

• 综述 •

肿瘤治疗的细胞药物递送系统的研究进展

马宝南, 孙丽娜, 韩美华*

中国医学科学院 北京协和医学院 药用植物研究所, 北京 100193

摘要: 目前, 肿瘤的临床治疗主要以手术、化疗和放射疗法为主, 但仍存在复发和不良反应明显等问题。细胞药物递送系统不仅可以避免纳米颗粒药物的毒性, 又可以增加药物的生物利用度, 提高生物相容性、靶向性。总结了活细胞、死细胞、外泌体及其药物递送系统的载药特点和在肿瘤治疗中的应用, 为肿瘤治疗提供了更多的治疗手段。

关键词: 细胞药物递送系统; 活细胞; 死细胞; 外泌体; 药物载体; 肿瘤治疗

中图分类号: R944; R979.1 **文献标志码:** A **文章编号:** 1674-5515(2024)02-0503-11

DOI: 10.7501/j.issn.1674-5515.2024.02.041

Research advances of cell drug delivery system in treatment of tumor

MA Baonan, SUN Lina, HAN Meihua

Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100193, China

Abstract: At present, the treatment of tumors is mainly based on surgery, chemotherapy, and radiotherapy, but there are still problems, such as recurrence and obvious side effects. Cell drug delivery system can not only avoid the toxicity of nanoparticle drugs, but also increase the bioavailability of drugs as well as improve biocompatibility and targeting. This article summarizes the drug loading characteristics of living cells, dead cells, exosomes, and their drug delivery systems, as well as their applications in tumor treatment, providing more therapeutic methods for tumor treatment.

Key words: cell drug delivery system; living cell; dead cell; exosomes; drug carrier; tumor therapy

根据世界卫生组织发布的《2022 年世界卫生组织统计报告》中的数据显示, 目前全球非传染性疾病中, 癌症的死亡率排名前 5 位^[1], 且死亡风险仍有升高的趋势^[2-4]。截止 2020 年底, 全球新发癌症病例约有 1 930 万, 癌症死亡病例近 1 000 万^[5-6]。癌症的传统的治疗方法主要为手术^[7]、化学疗法^[8-9]和放射疗法^[10]。但这些临床治疗手段效果仍然不理想, 存在治疗局限性^[11]、易复发^[12]、不良反应大^[13-16]、治疗窗口窄^[17]等问题。因此, 需要研发具有体内长循环、生物利用度高、可以特异性靶向肿瘤的递送系统, 来达到更好的治疗癌症的目的^[18-20]。纳米颗粒作为药物载体在癌症治疗的靶向递送方面取得了较深远的影响^[21], 其靶向作用可分为主动靶向和被

动靶向, 其中主动靶向可促进肿瘤细胞自身对纳米颗粒的主动摄取^[22], 如抗体-药物偶联物; 被动靶向向下, 由于肿瘤的增强渗透滞留效应 (EPR) 和增强的渗透效应, 使得纳米颗粒被允许优先积累在肿瘤细胞周围^[23-24]。目前临床上以被动靶向的纳米药物居多, 而主动靶向较难实现^[25], 并且这两者也由于肿瘤微环境中的高间质流体压力而限制了他们在肿瘤周围的积累^[26]。纳米颗粒对人体也存在一定的毒性和药效局限性问题^[27-28]。

近年来, 研究者们开始探索仿生药物递送系统, 其中基于细胞或其衍生物的纳米仿生给药系统是目前新型给药系统的研究热点^[29-30]。该纳米仿生给药系统利用细胞天然的同型或异型黏附性质^[31], 通

收稿日期: 2023-11-02

基金项目: 中国医学科学院医学与健康科技创新工程项目 (2021-I2M-1-031, 2021-I2M-1-071)

作者简介: 马宝南, 硕士研究生, 从事肿瘤药物靶向制剂研究。E-mail: 18813033698@163.com

*通信作者: 韩美华 E-mail: hanmeihua727@163.com

过物理或化学手段修饰细胞或其衍生物^[32-33],使药物进入其内部或负载在其表面,得到具有主动靶向性的药物递送载体^[34]。这种载体可具备高载药量、控释特性^[35];具有良好的生物相容性、低免疫原性和天然靶向性^[36-37];可与活细胞的柔性形态结合。在减少药物被免疫系统攻击的同时提高了药物在组织上积累和作用的效率以及靶向肿瘤能力^[38-40]。其中通常被用作药物载体的包括活细胞、死细胞和外泌体。不同的细胞具有不同的活性、靶向性^[41]。本文总结了活细胞、死细胞、外泌体及其药物递送系统的载药特点和在肿瘤治疗中的应用,为肿瘤治疗提供了更多的治疗手段。

1 活细胞及其药物递送系统

目前,人体中的一些功能细胞已经被研究应用于不同的领域,已知在药物递送方面,利用活细胞进行药物输送的载体主要有干细胞、血细胞、免疫细胞等,其原理分别为干细胞在损伤部位的修复能力、血细胞的循环能力以及免疫细胞的能力来延长药物在体内的循环时间,以进入肿瘤组织,进行靶向药物输送^[42](图 1)。血细胞来源于造血干细胞,主要分为红细胞、血小板和白细胞,其中白细胞包含了免疫细胞,分为中性粒细胞、T 淋巴细胞和巨噬细胞。



图 1 肿瘤微环境中的细胞 (由 Figdraw 绘制)

Fig. 1 Cells in tumor microenvironment (by Figdraw)

1.1 干细胞

干细胞是未分化的细胞,根据发育阶段分为胚胎干细胞和成体干细胞。其中成体干细胞中的间充质干细胞是一种多能前体细胞,具有高度的自我更新和多向分化潜能^[43];且有较好的自我增殖能力、肿瘤归巢能力、低免疫原性^[44-45];具有强大的肿瘤穿透能力和在肿瘤部位长期驻留能力^[46],可作为治疗癌症(如肺腺癌^[47])的药物递送载体。Cao 等^[48]

证明了使用间充质干细胞可以实现将生物相容性 SiO₂ 纳米颗粒封装的光敏剂递送至肿瘤后进行光热治疗,实现了有效的肿瘤破坏。Litvinova 等^[49]研究人类间充质干细胞包载微胶囊的实验显示,人类间充质干细胞可以在适当的条件下有效地装载合成的微胶囊,并且可以保留间充质干细胞细胞的完整性、运动性和孔迁移能力(8 μm)。Huang 等^[50]基于间充质干细胞的多功能平台,通过整合间充质干细胞的肿瘤靶向递送和介孔 SiO₂ 纳米粒子靶向原位胶质母细胞瘤证明了间充质干细胞载药纳米粒比单独的纳米粒子具有更高的肿瘤摄取效果。

同时,在研究间充质干细胞装载各种抗癌药物输送至肿瘤部位的实验中发现,间充质干细胞对一些细胞毒性较大的抗癌药物具有较高的耐药性。如 Pessina 等^[51]证明间充质干细胞可以在较高浓度的紫杉醇溶液中存活,并可以选择性将紫杉醇递送至白血病细胞中。Kalimuthu 等^[52]证实了阿霉素没有影响间充质干细胞的肿瘤归巢能力。

