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纳米药物递送系统：胰腺癌靶向策略的新选择*

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摘要 胰腺导管腺癌（PDAC）是一类进展迅速、早期诊断困难的恶性消化系统实体肿瘤，多数患者就诊时已失去根治性手术切除机会。PDAC组织中的多种细胞成分和非细胞成分组成复杂的调控网络，共同塑造了代谢异常的肿瘤微环境，导致临床化疗和免疫治疗等效果受限。纳米技术的发展为PDAC的高效药物递送和精准靶向治疗提供了新思路。本文从靶向肿瘤细胞与肿瘤微环境两个方面，综述了近年来基于纳米药物递送系统的PDAC治疗策略，并总结了本团队在相关领域的研究进展，为胰腺癌的治疗提供参考。

关键词 胰腺导管腺癌，纳米药物递送系统，肿瘤微环境，靶向治疗
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胰腺导管腺癌（pancreatic ductal adenocarcinoma，PDAC）是一种由非侵袭性癌前病变引起的恶性上皮性消化系统肿瘤[1-2]，患者五年生存率低于9%[3]，其发病人数占胰腺癌患者总数的90%以上[4]，通常被简称为胰腺癌。随着全球人口老龄化的加剧和人们生活习惯的变化，PDAC的发病率逐年上升，严重威胁公共健康，并造成巨大社会负担。

PDAC组织由肿瘤细胞及复杂的肿瘤微环境（tumor microenvironment，TME）构成，后者包括细胞成分（如基质细胞和免疫细胞等）和细胞外基质（extracellular matrix，ECM）[5]，具有过度结缔组织增生的典型特征[6]，是PDAC具有高度侵袭性与耐药性的重要病理基础[7]。胰腺星状细胞（pancreatic stellate cell，PSC）是PDAC微环境的重要成分和效应细胞，位于胰腺腺泡细胞的基底外侧[8]。在PDAC组织中被激活后，PSC表达α平滑肌肌动蛋白（α-smooth muscle actin，α-SMA）等标志性蛋白质，并释放各种细胞因子和代谢产物，直接促进PDAC细胞的增殖、侵袭和转移，同时在ECM产生、结缔组织增生、免疫耐受和促进耐药等过程中起关键作用[9]。PDAC细胞免疫原性低，不易被免疫细胞识别。此外，组织中获得性免疫细胞浸润困难，巨噬细胞和中性粒细胞等固有免疫细胞在微环境中发挥免疫抑制与促肿瘤作用，共同缔造了PDAC的免疫抑制微环境[10-11]。肿瘤相关巨噬细胞转化为促肿瘤表型后可激活PSC，并通过分泌基质金属蛋白酶（modified matrix metalloproteinase，MMP）等参与ECM的重塑[11-12]。ECM是由胶原蛋白、透明质酸和蛋白水解酶等组成的致密网状结构，作为天然的物理屏障，不仅引发间质高压和血供匮乏，阻碍药物瘤内递送，还为PDAC细胞的转移与分化提供适宜的环境[13-14]。近年来，除PDAC细胞外，PSC、肿瘤相关免疫细胞和ECM重要成分也已成为PDAC治疗的重要靶点。

目前，手术治疗与化疗仍是PDAC患者的临床标准治疗方案。然而，PDAC发病隐匿，早期诊断困难，约80%患者确诊时已处于局部进展期或晚期，因而失去根治性手术切除的机会；而术后患者也面临严重的复发问题[15]。吉西他滨等传统一线化疗药物往往存在血液稳定性差、细胞摄取率低、

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胞内代谢复杂以及严重耐药等问题，临床疗效不尽人意[16-17]。近十年来，新辅助化疗序贯手术后继续辅助化疗及各种联合治疗方案不断更新，AG（白蛋白紫杉醇联合吉西他滨）和FOLFIRINOX（5-氟尿嘧啶、亚叶酸、伊立替康和奥沙利铂四药联用）疗法成为晚期胰腺癌患者的一线治疗方案[18-19]。尽管这两种联合治疗方案能够延长PDAC患者的总生存期，然而患者用药后往往出现中性粒细胞与血小板减少、腹泻与感觉神经病变等症状，生活质量大大降低[20-21]。放射治疗也可以在一定程度上提高PDAC患者的生存率，但对于周围器官的毒性风险限制了该疗法的有效治疗时间与照射剂量[22]。作为新兴的肿瘤治疗手段，以靶向程序性死亡受体1（PD-1）或程序性死亡受体配体1（PD-L1）为代表的免疫检查点抑制疗法，在黑色素瘤等恶性肿瘤治疗中取得了良好的临床效果。然而，PDAC细胞固有的免疫逃逸特性及复杂的免疫抑制微环境造成PDAC患者对免疫治疗难以响应[23]。因此，PDAC也被称为免疫“冷”肿瘤。近年来，针对肿瘤细胞*KRAS*^{G12C}突变[24]、*BRCA*突变[25]和*NTRK*融合突变[26]等开发的一系列抑制剂，为PDAC的靶向治疗带来了新的希望。然而，抑制剂本身突出的毒副作用及受众有限等问题制约了相关疗法的广泛实施[6]。迄今没有一种*KRAS*抑制剂进入临床，也没有一种靶向治疗成为PDAC的一线非化疗选择[27]。目前，美国食品与药品管理局（FDA）已批准了奥拉帕尼（聚腺苷二磷酸核糖聚合酶抑制剂）用于PDAC的靶向治疗[28]。今后，相关靶向治疗仍需在肿瘤高度异质性的背景下，研发直接作用于靶细胞或靶分子的创新药物或者协同多样化的治疗策略，使PDAC患者得到更精准的个性化治疗。此外，核酸药物在体内稳定性不佳，其潜在的脱靶效应与安全性问题也限制了基因疗法在PDAC早期患者及无法手术患者中的临床应用[29-30]。PDAC的病理特征及其临床治疗现状小结见图1。

