基于纳米递送系统的PI3K-AKT信号通路治疗癌症的研究进展

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摘要: PI3K-AKT信号通路被发现在多种癌症中过度活跃, 致使细胞异常增殖, 抑制细胞凋亡, 促进肿瘤转移, 并与化疗和放疗耐药的出现息息相关。因此, 靶向PI3K-AKT信号通路治疗肿瘤成为当下研究的热点。目前针对PI3K-AKT信号通路常用小分子抑制剂、天然产物、siRNA、miRNA等进行抑制。但这些治疗手段往往由于不良反应明显、生物稳定性差、溶解度低或无靶向性等问题导致临床应用受限。将纳米技术应用于药物递送, 可以提高药物稳定性和溶解度, 减少药物在正常组织中的蓄积, 实现良好的靶向性。纳米载体搭载药物靶向PI3K-AKT通路治疗肿瘤可以优化治疗效果、减少药物所产生的不良反应, 还可以增加化疗或放疗的敏感性, 改善癌症患者的预后, 在治疗癌症方面具有广阔的发展前景。本文就PI3K-AKT信号通路的分子机制及其在肿瘤中所起到的作用进行了介绍, 详细综述了纳米递送系统在基于通路治疗癌症的最新进展, 并对未来的前景进行了分析展望, 以期为将来研究提供参考。

关键词: PI3K; AKT; 肿瘤治疗; 纳米给药系统; 癌症

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Research advances in nanodelivery system-mediated cancer treatment through the PI3K-AKT signaling pathway

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Abstract: Aberrant activation of the phosphoinositide 3-kinase (PI3K)-AKT signaling pathway has been identified in numerous cancer types, contributing to uncontrolled cellular proliferation, inhibition of apoptosis, enhanced metastatic potential, and the development of resistance to chemotherapy and radiotherapy. Consequently, targeting the PI3K-AKT pathway has emerged as a promising therapeutic strategy. Current approaches to inhibit this pathway include small-molecule inhibitors, natural compounds, siRNAs, and miRNAs. However, these therapeutic approaches are often limited in clinical application due to prominent adverse effects, poor biological stability, low solubility, or lack of targeting ability. The integration of nanotechnology into drug delivery systems offers a compelling solution by improving drug stability and solubility, minimizing off-target accumulation, and enhancing tumor-specific targeting. Nanocarrier-based delivery of agents targeting the PI3K-AKT pathway holds the potential to improve therapeutic efficacy, mitigate drug-induced toxicity, sensitize tumors to conventional therapies, and ultimately enhance patient outcomes. This review provides a comprehensive overview of the PI3K-AKT signaling pathway and its oncogenic role, provides a detailed review of the latest progress of nano-based drug delivery system in cancer treatment based on pathways, and discusses future directions, aiming to inform and guide ongoing research in this field.

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癌症是一种严重威胁人类生命健康的疾病, 其发病率和死亡率逐年上升。2024年最新发布的数据显示, 2022年全球癌症病例数约为2 000万, 癌症死亡人数约为970万。预计2050年全球癌症病例数将达到3 530万, 癌症死亡人数预计达到1 850万[1]。因此, 强化癌症的预防措施、提升诊断技术及优化治疗手段, 对于延长人类寿命和提高生活质量至关重要。

目前, 肿瘤治疗的主要手段包括化疗、放疗、手术切除、免疫治疗和靶向治疗等。但肿瘤异质性导致的治疗无效或耐药性、手术切除后的复发与转移, 以及免疫治疗引发的强烈不良反应, 仍使肿瘤难以彻底治愈。信号通路在细胞间信息传递和细胞生长、增殖、凋亡等生命活动中发挥着关键调控作用, 因此受到广泛关注[2]。研究表明, 癌症发生时许多信号通路会发生异常变化, 促进癌细胞增殖和存活, 同时对治疗产生抗性[3]。在多种肿瘤中, 磷脂酰肌醇-3激酶 (phosphatidylinositol-3 kinase, PI3K) 及其下游信号蛋白激酶B (protein kinase B, PKB, 又称AKT) 组成的PI3K-AKT信号通路被发现异常激活, 为靶向该通路提供了重要的治疗机会和依据。目前, 针对PI3K-AKT通路的治疗主要依赖小分子靶向抑制剂, 这些抑制剂大多处于不同的临床试验阶段, 少数已获批用于癌症的临床治疗[4]。此外, 天然产物、RNA干扰 (RNA interference, RNAi) 技术和基因治疗等手段对PI3K-AKT信号通路的调控也在积极研究中。然而, 靶向抑制PI3K-AKT通路存在诸多障碍: 靶向抑制剂的治疗窗口较窄且常伴随不良反应[5]、天然产物的难溶性差[6]、RNA类物质在体内递送困难[7]均增加了临床应用的难度。纳米递送系统凭借其小粒径、大比表面积、高强度、稳定性和可修饰性等优点, 被广泛应用于药物递送, 为癌症治疗提供了全新的策略[8]。通过将纳米递送系统与药物结合, 不仅可改善药物的溶解性和靶向递送, 还能增加药物在病灶部位的蓄积, 从而实现更理想的治疗效果。

本文详细阐述了PI3K-AKT信号通路在肿瘤发生与治疗中的作用, 分析了当前用于抑制该通路的多种物质, 如小分子抑制剂、天然产物、小干扰RNA (small interfering RNA, siRNA) 及微RNA (microRNA, miRNA)。在应用中遇到的挑战, 并探讨了纳米递送系统在克服这些障碍方面的潜力。最后, 本文展望了该领域的未来发展, 提出了对靶向PI3K-AKT通路抗肿瘤疗法的见解。

1 PI3K-AKT信号通路

1.1 PI3K-AKT信号通路简介

PI3K是一种胞内磷脂酰肌醇激酶, 根据结构特点和底物分子分为I、II、III 3类[9]。I类PI3K是由一个催化亚基p110和一个调节亚基p85构成的异二聚体, 包括IA型 (PI3Kα、PI3Kβ和PI3Kδ) 和IB型 (PI3Kγ)[10], PI3Kα和PI3Kβ在哺乳动物体内广泛表达, 而PI3Kδ和PI3Kγ则主要存在于造血系统中, 研究发现IA型PI3K与癌症的发展息息相关[11]。

PI3K信号可由一系列受体酪氨酸激酶 (receptor tyrosine kinase, RTKs) 激活, 包括驱动增殖和迁移的表皮生长因子受体 (epixdermal growth factor receptor, EGFR)、刺激血管生成的血管内皮细胞生长因子受体 (vascular endothelial growth factor receptor, VEGFR)、刺激生长和存活的胰岛素样生长因子受体 (insulin like growth factor receptor, IGFR) 等[11,12] (图1)。除此之外, 细胞黏附分子如整合素、G蛋白偶联受体 (G protein-coupled receptors, GPCR) 的刺激也可以使PI3K-AKT通路活化[13]。PI3K将磷脂酰肌醇4,5-二磷酸 (phosphatidylinositol-4,5-bisphosphate, PIP_2) 催化为磷脂酰肌醇3,4,5-三磷酸 (phosphatidylinositol 3,4,5-trisphosphate, PIP_3), PIP_3充当第二信使, 促进具有pH结构域的AKT和3-磷酸肌醇依赖性蛋白激酶-1 (3-phosphoinositide-dependent protein kinase-1, PDK1) 向质膜募集, 并使PDK1磷酸化AKT蛋白上的苏氨酸磷酸化位点和丝氨酸磷酸化位点, 激活AKT[10,13]。一旦活化, 激活的AKT通过磷酸化多种酶、激酶和转录因子, 直接或间接激活或抑制下游底物, 调节细胞功能。例如, AKT的苏氨酸磷酸化诱导下游分子哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 的磷酸化, 使mTOR二聚体 (mTORC1和mTORC2) 转录, mTORC1诱导下游核糖体蛋白S6激酶和eEF2K等的磷酸化, 促进血管生成和蛋白翻译, mTORC2继续通过激活AKT促进细胞增殖存活[14]。

在正常情况下, 由于PI3K-AKT通路严格的调控机制PIP_3水平几乎检测不到, 抑癌基因同源性磷酸酶-张力蛋白 (phosphatase and tensin homolog, PTEN) 可以对PI3K-AKT途径进行负向调节, PTEN通过将PIP_3去磷酸化为PIP_2, 减少PIP_3在细胞内的累积, 减少AKT的活化, 阻止AKT调控的下游信号传导, 抑制下游激酶激活[15]。PI3K及其下游分子AKT构成的PI3K-AKT信号通路是哺乳动物重要的信号通路之一, 可以调节细

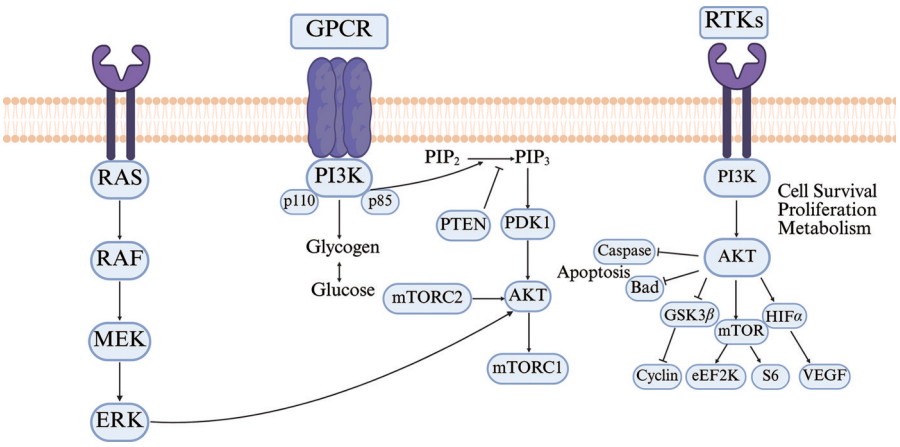


Figure 1 The overview of PI3K-AKT signaling pathway. GPCR: G protein-coupled receptors; RTKs: Kinase receptor tyrosine; PTEN: Phosphatase and tensin homolog; PIK3: Phosphatidylinositol-3 kinase; AKT: Rotein kinase B. Created with BioRender.com