1.2 血细胞

基于血细胞(红细胞、血小板和白细胞)的载体在肿瘤靶向药物输送方面具有很多特性,使其成为较理想的药物载体^[3],如降低免疫原性并延长药物在体内的循环时间;一般情况下,血细胞具有生物降解性,不会因载体生物降解而产生有毒产物^[54];由于其膜上具有特定的蛋白质标记,靶向递送血细胞是机体的本能^[55];由于血细胞膜的限制或亲和力,药物将以受控方式释放,使稳态浓度波动显著降低。因此,血细胞是载药细胞的重要来源之一。

1.2.1 红细胞 红细胞作为一类无核细胞呈双凹形,其整个内部体积和扩展表面均可用于运输各种化合物^[56];并且红细胞是血液中最丰富的血细胞类型,具有生物相容性、高载药量、低免疫原性等特点^[57-58]。由于红细胞表面的 CD47 蛋白与 SIRPα 的相互作用可以调节免疫系统中巨噬细胞的吞噬摄取^[59],使其可以在体内长时间循环。红细胞本身对机体无毒,可完全被生物降解^[60];同时其半透膜可以防止药物被快速清除而实现缓释^[61]。以红细胞为载体的递送系统,针对红细胞工程开发了多种策略,主要分为基因工程方法和非基因工程方法^[62]。基因工程方法中,可以在红细胞表面引入编码酶识别位点的非天然基因,从而使治疗性蛋白质或药物能够共价连接到红细胞表面^[63]。非基因工程方法主要包括封装、吸收和生物偶联^[64]。

在肿瘤的治疗方面,由于红细胞没有遗传物质,减少了肿瘤转化的可能性^[65]。红细胞作为药物载体,可通过细胞内酶的代谢将非渗透性药物转化为可扩散活性药物来实现递送一些抗癌分子的效果,既可提高其疗效,又能降低抗癌药物的毒性^[66]。Pierige 等^[67]将 2-Fluoro-ara-AMP 以游离形式封装在红细胞中,在乳腺癌细胞系(MCF-7、MDA-MB-435 细胞)上进行了测试,结果显示该药物可以抑制癌细胞的增殖,并可以实现缓慢而持续地输送到血液循环中。Bachet 等^[68]将 L-ASP 封装到红细胞(ERY-ASP)中以评估其对胰腺癌治疗效果,结果显示患者对其耐受性良好。此外,一些研究发现,可以利用红细胞制备用于治疗癌症的纳米递送载体疫苗^[69-70]。Han 等^[71]发现负载肿瘤抗原的纳米红细胞体可以与抗程序性死亡配体 1(PD-L1)阻断相结合,在体内引发抗原反应,从而抑制 B16F10、4T1 肿瘤模型中的肿瘤生长。

1.2.2 血小板 血小板同红细胞一样,是一种无核细胞^[72],寿命为 9~10 d,是药物递送载体的良好选择^[73]。其主要的生理作用为止血,可应对手术等相关的血管损伤^[74]以及在炎症和抗菌宿主防御方面发挥了重要作用^[75]。血小板内部含有多种因子以促进血管的生成和再生细胞的增殖,如生长因子、趋化因子和细胞因子^[76]。这些生理作用表明血小板作为药物载体具有高安全性和可再生性。另一方面,血小板微粒是循环系统中最丰富的微粒,具有消除合成和聚合物药物输送系统的不良反应^[77]。作为药物载体,血小板可以通过体外工程化进入血液循环,也可以通过在体内结合前药或纳米颗粒搭便车来实现靶向给药^[78]。

对于癌症的治疗,有大量研究表明血小板在提供刺激、激活趋化因子分泌方面发挥了重要作用,从而创造了促进转移性肿瘤种植和最终肿瘤过度生长所需的适宜微环境^[79]。因此,血小板具有维持肿瘤血管完整性和促进肿瘤转移的作用^[80]。Sarkar 等^[81]以血小板为递送载体将阿霉素递送到肺腺癌细胞系(A549)中,结果表明与游离药物相比,载药血小板在体外和体内模型中诱导细胞毒性的效率更高。由于血小板的存在,使得阿霉素等抗癌药物的毒性降低,并增强了对肿瘤细胞生长的抑制作用^[82]。此外,血小板还可以作为骨髓瘤异种移植体内成像的载体,Dai 等^[83]利用卡拉比拉胺来抑制血小板聚集,将血小板与抗肿瘤蛋白结合,以实现骨髓

瘤肿瘤体内外靶向和成像。

1.2.3 白细胞 白细胞作为血细胞之一,在血液中具有自由循环和选择性靶向发炎的血管系统以应对癌症等功能^[84]。白细胞最突出的作用体现在免疫方面。根据其染色时的形态、着色等特征,白细胞作为免疫细胞用于肿瘤靶向递送系统的药物载体有 3 种类型^[85]:多形核白细胞中的中性粒细胞、淋巴细胞中的 T 细胞和单核细胞巨噬细胞。这些免疫细胞具有先天性和特异性靶向作用、低免疫原性、提高疗效等特点^[86]。由于白细胞在肿瘤微环境中的作用^[87]和具有与肿瘤细胞共同的物理特性^[88],可以将纳米治疗药物输送到肿瘤部位。纳米粒子可以通过“搭便车策略”掺入到白细胞中或在其表面固定,也可以利用白细胞衍生的膜成分包裹纳米粒子^[89]。

(1) 中性粒细胞 人体中最丰富的白细胞为中性粒细胞,占到循环白细胞数量的 50%~70%^[90],是炎症反应中最早到达炎症部位的免疫细胞^[91],其从循环部位到炎症部位的迁移是一个自然过程,并具有高特异性和流动性^[92]。因此,中性粒细胞是运输药物或纳米药物的优秀细胞载体,可以延长药物在体内的循环时间,且不会被免疫系统清除^[93-94]。现有研究表明由于纳米粒内化不影响中性粒细胞的存活、凋亡或激活,中性粒细胞可以装载纳米药物复合物以解决药物本身的毒性^[95]。

研究显示,中性粒细胞不仅可以在炎症部位起作用,还存在于肿瘤微环境中,具有抗肿瘤功能^[96],并且显示出固有的肿瘤归巢和药物携带特性^[97]。Chu 等^[98-99]在研究中性粒细胞在肿瘤治疗中的作用时发现,纳米粒子可以通过在体内劫持中性粒细胞或通过控制肿瘤微环境促进中性粒细胞的浸润来增强治疗效果。Hao 等^[100]将 PLGA 纳米颗粒与 CXCL1 水凝胶组合,在黑色素瘤小鼠模型中进行实验证明了内源性嗜中性粒细胞可以在体内参与纳米粒子递送来实现抑制肿瘤的目的。也有研究发现,中性粒细胞可以穿透血脑屏障治疗脑部的相关疾病^[101]。Xue 等^[102]将含有紫杉醇的脂质体中性粒细胞递送到经手术切除的神经胶质瘤小鼠中,发现其可以抑制肿瘤的复发,从而证明了中性粒细胞介导的药物递送的有效性。

(2) T 细胞 T 细胞是人体中第 2 丰富的白细胞^[103]。因其作为适应性免疫系统的一部分,可以特异性识别抗原,且每个细胞仅呈递一种抗原,所以极具特异性,是一种优秀的靶向细胞^[104]。同时当 T

