用于肺部疾病治疗的细胞膜涂层仿生纳米粒递送体系研究进展

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摘要: 肺易受外界侵扰, 造成多种急性和慢性肺部疾病。采用功能化纳米粒作为载体可携带药物穿透多重肺生理屏障进入肺病变部位, 但存在靶向性差、治疗效率低等问题。细胞膜涂层仿生纳米粒作为药物载体, 由于保留其源细胞特性, 具有免疫系统逃逸、主动靶向、炎症趋化、穿过生理屏障等特点, 近年来被大量应用于肺部疾病的治疗研究。本综述总结了近年来多种细胞膜仿生纳米粒在肺部疾病治疗中的应用, 并进行了分类论述, 其中细胞膜来源包括红细胞膜、血小板膜、巨噬细胞膜、中性粒细胞膜、肺上皮细胞膜、肺表面活性剂、内皮细胞膜、癌细胞膜、细菌膜和混合膜等。本综述旨在为细胞膜涂层仿生纳米粒治疗肺部疾病提供新思路。

关键词: 细胞膜涂层; 仿生纳米粒; 药物递送系统; 肺部疾病; 生理屏障; 免疫逃逸

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Research progress of cell membrane-coated biomimetic nanoparticle delivery systems for the treatment of lung diseases

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Abstract: Lung is susceptible to external disturbance, resulting in a variety of acute and chronic lung diseases. Functionalized nanoparticles as carriers can carry drugs through multiple biological barriers of lung into lung lesions, but there are some problems such as poor targeting and low therapeutic efficiency. As a drug carrier, membrane-coated biomimetic nanoparticles have the characteristics of immune system escape, active targeting, inflammatory chemotaxis and crossing physiological barriers due to the retention of the characteristics of the source cells. Therefore, it has been widely used in the treatment of lung diseases in recent years. In this review, the application of membrane-coated biomimetic nanoparticles in the treatment of lung diseases in the recent years was summarized and classified. Cell membrane sources include erythrocyte membrane, platelet membrane, macrophage membrane, neutrophil membrane, lung epithelial membrane, lung surfactant, endothelial membrane, cancer cell membrane, bacterial membrane, hybrid membrane and so on. The purpose of this review is to provide a new idea for treating lung diseases with membrane-coated biomimetic nanoparticles.

Key words: cell membrane coated; biomimetic nanoparticle; drug delivery system; pulmonary disease; physiological barrier; immune escape

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各种环境因素如毒素、化学污染物、清洁剂、病毒、细菌、微生物菌群失调和过敏原等, 都会导致肺部疾病的发生和发展[1]。近期, 世界卫生组织 (https://www.who.int/en/) 在多项报告中指出, 每年有数百万人死于肺癌、肺炎、哮喘和慢性阻塞性肺病等肺部疾病。Herbst等[2]在《自然》杂志上发表的文章总结了肺癌的治疗进展, 总体治愈率和生存率仍很低, 尤其是转移性疾病。肺是实体瘤转移的最常见的部位之一[3]。目前, 正在大流行的新型冠状病毒肺炎 (Coronavirus disease 2019, COVID-19) 存在无症状或轻度上呼吸道疾病及严重的病毒性肺炎, 后者可能发生细胞因子风暴, 进而发展为急性呼吸窘迫综合征 (acute respiratory distress syndrome, ARDS) 并导致死亡, 几乎所有重症COVID-19患者均累及双侧肺, 而15%～40%的COVID-19患者会发展为ARDS[4]。对ARDS的药物治疗由病理过程决定, 例如, 抑制炎症可使用皮质类固醇、他汀类、西维来司他等, 减轻肺水肿可使用表面活性剂和β2激动剂等, 此外, 候选药物也在不断涌现, 由于独特的肺部生理屏障导致药物向肺部输送效率较低和存在诸多不良反应, 因此没有一种药物被证明可降低死亡率[5]。抗炎和支气管扩张是哮喘的主要治疗方法, 但长期使用吸入性糖皮质激素类药物可能导致发音障碍和骨质疏松等不良反应, 并且约半数患者的激素疗法不佳甚至无效, 需研究新型疗法[5-7]。