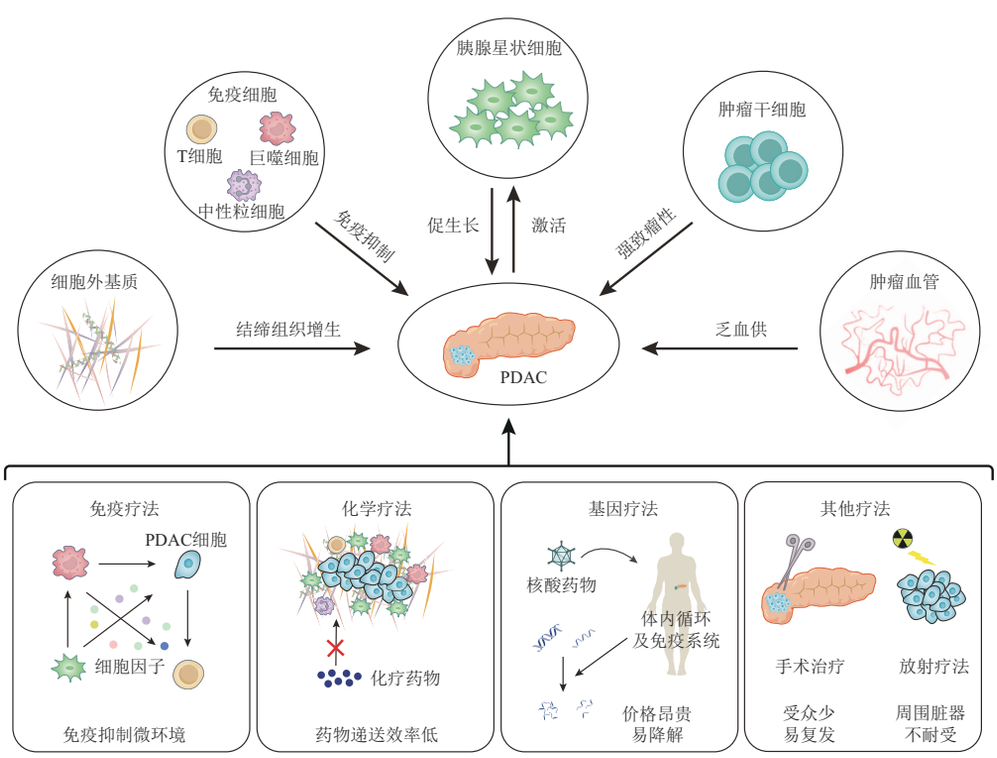

Fig. 1　Pathological features and clinical treatments of PDAC

图1　胰腺导管腺癌的病理特征及其临床治疗现状

PDAC细胞与其肿瘤微环境中的细胞成分和非细胞成分相互作用，形成复杂的调控网络，共同塑造了基质过度增生和免疫抑制的微环境，导致临床治疗方案的效果不佳。

纳米技术在生物医药领域的快速发展为PDAC治疗带来了新的机遇。纳米体系独特的尺寸效应有助于突破PDAC致密的基质屏障[31]；体系表面丰富的功能化修饰不仅能够延长药物的体内循环时

间[32]，还可以借助靶向分子将药物主动递送至TME，实现对PDAC细胞的精准杀伤[33]。基于PDAC病理特征和药物作用机制，以PDAC细胞及其微环境中特异性表达的蛋白质[34]、异常信号转导[35]和代谢途径[36]的关键分子等为靶点，精准设计和构筑纳米药物体系，有望突破现有疗法的局限，更加准确和高效地抑制肿瘤的生长和转移。目前，基于纳米递送系统构建的白蛋白紫杉醇和伊立替康脂质体等代表性纳米药物已经被写入胰腺癌患者的临床一线治疗方案[4]。利用天然人血清白蛋白纳米载体与TME中富含半胱氨酸的酸性分泌蛋白（SPARC）之间的特异性结合，白蛋白紫杉醇改善了传统化疗药物的药代动力学性质，显著促进了紫杉醇在肿瘤部位的富集[37]。将DNA拓扑异构酶I抑制剂伊立替康封装于聚乙二醇化的脂质体中，可明显延长药物的体内循环时间，提高传统酶抑制剂的临床疗效[38]。这些成功的临床范例显示了纳米药物递送系统在提高PDAC患者疗效方面的巨大潜力，也鼓舞了更多纳米药物的研发和转化[39]。

本文从靶向PDAC细胞及其肿瘤微环境的角度，综述了近年来基于纳米药物递送系统的胰腺癌治疗策略，并系统总结了本团队在相关领域的研究进展（图2），以期为PDAC的临床治疗提供新的思路。

