PDX模型在纳米递送系统评价中的应用

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摘要: 恶性肿瘤是影响人类健康的重大疾病, 纳米递送系统本身具有独特的尺寸效应, 对其功能化修饰后可实现药物分子的肿瘤靶向聚集、提高治疗效果、减小对正常组织和细胞的毒副作用。将源自患者的癌细胞或小肿瘤组织直接移植到免疫缺陷小鼠体内, 可建立患者来源的异种移植 (patient-derived xenografts, PDX) 模型。相比于肿瘤细胞系模型, 该模型可保持原发肿瘤的组织形态、异质性及基因异常等关键特征, 并使其在各代之间保持稳定。PDX模型被广泛应用于药物评估、靶标发现和生物标志物开发, 尤其为纳米递送系统的诊断和治疗评价提供了可靠研究平台。本综述总结了常见癌症PDX模型在纳米递送系统评价中的应用, 以期为本领域科研人员开展相关研究提供参考。

关键词: 纳米递送系统; 患者来源的异种移植模型; 癌症; 免疫缺陷小鼠; 药物评价

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Application of PDX model in the evaluation of nano-delivery systems

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Abstract: Malignant tumor is a major disease affecting human health. The nano-delivery system itself has a unique size effect and it can achieve tumor-targeted distribution of drug molecules, improve the therapeutic effect, and reduce the toxic and side effects on normal tissues and cells after functional modification. Patient-derived xenografts (PDX) models can be established by transplanting patient-derived cancer cells or small tumor tissue into immunodeficient mice directly. Compared with the tumor cell line model, this model can preserve the key features of the primary tumor such as histomorphology, heterogeneity, and genetic abnormalities, and keep them stable between generations. PDX models are widely used in drug evaluation, target discovery and biomarker development, especially providing a reliable research platform for the diagnosis and treatment evaluation of nano-delivery systems. This review summarizes the application of several common cancer PDX models in the evaluation of nano-delivery systems, in order to provide references for researchers to perform related research.

Key words: nano-delivery system; patient-derived xenografts model; cancer; immunodeficient mouse; drug evaluation

癌症是一种高度异质性疾病, 由具有多种特征的癌细胞组成。临床前研究中为避免异种移植模型与患者肿瘤之间的差异, 患者来源的异种移植 (patient-derived xenografts, PDX) 模型被广泛应用。PDX模型是指将来自患者的癌细胞或小肿瘤组织移植到免疫功

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能低下的小鼠体内[1] (图1), 常用的免疫缺陷小鼠有裸鼠 (nude mice)、重度联合免疫缺陷 (severe combined immunodeficiency, SCID) 小鼠、非肥胖糖尿病/重度联合免疫缺陷 (diabetes of non-obese diabetic/SCID, NOD/SCID) 小鼠及NSG/NOG小鼠 (在NOD/SCID基础上敲除白介素2受体) (表1)。