细胞遇到各自的抗原时,其受体会导致细胞表面还原电位增加,进而发出信号,分泌细胞,可诱导抗原呈递细胞死亡的蛋白质,最终导致细胞凋亡^[105]。T 细胞的这两个特性表明了其在药物递送和肿瘤治疗中的重要潜能^[39]。

在肿瘤治疗中,嵌合抗原受体 T 细胞是目前研究学者关注的一个热点,其被研究应用于治疗脑胶质瘤和黑色素瘤^[106],且被美国食品药品监督管理局批准用于淋巴瘤^[107]。Stephan 等^[108]证明了将载有辅助药物的纳米颗粒结合到过继性 T 细胞疗法模型中可以显著消除肿瘤,表明 T 细胞是一种可以用于主动靶向药物递送的、有前途的载体。此外, Pohl-Guimaraes 等^[109]证明了经过 RNA 修饰的 T 细胞可以穿过血脑屏障作为一个多功能平台,将治疗大分子药物递送到中枢神经系统恶性肿瘤部位。

(3) 巨噬细胞 巨噬细胞是最大的一种白细胞类型^[110],是先天免疫系统的主要吞噬细胞,根据其位置和宿主要求,巨噬细胞可以通过周围微环境的调节来表现出不同的表型和功能特性,具有功能特异性^[111]。在各种刺激下可被极化成不同功能的表型,一般可分为 M1 型和 M2 型^[112]。M1 型巨噬细胞可以捕获、吞噬和裂解肿瘤细胞,并表达一系列免疫刺激细胞因子;M2 型巨噬细胞则在肿瘤微环境中充当免疫抑制剂,表达多种抗炎分子^[113]。由于巨噬细胞具有良好的生物相容性,是丰富的表面受体;可以感知趋化信号,并高效地定位肿瘤^[114];在体内可以延长药物的循环和释放、增强药物稳定性、降低免疫原性^[115],因此其在癌症治疗药物递送方面具有巨大潜力。巨噬细胞特异性药物递送系统纳米载体的巨噬细胞靶向策略可分为两类:被动靶向(主要由含有大量巨噬细胞的单核吞噬系统驱动)和主动靶向(主要由配体受体相互作用驱动)^[116]。

肿瘤微环境主要呈低 pH 值和缺氧状态^[117-118],会吸引巨噬细胞积聚在肿瘤的血管缺氧部位^[119]。Pang 等^[120]利用巨噬细胞的内在归巢特性,使其作为“特洛伊木马”携带载药纳米颗粒穿过血脑障碍,最终到达脑肿瘤部位。肿瘤微环境中存在的肿瘤相关巨噬细胞可以增强或介导细胞毒剂和检查点抑制剂的抗肿瘤活性^[121],是影响进展、转移和肿瘤复发的癌症的关键参与者^[122]。Qiu 等^[123]开发了一种以巨噬细胞为载体来治疗三阴性乳腺癌术后复发的研究,将紫杉醇和白藜芦醇装载在 R8 修饰的聚乙二醇化脂质体中,通过巨噬细胞的摄取进行封

装,进而构建了具有高载药量和炎症/肿瘤趋向性的细胞介导载体,以达到增强术后肿瘤复发的治疗效果。

细胞载药过程和作用在不同生理条件下的作用优势见图 2。

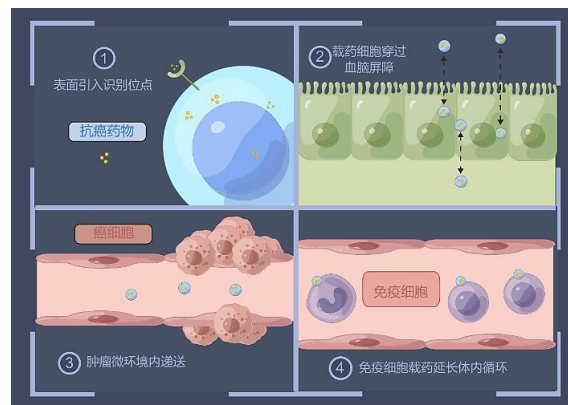


图 2 细胞载药过程和作用在不同生理条件下的作用优势
(由 Figdraw 绘制)

Fig. 2 Process of cell drug loading and its action advantages under different physiological conditions (by Figdraw)

2 死细胞及其药物递送系统

目前,细胞载药中多以活细胞载体为主,在治疗肿瘤时多依赖于肿瘤微环境的作用以及细胞本身的特点和作用,但在药物有效性、靶向性方面还有待提高,如活细胞内药物负载可能会导致细胞特性的变化、会改变细胞表面蛋白和细胞膜的流动性,从而影响细胞活性,并增加免疫原性^[124];或当活细胞用于靶向肿瘤的药物递送和癌症治疗中时,其与癌细胞载药相比不具有同源靶向性^[125]。因此,具有治疗性的死细胞(低温休克的癌细胞)成为了治疗肿瘤疾病的新选择。Ci 等^[126]基于急性髓性白血病癌变细胞本身“骨髓归巢”的特点将急性髓性白血病细胞用液氮处理使其冷冻休克(完全丧失增殖能力),构建具有骨髓靶向功能的递药系统,在消除致瘤性并保持细胞结构完整性的同时,提高化疗药物阿霉素在骨髓内的富集,并抑制急性髓性白血病细胞增殖。

3 细胞衍生物外泌体及其药物递送系统

外泌体是一种内源性细胞的外囊泡,是细胞衍生物中最常见、应用于载药最多的一类囊泡,其直径为 40~100 nm,含有蛋白质、脂质等生物分子^[127],其脂质双分子层可以保护药物的正常运输^[128],保证药物在体液中循环,具有血液循环稳定性强、长期安全等特点^[129-130]。由于不同细胞分泌的外泌体携带不同的信号分子,且基于本身尺寸小的特点,

因此外泌体是一种可以实现靶向递送的天然纳米药物载体^[131]。外泌体的来源主要是干细胞、免疫细胞（T 细胞、NK 细胞、巨噬细胞等）以及肿瘤细胞衍生的外泌体^[132]。此外，外泌体还具有“归巢”的能力，即可以靶向该外泌体的源细胞。

外泌体的分离纯化方法主要有超速离心法^[133]、免疫分离法^[134]和超滤法^[135]。载药方法分为两类(图 3^[136])，一类是在供体细胞中直接载药，分为转染和共孵育；另一类是形成外泌体后载药，主要有电穿孔和直接混合法。在癌症的治疗方面，外泌体可以通过表面的膜蛋白与受体细胞相互作用，将抗癌药物选择性地递送到癌细胞表面或内部，这种递送药物的方式可以克服多药耐药相关蛋白（如 P-糖蛋白）介导的耐药性^[137]。同时，外泌体还具备生物利用度高的特性，可以通过血脑屏障等生物屏障^[138]。

外泌体作为小分子药物递送载体已经被许多研究者进行了广泛的研究。外泌体可以递送多种药物，包括亲水性药物和疏水性药物，如阿霉素^[139]、多巴胺^[140]、姜黄素^[141]、紫杉醇^[142]。Haney 等^[143]基于巨噬细胞的外泌体载药紫杉醇和阿霉素在肺转移的小鼠模型中表现出高抗癌的效果，同时靶向三阴性乳腺癌在免疫活性 BALB/C 小鼠中的原位小鼠 T11 肿瘤和无胸腺 nu/nu 小鼠中显示出抗肿瘤作用。Osterman 等^[144]证明用胰腺癌的外泌体载姜黄素可