总之, 肺相关疾病的治疗方法受到靶部位药物浓度不足、细胞特异性靶向缺乏及肺生物屏障等限制[8]。全身给药需经过血液循环并穿过肺生理屏障, 吸入式药物则受到气道黏液和肺表面活性剂的阻碍而导致传统药物治疗效率低下[9]。纳米药物可改善小分子药物、蛋白质和核酸的临床疗效, 例如, Abraxane获批用于治疗肺癌, 提高靶部位紫杉醇浓度; 阳离子脂质体GL67A/pGM169可治疗肺囊性纤维化等[10]。然而, 未经功能化修饰纳米粒存在载药量低且突释, 稳定性和靶向性较差等问题[11-13]。通过载体表面偶联的抗体或配体与靶细胞膜表面受体间的相互作用为实现特异高效的药物递送提供了可行策略[14]。精氨酸-甘氨酸-天冬氨酸 (Arg-Gly-Asp, RGD) 肽修饰脂质-聚合物杂化纳米粒比非功能化纳米粒在肺转移灶中的浓度更高, 可治疗乳腺癌的肺转移[15]; E-选择素结合肽修饰牛血清白蛋白纳米粒更易被肺部吸收, 可治疗急性肺损伤[16]。由于某些配体的外生性或其他原因, 出现了免疫反应和细胞毒性等不良反应, 其生物结合的优化、适用性和毒理学方面还有待进一步研究[17]。

随着纳米技术的发展, 活细胞作为载体进行药物递送[18]、天然或工程化细胞外囊泡[19]、细胞膜涂层仿生纳米粒[5]等仿生纳米技术的开发为肺部疾病治疗带来新启发。本综述聚焦于细胞膜涂层仿生纳米粒, 将天然细胞膜材料与纳米载体相结合, 制备出各种仿生纳米药物递送系统, 同时具有内核的物理化学性质和源细胞固有的功能和特性[20,21]。不同来源的细胞膜涂层材料由于具有不同的膜蛋白、聚糖和脂质等成分而拥有不同功能。例如, 红细胞膜涂层纳米粒继承红细胞的长效血液循环能力, 比聚乙二醇 (polyethylene glycol, PEG) 化纳米粒表现出更优越的循环半衰期[22]。并且对于PEG引起的免疫原性和过敏反应, 细胞膜涂层仿生材料成为良好的屏蔽剂[21,23]。白细胞膜涂层仿生纳米粒则被赋予免疫逃逸和炎症趋化功能[24]。对于一些纳米粒如磁性氧化铁纳米粒, 存在聚集、代谢周期长和具有潜在毒性等缺点, 经细胞膜包裹后具有更高的稳定性和体内外生物相容性[25-28]。同时, 癌细胞膜涂层仿生纳米粒则具有免疫逃逸和同源靶向功能[29]; 细菌膜涂层仿生纳米粒可以和同源病菌竞争性与宿主的结合[30]等。本综述总结和归纳了近6年来不同来源的细胞膜, 主要为红细胞膜、白细胞膜、癌细胞膜等包被不同类型的纳米粒, 用于多种肺部疾病的治疗研究 (图1), 为肺部疾病治疗提供潜在思路和方法。

1 红细胞膜

红细胞是人体内最丰富的血细胞, 血液循环时间长达120天, 成熟的红细胞缺乏细胞核和各种细胞器, 有利于红细胞膜的提取和纯化[31]。将人类红细胞 (human red blood cells, hRBCs) 膜涂覆在聚合物纳米粒上得到仿生毒素纳米海绵 (RBC-NS) 充当细菌毒素诱饵, 吸收和中和溶血毒素, 可用于治疗细菌感染[32]。细菌感染易引发急性肺损伤 (acute lung injury, ALI), 严重者可能发展为ARDS, 威胁生命, 因此通过中和全身和肺中细菌毒素有望成为治疗ALI的有效策略。RBC-NS静脉注射对耐甲氧西林金葡菌 (methicillin-resistant *Staphylococcus aureus*, MRSA) 的全分泌毒素蛋白有强中和能力, 显著降低全分泌蛋白导致的致死率, 改善肺损伤症状[33]。红细胞膜涂层的聚乳酸-羟基乙酸共聚物 [poly(lactic-*co*-glycolic acid), PLGA] 纳米粒装载Bcl-2 (B-cell lymphoma/leukemia-2) 抑制剂, 静脉注射后可用于治疗皮下移植肺癌, 该仿生载体稳定性好, 有药物缓释作用, 显著延长了药物的血液循环时间, 提高药物的肿瘤组织靶向能力, 有效抑制癌细胞的增殖[34]。