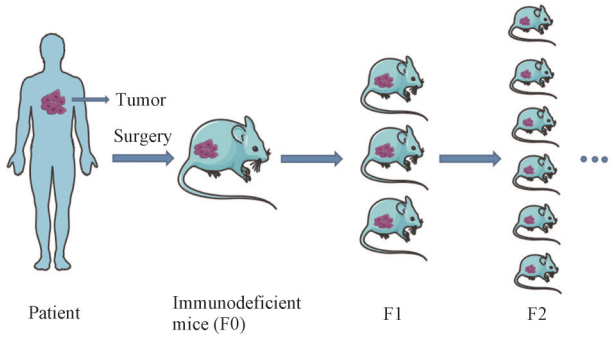

Figure 1 The establishment process of the patient-derived xenografts (PDX) model

在癌症诊疗领域, 脂质体 (liposomes, LP)、纳米粒 (nanoparticles, NP) 及纳米胶束 (nano micelles, NM) 等纳米递送系统显示出巨大的应用潜力。纳米系统可通过增强渗透性和滞留效应 (enhanced permeability and retention effect, EPR) 提高靶部位药物浓度、减少非特异性毒副作用[2]。肿瘤细胞系等传统肿瘤模型不能准确反映肿瘤的异质性, 导致临床前结果与实际临床结果有较大差异, 而PDX模型可保持原发肿瘤的组织形态、异质性、肿瘤组织基因型和表型多样性、肿瘤结构和肿瘤血管系统等关键特征, 更好地还原肿瘤生长微环境, 更准确反映患者肿瘤的发生发展机制, 更真实反映肿瘤患者的药物敏感性和耐受性[3]。目前, 研究者常建立皮下、原位 (patient-derived organoids xenografts, PDOX) 及肾下PDX模型来评估新型纳米药物的抗癌疗效, 为临床研究提供更真实的预测结果。

近年来, 癌症患者衍生模型发展迅速, 其在基础研究、药物开发和临床中的应用愈加广泛而深入, PDX模型相关研究在近10年来呈明显增长趋势。本综述总结了PDX模型在纳米递送系统治疗、诊断及诊疗一体化评价中的应用, 主要基于乳腺癌 (breast cancer, BC)、胰腺癌、肺癌 (lung cancer, LC)、胶质母细胞瘤 (glioblastoma, GBM)、结直肠癌 (colorectal cancer, CRC)、卵巢癌 (ovarian cancer, OC) 和肝癌 (hepatocarcinoma, HCC) 这7种癌症展开。

1 BC

三阴性乳腺癌 (triple-negative breast cancer, TNBC) 是BC预后最差的一个亚型, 其特点是雌激素受体、孕激素受体和人表皮生长因子受体-2缺乏表达[4]。通过开发新型纳米药物进行辅助治疗可减少TNBC患者因化疗产生的非特异性不良反应。研究者利用原位和皮下PDX模型进行了治疗、诊断和诊疗一体化研究。

1.1 原位移植 BC PDOX模型是指将患者肿瘤移植至免疫缺陷小鼠乳腺脂肪垫的模型。有研究者利用生物相容性良好的聚 (氰基丙烯酸酯) 化合物作为药物载体制备卡巴他塞 (cabazitaxel, CBZ) NP, 发现其在肿瘤部位聚集, 增强CBZ治疗效果[5,6]。纳米递送系统可降低某种药物的耐药性, Miller-Kleinhenz等[7]在Wnt和尿激酶型纤溶酶原激活物受体 (urokinase-type plasminogen activator receptor, uPAR) 过表达的耐药性BC PDX模型中证实双靶向的超小磁性氧化铁NP (iron oxide nanoparticles, IONP) 比单靶向NP及游离药物具备更强的肿瘤增殖和转移抑制能力, 为耐药性BC提供新的治疗方法。

NP中不同类别的治疗剂联用可增强疗效, 减少耐药性。Sulaiman等[8]将紫杉醇 (paclitaxel, PTK) 和维替泊芬 (verteporfin, CL 318952) 封装于同一NP, 利用PDX模型发现肿瘤对NP展示出EPR效应, 且通过抑制NF-κB (nuclear factor kappa-B)、Wnt和Yes相关蛋白 (Yes-associated protein, YAP) 通路来抑制肿瘤增殖。El-Sahli等[9]将PTK、CL 318952和康普立停A4三种药物共装封于聚合物−脂质杂化NP中, 在TNBC PDX模型中证实靶向乳腺癌细胞、癌症干细胞和肿瘤脉管系统的三药纳米疗法治疗效果更好。另有报道[10]将贝伐单抗 (bevacizumab, BEV) 与载荷抗肿瘤药物喜树碱 (camptothecin, CPT) 的NP-药物偶联物CRLX101联用, 在SCID小鼠体内, CRLX101可维持较高的肿瘤灌注并减少肿瘤缺氧, 减少BEV引起的耐药性。