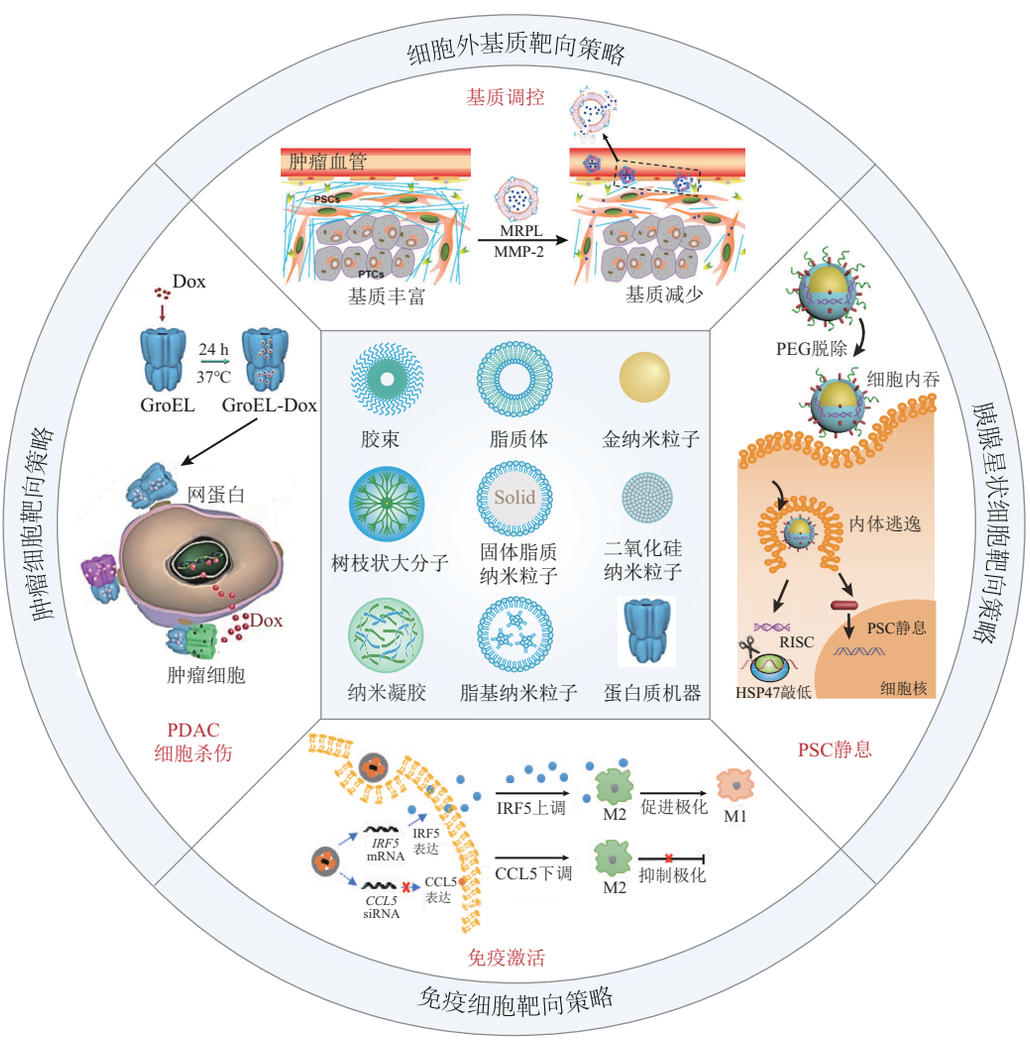

Fig. 2　Targeting strategies based on drug delivery nanosystems for PDAC treatment

图2　基于纳米药物递送体系的胰腺导管腺癌靶向策略

基于肿瘤细胞及其微环境病理特征与药物作用原理，按需设计和构筑多功能纳米递送体系，通过肿瘤细胞、胰腺星状细胞、免疫细胞及肿瘤微环境基质靶向的纳米策略，有助于实现PDAC的高效药物递送和精准靶向治疗。图中4种纳米策略代表性示意图分别选自参考文献［40］（左图）、参考文献［41］（右图）、参考文献［42］（上图）和参考文献［43］（下图），并进行了编辑。

1 靶向胰腺癌细胞的纳米药物递送策略

根据PDAC细胞生物学特征及药物治疗靶点，按需设计和构筑多功能纳米递送体系，能够提高药物对PDAC细胞的靶向输运和治疗效率，提高以PDAC细胞为靶点的化疗、分子靶向治疗、基因治疗、免疫治疗等多种疗法及其联合治疗的潜力。

1.1 细胞靶向化疗的纳米策略

针对PDAC细胞表面过表达的整合素αvβ3[44]、转铁蛋白受体（TfR）[33, 45]、表皮生长因子受体（EGFR）[46]、网蛋白（plectin）[40, 47]等特异性蛋白质，对纳米载体进行靶向分子修饰，是广泛用于化疗药物减毒增效的纳米靶向递送策略。本团队与临床团队合作，设计合成了表面修饰精氨酸-甘氨酸-天门冬氨酸（RGD）序列的多层脂质-聚合物杂化纳米颗粒，包载FOLFIRINOX化疗方案中的5-氟尿嘧啶、伊立替康和奥沙利铂，通过整合素αvβ3介导的PDAC细胞靶向杀伤，显著降低了该方案突出的毒副作用[48]。此外，本团队构建了金纳米壳包裹介孔二氧化硅纳米棒的药物递送体系，用于吉西他滨在PDAC组织内的靶向递送[49]。首先通过肿瘤局部特异性光热效应，增加药物在肿瘤血管的被动靶向富集与渗透；再通过纳米体系表面修饰的转铁蛋白，实现所载药物对PDAC细胞的主动靶向和杀伤。该纳米级联靶向策略有效促进了药物在肿瘤组织的累积，提高了PDAC细胞对吉西他滨的化疗敏感性。有研究显示，EGFR在PDAC中的表达率最高可达89%[46]，该特征在BxPc-3、PANC-1和HPAC等人胰腺癌细胞系中尤为突出[50]。基于EGFR的亲和体（affibody），Zhao等[51]合成了具有活性氧类和胰蛋白酶双重响应性的金纳米团簇，通过特异性靶向EGFR高表达的PDAC细胞，提高了化疗药物甲氨蝶呤的胞内浓度，抑制了癌细胞的增殖与转移。Greene等[52]发现，EGFR单抗的F(ab)片段可通过链间二硫键定向“点击”耦联到叠氮化物修饰的聚合物纳米颗粒表面，从而显著提高化疗药物喜树碱对PDAC细胞的靶向结合能力。通过配体与受体的特异性结合，实现药物靶向PDAC细胞的递送，已被大量纳米药物研究所证实。然而，该模式也存在一些潜在的问题。例如，转铁蛋白修饰的纳米载体可能与内源性的转铁蛋白分子竞争性结合TfR，从而影响机体正常代谢过程[53]。这也对纳米药物递送体系的发展提出了更加精准化和智能化的要求。