红细胞膜因其具有免疫逃避功能而被选择作为药物递送载体的膜涂层材料, 但红细胞缺乏主动靶向性,

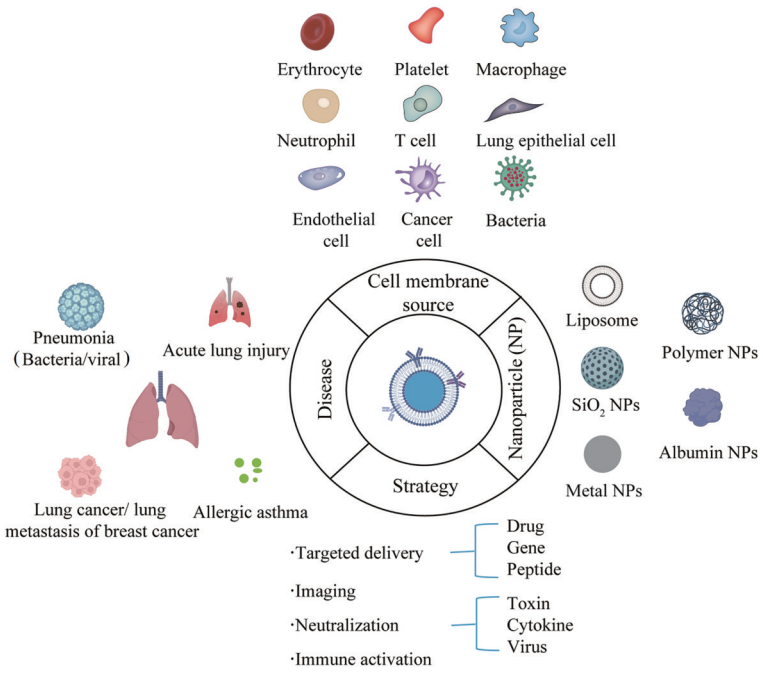

Figure 1　Application of cell membrane-coated biomimetic nanoparticles in pulmonary diseases

因此需对红细胞膜涂层的纳米载体进行功能化修饰, 使其能精准靶向和渗透到靶细胞内[21]。在白蛋白纳米粒表面的红细胞膜上修饰RGD肽序列, 经静脉注射到皮下移植肺癌模型小鼠体内, 其完整红细胞膜结构可使纳米粒在逃脱巨噬细胞吞噬的同时, 通过RGD肽靶向肿瘤细胞。此外, ^{99}TC标记的纳米粒选择性地在体内肿瘤组织中积累, 实现实时肿瘤成像功能[35]。集靶向−光热−化疗为一体的红细胞膜涂层仿生联合系统(R-RBC@BPtI)具有红细胞膜的隐身功能和靶向肽介导的肿瘤靶向功能, 白蛋白纳米粒负载1,2-二氨基环己烷−铂(II), 其可在近红外激光刺激下裂解, 触发药物在肿瘤深层的释放和积累, 该系统静脉注射后显著抑制乳腺癌的肺转移[36]。与外部触发释放相比, 红细胞膜仿生纳米粒也被优化以释放有效载荷, 响应肿瘤微环境变化, 如增加的局部酸度[37]。为了开发非小细胞肺癌治疗新策略, 在红细胞膜包裹的过程中添加pH敏感技术, 该纳米粒静脉注射后可在酸性肿瘤环境中及时触发药物释放, 用于治疗皮下移植非小细胞肺癌[38]。

笔者发现, 对于肺癌治疗策略的研究基本是通过皮下移植肿瘤模型来实现的。皮下移植瘤虽不能很好地体现临床转移特征和反映药物敏感性, 但由于原位肺癌模型的建立方法缺乏简便性和可重复性, 原位移植瘤的实时监测对实验条件、实验仪器有较高的依赖性, 成瘤不稳定等局限, 皮下移植瘤模型仍是最常见的[39,40]。以提高对原发性肿瘤和转移病灶的靶向能力, 增加药物的有效积累浓度为目标, 新型纳米递送系统的研究对于推动肺癌或肺转移癌治疗发展具有重要意义。

2　血小板膜

与红细胞膜功能相似, 血小板膜仿生纳米粒也能逃避免疫系统、延长血液循环及病原体相互作用, 此外血小板还具有增强的与白细胞和内皮细胞黏附的能力[41,42]。瘤内注射血小板膜涂层纳米粒将R848 [Toll样受体(Toll like receptor, TLR)激动剂]递送到侵袭性乳腺癌的实体肿瘤中, 借助血小板与白细胞的黏附特性可作用于主要表达TLR7的巨噬细胞、浆细胞样树突状细胞、自然杀伤细胞和B细胞, 最大限度发挥R848的活性, 抑制肿瘤的肺转移[43]。