Table 1 Comparison of immunodeficient mouse strains. SCID: Severe combined immunodeficiency; NOD/SCID: Diabetes of non-obese diabetic/SCID; NSG/NOG: NOD/SCID/IL2Rγ^{null}; s.c.: Subcutaneous; NK: Natural killer

Mouse strain	Advantage	Disadvantage	Success rate of PDX
Nude	Hairless; well characterized; easy to detect s.c. tumor	Functional B and NK cells; increased T cell leakage with age	Low
SCID	Better engraftment compared with nude mice	Functional NK cell; leakage of T cells; radiosensitive	Low
NOD/SCID	Better engraftment; multiple defects	High incidence of thymoma; short life span; radiosensitive	Moderate
NSG/NOG	Excellent engraftment of PDX	Breeding is not easy; expensive	High

PDX模型除用于评价纳米药物治疗效果外, 还可在癌症治疗过程中实时监测药物的体内吸收、分布、代谢和排泄。BC发生时常伴随某些受体数量增加, 例如黄体生成素释放激素 (luteinizing hormone-releasing hormone, LHRH) 受体、C-X-C基序趋化因子受体4 (C-X-C motif chemokine receptor 4, CXCR4) 等, Xiao等[11]选定合成的 (*D*-Lys)-LHRH作为靶向配体, 与二硫化物交联胶束 (disulfide crosslinking micelles, DCM) 载体结合来递送PTK, 在LHRH受体高表达的TNBC PDX模型中, 通过近红外光 (near infrared, NIR) 及核磁共振成像 (magnetic resonance imaging, MRI) 观察到PTK-LHRH-DCMs在肿瘤部位实现药物靶向释放。有研究者用牛血清白蛋白 (bovine serum albumin, BSA) 与3,4-二氟亚苄基姜黄素 (3,4-difluorobenzylidene curcumin, CDF)、乙酰唑胺结合制备NP, CDF水溶性得到改善, 近红外染料S0456标记的NP成像显示NP在NOD/SCID小鼠肿瘤部位的摄取增加, 在缺氧条件下发挥超高的治疗效果[12]。

BC晚期治疗效果差、复发率高, 为提高BC患者晚期生存率, 除开发新的治疗药物外, 提高诊断技术也是重中之重。有研究者用配体FC131与^{64}Cu标记的铜纳米簇结合形成^{64}Cu-CuNCs-FC131, 在CXCR4高或低表达的TNBC PDX模型中通过体内电子计算机断层扫描 (computed tomography, CT) 成像证实^{64}Cu-CuNCs-FC131可靶向CXCR4受体, 指示肿瘤位置[13]。虽然纳米递送系统已被报道用于临床前成像诊断研究, 但其潜在的毒性、肿瘤早期诊断准确性较低等不足限制了应用, 有待进一步的研究。

1.2 皮下移植 另有学者建立皮下PDX模型来诊断肿瘤发生, 将新鲜的患者肿瘤标本经过处理后移植于免疫缺陷小鼠皮下, 一般选择移植在双侧腹股沟、后侧面、前腋窝处。Yang等[14]向裸鼠皮下注射uPAR靶向纳米探针, 经新型内窥镜观察到肿瘤荧光信号增强了4倍, 在肿瘤诊断和精准切除方面显示出巨大潜力。

2 胰腺癌

胰腺癌患者中有80%～90%为胰腺导管腺癌 (pancreatic ductal adenocarcinoma, PDAC), 死亡率高, 预后极差, 且大多数PDAC患者在确诊时已是晚期, 往往只能接受化疗干预[15]。化疗耐药是胰腺癌治疗失败的最常见原因, 纳米递送系统可增加靶部位药物浓度, 提高疗效, 研究者常建立皮下和原位PDX模型进行研究。