胞的多种生理功能, 包括细胞周期、细胞存活、蛋白质合成和生长、代谢、运动和血管生成。PI3K-AKT信号通路在癌症中常被异常激活, 促进癌细胞生长存活, 增强肿瘤侵袭性[16]。

1.2 PI3K-AKT信号通路在肿瘤发展中的作用

PI3K-AKT途径是癌症中常被激活的途径之一, 几乎介导50%恶性肿瘤的发生[9]。癌症基因组图谱数据表明, 在乳腺癌[17]、卵巢癌[14]、非霍奇金淋巴瘤[18]等多种癌症中, 大量患者的PI3K-AKT通路的主要节点都被检测到发生突变或扩增[19]。其他的生理信号改变也会导致通路解除调控, 例如上游RTKs受体的激活, GPCR的刺激, 癌基因 (如RAS) 的诱导和其他信号通路之间的串扰[20]。另外, 肿瘤微环境 (tumor microenvironment, TME)[21]的缺氧可以导致活性氧的产生, 使PI3K-AKT/HIF-1α通路激活[15]。

1.2.1 PI3K-AKT通路在肿瘤生长、转移、耐药中的作用 随着对PI3K-AKT信号通路的深入研究, 其在肿瘤的生长、转移、耐药中所发挥的作用也被发现。PI3K-AKT通过下游mTOR等蛋白的介导, 促进了细胞增殖, 抑制凋亡, 增强了肿瘤细胞的自我保护功能[22,23]。肿瘤相关巨噬细胞 (tumor-associated macrophages, TAMs) 分泌的CCL18可通过激活PI3K-AKT通路诱导上皮间充质转化, 促进癌细胞转移[24]。尽管对肿瘤的研究治疗有了突破性进展, 但肿瘤细胞对化疗、放疗和免疫治疗的耐药性仍然是影响预后的重要因素[25]。由于肿瘤的异质性, 肿瘤细胞不但会对单一化疗药物产生耐药性, 还可能对其他具有不同化学结构或作用机制的药物产生交叉耐药性, 被异常激活的PI3K-AKT通路与癌细胞的耐药性息息相关[5]。临床前神经胶质母细胞瘤模型研究中发现, 超过50%的小鼠肿瘤复发是由于通过PI3K途径获得了耐药性, 阻断PI3K-AKT在一定程度上可以逆转耐药[22]。例如, pan-PI3K抑制剂LY294002能使多西紫杉醇 (docetaxel, DTX) 耐药细胞对DTX增敏, 改善耐药[26]。Yao等[27]揭示了外体miR-27A-3p通过PI3K-AKT途径调节巨噬细胞细胞程序性死亡−配体1 (programmed cell death 1 ligand 1, PD-L1) 的表达, 导致乳腺癌的免疫逃逸。PI3K信号通路的激活也促进了对内分泌治疗的耐药性[28]。

1.2.2 PI3K-AKT通路在免疫中的作用 PI3K-AKT信号通路除了可以调节肿瘤细胞的相关活动之外, 还与TME中存在大量的免疫细胞关系密切。PI3K-AKT是不同免疫细胞成熟和激活所必需的重要信号转导通路, 对TAMs和T细胞的调节起到尤为重要的作用[29]。TAMs具有不同的表型, M1型巨噬细胞具有促炎 (抗肿瘤) 功能, M2巨噬细胞具有抗炎 (促瘤) 功能[30]。PI3K-AKT信号通路是调节TAMs激活表型的中心因子, 可以促进巨噬细胞向M2型极化并调节巨噬细胞PD-L1的表达, 导致免疫逃逸[27,31]。例如胸腺素受体10就是通过PI3K-AKT通路促进M2 TAMs增殖, 导致肺腺癌的不良预后[32]。通过抑制PI3K-AKT途径, 能够促使M2巨噬细胞向M1重极化, 以扼制肿瘤进程[33]。研究人员发现, 位于GPCR和RAS下游的PI3Kγ信号对巨噬细胞的功能尤其关键[4]。由于PI3Kγ在TAMs中高表达, 抑制PI3Kγ可将巨噬细胞从免疫抑制的M2型转换为M1型, 重塑TME, 与细胞毒性T淋巴细胞协同消灭肿瘤[34,35]。PI3K-AKT通路在调节$CD8^+$T细胞新陈代谢和分化中起重要作用。通过体外阻断PI3Kγ或δ及抑制AKT信号可以阻止T细胞的终末分化, 并产生显著抗肿瘤特性的T细胞用于癌症的过继免疫治疗[35]。

2 纳米制剂在通过PI3K-AKT通路治疗肿瘤中的优势

由于PI3K-AKT在肿瘤发展过程中的重要作用, 利用PI3K及其信号通路治疗癌症具有广阔的前景, 研

究者们采用小分子抑制剂、天然产物、RNAi技术等各种手段对该通路进行抑制。然而小分子抑制剂狭窄的治疗窗口及常见的不良反应、天然产物的难溶性以及RNA在体内递送困难等原因限制了临床应用。如何改善药物的理化特性、减少药物的不良反应、安全有效输送药物是当前研究的热点也是难点。

纳米载体如脂质体和聚合物纳米粒等[36-40]可以提高药物的溶解性与稳定性, 保护药物不受体内降解, 延长其在血液中的循环时间, 并在肿瘤部位实现更高的药物浓度。此外, 纳米载体[41]通过控制药物释放速率, 能持续抑制PI3K-AKT通路, 增强治疗效果。PI3K-AKT通路的异常激活是肿瘤耐药性的重要原因, 传统化疗药物可能通过该通路逃逸失效。纳米制剂可以联合递送PI3K-AKT抑制剂与其他抗肿瘤药物, 通过多重机制协同抑制肿瘤生长。同时, 纳米制剂能够在肿瘤微环境中精准释放药物, 避免药物在正常组织中过早释放, 减少耐药性。PI3K-AKT通路在肿瘤细胞中异常活跃, 成为理想的靶点, 但PI3K-AKT抑制剂常面临靶向性差和药物分布不均的问题。纳米载体通过表面修饰[42](如抗体或肽段修饰) 能够精准靶向肿瘤细胞, 提高药物在肿瘤组织中的积累。纳米载体还利用肿瘤的 (enhanced permeability and retention effect, EPR效应)[43]和特异性受体将药物递送至肿瘤区域, 从而提高靶向治疗特异性, 并减少正常组织的毒性。此外, 智能纳米载体能够响应肿瘤微环境变化, 在特定条件下释放药物, 增强靶向治疗效果。纳米制剂通过提高PI3K-AKT抑制剂的稳定性、靶向性和疗效, 克服了传统治疗中的局限, 提供了更精准、更高效的治疗方案。随着技术的进步, 纳米制剂在靶向PI3K-AKT信号通路治疗中的应用将进一步推动癌症治疗的发展[44,45]。纳米递送系统见表1[36,37,39,40,46]。

3 基于PI3K-AKT通路的纳米制剂治疗肿瘤

以PI3K-AKT信号通路为靶点的癌症治疗是近年的研究热点, 但药物理化性质特殊、毒副作用较大、给药效率不高等问题制约了在临床上的应用。纳米递送系统递送药物可以克服生物屏障、提高药物的溶解度和靶向性、降低不良反应, 在最佳药物剂量和最小不良反应中治疗肿瘤。因此, 使用纳米系统靶向肿瘤组织, 调节PI3K-AKT信号通路可能是一种有效的癌症治疗方法。

3.1 PI3K小分子抑制剂纳米制剂

PI3K抑制剂[47]主要分为pan-PI3K抑制剂[48]、双靶点PI3K/mTOR抑制剂[49]和异构体特异性抑制剂。pan-PI3K抑制剂如GDC0941[22,50,51]、buparlisib[52]、ZSTK[53]选择性低或不具备选择性, GDC0941、buparlisib可以抑制所有I类PI3K亚型, PI3K/mTOR抑制剂如BEZ235[54-56]可以与PI3K和mTOR激酶的ATP结合裂隙结合, 抑制其催化活性[15], 二者在临床研究常出现药物诱导的严重不良反应。异构体特异性PI3K抑制剂会因同工酶的特异性产生不良反应, 例如, PI3Kα抑制剂与高血糖和皮疹有关, PI3Kδ抑制剂与胃肠道不良反应、骨髓抑制和转氨酶升高有关[57], 因此使用小分子

Table 1 Systematic comparison of different nanosystems

Nanoparticle delivery system	Drug loading efficiency	Stability	*In vivo* metabolism pathway	Drug loading capacity	Advantage	Disadvantage	Ref.
Lipid nanoparticles	High	To some extent affected by temperature and pH changes	Metabolized by the liver, possibly excreted through the kidneys	High	Good biocompatibility, high drug loading efficiency, suitable for the delivery of macromolecules such as RNA and DNA	Stability is affected by the environment, difficulty in large-scale production is relatively high, and the price is relatively high	[36]
Polymeric nanoparticles	Medium	High	Degraded by enzymes, metabolized by the liver, and excreted in urine	Medium	Good controllability, able to achieve sustained release of drugs, applicable to a variety of drugs	May have toxicity or immune reactions, high production cost, and may cause allergic reactions	[37]
Silica nanoparticles	Medium	High	Metabolized by the liver or excreted through the kidneys	Medium	High surface area, adjustable surface functionality, suitable for drug delivery and targeted therapy	May cause toxic reactions to cells, and the production cost is relatively high	[39]
Metal nanoparticles	Medium	High	Metabolized or excreted by the liver, which may lead to toxic accumulation	Low	High optical properties, can be used for imaging, and capable of targeted therapy	May have certain toxicity, long-term use may have negative effects on the human body, and high cost	[40]
Nanocarrier complexes	High	High	Can be metabolized and excreted through multiple pathways depending on the composite components	High	Multifunctional, able to adjust the release rate and targeting according to needs	The production process is complex, may trigger immune reactions, and high cost	[46]