以增强姜黄素的功效。Sun 等^[145]使用供体细胞为人腺癌细胞、小鼠乳腺肿瘤细胞的外泌体负载姜黄素，通过实验数据表明外泌体递送的姜黄素在血液中更稳定，且浓度更高，并增强了靶标特异性。

不同载药细胞的优势和应用的总结见表 1。

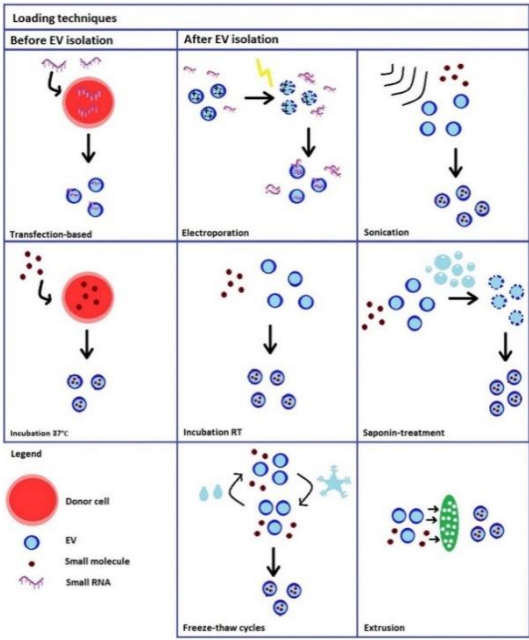


图 3 外泌体的两类载药方法
Fig. 3 Two kinds of drug loading methods of exosomes

表 1 不同载药细胞的优势和应用

Table 1 Advantages and applications of different drug-loaded cells				
载药细胞种类			优势	携载肿瘤药物
活细胞	干细胞	间充质干细胞	肿瘤归巢能力、低免疫原性、长期驻留肿瘤部位的能力 ^[45-46]	紫杉醇 ^[51] 、阿霉素 ^[52]
		红细胞	生物相容性、高载药量、低免疫原性 ^[57-58]	姜黄素 ^[146] 、阿霉素 ^[147]
	免疫细胞	血小板	高安全性和可再生性 ^[76]	阿霉素 ^[81-82]
		中性粒细胞	高特异性和流动性 ^[92]	紫杉醇 ^[102, 148]
		T 淋巴细胞	极具有特异性，一种优秀的靶向细胞 ^[104]	紫杉醇 ^[149]
死细胞	巨噬细胞		具有良好的生物相容性、增强药物稳定性、降低免疫原性 ^[114-115]	紫杉醇、白藜芦醇 ^[123]
	无活性肿瘤细胞		急性髓性白血病细胞的“骨髓归巢”能力	阿霉素 ^[126]
外泌体	来源于干细胞、免疫细胞、肿瘤细胞等		血液循环稳定性强、长期安全 ^[129]	阿霉素 ^[150]

4 结语和展望

在肿瘤的治疗中,细胞载药由于其内源性的特点,在靶向性、生物相容性等方面展现出了较多的优势,但该类给药系统应用于临床仍然面临着一些挑战:首先,药物负载在细胞内部可能会导致细胞特性的变化,会改变细胞表面蛋白和细胞膜的流动性,从而影响细胞活性,并增加免疫原性^[124]。如红细胞作为载体时,会影响细胞的生物相容性,从而导致药物暴露^[151]。其次,有些细胞类型如巨噬细胞,作为载体时需要细胞在体液中保持循环状态,从而达到迁移和归巢,并在肿瘤部位大量释放药物^[152],然而,体内的细胞保护机制可能会排泄游离的药物,并中和它们的内吞作用,导致治疗药物在到达肿瘤部位之前提前释放^[153]。此外,当细胞用于靶向肿瘤的药物递送和癌症治疗中时,其与癌细胞载药相比不具有同源靶向性^[125],会影响药物在肿瘤部位的释放效果。目前关于死细胞载药的相关研究较少,存在一定的不确定性,有关癌细胞在体内的代谢和安全性,即是否会诱导肿瘤的发生等都有待进一步探究。

利益冲突 所有作者均声明不存在利益冲突

参考文献

- [1] World health statistics 2022: Monitoring health for the SDGs, sustainable development goals [R/OL]. (2022-05-19) [2023-09-30]. <https://www.who.int/publications/i/item/9789240051157>.
- [2] Cheng S, Zhao Y, Wang F, *et al.* Comorbidities' potential impacts on severe and non-severe patients with COVID-19: A systematic review and meta-analysis [J]. *Medicine* (Baltimore), 2021, 100(12): e24971.
- [3] Al-Quteimat O M, Amer A M. The impact of the COVID-19 pandemic on cancer patients [J]. *Am J Clin Oncol*, 2020, 43(6): 452-455.
- [4] Siegel R L, Miller K D, Fuchs H E, *et al.* Cancer statistics, 2022 [J]. *CA Cancer J Clin*, 2022, 72(1): 7-33.
- [5] Sung H, Ferlay J, Siegel R L, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. *CA Cancer J Clin*, 2021, 71(3): 209-249.
- [6] Chhikara B S, Parang K. Global cancer statistics 2022: The trends projection analysis [J]. *Chem Biol Lett*, 2023, 10(1): 451.
- [7] Wyld L, Audisio R A, Poston G J. The evolution of cancer surgery and future perspectives [J]. *Nat Rev Clin Oncol*, 2015, 12(2): 115-124.
- [8] Cox J, Weinman S. Mechanisms of doxorubicin resistance in hepatocellular carcinoma [J]. *Hep Oncol*, 2016, 3(1): 57-59.
- [9] Yang M, Yang T, Mao C. Enhancement of photodynamic cancer therapy by physical and chemical factors [J]. *Angew Chem Int Ed Engl*, 2019, 58(40): 14066-14080.
- [10] Baskar R, Lee K A, Yeo R, *et al.* Cancer and radiation therapy: Current advances and future directions [J]. *Int J Med Sci*, 2012, 9(3): 193-199.
- [11] Strobel O, Neoptolemos J, Jager D, *et al.* Optimizing the outcomes of pancreatic cancer surgery [J]. *Nat Rev Clin Oncol*, 2019, 16(1): 11-26.
- [12] Wang J, Lei K, Han F. Tumor microenvironment: Recent advances in various cancer treatments [J]. *Eur Rev Med Pharmacol Sci*, 2018, 22(12): 3855-3864.
- [13] Schirrmacher V. From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment (Review) [J]. *Int J Oncol*, 2019, 54(2): 407-419.
- [14] Nurgali K, Jagoe R T, Abalo R. Editorial: adverse effects of cancer chemotherapy: Anything new to improve tolerance and reduce sequelae? [J]. *Front Pharmacol*, 2018, 9: 245.
- [15] Gomathi M, Ayisha H T P, Jijo A J, *et al.* Recent advances in radiotherapy and its associated side effects in cancer-A review [J]. *J Basic Appl Zool*, 2019, 80(1): 1-10.
- [16] Zhang Q Y, Wang F X, Jia K K, *et al.* Natural product interventions for chemotherapy and radiotherapy-induced side effects [J]. *Front Pharmacol*, 2018, 9: 1253.
- [17] Esfahani K, Roudaia L, Buhlaiga N, *et al.* A review of cancer immunotherapy: From the past, to the present, to the future [J]. *Curr Oncol*, 2020, 27(Suppl 2): S87-S97.
- [18] Li Z, Xiao C, Yong T, *et al.* Influence of nanomedicine mechanical properties on tumor targeting delivery [J]. *Chem Soc Rev*, 2020, 49(8): 2273-2290.
- [19] Kutova O M, Guryev E L, Sokolova E A, *et al.* Targeted delivery to tumors: Multidirectional strategies to improve treatment efficiency [J]. *Cancers* (Basel), 2019, 11(1): 68.
- [20] Li C, Wang J, Wang Y, *et al.* Recent progress in drug delivery [J]. *Acta Pharm Sin B*, 2019, 9(6): 1145-1162.
- [21] Masood F. Polymeric nanoparticles for targeted drug delivery system for cancer therapy [J]. *Mater Sci Eng C Mater Biol Appl*, 2016, 60: 569-578.
- [22] Bazak R, Hourri M, El Achy S, *et al.* Cancer active targeting by nanoparticles: A comprehensive review of literature [J]. *J Cancer Res Clin Oncol*, 2015, 141(5): 769-784.
- [23] Wang A Z, Langer R, Farokhzad O C. Nanoparticle