随着纳米技术与生物医学等多学科的深度交叉融合，各种人造或天然纳米机器等智能递送体系正逐渐成为纳米药物的发展方向。本团队长期关注利用生物纳米机器的药物递送在应对肿瘤异质性和微环境复杂性方面的巨大潜力，并取得了一系列原创性成果[54]。基于细菌天然ATP酶GroEL，本团队设计构筑了一种靶向PDAC细胞、递送疏水性化疗药物的智能分子机器（图3）[40]。GroEL是一种由14个亚基构成的、具有双层笼型结构的天然蛋白质，可通过其疏水性内腔便捷地包载疏水性药物。在TME中，高浓度ATP触发GroEL的构象转换，其内腔转变为亲水特性，从而将腔内的药物响应性释放到肿瘤组织。此外，GroEL还能够通过与PDAC细胞表面高表达的网蛋白特异性结合，实现对肿瘤细胞的靶向递送和精准治疗。该研究为基于天然蛋白质纳米机器的PDAC智能诊疗创造了新的研究范式。

肿瘤干细胞（cancer stem cell，CSC）是肿瘤组织中一小部分静止的、能够自我更新的、多功能的恶性细胞，与肿瘤复发和耐药高度相关[55]。研究发现，PDAC中存在具有干细胞特性的细胞群，表达CD24、CD44和上皮特异性抗原，具有强致瘤性和自我更新能力[56]。其中，表达上调的CD44可与胶原蛋白、纤连蛋白、骨桥蛋白等结合，并主要通过与透明质酸的相互作用，激活PDAC细胞内多个促癌信号通路，也因而成为纳米药物体系的重要治疗靶点[57]。Hu等[58]将阳离子白蛋白颗粒与带负电荷的透明质酸进行纳米组装，包载癌细胞抑制剂雷公藤红素，与吲哚胺2, 3-双加氧酶（indoleamine 2,3-dioxygenase 1，IDO）抑制剂1-甲基色氨酸联合使用，在异种和原位移植PDAC小鼠模型中实现了良好的肿瘤生长抑制。Kang等[59]设计了一种级联响应的纳米药物体系，在谷胱甘肽响应型抗菌聚合物外部包裹透明质酸，内部封装吉西他滨和光热试剂IR1048。该体系通过CD44靶向修饰富集在TME中，经基质透明质酸酶降解后体积变小，渗透进入肿瘤深部，通过化疗、光热治疗和免疫激活效应，协同抑制PDAC的快速发展。未来更多生物标志物的发现，将为PDAC干细胞的纳米靶向治疗提供新的研究思路。

1.2 细胞分子靶向治疗与基因治疗的纳米策略

分子靶向药物和基因药物正逐渐成为精准医疗时代的重要治疗手段，并在多种肿瘤治疗中取得了令人鼓舞的效果。然而，由于基因组的复杂性及

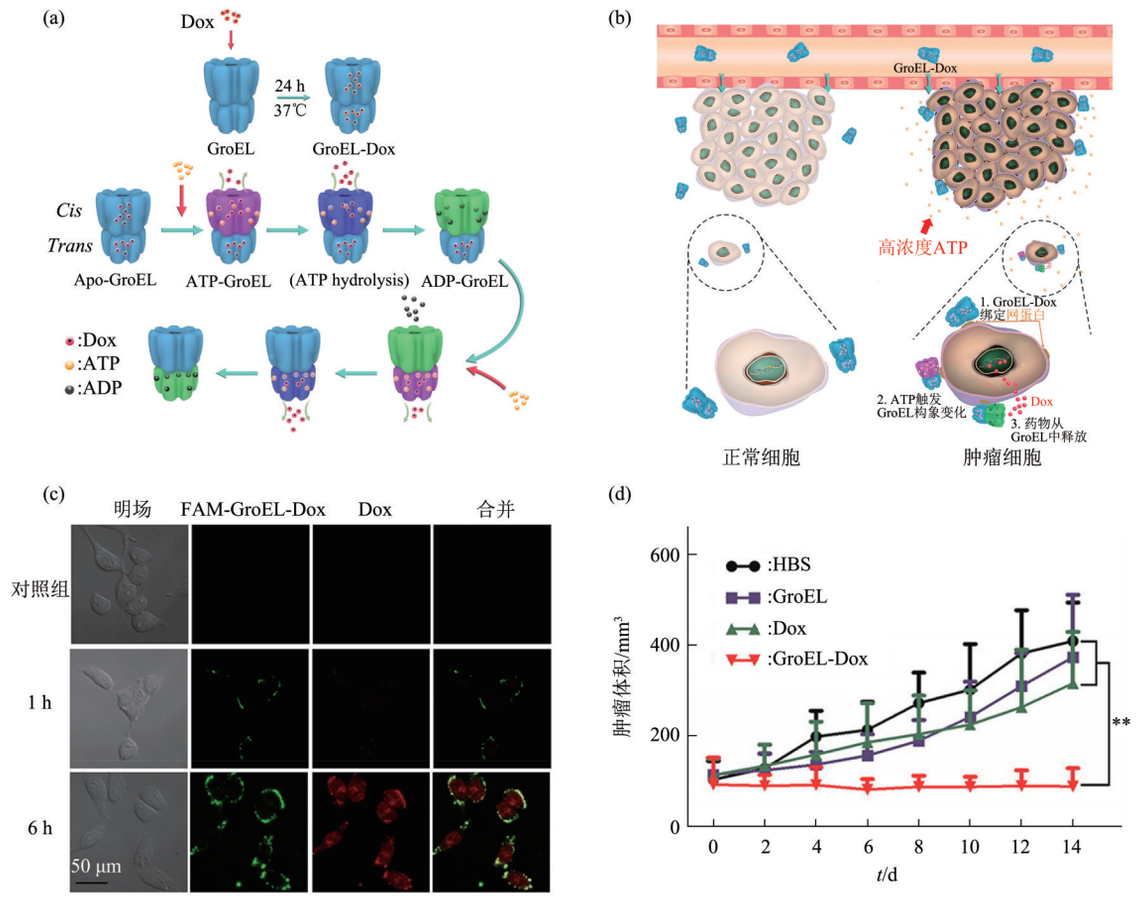

Fig. 3　An intelligent nanodrug delivery system GroEL−Dox−enhanced targeting chemotherapy for PDAC[40]