2.1 皮下移植 皮下移植方式简单、方便观察, 可用于评估单独用药治疗效果。Guo等[16]使用吉西他滨 (gemcitabine, GEM) 耐药PDX模型, 发现用人血清白蛋白 (human serum albumin, HSA) NP装封由肉豆蔻酰与GEM 4-氨基相偶联合成的GEM-C14, 对GEM耐药的患者抗肿瘤效果大于GEM。另有研究者设计了一种以血小板凝集素-1 (plectin-1, LRP-1) 为靶标、结合miR-9的新型嵌合肽超分子NP递送多柔比星 (doxorubicin, Dox), 发现该NP通过下调eIF5A2表达以抑制自噬并诱导PDAC体内凋亡, 改善Dox的抗癌作用[17]。有研究将生物活性物质siRNA-circFARSA设计成LP或NP, 利用PDX模型证实其可抑制circFARSA的表达, 为PDAC提供新的治疗工具[18]。

PDX模型也常用于评估联合用药治疗效果。Zhang等[19]使用该模型证明7-乙基-10-羟基CPT (SN-38)及其两亲性前药伊立替康 (irinotecan, Ir) 制成的纳米分散体治疗效果优于单独用药。有研究报道, PDAC多呈现出基因异常表达, 溴结构域蛋白4 (bromodomain containing 4, BRD4) 抑制剂JQ1与周期蛋白依赖性激酶 (cyclin-dependent kinase 7, CDK7) 抑制剂THZ1可通过靶向SE复合物影响致癌转录和肿瘤特征, 发挥协同作用, 如Huang等[20]发现由JQ1、THZ1与疏水性聚 (酯酰胺) 纳米载体结合制成的NP可在实现高载药量的同时满足靶向递送。另有研究用裸鼠建立了10个PDAC PDX模型, 将F_3代肿瘤分为4组 (对照、PTK-HSA-NP、S-1、S-1+PTK-HSA-NP), 证实联合用药不易产生耐药性[21]。

由于PDAC缺乏生物标志物, 很难在早期发现并进行治疗, MRI成为早期发现PDAC的重要手段。纳米造影剂在体外成像、延长体循环和提供最佳成像窗口等方面比传统造影剂更具优势, 有研究者使用皮下PDX模型来比较Mag和Mag脂质纳米粒造影剂在小鼠体内的成像强度, 证实纳米造影剂可延长成像时间, 增加小肿瘤的分辨度, 有利于更早发现肿瘤[22]。

2.2 原位移植 PDOX模型能更准确地模拟肿瘤微环境, 目前常用来评估药物联用的治疗效果。有研究者在裸鼠体内证实鼠伤寒沙门氏菌与GEM、PTK NP联用可改善治疗效果, 减少毒副作用[23]。

研究者常利用MRI、正电子发射型计算机断层显像 (positron emission computed tomography, PET)、NIR成像和在体生物光学成像 (*in vivo* optical imaging, IVIS) 等方法监测PDOX模型中纳米递送系统的治疗反应。Zhou等[24]将胰岛素样生长因子1受体与携带Dox的IONP结合制备NP, 通过对比MRI以及NIR成像发现该NP可增加药物的靶向递送量。Ventura等[25]通过MRI与PET成像发现PDOX模型中的肿瘤对Ir LP的摄取增加, 而Chen等[26]使用PET与IVIS成像监测到裸鼠体内PTK LP的生物分布。由此看来, 将不

同类型的成像技术进行融合, 能更准确地获得关于肿瘤的性质、大小、位置及边界等诊断信息, 为肿瘤的诊断、治疗指导及效果评估带来更多帮助。

3 LC

LC是男性死亡率最高的疾病, 分为小细胞肺癌 (small cell lung cancer, SCLC) 和非小细胞肺癌 (non-small cell lung cancer, NSCLC)。目前, 纳米制剂的开发已是LC研究的热点, 且研究者多用皮下PDX模型进行LC的新药筛选。