抑制剂靶向PI3K-AKT通路用于治疗癌症关键因素是如何减少药物在正常组织中的蓄积, 降低对全身的毒性, 同时实现在肿瘤部位的靶向阻断。另外, 蛋白激酶的内在机制可能使单一靶点的小分子药物在肿瘤的过程中失效, 并导致耐药[58]。临床数据显示, 与单靶点治疗相比, 联合疗法在提高疗效、降低药物的毒性、克服耐药性等方面具有很大的潜力。鉴于此, 越来越多的研究者以纳米递送系统作为药物载体, 递送PI3K小分子抑制剂, 并与化疗或放疗、抗体及其他小分子抑制剂组合, 以求改善耐药, 获得更好的疗效。

R_7是一种由7种精氨酸组成的细胞穿膜肽, 通过内吞作用促进纳米粒子内化进入肿瘤细胞, 并通过胞体逃逸加速药物在胞浆中的蓄积。Wang等[22]以磺胺二甲氧嘧啶衍生物为单体合成了PSD共聚物, 并用叶酸修饰, 形成pH敏感材料。随后将聚乳酸−乙醇酸−聚乙二醇−细胞穿膜肽R_7纳米粒与PSD共聚物连接得到R_7/PSD-Fol NPs, 用于DTX和GDC0941的共递送。结果显示, 在TME酸性条件下, PSD-叶酸脱落, R_7暴露出来, 促进纳米粒内吞, 并介导体内逃逸, GDC0941通过阻断PI3K-AKT通路诱导耐药细胞凋亡, 使其具有较好的抗肿瘤治疗效果。Neufeld等[52]合成了含高Z元素Hf (high-Z element Hf) 和配体1,4-苯二甲酸的纳米金属骨架对聚腺苷二磷酸核糖聚合酶抑制剂talazoparib和pan-PI3K抑制剂buparlisib靶向PI3K-AKT通路进行共递送以增强肿瘤放化疗。

BEZ23是一种有效的双重PI3K/mTOR抑制剂, 但因溶解性差和瘤外毒性而退出早期临床试验[18]。Yin等[54]研究开发了谷胱甘肽 (glutathione, GSH) 敏感纳米颗粒, 其可以靶向载有前药BEZ235的前列腺特异性膜抗原 (prostate-specific membrane antigen, PSMA)。PSMA-NP/BEZ可响应前列腺癌组织中GSH水平升高, 释放BEZ235, 靶向抑制PI3K/AKT/mTOR通路并损害下游细胞功能。此外, PSMA-NP/BEZ可以损害髓源性抑制细胞的免疫抑制功能, 重塑前列腺癌中的“冷”免疫微环境, 增强免疫治疗效果。PSMA-NP/BEZ为提高晚期前列腺癌化疗和免疫治疗效果, 提供了一种安全有效的策略。

临床显示, 同时靶向MAPK和PI3K途径可能是治疗癌症的有效方式, 但两种抑制剂的使用会产生剂量限制性的心脏和免疫毒性。Palvai等[59]设计了一种包载MAPK抑制剂AZD6244、PI3K/mTOR抑制剂PI103和顺铂的透明质酸包裹的脂质嵌合纳米粒 (hyaluronic acid layered lipid-based chimeric nanoparticle, HA-CNP)。实验发现HA-CNP与结肠癌细胞共孵育24 h后, p-ERK1/2和p-AKT的表达显著降低, 并且HA-CNP诱导的细胞早期和晚期凋亡明显增加, 对正常成纤维细胞无毒性, 说明HA-CNP通过抑制MAPK和PI3K-AKT信号通路与顺铂结合, 阻滞细胞周期、促进细胞凋亡。

随着研究深入, 具有异构体选择性的PI3K抑制剂显示出更好的安全性[60]。Juan等[61]首次报道了一种肿瘤细胞靶向方法, 使用聚乳酸作为原料将选择性抑制PI3Kα[62,63]的Alpelisib封装到聚合物纳米颗粒中, 生成NP-Alpelisib, 并通过碳二亚胺化学在其表面偶联西妥昔单抗组成抗体偶联纳米颗粒 (ACNP-Alpelisib)。研究结果显示包封的Alpelisib抑制了不同细胞系中的PI3K通路激活, 并增加了药物在细胞中的生物利用度, 可作为改善药物摄取和分布并降低药物毒性在健康组织中的潜在策略。TAMs是免疫抑制微环境中最重要的组成部分[64]。IPI549[34,65,66]是首个进入临床研究阶段的PI3Kγ抑制剂, 可以通过重极化TME中M2巨噬细胞使原本对程序性死亡受体1、细胞毒性T淋巴细胞相关蛋白4等免疫检查点抑制剂耐药的肿瘤丧失耐药性[35,67]。Yu等[34]将IPI549与MnO_2纳米粒结合, 用牛血清白蛋白为载体制备了一种多功能纳米调节器重塑TME。静脉注射纳米药物后发现其可以有效地在肿瘤积累并通过MnO_2与肿瘤中H_2O_2反应缓解缺氧, 随后可通过在TME释放IPI549来抑制骨髓来源的抑制性细胞上的PI3Kγ, 进而下调PD-L1的表达并将TAM极化为M1表型, 增强$CD4^+$T淋巴细胞和$CD8^+$T淋巴细胞的浸润, 从而增强肿瘤的免疫治疗。

小分子抑制剂纳米制剂相关详细信息见表2。

3.2 天然产物纳米制剂

天然产物资源丰富, 具有高效、低毒、结构多样、可作用于癌症多种机制途径等优点, 开辟了癌症治疗的新思路[68]。天然产物具有多靶向性, 能够激活PTEN, 抑制PI3K-AKT信号通路[69], 但生物利用度差的问题限制了许多天然产物在体内发挥其生物效应, 纳米递送系统的出现带来了全新的解决方式。姜黄素 (curcumin, CUR)[46,70-72]、大麻二酚 (cannabidiol, CBD)[73]、染料木素 (genistein)[74]、白杨素[75]、双氢青蒿素 (dihydroartemisinin, DHA)[76]、虾青素 (astraxanthin, AX)[77]和fabatin[78]等都可以调节PI3K-AKT的表达, 诱导细胞死亡。

姜黄素是从植物姜黄根茎中提取的一种天然多酚化合物, 可以通过抑制PI3K-AKT和其他信号通路产生抗癌活性, 抑制肿瘤的发展[70], 还被证明具有荧光定位和化疗增敏作用[79,80]。但CUR水溶性差等导致其生物利用度低限制了其临床应用。为克服这一问题, Ghalehkhondabi等[46]开发了一种新型的双pH/氧化还原敏感纳米载体, 首次合成了单分散透明质酸 (hyaluronic acid, HA) 偶联响应性空心介孔二氧化硅纳米颗粒

Table 2 Nanocarriers loaded PI3K inhibitors in the treatment of tumor. BRCA: Breast cancer; OC: Ovarian cancer; PCa: Prostatic cancer; PEG: Polyethylene glycol; PLGA: Poly (lactic-co-glycolic acid); PEI: Polyetherimide; PLA: Poly lactic acid; PCL: Polycaprolactone

No.	Nanocarrier	PI3K inhibitor	Inhibitor type	Combination therapy	Cancer type	Ref.
1	PEG-PLGA polymeric nanoparticles	BEZ235	PI3K/mTOR	None	Non-hodgkin's lymphoma	[18]
2	PEG-PLGA polymeric nanoparticles	GDC0941	pan-PI3K	Docetaxel	BRCA	[22]
3	Bovine serum albumin nanoparticles	IPI549	PI3Kγ	MnO_2	BRCA	[34]
4	Prodrug nanomicelle	PF-04691502	PI3K/mTOR	None	BRCA	[49]
5	PLGA-p-PEI polymeric nanoparticles	GDC0941	pan-PI3K	Docetaxel	BRCA	[50]
6	Chitosan nanoparticle	GDC0941	pan-PI3K	KRAS siRNA	OC	[51]
7	Metal-organic frameworks	Buparlisib	pan-PI3K	Talazoparib	BRCA	[52]
8	PEG	ZSTK	pan-PI3K	Indomethacin	PCa	[53]
9	Polymeric nanoparticles	BEZ235	PI3K/mTOR	Sorafenib	Hepatocellular carcinoma	[55]
10	PEG-PLGA polymeric nanoparticles	BEZ235	PI3K/mTOR	Radiation therapy	Hepatocellular carcinoma	[56]
11	Lipid-based chimeric nanoparticle	PI103	PI3K/mTOR	AZD6244 and cisplatin	Colon cancer	[59]
12	PLA	Alpelisib	PI3Kα	Cetuximab	Head and neck cancer	[61]
13	Fucoidan-based nanoparticles	BYL-719	PI3Kα	Radiotherapy	Head and neck squamous cell carcinoma	[62]
14	Gold nanoparticles	*N*-(4-Hydroxyphenyl)4-hydroxy-2-quinolone-3-carboxamide	PI3Kα	None	BRCA	[63]
15	Porous hollow iron oxide nanoparticles	3-Methyladenine	PI3Kγ	None	BRCA	[64]
16	PEG-PCL polymeric nanoparticles	IPI549	PI3Kγ	Silibinin	BRCA	[65]
17	PEG-PLGA polymeric nanoparticles	IPI549	PI3Kγ	None	Melanoma	[66]