- delivery of cancer drugs [J]. *Annu Rev Med*, 2012, 63: 185-198.
- [24] Hui Y, Yi X, Hou F, *et al.* Role of nanoparticle mechanical properties in cancer drug delivery [J]. *ACS Nano*, 2019, 13(7): 7410-7424.
- [25] Rosenblum D, Joshi N, Tao W, *et al.* Progress and challenges towards targeted delivery of cancer therapeutics [J]. *Nat Commun*, 2018, 9(1): 1410.
- [26] Minchinton A I, Tannock I F. Drug penetration in solid tumours [J]. *Nat Rev Cancer*, 2006, 6(8): 583-592.
- [27] Domingues C, Santos A, Alvarez-Lorenzo C, *et al.* Where is nano today and where is it headed? A review of nanomedicine and the dilemma of nanotoxicology [J]. *ACS Nano*, 2022, 16(7): 9994-10041.
- [28] Yetisgin A A, Cetinel S, Zuvin M, *et al.* Therapeutic nanoparticles and their targeted delivery applications [J]. *Molecules*, 2020, 25(9): 2193.
- [29] Wang R, Yan H, Yu A, *et al.* Cancer targeted biomimetic drug delivery system [J]. *J Drug Deliv Sci Technol*, 2021, 63: 102530.
- [30] Tong Q, Qiu N, Ji J, *et al.* Research progress in bioinspired drug delivery systems [J]. *Expert Opin Drug Del*, 2020, 17(9): 1269-1288.
- [31] Rao L, Bu LL, Cai B, *et al.* Cancer cell membrane-coated upconversion nanoprobe for highly specific tumor imaging [J]. *Adv Mater*, 2016, 28(18): 3460-3466.
- [32] Cheng H, Byrka-Bishop M, Zhang C T, *et al.* Stem cell membrane engineering for cell rolling using peptide conjugation and tuning of cell-selectin interaction kinetics [J]. *Biomaterials*, 2012, 33(20): 5004-5012.
- [33] Sarkar D, Vemula P K, Teo G S, *et al.* Chemical engineering of mesenchymal stem cells to induce a cell rolling response [J]. *Bioconjugate Chem*, 2008, 19(11): 2105-2109.
- [34] Stephan M T, Moon J J, Um S H, *et al.* Therapeutic cell engineering with surface-conjugated synthetic nanoparticles [J]. *Nat Med*, 2010, 16(9): 1035-1041.
- [35] 刘金虎, 刘永军, 张娜. 基于巨噬细胞的纳米仿生递药系统在肿瘤治疗中的应用 [J]. *药学报*, 2021, 56(9): 2505-2512.
- [36] Vijayan V, Uthaman S, Park I K. Cell membrane-camouflaged nanoparticles: A promising biomimetic strategy for cancer theragnostics [J]. *Polymers (Basel)*, 2018, 10(9): 983.
- [37] Wang Z, Wang X, Xu W, *et al.* Translational challenges and prospective solutions in the implementation of biomimetic delivery systems [J]. *Pharmaceutics*, 2023, 15(11): 2623.
- [38] Anchordoquy T J, Barenholz Y, Boraschi D, *et al.* *Mechanisms and Barriers in Cancer Nanomedicine: Addressing Challenges, Looking for Solutions* [M]. Columbia: ACS Publications, 2017.
- [39] Lutz H, Hu S, Dinh P U, *et al.* Cells and cell derivatives as drug carriers for targeted delivery [J]. *Med Drug Discov*, 2019, 3: 100014.
- [40] Kroll A V, Fang R H, Jiang Y, *et al.* Nanoparticulate delivery of cancer cell membrane elicits multiantigenic antitumor immunity [J]. *Adv Mater*, 2017, 29(47): 1703969.
- [41] Li R, He Y, Zhang S, *et al.* Cell membrane-based nanoparticles: A new biomimetic platform for tumor diagnosis and treatment [J]. *Acta Pharm Sin B*, 2018, 8(1): 14-22.
- [42] Fliervoet L A L, Mastrobattista E. Drug delivery with living cells [J]. *Adv Drug Deliv Rev*, 2016, 106(Pt A): 63-72.
- [43] Wang M, Xin Y, Cao H, *et al.* Recent advances in mesenchymal stem cell membrane-coated nanoparticles for enhanced drug delivery [J]. *Biomater Sci*, 2021, 9(4): 1088-1103.
- [44] Takayama Y, Kusamori K, Nishikawa M. Mesenchymal stem/stromal cells as next-generation drug delivery vehicles for cancer therapeutics [J]. *Expert Opin Drug Del*, 2021, 18(11): 1627-1642.
- [45] Ullah I, Subbarao R B, Rho G J. Human mesenchymal stem cells - current trends and future prospective [J]. *Biosci Rep*, 2015, 35(2): e00191.
- [46] Zhang T, Lin R, Wu H, *et al.* Mesenchymal stem cells: A living carrier for active tumor-targeted delivery [J]. *Adv Drug Deliv Rev*, 2022, 185: 114300.
- [47] Layek B, Sadhukha T, Panyam J, *et al.* Nano-engineered mesenchymal stem cells increase therapeutic efficacy of anticancer drug through true active tumor targeting [J]. *Mol Cancer Ther*, 2018, 17(6): 1196-1206.
- [48] Cao B, Yang M, Zhu Y, *et al.* Stem cells loaded with nanoparticles as a drug carrier for *in vivo* breast cancer therapy [J]. *Adv Mater*, 2014, 26(27): 4627-4631.
- [49] Litvinova L S, Shupletsova V V, Khaziakhmatova O G, *et al.* Human mesenchymal stem cells as a carrier for a cell-mediated drug delivery [J]. *Front Bioeng Biotechnol*, 2022, 10: 796111.
- [50] Huang X, Zhang F, Wang H, *et al.* Mesenchymal stem cell-based cell engineering with multifunctional mesoporous silica nanoparticles for tumor delivery [J]. *Biomaterials*, 2013, 34(7): 1772-1780.
- [51] Pessina A, Cocce V, Pascucci L, *et al.* Mesenchymal stromal cells primed with paclitaxel attract and kill