3　白细胞膜

白细胞作为免疫细胞, 负责保护身体免受感染, 吞噬外来入侵者, 修复组织损伤, 如巨噬细胞、中性粒细胞、T细胞和自然杀伤细胞等白细胞是预防和治疗诸多疾病的重要参与者[44]。巨噬细胞和中性粒细胞参与多种肺部疾病的发展甚至起决定性作用[45,46]。在肺部受到感染或损伤时, 这些细胞能迅速被激活且招募至肺泡和呼吸道中[47]。这些特性使它们尤其是巨噬细胞成为细胞膜仿生纳米粒设计中最受欢迎的细胞膜来源之一。由于T细胞在肿瘤中的关键作用如免疫监测、靶向肿瘤和分泌细胞毒性分子杀伤肿瘤细胞, T细胞膜涂层仿生纳米粒也被用于治疗癌症[48]。

3.1　巨噬细胞膜　纳米治疗药物的增强渗透滞留效

应 (enhanced permeability and retention effect, EPR) 受限于小而无血管化的转移灶, 而巨噬细胞可通过α4整合素与癌细胞膜表面表达的血管细胞黏附分子1 (vascular cell adhesion molecule 1, VCAM-1) 相互作用, 从而可主动靶向转移性癌细胞。因此, 在通过尾静脉注射乳腺癌细胞建立的乳腺癌肺转移模型中, 静脉注射巨噬细胞膜仿生pH敏感型负载曲妥珠单抗DOPE-DSPE-PEG脂质体, 利用巨噬细胞膜主动靶向肺肿瘤部位进行药物递送来杀伤癌细胞[49]。巨噬细胞膜涂层、负载槲皮素的空心硒化铋纳米粒通过静脉注射用于皮下移植乳腺癌肺转移的联合治疗, 凭借癌细胞分泌的CCL2 (C-C chemokine ligand 2) 介导的巨噬细胞趋化特性和巨噬细胞的主动靶向能力, 增强纳米粒向病灶内蓄积, 随后铋基纳米粒在近红外激光照射下触发槲皮素释放, 消耗癌细胞的热休克蛋白70 (heat shock protein 70, HSP-70), 使癌细胞对光热敏感, 实现级联协同效应[50]。静脉注射仿生抗炎纳米脂质体, 治疗气管滴注脂多糖 (lipopolysaccharide, LPS) 诱导的ALI, 巨噬细胞膜包裹的脂质体模拟巨噬细胞在炎症组织中募集, 通过CD47阻断巨噬细胞的非特异性吞噬作用, 提高靶部位药物积累[51]。

巨噬细胞表型的变化对疾病的发生发展至关重要。在急性炎症性疾病中, M1巨噬细胞参与放大的促炎反应[52]。在慢性肺部疾病如肺纤维化、哮喘和肺癌中, 过多的M2巨噬细胞会促进纤维微环境的形成及肺肿瘤细胞的发生和转移[53,54]。因此, 从细胞表型出发的靶向疗法更有针对性。分离M2巨噬细胞衍生的外泌体, 包裹PLGA纳米粒, 静脉注射后可靶向肺炎症部位的M2巨噬细胞, 通过基因递送抑制M2巨噬细胞的转分化, 治疗小鼠过敏性哮喘[55]。

在最新的相关研究中, Tan等[56]开发了用于治疗COVID-19的仿生纳米药物递送系统, 巨噬细胞膜赋予纳米粒中和多种细胞因子的作用, 静脉注射后有效抑制巨噬细胞和中性粒细胞的激活, 联合负载的抗病毒药物洛匹那韦, 显著抑制鼻内滴注冠状病毒感染小鼠的肺部炎症并减少病毒载量。随后, 该团队[57]又报道雾化吸入式多功能肺泡巨噬细胞涂层纳米粒, 用来伪装会遭受病毒攻击的肺泡巨噬细胞, 从而阻断冠状病毒进入真正的肺泡巨噬细胞, 实现抗炎和抗病毒作用, 在纳米粒中还掺入了高效光热材料, 可在外界近红外辐射协助下, 利用光热破坏病毒。

3.2 中性粒细胞膜 中性粒细胞在免疫监测中发挥重要作用, 对炎症信号作出迅速反应并快速迁移至炎症部位, 尽管中性粒细胞寿命短暂, 但在炎症刺激下可被激活而延长寿命[58]。中性粒细胞膜涂层的负载司帕沙星的纳米粒与普通纳米粒相比, 具有更精确的炎症部位靶向能力和更高的生物相容性, 用来促进气管滴注MRSA感染的肺组织快速修复[59]。