对于LC, 有很多具有广阔应用前景的纳米药物。Zhang等[27]制备负载表没食子儿茶素没食子酸酯 (epigallocatechin gallate, EGCG) 的聚乳酸-乙醇酸共聚物 [poly(lactic-*co*-glycolic acid), PLGA] NP, 基于皮下PDX模型的体内研究显示, EGCG-NPs的肿瘤抑制效果显著强于游离EGCG。Ir可用来治疗SCLC, 但易产生耐药性, 有研究用长循环LP装封Ir, 增加Ir循环时间, 使其转化为活性产物SN-38, 在SCLC PDX模型中发挥疗效[28]。还有研究者用BSA NP递送伊曲康唑 (itraconazole, ITA), 在NSG小鼠中发挥更好的治疗效果[29]。miRNA也可治疗LC, 在SCID小鼠建立的PDX模型中发现, 使用NP递送miR-486-5p的模拟物可通过诱导$CD133^+$肿瘤干细胞凋亡, 改善治疗效果[30]。Makita等[31]通过PDX模型发现, 用脂质NP封装动力相关蛋白2 miRNA可抑制肿瘤生长, 增强肿瘤对厄洛替尔的敏感性。上述研究表明, miRNA在LC治疗中发挥重要作用, 借助纳米递送系统靶向输送miRNA进而抑制肿瘤的生长和转移, 将成为一种极具潜力的肺部疾病治疗方法。另有研究发现, 溶酶体细胞死亡调节因子 (lysosomal cell death regulator, LCDR) 可介导癌症的凋亡, Yang等[32]用NP递送si-LCDR, 在NSG小鼠体内研究表明其可发挥靶向作用并抑制肿瘤生长。

纳米递送系统共载或与其他疗法联用能最大限度地发挥抗癌疗效。研究者在NSCLC PDX模型发现用聚乙二醇NM共装封PTK和ITA的治疗效果大于游离药物[33]。Cao等[34]则用LP共装封β-榄香烯和顺铂 (cisplatin, CDDP), 在NOD/SCID小鼠体内发现共载LP比单载LP对肿瘤细胞的毒性更大。研究发现, 可使用NP共同递送miRNA发挥治疗作用。Di Paolo等[35]利用PDX模型发现用脂质NP包裹的miR-126-3p和miR-221-3p抑制剂的联合系统性传递通过阻断PIK_3R_2-AKT通路降低肿瘤生长。另有研究用重组RNA分子剂递送let-7c/miR-124, 使用相同建模方式证实其可治疗NSCLC, 有望开发治疗致命性NSCLC的新RNA疗法[36]。为改善CDDP对LC晚期的治疗, Wang等[37]用NP递送铂的前药, 在耐药性PDX模型中发现, 其通过NIR照射可变为CDDP, 增强抗肿瘤作用, 实现光热疗和化疗联用。

4 GBM

GBM是成人中最具侵袭性和致命性的脑肿瘤, 具有快速增殖、高浸润能力、化学抗性和快速形成复发的能力。治疗方法包括手术切除肿瘤、放疗和替莫唑胺 (temozolomide, TMZ) 化疗, 但预后很差, 目前常用皮下和原位移植的方式建立PDX模型来开发新治疗方案。

4.1 皮下移植 目前, 各种siRNA常被用来治疗GBM, 可使用皮下PDX模型来检验其治疗效果。Manju等[38]向建立皮下PDX模型的裸鼠脑内注射siRNA NP凝胶, 发现其可抑制裸鼠脑肿瘤生长。有研究使用同种模型证实用LP来递送铁蛋白重链1 (ferritin heavy polypeptide 1, FTH1) siRNA可使FTH1下调, 延缓癌细胞生长[39]。还有研究发现用纳米聚合物来递送siRNA, 对肿瘤进行多RNA治疗, 能抑制肿瘤的发展[40]。多项PDX模型研究说明纳米药物-siRNA偶联物可靶向抑制GBM癌症干细胞的异常基因, 相比化疗毒副作用更小, 是一种很有潜力的临床治疗策略。

