疫苗靶向性和有效性的提高。在一项开发微阵列电穿孔设备用于癌症免疫治疗的研究中,电穿孔附近的细胞表现了50%以上的体内高转染性,诱导了强大的细胞和体液免疫反应,有效抑制了啮齿动物的肿瘤生长^[59]。在一项递送核酸疫苗治

疗癌症的研究中,设计了包含微针电极的水凝胶有机电子设备(μ EPO),实现了表皮和真皮层50%以上细胞的体内转染,有效抑制了啮齿动物的肿瘤生长^[59]。

3.4 微针临床试验的进展 自2015年在I期临床试验中成功使用微注射递送流感疫苗以来^[55],许多临床和临床前研究都利用相同的原理,用微针靶向皮肤驻留免疫细胞来对抗病毒和过敏性疾病。这些研究旨在全面探索药物的疗效机制以及人体产生免疫反应的机制^[51,60-62],收集微针在临床应用中的安全性^[63]、有效性^[64]、顺应性^[60]等方面的真实数据。表3^[52,62,63,65,66]总结了近几年与微针相关的临床试验和研究进展。

4 微针疫苗的展望与挑战

微针在免疫递送以及临床应用中具有诸多优势,这些独特的优势让微针的应用潜能备受关注。然而,从免疫学和实际应用考虑,微针并不是所有疫苗的最佳给药途径。研究发现,与皮内注射相比,微针疫苗接种可改善对破伤风类毒素和亚单位流感疫苗的免疫反应,但不能改善减毒活病毒麻疹疫苗^[67]。这可能与这些疫苗输送到真皮层和免疫系统之间的机制有关。

随着微针疫苗研究的不断深入和推进,其所面临的问题和挑战也亟待解决。比如,受体积的限制,微针往往难以承担毫克级及以上的给药量,而如果增加微针的面积,就需要考虑保证微针完整性的方法,因为较大的表面积会增加微针受损出现开裂和缺失的风险。同时,受材料机械性能的限制,单纯增加微针的面积可能造成其无法完全紧密而完美地贴合皮肤,导致部分药物的浪费和给药剂量的不准确。另外,微针的制备工艺使得其在大规模生产上以及保证无菌级上存在较大困难,并且,与传统制剂相比,微针的制备成本相对不具备竞争力。虽然微针在运输上降低了一部分成本,但其生产制造所引进的设备和技术成本,于企业而言亦是大量的投入。微针疫苗涉及的安全性、稳定性以及可接受性方面的挑战也有待解决。

4.1 疫苗安全性 微针疫苗的无菌性难以保证和实现。疫苗作为一种生物制品,保证在制备、包装和运输过程中的无菌性,是保证其安全性的必要手段。而在微针疫苗的生产中,由于向设备中添加疫苗和其他佐剂的复杂性和开放性,如何确保无菌性或将成为微针生产中一个大且棘手的问题。更不利的是,相较于传统注射剂,微针在药品生产质量管理规范(Good Manufacturing Practice for Drugs, GMP)中的相关标准以及关于患者自行给药的标准和法规均尚未建立,导致微针疫苗在安全有效性、质量可控性、产业规范性等方面未能形成明确的标准,影响了微针疫苗的安全可靠。

给药剂量准确性有待提高。相比于传统注射剂或

Table 3 Recent microneedle clinical trials

Clinical trial	Microneedle design	Result	Year	Ref.
A phase II, double-blind, double-simulated, randomized, active controlled, age-decreasing microneedle clinical trial of rubella vaccine mRNA COVID-19 vaccine microneedle	Soluble microneedle	Microneedle delivery vaccine is safe and effective, but it is necessary to further understand the patient's acceptability of microneedle and the effect of wearing time on drug efficacy	2024	[63]
	Alumina nano-porous ceramic microneedle	Microneedle delivery of 20 µg mRNA-1273 vaccine failed to induce antibody and T cell response. However, because of its application potential, it is valuable to further explore the adjustment scheme	2023	[65]
A phase I randomized, single-center clinical trial on the efficacy and safety of inactivated influenza virus vaccines	Soluble microneedle	The humoral and cellular immune response induced by microneedle vaccination is similar to or even greater than that of intramuscular injection. At the same time, the microneedle showed thermal stability for 4 months at 37 °C	2021	[62]
Acceptability of inactivated influenza vaccine by microneedle vaccination in population	Inactivated influenza vaccine coated microneedle	98.6% of the participants in the microneedle group reported their overall positive experience with microneedles, and vaccination through microneedles may help to increase vaccination coverage	2020	[52]
Clinical trial of anti-milk allergy skin immunotherapy gel patch	Solid microneedle with diameter of 1 cm, needle length of 300 µm and needle number of 481	The delivery of milk protein concentrate after piercing the skin with a microneedle can target immune cells, increasing the symptom induction threshold of half the subjects so that they can eat milk and switch to oral immunotherapy	2020	[66]