3.3 T淋巴细胞膜 T淋巴细胞是非吞噬性白细胞, 在免疫反应中起核心作用, T细胞可通过其高度特异性的T细胞抗原受体攻击和破坏肿瘤细胞[60]。但T细胞长时间暴露于其同源抗原会导致抑制性受体 [如程序性细胞死亡蛋白1 (programmed cell death protein 1, PD-1)] 的升高和持续表达, 出现T细胞功能障碍[61]。过继转移T细胞疗法往往被耗竭, 并存在体外T细胞增殖过程昂贵、基因编辑复杂等挑战, 因此T细胞膜涂层纳米粒被开发用于癌症免疫治疗[48]。去除EL4细胞系细胞膜的致癌基因, 构建T细胞膜仿生纳米粒, 静脉注射后, 其不受体内免疫的抑制, 通过阻断免疫检查点相互作用 [如程序性细胞死亡蛋白1配体1 (programmed cell death 1 ligand 1, PD-L1)] 和通过细胞膜上的PD-1或转化生长因子β1受体 (transforming growth factor β1 receptor, TGF-β1R) 蛋白清除免疫抑制分子 (如TGF-β1) 来帮助恢复T细胞的癌细胞杀伤功能, 在静脉注射癌细胞建立的肺转移模型中具有肿瘤抗原非特异性治疗作用[48]。

4 肺细胞膜

除了来自血液循环中的细胞, 肺上皮细胞膜和肺表面活性剂也相继被用来帮助纳米粒顺利到达肺部并跨越肺生理屏障。

4.1 肺上皮细胞膜 肺部给药通常能减少药物总剂量和全身不良反应, 但依然面临肺生理屏障的阻碍。吸入式纳米药物需穿越肺上皮细胞进入血液, 在体外, 肺上皮细胞膜仿生纳米粒可部分转移到上皮细胞层上, 从而可自由漫过受损的上皮细胞层[62]。对包括肺上皮细胞膜在内的6种不同功能化涂层纳米粒在H441细胞中的内化和转运进行比较, 结果揭示肺上皮细胞膜涂层最有利于纳米粒转运并穿过肺上皮屏障[63]。

4.2 类肺细胞膜 为了将肺作为靶器官进行药物的靶向递送, 在优化针对肺部给药途径策略的同时, 有必要考虑肺表面活性剂的作用。肺表面活性剂是哺乳动物肺部呼吸表面的一种薄脂质蛋白膜, 药物或纳米粒被吸入后, 首先接触表面活性剂层, 发生相互作用或阻碍而严重影响其寿命和效力[64]。肺表面活性剂涂层非天然生物膜, 而是由哺乳动物分泌的各种脂质和脂蛋白组成[65]。

2020年, Wang等[66]在《科学》杂志上发表了与肺表面活性剂仿生纳米粒相关的报道, 构建了包封2,3-环一磷酸鸟苷−一磷酸腺苷 (2,3-cyclic guanosine mono-

phosphate adenosine monophosphate, cGAMP) 的肺表面活性剂仿生脂质体, 鼻内给药, 由于其相似性, 可与肺特异性表面活性蛋白 (surfactant protein, SP)-A 和 SP-B 一起进入肺泡巨噬细胞, cGAMP 随后被释放到细胞质中, 并通过缝隙连接的方式进入肺泡上皮细胞, 在不破坏肺表面活性剂和肺泡上皮屏障的情况下, 激活肺泡巨噬细胞和肺泡上皮细胞中的干扰素基因蛋白的刺激因子 (stimulator of interferon genes protein, STING) 通路, 导致I型免疫介质的大量产生, 这些介质促进 $CD11b^+$树突状细胞的招募和分化, 进而引导 $CD8^+$ T细胞和体液免疫反应, 对鼻内接种 H1N1、H3N2、H5N1 或 H7N9 等多种流感病毒产生至少 6 个月的强交叉保护。

5 内皮细胞膜

内皮细胞在血管内表面形成一层薄的细胞单层, 并在血液和组织之间形成第一层界面, 来调节血管通透性、物质交换、血管张力、信号传导和血管生成, 内皮细胞损伤后能吸引多种免疫细胞[67,68]。利用炎症反应中激活的内皮细胞和固有免疫细胞之间的亲和力和黏附性, 将含有黏附分子的内皮细胞膜涂层 PLGA 纳米粒静脉注射到鼻内滴注 LPS 诱导的肺炎模型小鼠体内, 其在体循环中优先与中性粒细胞和单核细胞相互作用, 随后通过中性粒细胞和单核细胞靶向输送到肺炎症部位[69]。