图3　基于智能纳米药物体系GroEL−DOX的胰腺导管腺癌靶向化疗[40]

（a）GroEL−Dox的组装和ATP触发的药物释放原理；（b）GroEL-Dox的PDAC细胞靶向机制；（c）GroEL-Dox的细胞靶向摄取；（d）GroEL-DOX抑制PDAC生长。**P<0.01。

TME的异质性，PDAC患者并未从分子靶向治疗中显著获益。近年来，靶向DNA损伤修复机制的药物为晚期PDAC患者提供了新的选择。BRCA1/2和聚腺苷二磷酸核糖聚合酶（poly adenosine diphosphate-ribose polymerase，PARP）分别通过同源重组和碱基切除方式共同调控DNA损伤的修复，而BRCA1/2突变存在于5%~10%的家族性PDAC患者和3%的散发性PDAC患者中[60]。因此，靶向PARP修复为该类BRCA1/2突变患者提供了一种具有潜力的治疗选择。本团队制备了一种靶向EGFR的两亲性多肽纳米载体，以最佳的治疗剂量和比例，将吉西他滨和PARP抑制剂奥拉帕尼共同递送至PDAC细胞，通过抑制化疗药物引起的DNA单链断裂的修复，引发大规模DNA双链断裂，诱导PDAC细胞的合成致死效应，从而实现对一类DNA双链断裂缺少修复机制的BRCA1/2突变型胰腺癌的精准治疗[61]。然而，由于80%以上的PDAC是散发性的，BRCA1/2突变的人群在PDAC患者中所占的比例不到10%。为了使更多的非BRCA突变PDAC患者从奥拉帕尼疗法中获益，本团队与合作者基于PDAC特异分子标志物plectin-1，进一步构建了自组装多肽纳米体系，靶向递送具有不同作用机制的DNA损伤修复抑制剂奥拉帕尼和JQ1[47]。奥拉帕尼通过抑制DNA单链损伤的修复，增加DNA双链损伤的累积；而JQ1则抑制通过同源重组修复途径的DNA双链损伤的修复，进而诱导非BRCA1/2突变型PDAC细胞的凋亡。上述“诱捕-杀伤”纳米策略也为广泛的PDAC患者的分子靶向治疗带来了新的思路。

核酸药物在体内递送过程中长期面临稳定性差和靶向性不足的难题。纳米递送体系为突破这一困境提供了技术手段，并通过基因疗法与多种其他疗法的联合使用增强了PDAC的疗效[29，39，62]。Wu等[63]采用一种新型嵌合肽缩合的超分子纳米颗粒

递送系统，将miR-9 miRNA特异性递送至plectin-1过表达的PDAC细胞中，通过减少自噬和促进细胞凋亡，增强了肿瘤细胞对多柔比星的化疗敏感性。Yan等[64]制备了RGD靶向分子修饰的DSPE-PEG纳米胶束，在TME酸性条件下可释放负载的多组分脱氧核酶，联合共同递送的钙外排泵抑制剂，协同沉默热休克蛋白（heat shock protein，HSP）70 miRNA，并增强肿瘤抑制基因PTEN的表达，多重提高PDAC细胞对IR 780介导的光热治疗的敏感性。基因治疗相关的效率与安全性等问题也正随着纳米药物递送体系的不断迭代获得更优的解决方案[65]。

1.3 细胞靶向免疫治疗的纳米策略

免疫疗法主要利用免疫刺激因子、溶瘤病毒、过继性免疫细胞和肿瘤靶向抗体等发挥抗肿瘤作用，目前临床应用最为广泛的是免疫检查点抑制剂，并在多种实体瘤中展现出令人鼓舞的应用前景[66]。然而，免疫抑制微环境严重阻碍了PDAC患者从各种免疫疗法中获益[67]。通过纳米药物递送体系靶向调控PDAC细胞诱导的免疫抑制因子，促进肿瘤相关抗原的释放，能够更加有效地克服肿瘤免疫逃逸，协同提高免疫治疗效果[68]。本团队将吉西他滨和免疫原性细胞死亡诱导剂奥沙利铂共同包载于两亲性二嵌段共聚物纳米颗粒中，可刺激肿瘤细胞释放免疫刺激损伤相关分子模式，并诱导树突状细胞和T淋巴细胞更强的免疫反应[69]。针对IDO调控通路在塑造PDAC免疫抑制微环境中的核心作用，本团队通过模块化设计的多肽-药物偶联物自组装，合成了肿瘤靶向的IDO纳米抑制剂[70]。该体系由亲水性的靶向多肽RGD、两个可质子化的组氨酸和一个酯键连接的疏水性IDO小分子抑制剂偶联而成，具有pH响应的解组装和酯酶响应的药物释放功能。在有效降低小分子抑制剂系统毒性的同时，可显著提高PD-L1单克隆抗体的治疗效果。近期，本团队基于3种对免疫检查点疗法具有良好响应性的结肠细菌原生质体膜制备了杂化纳米囊泡，联合PD-1抗体阻断疗法，在PDAC小鼠模型中有效遏制了肿瘤的快速生长[71]。Jung等[72]构建了包载PD-L1 siRNA的乳酸-羟基乙酸共聚物纳米颗粒，通过抑制PD-L1的表达，提高肿瘤细胞对抗原特异性免疫细胞的敏感性，显著抑制了PDAC的进展。上述研究展示了纳米药物体系在增强PDAC免疫应答、发展抗肿瘤免疫正常化联合治疗方面的良好潜力。