为解决长期使用TMZ带来的耐药性问题, Wang等[41]借助PDX动物模型, 对多药联用策略的抗肿瘤效果进行评价。首先用二硫键修饰的纳米载体递送奥沙利铂前药和阳离子DNA嵌入剂来调节SCID小鼠的体内代谢, 再利用TMZ进行干预, 发现TMZ的抗肿瘤效果增强。

为提高纳米递送系统的疗效, 可结合其他疗法进行联合干预。Borah等[42]使用PDX模型评价发现, 阳离子聚丙烯酰胺NP可实现靶向递送药物HPPH, 且能与光、声动力疗法结合共同影响肿瘤血管系统。还有研究用卟啉衍生物脱镁叶酸A与Ir制备完全活性药物NP, 发现其在裸鼠体内药物释放增加, 且实现光动力疗法、光热疗法和化疗的癌症三联疗法[43]。

4.2 原位移植 为降低TMZ的耐药性, 研究者采用TMZ与生物活性物质联用的方法。Wang等[44]开发了一种IONP, 基于GEM PDOX的研究模型发现, 该NP可靶向递送siRNA, 抑制裸鼠TMZ抗性基因, 与TMZ联用可增加肿瘤细胞凋亡, 减少肿瘤生长。另有研究在同种模型证实, 纳米细胞介导的递送系统递送miR 34a与TMZ联合治疗可提高TMZ的敏感性, 有望成为一种新型治疗方法[45]。

5 CRC

CRC占全球癌症死亡人数的第3位。研究者使用皮下移植方式建立PDX模型模拟肿瘤的发生, 如在裸

鼠中建模, 用金纳米粒递送MDM2和MDMX十二聚体肽拮抗剂, 发现该NP在转移过程中有效抑制肿瘤生长, 具有良好的安全性[46]。纳米载体经过修饰可同时递送两种药物, 达到治疗目的。有研究证实纳米凝胶物装封考布他汀磷酸盐和蛋白酶体抑制剂硼替佐米制备壳堆叠NP用来治疗肿瘤[47]。而Sun等[48]用共轭聚合物POEG-*co*-PVDGEM (PGEM) 修饰纳米载体, 递送GEM和PTX, 基于皮下CRC模型研究发现, PTX/PGEM NPs可增加GEM的治疗作用。还有研究使用自组装多功能纳米载体共同递送5-氟尿嘧啶 (5-fluorouracil, 5-FU) 和microRNA-34a, 在裸鼠体内证实其协同治疗作用[49]。

通过对纳米材料表面修饰一些光敏分子等功能性基团, 可在成像指导下提供可视化治疗, 来追踪PDX模型中纳米药物的吸收、分布和代谢。MRI和荧光成像技术常用于反馈NP在皮下PDX模型中的治疗效果。有研究制备了TRAIL/Apo2L IONP, MRI图像显示其在肿瘤部位聚集, 提高肿瘤对药物的敏感性[50]。Lee等[51]开发了一种靶向LRP-1的含5-FU的HSA NP, 并装饰Cy7荧光团, 通过荧光成像发现该诊断治疗剂可准确靶向LRP-1响应辐射所指定的肿瘤, 增强CRC新辅助放疗的效果。

皮下PDX模型也可用来诊断PDAC, Reichel等[52]开发了含氟染料修饰的聚合物NP, 结合PDX模型体内荧光成像实验和计算数据, 确定该NP可用于鉴别转移性CRC肿瘤。