6 癌细胞膜

细胞膜的另一个主要来源是肿瘤细胞, 肿瘤细胞具备许多特性如同源靶向能力和异常增殖特性, 使其易于体外培养和获得膜材料[37]。EPR 效应高度依赖于血管化, 但纳米粒在转移灶无血管化细胞簇中的分布受到限制, 静脉注射乳腺癌细胞膜仿生聚合物纳米粒可主动靶向同型皮下移植乳腺癌肺转移癌的治疗[70]。利用癌细胞膜涂层二氧化硅纳米粒递送 miR495 和多柔比星, 静脉注射后, 利用癌细胞膜涂层的肿瘤归巢特性绕过细胞外屏障, 用于治疗皮下移植肺癌, 解决肺癌治疗过程中非靶向分布和多药耐药的困难[17]。近期, 转移性乳腺癌外泌体包裹的聚合物纳米粒被证明具有天然亲肺性, 静脉注射后, 其携带地塞米松可有效治疗气管滴注 LPS 诱导的 ALI, 减轻肺部炎症反应, 该项研究将癌细胞源生物膜材料扩展到非肿瘤的肺部炎症疾病中[71]。

细胞膜涂层方式大多是由右向外, 利用来自细胞质蛋白 P4.2 的肽配体, 固定在脂质体表面, 可特异性识别红细胞关键跨膜受体 3 的细胞质结构域, 确保形成由右向外的癌细胞膜涂层 (图 2A)[72]。当药物靶点处于跨膜受体的胞内区域时, 这种方式会成为药物发现的阻力。将生物素化的人肺腺癌上皮细胞膜与链霉亲和素修饰的 Fe_3O_4 磁性纳米粒进行特异性连接, 形成了由内向外定向的细胞膜包裹的磁性纳米粒 (图 2B), 用于体内酪氨酸激酶抑制剂的筛选[73]。

7 细菌膜

细菌膜含有大量具有内在佐剂特性的免疫原性抗原, 也表达各种病原体相关的分子模式, 在刺激先天免疫和促进适应性免疫应答中发挥关键作用, 是一种非常有吸引力的疫苗接种材料。同时, 合成的纳米粒核提供广泛可调节的物理化学性质, 以有效地将抗原呈递给免疫细胞。因此, 细菌膜涂层仿生纳米粒有望调节机体免疫反应[74]。

细菌外膜囊泡 (outer membrane vesicles, OMV) 存在病原体相关分子模式的致病性、保护性抗原表达水平低、分子免疫抑制或干扰保护性免疫反应等问题, 限制了 OMV 的直接使用[75]。将革兰阴性菌大肠杆菌的 OMV 包裹在粒径为 30 nm 的金纳米粒上, 通过皮下注射后可诱导小鼠淋巴结中树突状细胞的快速激活和成熟, 产生强烈的偏向 Th1 和 Th17 细胞免疫反应[76]。革兰阳性菌金葡菌胞外囊泡 (extracellular vesicles, EV) 包裹的 PLGA 纳米粒 (NP@EV) 在体外提高了被金葡菌感染的巨噬细胞的内化效率, 高于大肠杆菌感染的巨噬细胞对大肠杆菌 OMV 包裹纳米粒 (NP@OMV) 及 PEG 化脂质纳米粒 (NP@Lipo) 的内化效率, 在金葡菌血症小鼠模型中, NP@EV 对肺器官感染的疗效更显著, 这可能是因为革兰阳性菌分泌的 EV 刺激小鼠通常会引起 EV 组分特异性免疫反应[77]。

8 混合膜

通过融合不同细胞的细胞膜获得的混合膜用于伪装纳米粒, 这可充分发挥不同细胞膜的优势, 整合各种细胞膜的优点, 赋予纳米粒更多功能, 将不同来源的细胞膜融合在一起制备膜涂层仿生纳米粒逐渐成为趋势[78-80]。融合 RAW264.7 巨噬细胞和 4T1 细胞的细胞膜制备的仿生 PLGA 纳米粒结合了巨噬细胞膜和癌细胞膜的优点, 在静脉注射建立的乳腺癌肺转移模型中, 其同时具有炎症部位趋化、同源肿瘤靶向、对癌细胞特异性转移的靶向和多靶点增强的能力[81]。