(hollow mesoporous silica nanoparticles, HMSNs)/聚甲基丙烯酸 (polymethacrylic acid, PMAA) 核壳纳米球, 负载CUR组成CUR@HA-PMAA/HMON纳米球, 具有优异的生物利用度, 在癌症治疗方面具有巨大潜力。研究发现CUR可以协同顺铂治疗肿瘤并减少毒副作用[81-83]。Sripetthong等[82]将缩水甘油三甲基铵四分化壳聚糖与香兰素偶联制备QCS-Vani亚胺纳米胶束负载CUR。将顺铂与CUR负载的纳米胶束联合使用, 不仅在抗癌活性方面具有协同作用, 而且对正常细胞的毒性较小, 减少使用顺铂等抗癌药物的不良反应。

大麻二酚[84]是从大麻中提取的一种天然成分, 能通过使PI3K-AKT通路失活, 抑制膀胱癌细胞增殖迁移, 促进膀胱癌细胞死亡, 但膀胱生理特性导致药物利用率较低。壳聚糖可以通过与膀胱壁表面的糖胺多聚糖反应增加黏附时间。使用壳聚糖包裹CBD-聚乳酸-羟基乙酸共聚物 [poly(lactic-*co*-glycolic acid), PLGA] 纳米粒显著增强材料与膀胱壁的黏附性, 改善了治疗效果[73]。

Genistein是一种天然的异黄酮类化合物, 主要存在于豆类植物中, 通过下调p-PI3K、p-AKT抑制肺癌的生长。Sacko等[74]制备了负载Genistein和miRNA-29b的免疫球蛋白杂化纳米粒 (genistein-miRNA-29b-loaded hybrid nanoparticles, GMLHN), 并用黏蛋白-1适体 [mucin-1 (MUC-1)-aptamer] 修饰偶联, 与非小细胞肺癌 (non-small cell lung cancer, NSCLC) 细胞膜表面过表达的MUC-1作用以提高癌细胞对纳米粒的内吞, 定向输送药物, 同时GMLHN能诱导细胞的凋亡, 抑制p-PI3K和p-AKT的表达, 降低PI3K-AKT通路活性, 提高对NSCLC的治疗效果。白杨素也是一种黄酮类化合物, 可以通过靶向PI3K-AKT等通路减少癌细胞的迁移和侵袭。但其不溶于水, 生物利用度低[85]。Kim等[75]将疏水性聚ε-己内酯和亲水性PEG组成的共聚物与白杨素混合, 得到白杨素纳米粒以增强白杨素生物利用度, 同时发现载药纳米粒降低了PI3K和核因子κB (nuclear factor kappa-B, NF-κB) 的表达, 减缓肿瘤生长。

青蒿素[86]是一种萜类化合物, 存在于中草药青蒿的花叶中, DHA[76,87]是青蒿素的衍生物, 因具有肿瘤治疗活性而受到关注。Zhang等[87]将DHA负载到聚谷氨酸稳定的Fe_3O_4磁 (Fe_3O_4-PGA) 得到Fe_3O_4-PGA-DHA纳米颗粒与负载多柔比星 (doxorubicin, DOX) 的聚天冬氨酸稳定的Fe_3O_4磁性纳米粒子 (Fe_3O_4-PASP-DOX) 结合用于三阴性乳腺癌 (triple-negative breast cancer, TNBC) 的脱铁, 增强化疗, 为TNBC的治疗提供了一种前景广泛治疗方法。

Sun等[77]在研究中发现AX对二甲基苯蒽 [7,12-dimethylbenz(a)anthracene, DMBA] 引起的癌症具有抑制作用, 研究人员制备了灵芝酸固体脂质纳米粒载虾青素 (SLN-AX), 实验中DMBA诱导的乳腺癌大鼠PTEN表达降低, PI3K、p-AKT、p-mTOR表达增加, 而SLN-AX治疗使PTEN表达显著增加, PI3K、p-AKT、p-mTOR表达显著降低, 重新抑制了PI3K-AKT信号通

路, 有效抑制大鼠肿瘤。Ramya等[78]从蚕豆种子中分离植物防御素阳离子抗菌肽fabatin, 将其负载到介孔二氧化硅纳米颗粒中以提高生物利用度, 保护其不被蛋白质水解。Chen等[88]合成了直径约为40～45 nm鱼腥草纳米氧化铜颗粒 (Hc-CuONPs), Hc-CuONPs对HeLa细胞有明显的细胞毒作用, 可通过抑制PI3K-AKT通路诱细胞凋亡, 抑制肿瘤生长。天然产物纳米制剂相关研究成果见表3[89]。

3.3 RNAi技术纳米制剂

在细胞内DNA被转录为mRNA, mRNA被翻译为蛋白质。部分蛋白质表达过少或过多, 就可能促进癌症发生, 而对mRNA进行递送或控制此类蛋白的合成可能是解决方法[90]。研究者用聚酰胺–胺型树枝状高分子 [poly(amidoamine), PAMAM] 第0代树枝状大分子 (G0) 与1,2环氧十四烷合成阳离子类脂化合物G0-C14, 将PLGA与G0-C14和mRNA络合并用lipid-PEG包裹形成聚合物脂质杂化纳米粒, 用于递送PTEN的mRNA至PTEN缺失的前列腺癌细胞中, 产生的PTEN的功能性表达, 重新抑制了PI3K-AKT信号通路, 增加细胞凋亡[91]。RNAi是近年来生命科学领域重大的发现之一, 常用其对mRNA进行调节, 通过使用miRNA[44,92-94]、siRNA等非编码RNA特异性地降解或抑制同源mRNA, 从而抑制或关闭特定基因表达[95,96], 直接或间接地调节靶基因的转录翻译[97]。miRNA是一种长度为20～25个核苷酸的非编码RNA, 参与人体内多种生物学过程, 可以通过与特定位点结合调节靶基因的水平和各种信号通路的激活程度发挥作用。miR-22等miRNA在癌症中过表达, 参与癌症进展, 还有一些miRNA如miR126作为肿瘤抑制因子发挥作用, 在肿瘤中表达下调[92,93], 但miRNA不稳定的性质和较短的循环半衰期严重阻碍了应用, 将miRNA安全地输送到靶向作用部位是达到理想治疗效果关键的一步。

Liu等[44]为了延长miRNA在血液中的循环时间, 将miR-128-3p包裹在poly (ethylene glycol)-poly[2-(*N*, *N*′-dimethylamino) ethylmethacrylate] (PEG-PDMAEMA)中制备成纳米复合物PDMAEMA-NP, 并在表面修饰了可以特异性靶向结直肠癌中过表达的单羧酸转运蛋白1的肿瘤归巢肽CPKSNNGVC (CPDMAEMA-NP)。miR-128-3p在进入体内2 h内迅速代谢, 但CPDMAEMA-NP循环时间可以延长至8 h。CPDMAEMA-NP组miR-128-3p升高显著降低p-PI3K、p-AKT和p-mTOR的表达, 且PI3K-AKT通路被抑制程度最强, 诱导细胞凋亡。

siRNA[98-101]是RNAi的关键介导因子, 由21～23个双链核苷酸组成, 在极低的细胞内浓度下提供高效的基因沉默, 并且几乎没有毒性作用。2018年美国食品药品监督管理局批准了首个基于RNAi机制的药物Onpattro, 标志着siRNA药物的研发有了新的突破。Onpattro可以靶向甲状腺素运载蛋白, 抑制mRNA的表达, 治疗由遗传性转甲状腺素蛋白淀粉样变性引起的多发性周围神经疾病。随后基于RNAi技术的Givlaari和Oxlumo也相继被批准上市, 激发了人们的研究热情。但siRNA是一种带负电的水溶性大分子, 不具备组织和肿瘤靶向的能力, 且很难通过带负电的细胞膜被细胞内化[102]。即使少量通过内吞途径进入细胞, 也

Table 3 Recent progress on inhibition of PI3K-AKT signal pathway by using nanoparticles for delivering of natural products. HA: Hyaluronic acid; PMAA: Polymethacrylic acid; HMON: Hollow mesoporous orgnosilica nanoparticles; MSN: Mesoprous silica nanoparticles; NSCLC: Non-small cell lung cancer; TNBC: Triple-negative breast cancer; PVP: Ployvinyl pyrrolidone; GTAMAC: Glycerol trimethylammonium chloride; QCS: Quaternized chitosan

No.	Natural product	Nanocarrier	Combination therapy	Cancer type	Ref.
1	Curcumin	HA-PMAA/HMON	None	BRCA	[46]
2	Curcumin	PEG-MSN	None	Pancreatic cancer	[70]
3	Curcumin	α-Fe_2O_3/Fe_3O_4	None	Gastric cancer	[71]
4	Curcumin	Calcium-doped dendritic MSN	None	BRCA	[72]
5	Cannabidiol	PLGA polymeric nanoparticles	None	Bladder cancer	[73]
6	Genistein	Hybrid nanoparticles	miRNA-29b	NSCLC	[74]
7	Chrysin	PCL-PEG polymeric nanoparticles	None	TNBC	[75]
8	Dihydroartemisinin	Zeolitic imidazolate framework-8	None	Liver cancer	[76]
9	Astraxanthin	Solid lipid nanoparticles	None	Liver cancer	[77]
10	Fabatin	MSN	None	BRCA	[78]
11	Curcumin	Chitosan nanoparticle	Cisplatin	OC	[79]
12	Curcumin	PLGA/PVP polymeric nanoparticles	GANT61	BRCA	[80]
13	Curcumin	GTAMAC-QCS	Pt	Lung cancer	[82]
14	Curcumin	PEG-PLGA	Cisplatin	NSCLC	[83]
15	Dihydroartemisinin	Fe_3O_4-PGA	DOX	TNBC	[87]
16	Houttuynia cordata	Copper oxide nanoparticles	None	Cervical cancer	[88]
17	Turmeric	Turmeric silver nanoparticles	Electrochemotherapy	TNBC	[89]