- leukaemia cells, inhibit angiogenesis and improve survival of leukaemia-bearing mice [J]. *Br J Haematol*, 2013, 160(6): 766-778.
- [52] Kalimuthu S, Zhu L, Oh J M, *et al.* Migration of mesenchymal stem cells to tumor xenograft models and *in vitro* drug delivery by doxorubicin [J]. *Int J Med Sci*, 2018, 15(10): 1051-1061.
- [53] Sun Y, Su J, Liu G, *et al.* Advances of blood cell-based drug delivery systems [J]. *Eur J Pharm Sci*, 2017, 96: 115-128.
- [54] Serafini S, Rossi L, Antonelli A, *et al.* Drug delivery through phagocytosis of red blood cells [J]. *Transfusion Med Hemother*, 2004, 31(2): 92-101.
- [55] Kolesnikova T A, Skirtach A G, Mähwald H. Red blood cells and polyelectrolyte multilayer capsules: Natural carriers versus polymer-based drug delivery vehicles [J]. *Exp Opin Drug Del*, 2013, 10(1): 47-58.
- [56] Villa C H, Pan D C, Zaitsev S, *et al.* Delivery of drugs bound to erythrocytes: New avenues for an old intravascular carrier [J]. *Ther Deliv*, 2015, 6(7): 795-826.
- [57] Tan S, Wu T, Zhang D, *et al.* Cell or cell membrane-based drug delivery systems [J]. *Theranostics*, 2015, 5(8): 863-881.
- [58] Zhang W, Zhao M, Gao Y, *et al.* Biomimetic erythrocytes engineered drug delivery for cancer therapy [J]. *Chem Eng J*, 2022, 433: 133498.
- [59] Oldenborg P A, Zheleznyak A, Fang Y F, *et al.* Role of CD47 as a marker of self on red blood cells [J]. *Science*, 2000, 288(5473): 2051-2054.
- [60] Pierige F, Serafini S, Rossi L, *et al.* Cell-based drug delivery [J]. *Adv Drug Deliv Rev*, 2008, 60(2): 286-295.
- [61] Rossi L, Pierige F, Antonelli A, *et al.* Engineering erythrocytes for the modulation of drugs' and contrasting agents' pharmacokinetics and biodistribution [J]. *Adv Drug Deliv Rev*, 2016, 106(Pt A): 73-87.
- [62] Han X, Wang C, Liu Z. Red blood cells as smart delivery systems [J]. *Bioconjug Chem*, 2018, 29(4): 852-860.
- [63] Bush L M, Healy C P, Javdan S B, *et al.* Biological cells as therapeutic delivery vehicles [J]. *Trends Pharmacol Sci*, 2021, 42(2): 106-118.
- [64] Wang Q, Cheng H, Peng H, *et al.* Non-genetic engineering of cells for drug delivery and cell-based therapy [J]. *Adv Drug Deliv Rev*, 2015, 91: 125-140.
- [65] Villa C H, Anselmo A C, Mitragotri S, *et al.* Red blood cells: Supercarriers for drugs, biologicals, and nanoparticles and inspiration for advanced delivery systems [J]. *Adv Drug Deliv Rev*, 2016, 106(Pt A): 88-103.
- [66] Biagiotti S, Paoletti M F, Fraternale A, *et al.* Drug delivery by red blood cells [J]. *IUBMB Life*, 2011, 63(8): 621-631.
- [67] Pierige F, De Marco C, Orlotti N, *et al.* Cytotoxic activity of 2-fluoro-ara-AMP and 2-fluoro-ara-AMP-loaded erythrocytes against human breast carcinoma cell lines [J]. *Int J Oncol*, 2010, 37(1): 133-142.
- [68] Bachet J B, Gay F, Maréchal R, *et al.* Asparagine synthetase expression and phase I study with *L*-asparaginase encapsulated in red blood cells in patients with pancreatic adenocarcinoma [J]. *Pancreas*, 2015, 44(7): 1141-1147.
- [69] Izzati Mat Rani N N, Alzubaidi Z M, Azhari H, *et al.* Novel engineering: Biomimicking erythrocyte as a revolutionary platform for drugs and vaccines delivery [J]. *Eur J Pharmacol*, 2021, 900: 174009.
- [70] Li Y, Raza F, Liu Y, *et al.* Clinical progress and advanced research of red blood cells based drug delivery system [J]. *Biomaterials*, 2021, 279: 121202.
- [71] Han X, Shen S, Fan Q, *et al.* Red blood cell-derived nanoerythrocyte for antigen delivery with enhanced cancer immunotherapy [J]. *Sci Adv*, 2019, 5(10): eaaw6870.
- [72] Semple J W, Italiano J E, Jr. Freedman J. Platelets and the immune continuum [J]. *Nat Rev Immunol*, 2011, 11(4): 264-274.
- [73] Shi Q, Montgomery R R. Platelets as delivery systems for disease treatments [J]. *Adv Drug Deliv Rev*, 2010, 62(12): 1196-1203.
- [74] Jurk K, Kehrel B E. *Platelets: Physiology and Biochemistry. Seminars in Thrombosis and Hemostasis* [M]. New York: Thieme Medical Publishers, Inc., 2005: 381-392.
- [75] Kapur R, Semple J W. The nonhemostatic immune functions of platelets [J]. *Semin Hematol*, 2016, 53(Suppl 1): S2-6.
- [76] Lu Y, Hu Q, Jiang C, *et al.* Platelet for drug delivery [J]. *Cur Opin Biotechnol*, 2019, 58: 81-91.
- [77] Soleymani S, Yari F, Bolhassani A, *et al.* Platelet microparticles: An effective delivery system for anti-viral drugs [J]. *J Drug Deliv Sci Technol*, 2019, 51: 290-296.
- [78] Dovizio M, Ballerini P, Fullone R, *et al.* Multifaceted functions of platelets in cancer: From tumorigenesis to liquid biopsy tool and drug delivery system [J]. *Int J Mol Sci*, 2020, 21(24): 9585.
- [79] Ortiz-Otero N, Mohamed Z, King M R. Platelet-based drug delivery for cancer applications [J]. *Biomechan Oncol*, 2018: 235-251.
- [80] Zhang Y, Liu G, Wei J, *et al.* Platelet membrane-based and tumor-associated platelet-targeted drug delivery systems for cancer therapy [J]. *Front Med*, 2018, 12(6): 667-677.
- [81] Sarkar S, Alam M A, Shaw J, *et al.* Drug delivery using platelet cancer cell interaction [J]. *Pharm Res*, 2013,