由于细胞膜纳米囊泡稳定性较差, 因此需涂层在纳米载体表面, 或与脂质体进行混合, 由于人工合成的脂质体具有同细胞膜相同的磷脂双分子结构, 因此可将细胞膜与脂质体进行混合构建稳定且具有细胞膜功能的纳米囊泡[82,83]。融合 A549 细胞膜和修饰基质金属蛋白酶 9 (matrix metalloproteinase 9, MMP9) 敏感肽的人工脂质体膜, 负载硫辛酸修饰的多肽胶束构建功

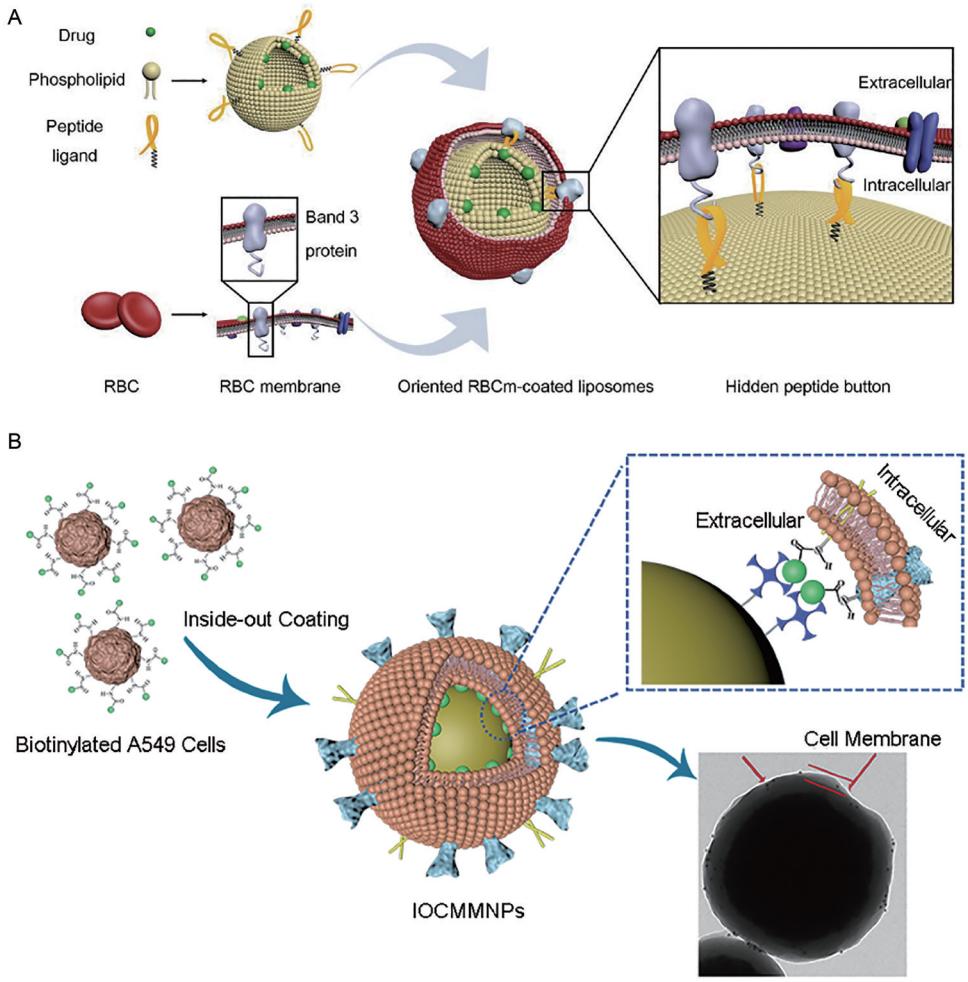

Figure 2 A: Right-side-out-oriented cell membrane coating methods. RBC: Red blood cell. Adapted from Ref. 72 with permission. Copyright © 2019 American Chemical Society. B: Inside-out-oriented cell membrane coating methods. IOCMMNPs: Inside-out-oriented cell membrane-coated magnetic nanoparticles. Adapted from Ref. 73 with permission. Copyright © 2021 American Chemical Society

能化混合纳米囊泡, 利用肿瘤细胞膜的同源靶向能力和脂质体膜较细胞膜更易进行修饰的优点, 肿瘤酸性环境触发脂质体膜电荷转换而破裂, 暴露的MMP9激活囊泡表面的细胞穿透肽, 同时释放内部药物, 导致糖酵解和高效靶基因沉默, 用于皮下移植肺癌的治疗[83]。