会被溶酶体降解, 达不到治疗作用[103]。除此之外, 网状内皮系统的摄取、血液中循环的核酸酶的降解、肾脏肝脏的滤过排出作用都导致siRNA在血液中的半衰期较短, 难以持续发挥作用。纳米载体与siRNA结合或包裹, 从而进入TME, 能提升治疗效果[20]。Fernandez-Alarcon等[101]开发了一个金属海藻酸盐水凝胶库, 其中含有高浓度的金属离子, 通过局部高温破坏癌细胞线粒体中的Ca^{2+}稳态。将致癌基因沉默核酸装载到由聚 (R-氨基酯) 组成的聚合物纳米颗粒中, 嵌入金属海藻酸盐水凝胶中, 靶向激活PI3K/AKT/mTOR等多药耐药途径的癌细胞, 安全有效地消除残留的癌细胞并增强抗肿瘤免疫力。

长链非编码RNA (long non-coding RNA, lncRNA) 是长度大于200个核苷酸的非编码RNA。研究表明, lncRNA在剂量补偿效应、表观遗传调控、细胞周期调控和细胞分化调控等众多生命活动中发挥作用。临床研究发现, PRKAR1B-AS2长非编码RNA的表达与OC患者的不良预后紧密相关, PRKAR1B-AS2通过直接调节PI3Kα激活PI3K-AKT信号通路, 促进肿瘤发生, 产生化疗耐药。Elsayed等[14]制备了载PRKAR1B-AS2 siRNA的1,2-二油酰-甘油-3-磷脂酰胆碱 (1,2-dioleoyl-*sn*-glycero-3-phosphatidylcholine, DOPC) 纳米脂质体。实验发现沉默PRKAR1B-AS2后显著抑制了PRKAR1B-AS2的表达, siRNA被有效递送。DOPC-PRKAR1B-AS2-siRNA处理的小鼠PI3Kα蛋白表达被抑制, 降低了PDK1、AKT和mTOR的磷酸化, 有效抑制了肿瘤生长, 并提高了肿瘤细胞对顺铂的敏感性。

整合素β1能激活PI3K-AKT信号通路, 促进多种癌细胞的增殖, 下调EF2K可降低整合素β1的表达, 降低Src、PI3K/AKT和NF-κB信号通路的活性。基于此, Erdogan等[104]设计了EF2K siRNA, 并用脂质体纳米粒包裹, siRNA沉默EF2K后, 诱导了卵巢癌细胞整合素β1的表达下调, 抑制了PI3K-AKT信号通路的活性。RNAi技术纳米制剂相关研究成果见表4。

3.4 功能纳米制剂

纳米材料不仅可以输送药物, 还可能作为药物发挥作用[105,106]。Wang等[105]发现将$HAuCl_4$与癌细胞孵育后, 通过一系列高度活跃的酶如NADPH氧化酶、谷胱甘肽还原酶、一氧化氮合酶产生的氧化还原反应可以将Au (III) 还原为Au (0), 自发合成荧光纳米金团簇。实验表明原位合成的Au-NCs通过抑制PI3K-AKT信号通路而抑制肿瘤的发展。Gd_2O_3常被用来作为磁共振成像的造影剂。Liu等[107]合成了掺杂镧系离子Eu^{3+}的Gd_2O_3粒子, 形成高效的双模纳米探针。Zheng等[108]发现注射Gd_2O_3: Eu^{3+}纳米粒后, 小鼠PI3K的mRNA水平下降, 转录受到抑制, 蛋白表达水平降低, 抑制PI3K相关通路, 对癌症治疗产生作用。

Du以金纳米棒作为内核, 外层用二氧化硅包覆, 表面固定超小氧化铁纳米粒 (iron oxide nanoparticles, IONPs), 创新性的开发了近红外光触发的核−壳−卫星纳米棒 (core-shell-satellite nanomaces, Au@MSN@IONP)[109]。金纳米棒将近红外光能转化为热能以诱导细胞产生H_2O_2, 与纳米粒表面的IONPs发生芬顿反应, 产生·OH, 从而抑制PI3K-AKT信号通路, 诱导细胞死亡。Liu等[110]开发了$CoFe_2O_4$量子点协同光热和光动力通过调节PI3K-AKT通路治疗非小细胞肺癌。You等[111]制备的Bi_2Se_3粒子具有高效的光吸收能力, 光热治疗后, 在Bi_2Se_3中暴露的细胞PI3K-AKT信号显著减弱。Guo等[112]利用脉冲激光烧蚀技术合成氧化锡纳米粒子, 纳米粒通过下调PI3K/AKT信号通路增强抗癌作用。

3.5 其他纳米制剂

随着人们对基因了解的深入, 利用基因工具更好的治疗癌症成为研究的热点。CRISPR/Cas9是近年来发展迅速的基因敲除技术, 比siRNA具有更高的基因沉默效率。Zhang等[113]利用聚酰胺胺适配子包裹负载索拉非尼和CRISPR/Cas9的中空介孔二氧化硅, 敲除EGFR基因, 抑制EGFR-PI3K-AKT通路, 实现肿瘤抑

Table 4 Delivery of RNA substances by nano-carriers. PAMAM: Poly (amidoamine); PTEN: Phosphatase and tensin homolog; EGFR: Epixdermal growth factor receptor

No.	RNA	Nano-carrier	Combination therapy	Cancer type	Ref.
1	PARKAR1B-AS2 siRNA	Liposomes	None	OC	[14]
2	miRNA-128-3p	PEG-PDMAEMA polymeric nanoparticles	None	Colorectal cancer	[44]
3	PTEN mRNA	PAMAM-PLGA-PEG	None	PCa	[91]
4	miR126	Chitosan	None	Melanoma	[92]
5	miRNA-22-3p	Single lipid-based nanoparticles	None	TNBC	[93]
6	as-miR-21	PAMAM	5-Fluorouracil	Glioblastoma	[94]
7	PI3K p110β siRNA	PEG-chitosan nanoparticle	Rac1 siRNA	Colon cancer	[98]
8	siRNA	Chitosan	Salinomycin	Gastric carcinoma	[99]
9	EGFR siRNA	PEG-PEI polymeric nanoparticles	BRD4siRNA	TNBC	[100]
10	siRNA	Nanoparticles	Metal ion	Melanoma	[101]
11	EF2K siRNA	Single lipid-based nanoparticles	None	OC	[104]

制。钙调素 (calmodulin, CaM) 是一种钙结合蛋白, 与细胞增殖、代谢、运动和凋亡密切相关。CaM可以诱导PI3K的磷酸化, 促进下游蛋白的活化, 还能与AKT的pH结构域结合, 直接激活AKT, 导致PI3K-AKT途径完全激活。Bao等[114]将聚吡咯二酮和二棕榈酰磷脂酰乙醇胺–聚乙二醇–马来酰亚胺组装起来, 并用CaM抗体修饰, 构建了近红外光响应的共轭聚合物纳米粒 (conjugated polymer nanoparticle, CPNs-C) 与CaM结合形成CaM/CPNs-C, CaM/CPNs-C与细胞膜上的PI3K和AKT结合, 在近红外光的照射下, CaM/CPNs-C产生光热效应, 抑制PI3K和AKT的磷酸化, 减少PIP_3的积聚, 抑制PI3K-AKT信号通路, 促进细胞凋亡。

仿生纳米粒子具有超强生物相容性和免疫逃逸能力, 在肿瘤靶向治疗中受到广泛关注。Ji等[115]将抗血管内皮生长因子受体修饰到癌细胞–巨噬细胞杂化膜包裹的载索拉非尼中空硫化铜纳米粒子中用于肝癌的光热治疗。巨噬细胞膜帮助纳米粒进行免疫逃逸, 而肿瘤细胞膜则产生归巢作用, 协助癌细胞对纳米粒的摄取。杂化膜包裹的纳米粒VEGFR抗体与索拉非尼通过协同抑制PI3K/AKT和Ras/Raf/MEK/ERK途径, 联合光热治疗肿瘤。

功能纳米制剂及其他纳米制剂研究成果见表5。

Table 5 Summary of other nanodelivery system applications

No.	Nanocarrier	Combination therapy	Cancer type	Ref.
1	Gold nanoclusters	None	Cervical cancer	[105]
2	Gd_2O_3:Eu^{3+} nanoparticles	None	None	[108]
3	Core-shell-satellite nanomaces	Photothermal therapy	NSCLC	[109]
4	$CoFe_2O_4$-quantum dots	Photothermal therapy	NSCLC	[110]
5	Bi_2Se_3 nanoparticles	Photothermal therapy	NSCLC	[111]
6	Tin oxide nanoparticles	Photothermal therapy	BRCA	[112]
7	Hollow mesoporous silica nanoparticles	Sorafenib	Hepatocellular carcinoma	[113]
8	Polymer nanoparticle	None	BRCA	[114]
9	Hybrid membrane camouflaged copper sulfide nanoparticles	Sorafenib	Hepatocellular carcinoma	[115]