- 30(11): 2785-2794.
- [82] Xu P, Zuo H, Chen B, *et al.* Doxorubicin-loaded platelets as a smart drug delivery system: An improved therapy for lymphoma [J]. *Sci Rep*, 2017, 7(1): 42632.
- [83] Dai L, Gu N, Chen B A, *et al.* Human platelets repurposed as vehicles for *in vivo* imaging of myeloma xenotransplants [J]. *Oncotarget*, 2016, 7(16): 21076.
- [84] Molinaro R, Martinez J O, Zinger A, *et al.* Leukocyte-mimicking nanovesicles for effective doxorubicin delivery to treat breast cancer and melanoma [J]. *Biomater Sci*, 2020, 8(1): 333-341.
- [85] Dong X, Chu D, Wang Z. Leukocyte-mediated delivery of nanotherapeutics in inflammatory and tumor sites [J]. *Theranostics*, 2017, 7(3): 751-763.
- [86] Chen Y, Qin D, Zou J, *et al.* Living leukocyte - based drug delivery systems [J]. *Adv Mater*, 2022, 35(17): 2207787.
- [87] Turley S J, Cremasco V, Astarita J L. Immunological hallmarks of stromal cells in the tumour microenvironment [J]. *Nat Rev Immunol*, 2015, 15(11): 669-682.
- [88] Mitchell M J, King M R. Leukocytes as carriers for targeted cancer drug delivery [J]. *Exp Opin Drug Del*, 2015, 12(3): 375-392.
- [89] Huang Y, Gao X, Chen J. Leukocyte-derived biomimetic nanoparticulate drug delivery systems for cancer therapy [J]. *Acta Pharm Sin B*, 2018, 8(1): 4-13.
- [90] Mayadas T N, Cullere X, Lowell C A. The multifaceted functions of neutrophils [J]. *Annu Rev Pathol*, 2014, 9: 181-218.
- [91] Kolaczowska E, Kubes P. Neutrophil recruitment and function in health and inflammation [J]. *Nat Rev Immunol*, 2013, 13(3): 159-175.
- [92] Chu D, Dong X, Shi X, *et al.* Neutrophil-based drug delivery systems [J]. *Adv Mater*, 2018, 30(22): e1706245.
- [93] Han Y, Zhao R, Xu F. Neutrophil-based delivery systems for nanotherapeutics [J]. *Small*, 2018, 14(42): e1801674.
- [94] Wang H, Zang J, Zhao Z, *et al.* The advances of neutrophil-derived effective drug delivery systems: A key review of managing tumors and inflammation [J]. *Int J Nanomedicine*, 2021, 16: 7663-7681.
- [95] Zhang C Y, Dong X, Gao J, *et al.* Nanoparticle-induced neutrophil apoptosis increases survival in sepsis and alleviates neurological damage in stroke [J]. *Sci Adv*, 2019, 5(11): eaax7964.
- [96] Rosowski E E, Huttenlocher A. Neutrophils, wounds, and cancer progression [J]. *Dev Cell*, 2015, 34(2): 134-136.
- [97] Hosseinalizadeh H, Mahmoodpour M, Razaghi Bahabadi Z, *et al.* Neutrophil mediated drug delivery for targeted glioblastoma therapy: A comprehensive review [J]. *Biomed Pharmacother*, 2022, 156: 113841.
- [98] Chu D, Zhao Q, Yu J, *et al.* Nanoparticle targeting of neutrophils for improved cancer immunotherapy [J]. *Adv Healthc Mater*, 2016, 5(9): 1088-1093.
- [99] Chu D, Dong X, Zhao Q, *et al.* Photosensitization priming of tumor microenvironments improves delivery of nanotherapeutics via neutrophil infiltration [J]. *Adv Mater*, 2017, 29(27): 1701021.
- [100] Hao J, Chen J, Wang M, *et al.* Neutrophils, as “Trojan horses”, participate in the delivery of therapeutical PLGA nanoparticles into a tumor based on the chemotactic effect [J]. *Drug Deliv*, 2020, 27(1): 1-14.
- [101] Qin J, Chen D, Hu H, *et al.* Surface modification of RGD-liposomes for selective drug delivery to monocytes/neutrophils in brain [J]. *Chem Pharm Bull*, 2007, 55(8): 1192-1197.
- [102] Xue J, Zhao Z, Zhang L, *et al.* Neutrophil-mediated anticancer drug delivery for suppression of postoperative malignant glioma recurrence [J]. *Nat Nanotechnol*, 2017, 12(7): 692-700.
- [103] Masopust D, Soerens A G. Tissue-resident T cells and other resident leukocytes [J]. *Ann Rev Immunol*, 2019, 37: 521-546.
- [104] Jones R B, Mueller S, Kumari S, *et al.* Antigen recognition-triggered drug delivery mediated by nanocapsule-functionalized cytotoxic T-cells [J]. *Biomaterials*, 2017, 117: 44-53.
- [105] Tang L, Zheng Y, Melo M B, *et al.* Enhancing T cell therapy through TCR-signaling-responsive nanoparticle drug delivery [J]. *Nat Biotechnol*, 2018, 36(8): 707-716.
- [106] Soltantoyeh T, Akbari B, Karimi A, *et al.* Chimeric antigen receptor (CAR) T cell therapy for metastatic melanoma: Challenges and road ahead [J]. *Cells*, 2021, 10(6): 1450.
- [107] Zhao Z, Ukidve A, Kim J, *et al.* Targeting strategies for tissue-specific drug delivery [J]. *Cell*, 2020, 181(1): 151-167.
- [108] Stephan M T, Moon J J, Um S H, *et al.* Therapeutic cell engineering with surface-conjugated synthetic nanoparticles [J]. *Nat Med*, 2010, 16(9): 1035-1041.
- [109] Pohl-Guimaraes F, Yang C, Dyson K A, *et al.* RNA-modified T cells mediate effective delivery of immunomodulatory cytokines to brain tumors [J]. *Mol Ther*, 2019, 27(4): 837-849.
- [110] Murray P J, Allen J E, Biswas S K, *et al.* Macrophage activation and polarization: Nomenclature and experimental guidelines [J]. *Immunity*, 2014, 41(1): 14-20.
- [111] Wang H F, Liu Y, Yang G, *et al.* Macrophage-mediated cancer drug delivery [J]. *Mate. Today Sustain*, 2021: 11-