如上所述，纳米药物递送体系能够通过配体-受体的特异性结合，提高传统化疗药物在PDAC细胞中的富集，通过高效的“合成致死”纳米策略，为特定基因突变PDAC患者提供更多治疗选择，通过功能化设计，改善核酸药物的体内代谢行为、提高靶向性[73]，通过综合调控免疫抑制因子，提高PDAC细胞的免疫应答，改善免疫抑制微环境。此外，未来还需要更加智能化的纳米药物递送体系，以克服目前靶向PDAC细胞的纳米策略中存在的问题，如：纳米体系与内源性生物分子共同竞争结合受体时可能影响机体的正常代谢；纳米体系中的药物分子可能影响载体的细胞摄取和清除机制，从而导致细胞损伤和炎症反应；功能化纳米药物体系的复杂特性使其缺乏全面的安全性评估数据，导致临床转化困难等[74]。

2 靶向胰腺癌微环境的纳米药物递送策略

胰腺癌微环境是促进PDAC细胞生长、转移和治疗耐受的关键因素，其重要作用在PDAC研究领域日益受到关注[75]。微环境中的各种细胞成分与非细胞成分占整个肿瘤组织的比例高达90%[9, 76]，为基于纳米体系的药物递送和PDAC治疗提供了丰富的作用靶点。下文将详细介绍以PSC、免疫细胞和细胞外基质等微环境重要成分为靶点的纳米药物递送策略。

2.1 靶向胰腺星状细胞的纳米策略

作为PDAC微环境中最重要的基质细胞之一，PSC约占整个基质成分的50%[9, 77-78]。在TME中被活化的PSC失去细胞质中储存的维生素A脂滴，表达α-SMA，获得肌成纤维细胞特性[75]，大量分泌胶原、纤连蛋白、透明质酸和MMP等ECM，诱导广泛的结缔组织增生[79-80]，通过与PDAC细胞和其他基质细胞广泛的相互作用，促进多种促癌细胞因子（如IL-1、IL-6、IL-8等）和生长因子（如血管内皮生长因子、成纤维细胞生长因子等）分泌，是PDAC高度侵袭性和转移性的主要贡献者[9, 81]，也是TME调控的重要靶点。

研究发现，单纯清除PSC会诱导PDAC的免疫抑制，同时增加肿瘤转移的风险[82]。因此，使激活的PSC重返正常的静息状态成为更理想的PDAC基质调控策略。本团队构建了一种表面修饰聚乙二醇的阳离子金纳米颗粒体系，同时递送PSC调控药物全反式维甲酸及降低基质分泌的HSP47 siRNA（图4）[41, 83]。体系设计中引入了肿瘤微环境低pH