4 结语与展望

癌症不仅从生理上破坏人体机能, 还影响人的心理和情绪, 严重时夺走人们的生命, 使用手术、化疗、放疗等传统的治疗方法可能收效甚微。PI3K-AKT信号通路在肿瘤细胞的增殖、迁移和耐药性中起着关键作用, 为癌症治疗提供了新的思路。然而, 传统靶向药物面临药物溶解性差、靶向性差和不良反应大等问题。纳米制剂作为新兴的药物递送平台, 通过优化药物递送系统, 显著提高药物的稳定性和生物利用度, 并能够精准靶向肿瘤组织, 克服传统治疗的局限性。此外, 纳米载体还可以联合使用其他抗肿瘤药物, 增强治疗效果, 克服耐药性。尽管纳米制剂展现了巨大的潜力, 但仍面临载体毒性、免疫原性和大规模生产一致性等临床转化障碍。通过优化载体设计和改进生产工艺, 这些障碍有望得到解决, 推动纳米载体在肿瘤治疗中的广泛应用。通过包裹聚乙二醇外壳延长纳米颗粒的循环时间[42]; 设计特殊结构如二硫键使纳米粒参与TME响应[21]; 通过设计配体或连接具有靶向性的物质, 如透明质酸[116]增强纳米粒靶向性; 使用细胞穿膜肽增加纳米粒内吞和溶酶体逃逸[22]; 联合超声、光热[110]等技术增强对肿瘤的杀伤性等。随着纳米技术的不断进步, 未来更多基于纳米载体的治疗手段将在靶向PI3K-AKT通路的肿瘤治疗中得到应用, 极大地改善癌症患者的治疗效果。

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References

[1] Bizuayehu HM, Ahmed KY, Kibret GD, et al. Global disparities of cancer and its projected burden in 2050 [J]. JAMA Netw Open, 2024, 7: e2443198.

[2] Nisar S, Hashem S, Macha MA, et al. Exploring dysregulated signaling pathways in cancer [J]. Curr Pharm Des, 2020, 26: 429-445.

[3] Cheng Z, Li MY, Dey R, et al. Nanomaterials for cancer therapy: Current progress and perspectives [J]. J Hematol Oncol, 2021, 14: 85.

[4] Castel P, Toska E, Engelman JA, et al. The present and future of PI3K inhibitors for cancer therapy [J]. Nat Cancer, 2021, 2: 587-597.

[5] Vanhaesebroeck B, Perry MWD, Brown JR, et al. PI3K inhibitors are finally coming of age [J]. Nat Rev Drug Discov, 2021, 20: 741-769.

[6] Liang Y, Liu ZY, Wang PY, et al. Nanoplatform-based natural products co-delivery system to surmount cancer multidrug-resistant [J]. J Control Release, 2021, 336: 396-409.

[7] Kim B, Park JH, Sailor MJ. Rekindling RNAi therapy: materials design requirements for *in vivo* siRNA delivery [J]. Adv Mater, 2019, 31: e1903637.

[8] Mu WW, Chu QH, Liu YJ, et al. A review on nano-based drug

delivery system for cancer chemoimmunotherapy [J]. Nanomicro Lett, 2020, 12: 142.

[9] Zhang MZ, Jang H, Nussinov R. PI3K inhibitors: Review and new strategies [J]. Chem Sci, 2020, 11: 5855-5865.

[10] Vivanco I, Sawyers CL. The phosphatidylinositol 3-kinase AKT pathway in human cancer [J]. Nat Rev Cancer, 2002, 2: 489-501.

[11] Garces AE, Stocks MJ. Class 1 PI3K clinical candidates and recent inhibitor design strategies: A medicinal chemistry perspective [J]. J Med Chem, 2019, 62: 4815-4850.

[12] Thapa N, Chen M, Horn HT, et al. Phosphatidylinositol-3-OH kinase signalling is spatially organized at endosomal compartments by microtubule-associated protein 4 [J]. Nat Cell Biol, 2020, 22: 1357-1370.

[13] Fruman DA, Chiu H, Hopkins BD, et al. The PI3K pathway in human disease [J]. Cell, 2017, 170: 605-635.

[14] Elsayed AM, Bayraktar E, Amero P, et al. PRKAR1B-AS2 long noncoding RNA promotes tumorigenesis, survival, and chemoresistance *via* the PI3K/AKT/mTOR pathway [J]. Int J Mol Sci, 2021, 22: 4.

[15] Yang J, Nie J, Ma XL, et al. Targeting PI3K in cancer: Mechanisms and advances in clinical trials [J]. Mol Cancer, 2019, 18: 26.

[16] Janku F, Yap TA, Meric-Bernstam F. Targeting the PI3K pathway in cancer: Are we making headway? [J]. Nat Rev Clin Oncol, 2018, 15: 273-291.

[17] Tian Y, Zhao L, Gui ZW, et al. PI3K/AKT signaling activates HIF1*α* to modulate the biological effects of invasive breast cancer with microcalcification [J]. NPJ Breast Cancer, 2023, 9: 93.

[18] Au KM, Wang AZ, Park SI. Pretargeted delivery of PI3K/mTOR small-molecule inhibitor – loaded nanoparticles for treatment of non-Hodgkin′s lymphoma [J]. Sci Adv, 2020, 6: eaaz9798.

[19] Yuan TL, Cantley LC. PI3K pathway alterations in cancer: Variations on a theme [J]. Oncogene, 2008, 27: 5497-5510.

[20] Singh P, Singh A, Shah S, et al. RNA interference nanotherapeutics for treatment of glioblastoma multiforme [J]. Mol Pharm, 2020, 17: 4040-4066.

[21] Zhuang JL, Chen SQ, Hu Y, et al. Tumour-targeted and redox-responsive mesoporous silica nanoparticles for controlled release of doxorubicin and an siRNA against metastatic breast cancer [J]. Int J Nanomedicine, 2021, 16: 1961-1976.

[22] Wang YY, Li J, Chen JJ, et al. Multifunctional nanoparticles loading with docetaxel and GDC0941 for reversing multidrug resistance mediated by PI3K/Akt signal pathway [J]. Mol Pharm, 2017, 14: 1120-1132.

[23] Yi JM, Zhu JJ, Wu J, et al. Oncogenic activation of PI3K-AKT-mTOR signaling suppresses ferroptosis *via* SREBP-mediated lipogenesis [J]. Proc Natl Acad Sci U S A, 2020, 117: 31189-31197.

[24] Zhao CL, Zheng SX, Yan ZQ, et al. CCL18 promotes the invasion and metastasis of breast cancer through Annexin A2 [J]. Oncol Rep, 2020, 43: 571-580.

[25] Vasan N, Baselga J, Hyman DM. A view on drug resistance in cancer [J]. Nature, 2019, 575: 299-309.

[26] Sekino Y, Han XR, Kawaguchi T, et al. TUBB3 reverses resistance to docetaxel and cabazitaxel in prostate cancer [J]. Int J Mol Sci, 2019, 20: 3936.

[27] Yao XL, Tu Y, Xu YL, et al. Endoplasmic reticulum stress-induced exosomal miR-27a-3p promotes immune escape in breast cancer *via* regulating PD-L1 expression in macrophages [J]. J Cell Mol Med, 2020, 24: 9560-9573.

[28] Mayer IA, Abramson VG, Isakoff SJ, et al. Stand up to cancer phase Ib study of pan-phosphoinositide-3-kinase inhibitor buparlisib with letrozole in estrogen receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer [J]. J Clin Oncol, 2014, 32: 1202-1209.

[29] Lin YX, Xu JX, Lan HY. Tumor-associated macrophages in tumor metastasis: Biological roles and clinical therapeutic applications [J]. J Hematol Oncol, 2019, 12: 76.

[30] Elia I, Haigis MC. Metabolites and the tumour microenvironment: From cellular mechanisms to systemic metabolism [J]. Nat Metab, 2021, 3: 21-32.

[31] Vergadi E, Ieronymaki E, Lyroni K, et al. Akt signaling pathway in macrophage activation and M1/M2 polarization [J]. J Immunol, 2017, 198: 1006-1014.

[32] Zeng J, Yang XG, Yang L, et al. Thymosin *β*10 promotes tumor-associated macrophages M2 conversion and proliferation *via* the PI3K/Akt pathway in lung adenocarcinoma [J]. Respir Res, 2020, 21: 328.

[33] Chen MM, Lai RM, Lin XY, et al. Downregulation of triggering receptor expressed on myeloid cells 1 inhibits invasion and migration of liver cancer cells by mediating macrophage polarization [J]. Oncol Rep, 2021, 45: 37.

[34] Yu M, Duan XH, Cai YJ, et al. Multifunctional nanoregulator reshapes immune microenvironment and enhances immune memory for tumor immunotherapy [J]. Adv Sci (Weinh), 2019, 6: 1900037.

[35] Dwyer CJ, Arhontoulis DC, Rangel Rivera GO, et al. *Ex vivo* blockade of PI3K gamma or delta signaling enhances the antitumor potency of adoptively transferred $CD8^+$ T cells [J]. Eur J Immunol, 2020, 50: 1386-1399.

[36] Lei M, Ma GL, Sha SJ, et al. Dual-functionalized liposome by co-delivery of paclitaxel with sorafenib for synergistic antitumor efficacy and reversion of multidrug resistance [J]. Drug Deliv, 2019, 26: 262-272.

[37] Deirram N, Zhang CH, Kermaniyan SS, et al. pH-responsive polymer nanoparticles for drug delivery [J]. Macromol Rapid Commun, 2019, 40: e1800917.

[38] Chen K, Xin X, Qiu LP, et al. Co-delivery of p53 and MDM2 inhibitor RG7388 using a hydroxyl terminal PAMAM dendrimer derivative for synergistic cancer therapy [J]. Acta Biomater,

2019, 100: 118-131.

[39] Kankala RK, Han YH, Na J, et al. Nanoarchitectured structure and surface biofunctionality of mesoporous silica nanoparticles [J]. Adv Mater, 2020, 32: e1907035.