6 OC

OC是女性第3大常见妇科癌症, 也是女性癌症死亡的第5大原因。为克服静脉注射含铂类和紫杉类药物化疗时产生的耐药性, 常利用皮下和肾下PDX模型筛选新药。

6.1 皮下移植 多种基于纳米技术的治疗方法已被开发, 以减少非特异性毒性和延长抗癌药物的体内停留时间。Qi等[53]设计单甲基澳瑞他汀E (monomethyl oriostatin E, MMAE) 的NP−药物偶联物 (nanoparticles-drug conjugates, NDC), 基于耐药性上皮性OC PDX模型研究, 发现该NDC可提高载药量, 并在腹腔内触发活性MMAE毒素释放。Layek等[54]使用二苄基环辛炔功能化的NP递送PTK, 该NP靶向定位于肿瘤组织中的带有叠氮化物的间充质干细胞, 抑制肿瘤生长, 提高小鼠存活率。而Zhang等[55]用OC PDX模型验证载有CPG的PLAG NP与细胞膜结合, 也可提高治疗作用。用siRNA进行基因沉默也是一种可行的治疗方法, 如有研究进行了在NOD/SCID小鼠体内的金纳米粒与MICU1-siRNA制成的自组装LP的疗效评估[56]。

6.2 肾下移植 目前载药NP在OC治疗中应用非常广泛, 可用肾下移植进行药物评价。Kim等[57]设计了一种组织蛋白酶B特异性Dox前药NP, 利用此模型发现该NP在靶部位的停留时间延长, 不良反应减小。Byeon等[58]开发了透明质酸标记的聚 (*D*,*L*-丙交酯−乙交酯) NP来递送PTX和黏着斑激酶siRNA, 提高化疗耐药OC的治疗效果。

7 HCC

HCC是世界范围内高死亡率的恶性肿瘤之一, 手术治疗是治愈HCC的唯一方法, 但其发现常在晚期, 往往已失去手术机会。药物治疗成为晚期患者主要治疗手段, 可通过皮下或原位移植建立PDX模型来预测纳米药物治疗效果。

7.1 皮下移植 目前, 用于HCC治疗的纳米药物被陆续开发, 并用皮下PDX模型进行疗效评估。Wang等[59]使用不同分子质量的聚丙交酯 (polypropyl ester, PLA) 链段与SN-38嵌合成纳米药物来改善药物溶解性, 在裸鼠体内研究发现, PLA越长, SN-38共轭物在NP中的保留时间越长, 抗肿瘤活性越高。长编码RNA (long non-coding RNA, LncRNA) 在癌症中有重要的调节功能, Oh等[60]开发了一种装封LINC00598 siRNA的PLAG纳米平台, 在PDX模型中发现LncRNA LINC00598可作为治疗靶标, 提高治疗效果。联合用药可降低由大量DNA修复引起的CDDP耐药性, 如用LP递送铂的前药、葡萄糖氧化酶和替拉帕明, 在裸鼠体内发现其可抑制缺氧DNA修复[61]。

根据纳米材料独特的理化性质, 进行适当功能化修饰可实现刺激响应型的智能纳米给药系统靶向释药, 为多种疗法联合给药提供契机。雷公藤甲素 (triptolide, TP) 具有较强的抗肿瘤作用, 但其严重的全身毒性、低溶解度和极短的体内半衰期限制了其广泛应用[62]。利用裸鼠构建皮下HCC PDX模型, 以此考察光敏剂Ce6和TP制成的光激活LP, 发现该LP在NIR激光照射下可展示最佳的治疗效果, 显著降低了TP的不良反应[63]。

7.2 原位移植 多项临床研究表明, PDOX模型能更好地保持原发肿瘤的基因特征, 反映更真实的药物治疗效果, Chen等[64]利用此模型对载有羟基PCT和Dox的NP进行体内研究, 发现其在pH及NIR双重刺激下释放药物, 通过MRI/CT成像显示NP在肿瘤部位聚集。

对于BC、胰腺癌、LC、GBM、CRC、OC和HCC这7种癌症的PDX模型在纳米递送系统治疗、诊断及诊疗一体化评价中的应用, 总结见表2[5-14,16-61,63,64]。