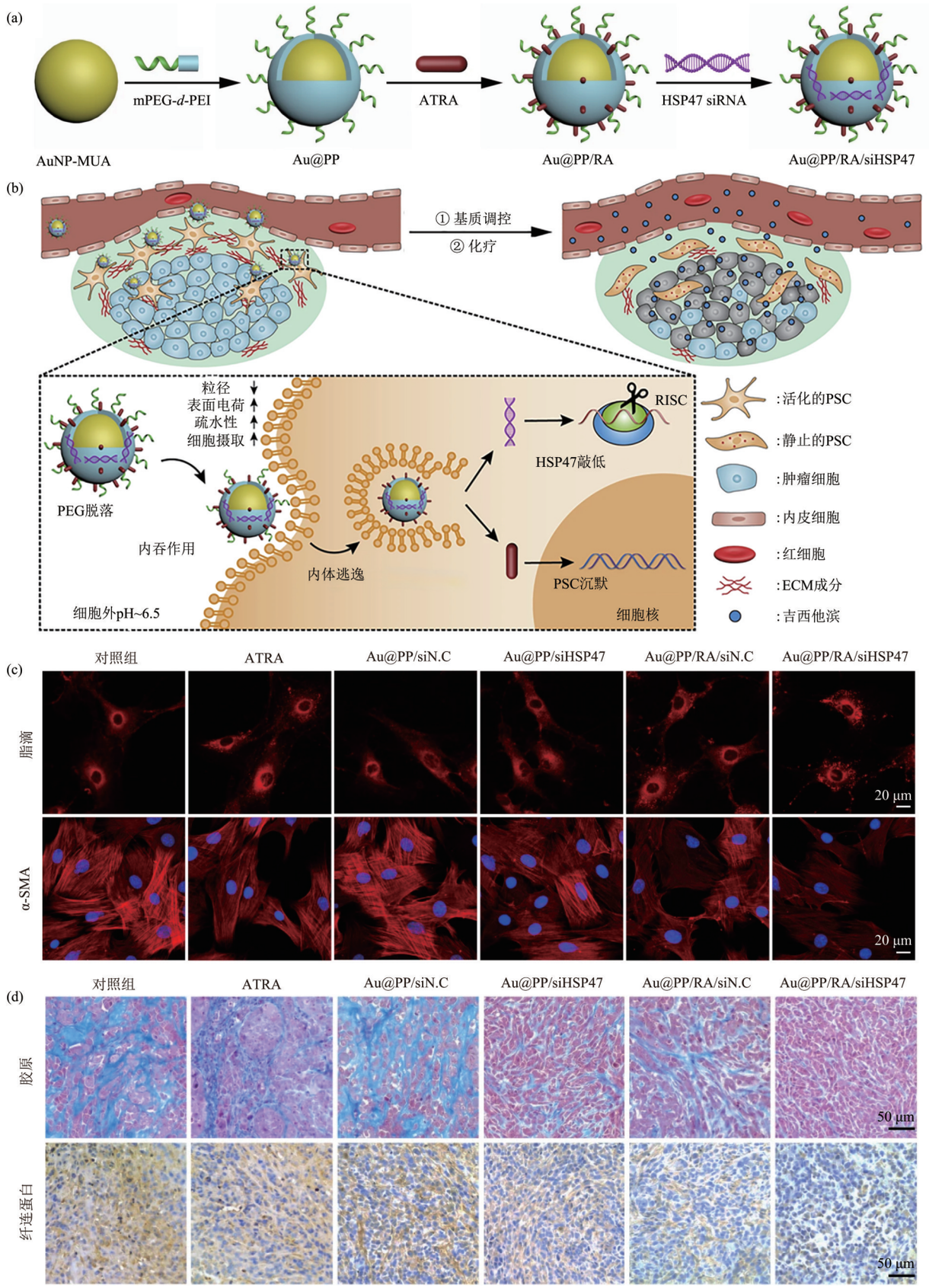

Fig. 4　Gold nanosystem promotes PSC quiescence and restores homoeostatic stroma of PDAC[41]

图4　金纳米药物体系促进PSC静息和PDAC基质平衡[41]

（a）金纳米药物体系的构建；（b）金纳米药物体系的作用机制；（c）金纳米药物体系诱导PSC静息；（d）金纳米药物体系降低肿瘤微环境基质。

响应的聚乙二醇脱除机制，能够在保证其体内输运稳定性的同时，提高癌细胞的药物摄取和siRNA的转染效率。在PDAC细胞与患者来源的PSC共接种的小鼠原位PDAC模型中，该纳米体系均实现了对PSC异常活化状态的高效逆转，通过对微环境基质代谢的稳态调控，显著增加药物在肿瘤内的输运效率，提高后续吉西他滨的化疗效果。随后，团队还尝试通过TGF-β1信号通路抑制，促进激活的PSC复归正常状态[31]。我们设计了一种尺寸可变的级联递送纳米体系，将化疗药物包载于粒径约40 nm的PEG-PLGA纳米小球中，并与TGF-β1受体激酶抑制剂共同封装在粒径约200 nm的脂质体内。通过表面靶向肽修饰，该纳米体系首先结合TME中含量丰富的纤连蛋白，实现对肿瘤基质的一级输运和靶向富集，进而释放TGF-β1抑制剂，高效降低PSC的活化程度，促进PEG-PLGA纳米小球向组织深部的PDAC细胞进行二级输运，通过释放化疗药物，实现对小鼠原位PDAC生长的有效抑制。Wang等[84]利用聚乙二醇和胆固醇组成嵌段聚合物纳米颗粒，共递送卡泊三醇和化疗药物喜树碱，通过激活PSC表面高表达的维生素D受体诱导PSC静息，促进化疗药物的瘤内输运，有效抑制了小鼠PDAC的生长和转移。Wang等[85]则构建了一种由聚乙二醇、聚赖氨酸和聚天冬酰胺苯丙氨酸构成的两亲性三嵌段聚合物，载带卡泊三醇与C-X-C基序趋化因子12（CXCL12）siRNA，通过抑制PSC的活化和调节性T细胞的肿瘤浸润，促进PDAC的免疫治疗。

2.2 靶向免疫细胞的纳米策略

PDAC具有突出的免疫抑制特征[86]。肿瘤细胞募集并激活多种免疫抑制细胞（如巨噬细胞、髓系抑制性细胞等），分泌免疫抑制因子，诱导肿瘤的免疫逃逸，进而促进肿瘤的生长和转移[87]。巨噬细胞是PDAC组织浸润免疫细胞的主要组成部分[75, 88]，根据其激活状态和功能可分为经典激活的巨噬细胞与选择激活的巨噬细胞，分别具有M1抗肿瘤表型和M2促肿瘤表型[86, 89-90]。

免疫调节因子5（IRF5）在巨噬细胞的极化过程中起重要的调控作用，能够将M2型肿瘤相关巨噬细胞（TAM）重新极化成M1型，从而抑制肿瘤发生和转移[88]。此外，趋化因子配体5（CCL5）能够以多种方式促进PDAC的发生，诱导基质细胞和炎症细胞参与免疫逃逸[91-92]。基于此，本团队构建了原位可注射的壳聚糖水凝胶纳米体系，同时负载IRF5 mRNA及CCL5 siRNA脂质体纳米颗粒[43]。该平台具有温敏性、可降解和药物控释等诸多优势，实现了RNA药物的体内可控释放，通过上调IRF5、下调CCL5，促进TME中的M2型TAM向M1型转化，进而增强CD8+ T细胞的浸润，重塑肿瘤免疫微环境，有效抑制了PDAC术后复发和转移（图5）。Chen等[93]合成了一种β葡聚糖功能化锌-多柔比星口服纳米颗粒，可靶向肠道相关淋巴组织中的微皱褶细胞。经转胞吞作用后，纳米颗粒被肠道淋巴系统中的内源性巨噬细胞吞噬，进而富集在PDAC组织中，促进M2型TAM极化为M1表型，重塑免疫抑制TME，降低基质纤维化程度，促进T细胞向肿瘤组织的浸润，最终诱导PDAC细胞凋亡。此外，靶向巨噬细胞的纳米策略还可以与免疫检查点阻断疗法相结合，以激活T细胞介导的抗肿瘤免疫，协同提高PDAC的疗效[94]。