[40] Kankala RK, Zhang H, Liu CG, et al. Metal species-encapsulated mesoporous silica nanoparticles: Current advancements and latest breakthroughs [J]. Adv Funct Mater, 2019, 29: 1902652.

[41] Dong CH, Feng W, Xu WW, et al. The coppery age: Copper (Cu) -involved nanotheranostics [J]. Adv Sci (Weinh), 2020, 7: 2001549.

[42] Tang YX, Wang XY, Li J, et al. Overcoming the reticuloendothelial system barrier to drug delivery with a "Don't-Eat-Us" strategy [J]. ACS Nano, 2019, 13: 13015-13026.

[43] Kalyane D, Raval N, Maheshwari R, et al. Employment of enhanced permeability and retention effect (EPR): Nanoparticle-based precision tools for targeting of therapeutic and diagnostic agent in cancer [J]. Mater Sci Eng C Mater Biol Appl, 2019, 98: 1252-1276.

[44] Liu X, Dong C, Ma SP, et al. Nanocomplexes loaded with miR-128-3p for enhancing chemotherapy effect of colorectal cancer through dual-targeting silence the activity of PI3K/AKT and MEK/ERK pathway [J]. Drug Deliv, 2020, 27: 323-333.

[45] Schroeder A, Heller DA, Winslow MM, et al. Treating metastatic cancer with nanotechnology [J]. Nat Rev Cancer, 2011, 12: 39-50.

[46] Ghalehkhondabi V, Fazlali A, Soleymani M. Preparation of hyaluronic acid-decorated hollow meso-organosilica/poly (methacrylic acid) nanospheres with redox/pH dual responsivity for delivery of curcumin to breast cancer cells [J]. Mater Today Chem, 2023, 34: 101780.

[47] Li HY, Wen X, Ren YT, et al. Targeting PI3K family with small-molecule inhibitors in cancer therapy: Current clinical status and future directions [J]. Mol Cancer, 2024, 23: 164.

[48] Peng X, Huang X, Lulu TB, et al. A novel pan-PI3K inhibitor KTC1101 synergizes with anti-PD-1 therapy by targeting tumor suppression and immune activation [J]. Mol Cancer, 2024, 23: 54.

[49] Yang QC, Ma XB, Xiao Y, et al. Engineering prodrug nanomicelles as pyroptosis inducer for codelivery of PI3K/mTOR and CDK inhibitors to enhance antitumor immunity [J]. Acta Pharm Sin B, 2022, 12: 3139-3155.

[50] Zuo TT, Li J, Zhang J, et al. Coadministration of chemotherapy and PI3K/Akt pathway treatment with multistage acidity/CathB enzyme-responsive nanocarriers for inhibiting the metastasis of breast cancer [J]. Biomater Sci, 2019, 7: 5054-5067.

[51] Kim MJ, Lee SJ, Ryu JH, et al. Combination of KRAS gene silencing and PI3K inhibition for ovarian cancer treatment [J]. J Control Release, 2020, 318: 98-108.

[52] Neufeld MJ, DuRoss AN, Landry MR, et al. Co-delivery of PARP and PI3K inhibitors by nanoscale metal-organic frameworks for enhanced tumor chemoradiation [J]. Nano Res, 2019, 12: 3003-3017.

[53] Zhang Z, Hou L, Yu Z, et al. Biomimetic small-molecule self-assembly of PI3K inhibitor integrated with immunomodulator to amplify anticancer efficacy [J]. Chem Eng J, 2022, 433: 133747.

[54] Yin L, Yang FY, Wang WK, et al. PSMA-targeted nanoparticles with PI3K/mTOR dual inhibitor downregulate P-glycoprotein and inactivate myeloid-derived suppressor cells for enhanced chemotherapy and immunotherapy in prostate cancer [J]. Adv Mater, 2025, 37: e2415322.

[55] Wu BQ, Li AM, Zhang YC, et al. Resistance of hepatocellular carcinoma to sorafenib can be overcome with co-delivery of PI3K/mTOR inhibitor BEZ235 and sorafenib in nanoparticles [J]. Expert Opin Drug Deliv, 2020, 17: 573-587.

[56] Tang XL, Li AM, Xie CM, et al. The PI3K/mTOR dual inhibitor BEZ235 nanoparticles improve radiosensitization of hepatoma cells through apoptosis and regulation DNA repair pathway [J]. Nanoscale Res Lett, 2020, 15: 63.

[57] Hosford SR, Dillon LM, Bouley SJ, et al. Combined inhibition of both p110α and p110β isoforms of phosphatidylinositol 3-kinase is required for sustained therapeutic effect in PTEN-deficient, ER^+ breast cancer [J]. Clin Cancer Res, 2017, 23: 2795-2805.

[58] Liao MR, Zhang J, Wang G, et al. Small-molecule drug discovery in triple negative breast cancer: Current situation and future directions [J]. J Med Chem, 2021, 64: 2382-2418.

[59] Palvai S, Kuman MM, Sengupta P, et al. Hyaluronic acid layered chimeric nanoparticles: Targeting MAPK-PI3K signaling hub in colon cancer cells [J]. ACS Omega, 2017, 2: 7868-7880.

[60] Zhang MQ, Zhou FM, Qi ZP, et al. Synthesis and anti-tumor activity of pyrazole pyrimidine PI3Kγ/δ inhibitors [J]. Acta Pharm Sin (药学学报), 2024, 59: 2041-2052.

[61] Juan A, Segrelles C, del Campo-Balguerías A, et al. Anti-EGFR conjugated nanoparticles to deliver alpelisib as targeted therapy for head and neck cancer [J]. Cancer Nanotechnol, 2023, 14: 29.

[62] Mizrachi A, Shamay Y, Shah J, et al. Tumour-specific PI3K inhibition *via* nanoparticle-targeted delivery in head and neck squamous cell carcinoma [J]. Nat Commun, 2017, 8: 14292.

[63] Mahmoud NN, Abuarqoub D, Zaza R, et al. Gold nanocomplex strongly modulates the PI3K/Akt pathway and other pathways in MCF-7 breast cancer cell Line [J]. Int J Mol Sci, 2020, 21: 9.

[64] Li K, Lu L, Xue CC, et al. Polarization of tumor-associated macrophage phenotype *via* porous hollow iron nanoparticles for tumor immunotherapy *in vivo* [J]. Nanoscale, 2020, 12: 130-144.

[65] Jiang M, He KY, Qiu T, et al. Tumor-targeted delivery of silibinin and IPI-549 synergistically inhibit breast cancer by remodeling the microenvironment [J]. Int J Pharm, 2020, 581: 119239.

[66] Zhang XQ, Shen LM, Liu Q, et al. Inhibiting PI3 kinase-γ in both myeloid and plasma cells remodels the suppressive tumor microenvironment in desmoplastic tumors [J]. J Control Release, 2019, 309: 173-180.

[67] Kaneda MM, Messer KS, Ralainirina N, et al. PI3Kγ is a molecular switch that controls immune suppression [J]. Nature, 2016, 539: 437-442.

[68] Tan P, Zhang YF, Wang LY, et al. A novel chalcone derivative C13 inhibits the growth of humangastric cancer cells through suppressing ErbB4/PI3K/AKTsignaling pathway [J]. Acta Pharm Sin (药学学报), 2024, 59: 957-964.

[69] Ashrafizadeh M, Zarrabi A, Hushmandi K, et al. Progress in natural Compounds/siRNA co-delivery employing nanovehicles for cancer therapy [J]. ACS Comb Sci, 2020, 22: 669-700.

[70] Prabhuraj RS, Mal A, Valvi SK, et al. Noninvasive preclinical evaluation of targeted nanoparticles for the delivery of curcumin in treating pancreatic cancer [J]. ACS Appl Bio Mater, 2020, 3: 4643-4654.

[71] Ma M, Lv Z, Li Y, et al. Enhanced anti-cancer effects of magnetic targeted pH-sensitive curcumin delivery system based on heterogeneous magnetic α-Fe_2O_3/Fe_3O_4 nanoparticles on gastric cancer SGC-7901 cells [J]. Arab J Chem, 2023, 16: 105352.

[72] Wang J, Wang Y, Liu Q, et al. Rational design of multifunctional dendritic mesoporous silica nanoparticles to load curcumin and Enhance efficacy for breast cancer therapy [J]. ACS Appl Mater Interfaces, 2016, 8: 26511-26523.

[73] Chen SS, Deng CP, Zheng WY, et al. Cannabidiol effectively promoted cell death in bladder cancer and the improved intravesical adhesion drugs delivery strategy could be better used for treatment [J]. Pharmaceutics, 2021, 13: 1415.

[74] Sacko K, Thangavel K, Shoyele SA. Codelivery of genistein and miRNA-29b to A549 cells using aptamer-hybrid nanoparticle bioconjugates [J]. Nanomaterials (Basel), 2019, 9: 1052.

[75] Kim KM, Jung J. Upregulation of G protein-coupled estrogen receptor by chrysin-nanoparticles inhibits tumor proliferation and metastasis in triple negative breast cancer xenograft model [J]. Front Endocrinol (Lausanne), 2020, 11: 560605.

[76] Li YW, Song Y, Zhang W, et al. MOF nanoparticles with encapsulated dihydroartemisinin as a controlled drug delivery system for enhanced cancer therapy and mechanism analysis [J]. J Mater Chem B, 2020, 8: 7382-7389.

[77] Sun T, Gao J, Han D, et al. Fabrication and characterization of solid lipid nano-formulation of astraxanthin against DMBA-induced breast cancer *via* Nrf-2-Keap1 and NF-κB and mTOR/Maf-1/PTEN pathway [J]. Drug Deliv, 2019, 26: 975-988.