9 总结与展望

本综述提到了纳米医药的发展过程, 对传统纳米粒的优缺点进行了总结; 强调了细胞膜涂层仿生纳米粒用于有效治疗肺部疾病的巨大潜力, 且详细汇总了红细胞膜、血小板膜、白细胞膜、肺细胞膜、癌细胞膜、细菌膜和混合膜等细胞膜涂层仿生纳米粒在肺部疾病治疗中的研究进展 (表1[17,33-36,38,43,48-51,55-57,59,62,63,66,69-71,76,77,81,83]), 为未来细胞膜涂层仿生纳米粒的发展提供更多科学依据。

细胞膜涂层仿生纳米粒在肺部疾病中的应用可归纳为以下几点: ① 延长血液循环时间; ② 逃避免疫系统清除; ③ 靶向炎症部位或同源细胞; ④ 肿瘤微环境和炎症环境的免疫调节; ⑤ 克服多重肺屏障; ⑥ 与病原体或毒素相互作用。尽管细胞膜涂层仿生纳米药物具有多种治疗优势和高生物相容性, 但目前在肺部疾病中的应用并不广泛, 细胞膜来源集中在红细胞膜、巨噬细胞膜和癌细胞膜上, 主要用于治疗肺癌、乳腺癌肺转移, 少量研究聚焦于肺炎、急性肺损伤和过敏性哮喘等肺部疾病, 对于其他肺部疾病如常见的肺纤维化开发针对性的细胞膜仿生系统仍存在明显空白。这些细胞膜仿生纳米粒离临床试验还有较远的距离, 肺部疾病的有效治疗策略仍面临巨大挑战。

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Table 1 Research progress of cell membrane-coated biomimetic nanoparticles in pulmonary diseases. PLGA: Poly(lactic-*co*-glycolic acid); PGSC: Poly(*L*-γ-glutamylcarbocistein); PLA: Polylactic acid; PCL: Poly(caprolactone); PCL-PEG: Polycaprolactone-poly(ethylene glycol); SPIO: Superparamagnetic iron oxide; MRSA: Methicillin-resistant *Staphylococcus aureus*; ALI: Acute lung injury

Cell membrane	Nano-carrier	Application	Therapeutic strategy	Ref.
Erythrocyte membrane	PLGA NPs	MRSA infected lung injury	Toxin neutralization	[33]
	PLGA NPs	Lung cancer	Targeted drug delivery	[34]
	Albumin NPs	Lung cancer	Targeted drug delivery, tumor imaging	[35]
	Albumin NPs	Lung metastasis of breast cancer	Targeted drug delivery	[36]
	PGSC NPs	Lung cancer	Targeted drug delivery	[38]
Platelet membrane	PLA NPs	Lung metastasis of breast cancer	Targeted drug delivery	[43]
Macrophage membrane	Lipidosome	Lung metastasis of breast cancer	Targeted drug delivery	[49]
	Bismuth selenide NPs	Lung metastasis of breast cancer	Targeted drug delivery	[50]
	Liposome	ALI	Targeted drug delivery	[51]
	PLGA NPs	Viral pneumonia	Cytokines/virus neutralization, Targeted drug delivery	[56,57]
Macrophage exosomal membrane	PLGA NPs	Allergic asthma	Targeted gene delivery	[55]
Neutrophil membrane	PCL-PEG NPs	MRSA infected pneumonia	Targeted drug delivery	[59]
T cell membrane	PLGA NPs	Lung cancer	Targeted drug delivery	[48]
Lung epithelial cell membrane	TiO_2 NPs	Injury of epithelial cells	Across pulmonary epithelial barrier	[62]
	Acetalated dextran-based NPs	Air-blood barrier	Across pulmonary epithelial barrier	[63]
Pulmonary surfactant	Lipidosome	Adjuvants for influenza vaccines	Across pulmonary epithelial barrier	[66]
Endothelial cell membrane	PLGA NPs	ALI	Targeted drug delivery	[69]
Cancer cell membrane	PCL NPs	Lung metastasis of breast cancer	Targeted drug delivery	[70]
	SiO_2 NPs	Lung cancer	Targeted drug/gene delivery	[17]
Exosomal membrane of cancer cells	PLGA NPs	ALI	Targeted drug delivery	[71]
Bacterial membrane	AuNPs	Vaccine	Immune activation	[76]
	PLGA NPs	*Staphylococcus aureus* bacteremia	Targeted drug delivery	[77]
Hybrid membrane	PLGA NPs	Lung metastasis of breast cancer	Targeted drug delivery	[81]
	Liposome	Lung cancer	Targeted drug delivery	[83]

修改。

利益冲突: 所有作者均声明不存在利益冲突。

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