Table 2 Application of nano-delivery systems in different PDX models. BC: Breast cancer; PDAC: Pancreatic ductal carcinoma; LC: Lung cancer; SCLC: Small cell lung cancer; NSCLC: Non-small cell lung cancer; LUAD: Lung adenocarcinoma; GBM: Glioblastomas; CRC: Colorectal cancer; OC: Ovarian cancer; HCC: Hepatocarcinoma; NP: Nanoparticles; NM: Nano micelles; LP: Liposomes; LPP: Lipopolyplex

Cancer	Implantation site	Nano preparation	Ref.
BC	Mammary fat pad	NP	[5-10,12,13]
	Mammary fat pad	NM	[11]
	s.c.	Nano probes	[14]
PDAC	s.c.	NP	[16,17,19-22]
	s.c.	NP/LP	[18]
	Pancreatic	NP	[23,24]
	Pancreatic	LP	[25,26]
LC	s.c.	NP	[27]
	s.c.	LP	[34]
SCLC	s.c.	LP	[28]
NSCLC	s.c.	NP	[29-31,35,37]
	s.c.	NM	[33]
	s.c.	LPP	[36]
LUAD	s.c.	NP	[32]
GBM	s.c.	NP	[38-41]
	s.c.	LP	[42,43]
	Glioblastoma	NM	[44]
	Glioblastoma	Nanocell	[45]
CRC	s.c.	NP	[46-52]
OC	s.c.	NP	[53-55]
	s.c.	LP	[56]
	Renal capsule	NP	[57]
	Renal capsule	LP	[58]
HCC	s.c.	NP	[59]
	s.c.	Nano platform	[60]
	s.c.	LP	[61,63]
	Liver	NP	[64]

8 总结与展望

PDX模型是目前为止最为接近临床研究的相关肿瘤模型, 除上述癌症外, 该模型在前列腺癌[65]、胃癌[66]、黑色素瘤[67]和宫颈癌[68]等癌症临床研究中均有应用, 借助PDX模型进行新药的初步评价、验证, 有利于提高新药临床转化的成功率, 此外, 还可用于在临床应用前发现和测试与癌症治疗相关的新抗体、抗癌微生物、毒性细胞的作用。由于PDX模型保留了原发肿瘤和微环境的异质性, 可应用于分析患者的临床表型并模拟不同阶段疾病的表型, 因此该模型在个体化治疗和肿瘤转移分析方面具有巨大潜力。

尽管PDX模型是研究癌症的相对简单且理想的模型, 但仍存在一定局限性。① 样本获取有限且不可重复, 其主要通过手术切除获取, 大块肿瘤组织对于PDX建立有益, 但较小的样本如肿瘤活检或细针穿刺更适合个性化医学应用; ② 移植成功率低, 肿瘤类型、肿瘤恶性程度、组织中肿瘤细胞比例、组织离体时间、受体鼠、操作技术、移植部位、饲养环境等多种因素皆会影响建模成功率, 也是制约其广泛应用的关键因素; ③ 建模耗费时间长, 需花费时间进行伦理评估, 与患者的治疗匹配性低, 因此并不适用于所有癌症, 尤其是需要短时间获得治疗方案的情况; ④ PDX模型建立和维持的成本较高, 但相对建成后的使用价值也非常高; ⑤ PDX模型并不能完全模拟体内微环境, 在肿瘤移植过程中, PDX肿瘤的克隆型分布与患者原始肿瘤相比依然不同, PDX的基因表达图谱与转移复发灶是重叠的, 与原发灶肿瘤有较大区别, 这些方面对临床肿瘤样本筛选、组织取材技术运用、移植和分析水平等均提出了更高要求。为进一步发挥PDX模型的优势, 可在全球范围内建立PDX模型共享数据库, 通过将临床样品与数据库中的样品进行比较, 在患者间的基因组特征相似或一致的情况下, 可从共享数据库中确定最佳治疗方案, 有望使个体化治疗转化为程序性治疗。

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