[78] Ramya S, Paulpandi M, Kavithaa K, et al. Fabatin-loaded silica nanoparticle-induced apoptosis *via* mitochondrial dysfunction: Targeting the PI3K/AKT molecular pathway as a therapeutic implication against triple negative breast cancer [J]. New J Chem, 2021, 45: 17847-17861.

[79] Sandhiutami NMD, Arozal W, Louisa M, et al. Curcumin nanoparticle enhances the anticancer effect of cisplatin by inhibiting PI3K/AKT and JAK/STAT3 pathway in rat ovarian carcinoma induced by DMBA [J]. Front Pharmacol, 2020, 11: 603235.

[80] Borah A, Pillai SC, Rochani AK, et al. GANT61 and curcumin-loaded PLGA nanoparticles for GLI1 and PI3K/Akt-mediated inhibition in breast adenocarcinoma [J]. Nanotechnology, 2020, 31: 185102.

[81] Kuhad A, Pilkhwal S, Sharma S, et al. Effect of curcumin on inflammation and oxidative stress in cisplatin-induced experimental nephrotoxicity [J]. J Agric Food Chem, 2007, 55: 10150-10155.

[82] Sripetthong S, Nalinbenjapun S, Basit A, et al. Preparation of self-assembled, curcumin-loaded nano-micelles using quarternized chitosan-vanillin imine (QCS-Vani imine) conjugate and evaluation of synergistic anticancer effect with cisplatin [J]. J Funct Biomater, 2023, 14: 525.

[83] Chen Y, Chen C, Zhang XJ, et al. Platinum complexes of curcumin delivered by dual-responsive polymeric nanoparticles improve chemotherapeutic efficacy based on the enhanced anti-metastasis activity and reduce side effects [J]. Acta Pharm Sin B, 2020, 10: 1106-1121.

[84] Esmaeli M, Dehabadi MD, Khaleghi AA. Cannabidiol as a novel therapeutic agent in breast cancer: Evidence from literature [J]. BMC Cancer, 2025, 25: 772.

[85] Moghadam ER, Ang HL, Asnaf SE, et al. Broad-spectrum preclinical antitumor activity of chrysin: Current trends and Future perspectives [J]. Biomolecules, 2020, 10: 1374.

[86] Zhou ZW, Farhan M, Xing XG, et al. Artemisinin suppressed melanoma recurrence and metastasis after radical surgery through the KIT/PI3K/AKT pathway [J]. Int J Biol Sci, 2025, 21: 75-94.

[87] Zhang J, Zhou K, Lin J, et al. Ferroptosis-enhanced chemotherapy for triple-negative breast cancer with magnetic composite nanoparticles [J]. Biomaterials, 2023, 303: 122395.

[88] Chen HM, Feng XJ, Gao L, et al. Inhibiting the PI3K/AKT/mTOR signalling pathway with copper oxide nanoparticles from *Houttuynia cordata* plant: Attenuating the proliferation of cervical cancer cells [J]. Artif Cells Nanomed Biotechnol, 2021, 49: 240-249.

[89] Mittal L, Camarillo IG, Varadarajan GS, et al. High-throughput, label-free quantitative proteomic studies of the anticancer effects of electrical pulses with turmeric silver nanoparticles: An *in vitro* model study [J]. Sci Rep, 2020, 10: 7258.

[90] Buschmann MD, Carrasco MJ, Alishetty S, et al. Nanomaterial delivery systems for mRNA vaccines [J]. Vaccines (Basel), 2021, 9: 65.

[91] Islam MA, Xu YJ, Tao W, et al. Restoration of tumour-growth suppression *in vivo via* systemic nanoparticle-mediated delivery of PTEN mRNA [J]. Nat Biomed Eng, 2018, 2: 850-864.

[92] Arasi MB, De Luca G, Chronopoulou L, et al. MiR126-targeted-nanoparticles combined with PI3K/AKT inhibitor as a new strategy to overcome melanoma resistance [J]. Mol Ther Nucleic

Acids, 2023, 32: 152-167.

[93] Gorur A, Bayraktar R, Ivan C, et al. ncRNA therapy with miRNA-22-3p suppresses the growth of triple-negative breast cancer [J]. Mol Ther Nucleic Acids, 2021, 23: 930-943.

[94] Ren Y, Kang CS, Yuan XB, et al. Co-delivery of as-miR-21 and 5-FU by poly(amidoamine) dendrimer attenuates human glioma cell growth *in vitro* [J]. J Biomater Sci Polym Ed, 2010, 21: 303-314.

[95] Bhan A, Soleimani M, Mandal SS. Long noncoding RNA and cancer: A new paradigm [J]. Cancer Res, 2017, 77: 3965-3981.

[96] Li K, Zhang YQ, Hussain A, et al. Progress of photodynamic and RNAi combination therapy in cancer treatment [J]. ACS Biomater Sci Eng, 2021, 7: 4420-4429.

[97] Meng X, Lou QY, Yang WY, et al. The role of non-coding RNAs in drug resistance of oral squamous cell carcinoma and therapeutic potential [J]. Cancer Commun (Lond), 2021, 41: 981-1006.

[98] Kim MJ, Kim H, Gao X, et al. Multi-targeting siRNA nanoparticles for simultaneous inhibition of PI3K and Rac1 in PTEN-deficient prostate cancer [J]. J Ind Eng Chem, 2021, 99: 196-203.

[99] Wu C, Zhang Y, Li F, et al. Precise engineering of cholesterol-loaded chitosan micelles as a promising nanocarrier system for co-delivery drug-siRNA for the treatment of gastric cancer therapy [J]. Process Biochem, 2022, 120: 265-274.

[100] Zhang C, Yuan W, Wu Y, et al. Co-delivery of EGFR and BRD4 siRNA by cell-penetrating peptides-modified redox-responsive complex in triple negative breast cancer cells [J]. Life Sci, 2021, 266: 118886.

[101] Fernandez-Alarcon J, Cladera MA, Rodriguez-Camenforte N, et al. Regulation of mitochondrial apoptosis *via* siRNA-loaded metallo-alginate hydrogels: A localized and synergistic antitumor therapy [J]. Biomaterials, 2025, 318: 123164.

[102] Cummings JC, Zhang HW, Jakymiw A. Peptide carriers to the rescue: Overcoming the barriers to siRNA delivery for cancer treatment [J]. Transl Res, 2019, 214: 92-104.

[103] Subhan MA, Torchilin VP. Efficient nanocarriers of siRNA therapeutics for cancer treatment [J]. Transl Res, 2019, 214: 62-91.

[104] Erdogan MA, Ashour A, Yuca E, et al. Targeting eukaryotic elongation factor-2 kinase suppresses the growth and peritoneal metastasis of ovarian cancer [J]. Cell Signal, 2021, 81: 109938.

[105] Wang MN, Yu ZQ, Feng H, et al. *In situ* biosynthesized gold nanoclusters inhibiting cancer development *via* the PI3K-AKT signaling pathway [J]. J Mater Chem B, 2019, 7: 5336-5344.

[106] Wang JL, Zhang G, Li QW, et al. *In vivo* self-bio-imaging of tumors through *in situ* biosynthesized fluorescent gold nanoclusters [J]. Sci Rep, 2013, 3: 1157.

[107] Liu J, Tian XM, Luo NQ, et al. Sub-10 nm monoclinic Gd_2O_3: $Eu3^+$ nanoparticles as dual-modal nanoprobes for magnetic resonance and fluorescence imaging [J]. Langmuir, 2014, 30: 13005-13013.

[108] Zheng CJ, Tian XM, Cai J, et al. *In vivo* immunotoxicity of Gd_2O_3: Eu^{3+} nanoparticles and the associated molecular mechanism [J]. J Biochem Mol Toxicol, 2020, 34: e22562.

[109] Du Y, Yang C, Li FY, et al. Core-shell-satellite nanomaces as remotely controlled self-fueling Fenton reagents for imaging-guided triple-negative breast cancer-specific therapy [J]. Small, 2020, 16: e2002537.

[110] Liu JF, Shi XY, Zhang RJ, et al. $CoFe_2O_4$-quantum dots for synergistic photothermal/photodynamic therapy of non-small-cell lung cancer *via* triggering apoptosis by regulating PI3K/AKT pathway [J]. Nanoscale Res Lett, 2021, 16: 120.

[111] You Y, Li JX, Chen LL, et al. Photothermal killing of A549 cells and autophagy induction by bismuth Selenide particles [J]. Materials (Basel), 2021, 14: 33373.

[112] Guo Y, Zhao Y, Zhao X, et al. Exploring the anticancer effects of tin oxide nanoparticles synthesized by pulsed laser ablation technique against breast cancer cell line through downregulation of PI3K/AKT/mTOR signaling pathway [J]. Arab J Chem, 2021, 14: 103212.

[113] Zhang BC, Luo BY, Zou JJ, et al. Co-delivery of sorafenib and CRISPR/Cas9 based on targeted core-shell hollow mesoporous organosilica nanoparticles for synergistic HCC therapy [J]. ACS Appl Mater Interfaces, 2020, 12: 57362-57372.

[114] Bao BK, Gao D, Li N, et al. Near-infrared light regulation of tumor PI3K/Akt signaling pathway for enhancing cancer cell apoptosis through conjugated polymer nanoparticles [J]. ACS Appl Bio Mater, 2020, 3: 2428-2437.

[115] Ji B, Cai HQ, Yang Y, et al. Hybrid membrane camouflaged copper sulfide nanoparticles for photothermal-chemotherapy of hepatocellular carcinoma [J]. Acta Biomater, 2020, 111: 363-372.

[116] Kang Y, Sun W, Li SY, et al. Oligo hyaluronan-coated silica/hydroxyapatite degradable nanoparticles for targeted cancer treatment [J]. Adv Sci (Weinh), 2019, 6: 1900716.