- 12.
- [112] Hao N B, Lu M H, Fan Y H, *et al.* Macrophages in tumor microenvironments and the progression of tumors [J]. *Clin Dev Immunol*, 2012, 2012: 948098.
- [113] Liu J, Geng X, Hou J, *et al.* New insights into M1/M2 macrophages: Key modulators in cancer progression [J]. *Cancer Cell Int*, 2021, 21(1): 389.
- [114] Zhang W, Wang M, Tang W, *et al.* Nanoparticle-laden macrophages for tumor-tropic drug delivery [J]. *Adv Mater*, 2018, 30(50): e1805557.
- [115] Liang T, Zhang R, Liu X, *et al.* Recent advances in macrophage-mediated drug delivery systems [J]. *Int J Nanomedicine*, 2021, 16: 2703-2714.
- [116] Li H, Tatematsu K, Somya M, *et al.* Development of a macrophage-targeting and phagocytosis-inducing bio-nanocapsule-based nanocarrier for drug delivery [J]. *Acta Biomater*, 2018, 73: 412-423.
- [117] Anderson N M, Simon M C. The tumor microenvironment [J]. *Curr Biol*, 2020, 30(16): R921-R925.
- [118] Balkwill F R, Capasso M, Hagemann T. The tumor microenvironment at a glance [J]. *J Cell Sci*, 2012, 125(Pt 23): 5591-5596.
- [119] Batrakova E V, Gendelman H E, Kabanov A V. Cell-mediated drug delivery [J]. *Exp Opin Drug Del*, 2011, 8(4): 415-433.
- [120] Pang L, Qin J, Han L, *et al.* Exploiting macrophages as targeted carrier to guide nanoparticles into glioma [J]. *Oncotarget*, 2016, 7(24): 37081.
- [121] Arneth B. Tumor microenvironment [J]. *Medicina* (Kaunas), 2019, 56(1): 15.
- [122] Malfitano A M, Pisanti S, Napolitano F, *et al.* Tumor-associated macrophage status in cancer treatment [J]. *Cancers* (Basel), 2020, 12(7): 1987.
- [123] Qiu Y, Ren K, Zhao W, *et al.* A "dual-guide" bioinspired drug delivery strategy of a macrophage-based carrier against postoperative triple-negative breast cancer recurrence [J]. *J Control Release*, 2021, 329: 191-204.
- [124] Wu Y, Liu Y, Wang T, *et al.* Living cell for drug delivery [J]. *Eng Regener*, 2022, 3(2): 131-148.
- [125] Xu L, Wu S, Wang J. Cancer cell membrane-coated nanocarriers for homologous target inhibiting the growth of hepatocellular carcinoma [J]. *J Bioactive Compatible Polym*, 2018, 34(1): 58-71.
- [126] Ci T, Li H, Chen G, *et al.* Cryo-shocked cancer cells for targeted drug delivery and vaccination [J]. *Sci Adv*, 2020, 6(50): eabc3013.
- [127] Valadi H, Ekstrom K, Bossios A, *et al.* Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells [J]. *Nat Cell Biol*, 2007, 9(6): 654-659.
- [128] Kim M S, Haney M J, Zhao Y, *et al.* Engineering macrophage-derived exosomes for targeted paclitaxel delivery to pulmonary metastases: *In vitro* and *in vivo* evaluations [J]. *Nanomedicine*, 2018, 14(1): 195-204.
- [129] Alyamani H, Obeid M A, Tate R J, *et al.* Exosomes: Fighting cancer with cancer [J]. *Ther Deliv*, 2019, 10(1): 37-61.
- [130] Zhao X, Wu D, Ma X, *et al.* Exosomes as drug carriers for cancer therapy and challenges regarding exosome uptake [J]. *Biomed Pharmacother*, 2020, 128: 110237.
- [131] Liao W, Du Y, Zhang C, *et al.* Exosomes: The next generation of endogenous nanomaterials for advanced drug delivery and therapy [J]. *Acta Biomater*, 2019, 86: 1-14.
- [132] Kim H, Kim E H, Kwak G, *et al.* Exosomes: Cell-derived nanoplatforams for the delivery of cancer therapeutics [J]. *Int J Mol Sci*, 2020, 22(1): 14.
- [133] Greening D W, Xu R, Ji H, *et al.* A protocol for exosome isolation and characterization: Evaluation of ultracentrifugation, density-gradient separation, and immunoaffinity capture methods [J]. *Methods Mol Biol*, 2015, 1295: 179-209.
- [134] Söderberg A, Barral A M, Söderström M, *et al.* Redox-signaling transmitted in trans to neighboring cells by melanoma-derived TNF-containing exosomes [J]. *Free Radic Biol Med*, 2007, 43(1): 90-99.
- [135] Blázquez R, Sánchez-Margallo F M, Álvarez V, *et al.* Fibrin glue mesh fixation combined with mesenchymal stem cells or exosomes modulates the inflammatory reaction in a murine model of incisional hernia [J]. *Acta Biomater*, 2018, 71: 318-329.
- [136] Vader P, Mol E A, Pasterkamp G, *et al.* Extracellular vesicles for drug delivery [J]. *Adv Drug Deliv Rev*, 2016, 106(Pt A): 148-156.
- [137] Chen L, Wang L, Zhu L, *et al.* Exosomes as drug carriers in anti-cancer therapy [J]. *Front Cell Dev Biol*, 2022, 10: 728616.
- [138] Kim M S, Haney M J, Zhao Y, *et al.* Development of exosome-encapsulated paclitaxel to overcome MDR in cancer cells [J]. *Nanomedicine*, 2016, 12(3): 655-664.
- [139] Tian Y, Li S, Song J, *et al.* A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy [J]. *Biomaterials*, 2014, 35(7): 2383-2390.
- [140] Qu M, Lin Q, Huang L, *et al.* Dopamine-loaded blood exosomes targeted to brain for better treatment of

- Parkinson's disease [J]. *J Control Release*, 2018, 287: 156-166.
- [141] Zhuang X, Xiang X, Grizzle W, *et al.* Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain [J]. *Mol Ther*, 2011, 19(10): 1769-1779.
- [142] Pascucci L, Cocce V, Bonomi A, *et al.* Paclitaxel is incorporated by mesenchymal stromal cells and released in exosomes that inhibit *in vitro* tumor growth: A new approach for drug delivery [J]. *J Control Release*, 2014, 192: 262-270.
- [143] Haney M J, Zhao Y, Jin Y S, *et al.* Macrophage-derived extracellular vesicles as drug delivery systems for triple negative breast cancer (TNBC) therapy [J]. *J Neuroimmune Pharmacol*, 2020, 15(3): 487-500.
- [144] Osterman C J, Lynch J C, Leaf P, *et al.* Curcumin modulates pancreatic adenocarcinoma cell-derived exosomal function [J]. *PLoS One*, 2015, 10(7): e0132845.
- [145] Sun D, Zhuang X, Xiang X, *et al.* A novel nanoparticle drug delivery system: The anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes [J]. *Mol Ther*, 2010, 18(9): 1606-1614.
- [146] Xie X, Wang H, Williams G R, *et al.* Erythrocyte membrane cloaked curcumin-loaded nanoparticles for enhanced chemotherapy [J]. *Pharmaceutics*, 2019, 11(9): 429.
- [147] Aryal S, Hu C M, Fang R H, *et al.* Erythrocyte membrane-cloaked polymeric nanoparticles for controlled drug loading and release [J]. *Nanomedicine (Lond)*, 2013, 8(8): 1271-1280.
- [148] Wang J, Gu X, Ouyang Y, *et al.* Engineering of neutrophil membrane camouflaging nanoparticles realizes targeted drug delivery for amplified antitumor therapy [J]. *Int J Nanomedicine*, 2021: 1175-1187.
- [149] Zhang L, Li R, Chen H, *et al.* Human cytotoxic T-lymphocyte membrane-camouflaged nanoparticles combined with low-dose irradiation: A new approach to enhance drug targeting in gastric cancer [J]. *Int J Nanomedicine*, 2017, 12: 2129-2142.
- [150] Wang J, Tang W, Yang M, *et al.* Inflammatory tumor microenvironment responsive neutrophil exosomes-based drug delivery system for targeted glioma therapy [J]. *Biomaterials*, 2021, 273: 120784.
- [151] Villa C H, Seghatchian J, Muzykantov V. Drug delivery by erythrocytes: "Primum non nocere" [J]. *Transfus Apher Sci*, 2016, 55(3): 275-280.
- [152] Si J, Shao S, Shen Y, *et al.* Macrophages as active nanocarriers for targeted early and adjuvant cancer chemotherapy [J]. *Small*, 2016, 12(37): 5108-5119.
- [153] Zhang X, Yao S, Liu C, *et al.* Tumor tropic delivery of doxorubicin-polymer conjugates using mesenchymal stem cells for glioma therapy [J]. *Biomaterials*, 2015, 39: 269-281.

[责任编辑 解学星]