贴剂,微针在给药剂量的准确性上,还具有一定差距,这可能引起微针疫苗的有效性和安全性问题。一方面,微针可能无法完全紧密地贴合柔软立体的皮肤,造成部分微针未能进入皮肤并递送药物;另一方面,微针本身在制造、运输或是给药过程中,可能造成微针的开裂或缺损,最终给药剂量低于预期。

皮肤刺激可能引起未知的过敏反应。研究发现,在某些情况,微针在给药部位会引起皮肤刺激^[68]。这可能是由于皮肤中的LC细胞被破坏引发的感染所致。I期临床试验发现,与肌肉注射治疗的患者相比,接受微针治疗的患者中与过敏反应有关的循环细胞因子(IL-5和IL-13)水平较高,同样会导致给药部位出现短期刺激。有研究显示,较长的针尖虽然可以递送药物到富含DC细胞的位置,但会破坏表皮,引起红斑。而较短的针尖可直接递送药物到含LC的表皮,减少红斑情况的出现^[69]。

4.2 疫苗稳定性 确保抗原的完整性和稳定性对微针引发保护性免疫反应至关重要,关系疫苗的安全性和有效性。尤其在特殊地区(如战争地区或发展中国家等运输条件受限的地区),解除疫苗冷链运输的限制具有深刻的现实意义。在一项流感疫苗可溶性微针的稳定性研究中,将微针分别于4种不同的条件下,即25 °C下存24个月、60 °C下存4个月、进行5次冻融循环储存和电子束辐照储存,发现疫苗活性均无显著变化^[70]。

在微针疫苗中,稳定性还包含微针保持足够的机械性能,即微针在储存和运输过程中,仍然拥有穿透皮

肤递送药物的能力。例如,有研究将卡介苗的冻干粉未制备成可溶解微针,保证了微针在室温下储存至少两个月而不影响卡介苗的存活率和微针的机械强度^[71]。目前,对于微针储存后机械强度的评估的重视度有待提高。

4.3 疫苗可接受性 在多个微针疫苗的临床试验中,对比肌肉注射,受试者表现出对微针接种更喜爱的意愿^[72]。这得益于微针在疫苗递送中的诸多优势,尤其在许多临床试验中也证实了这些优势,如更小的疼痛、避免针头引起的恐惧、更低的过敏反应,甚至用以改善免疫疗法对患者生活的影响。在一项调查患者对流感疫苗微针的使用体验中,自行接种疫苗(经过PPT简短教学)组相较于由医务人员接种疫苗组,表现出明显的放松和舒适^[60]。一项将抗逆转录病毒药物用微针递送到阴道黏膜层的研究发现,在南非的用户市场调研中,用户对于长效药物的阴道微针递送持积极态度^[73]。更有数据显示,相比于注射给药,70%的临床I期受试者更倾向于微针给药^[60]。由此可见,微针递送在患者的可接受度方面形势乐观。

虽然微针在保证无菌性、给药剂量的准确性、皮肤刺激引起的过敏反应,以及适用的疫苗种类这几方面,仍然存在挑战。但上述问题在寻求解决办法中并非毫无头绪。在法规和质量标准的建立方面,已经有相关文献进行质量标准的总结,如Li等^[74]对可溶性微针的质量标准进行了总结;给药剂量准确性方面,设计更贴合实际应用的结构和寻找更具韧性或强度的材料可能为微针的应用注入新动力;过敏反应有希望通过调节

针尖长度和材料而减轻或消除。结合微针在免疫递送和临床顺应性上的优势,如更高的效价强度、非冷藏条件下储存与运输的稳定性、可自行给药的便捷接种方式,以及微针的给药特性(针长只到达浅表层)有效避免了重复注射引起的瘢痕等。可以预见微针是具有广阔应用前景的递送系统。

在未来的研究中,需要更多的证据证明微针的有效性、安全性以及质量可控性。同时,更深入地了解微针为何在递送某些佐剂和抗原方面能够引发更强的免疫反应,以及补充或阐明微针具有前述优势的证据和机制,将是微针蓬勃发展的基石。

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