2.3 靶向细胞外基质的纳米策略

丰富的胶原蛋白与透明质酸等ECM成分围绕在肿瘤实质周围，形成了药物难以渗透的天然物理屏障，同时促进PDAC细胞的增殖与侵袭[6, 95]。随着对肿瘤基质生物学认识的不断深入，越来越多的ECM调控靶点被发现，为纳米药物递送系统的设计提供了新思路[96]。

PDAC微环境中富含MMP，在组织重塑与肿瘤生长中起重要促进作用[13]。本团队早期制备了一种β环糊精修饰的MMP2响应性脂质体，共递送抗纤维化药物吡非尼酮和化疗药物吉西他滨，突破PDAC基质屏障，提高化疗敏感性[97]。其后，我们将MMP2响应性两亲性多肽与TME响应性的磷脂共组装，构建了载带吡非尼酮的杂化脂质体纳米体系，同样获得了良好的ECM调控效果[42]。为了应对基质含量减少可能引发的肿瘤转移风险，本团队近期构建了TME响应的级联递送纳米药物系统，包载LOXL2及DDR1小分子抑制剂，在不影响PDAC组织胶原含量的情况下，将其由病理性的线性化排列逆转为正常的非线性化排列形式[98]。在小鼠PDAC原位模型中，该纳米体系显著提高了白蛋白紫杉醇的瘤内递送和肿瘤杀伤效率，同时有效抑制了PDAC细胞对肺部的迁移和侵袭。此外，针对ECM中特异表达的纤连蛋白可变剪接片段[99]，我们设计了载带有氧糖酵解抑制剂3-溴丙酮酸的脂质体纳米体系[100]，通过共价偶联肿瘤靶向肽CREKA，特异性识别PDAC微环境中的纤维蛋白-纤连蛋白复合物，显著降低3-溴丙酮酸的毒副作

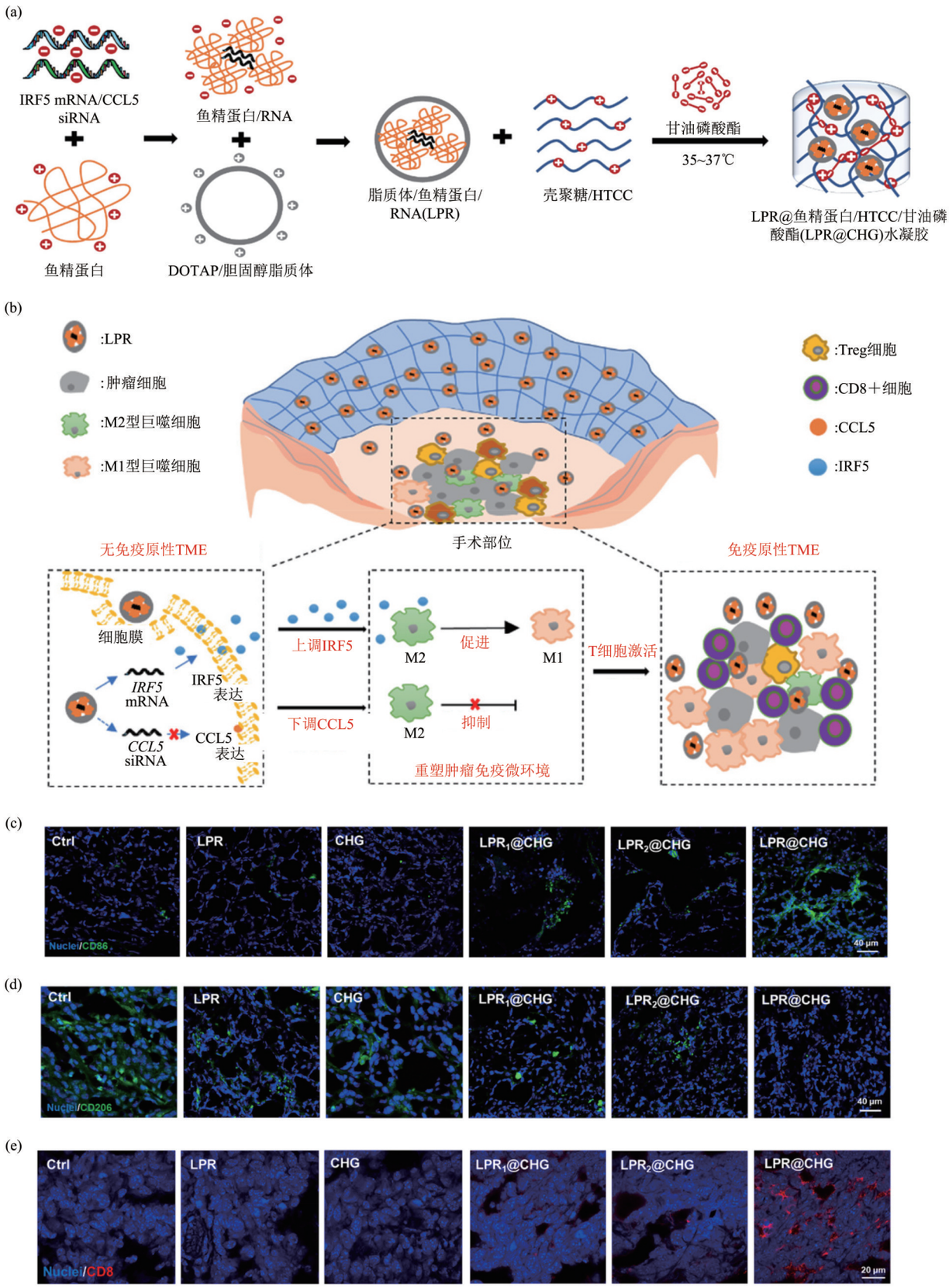

Fig. 5　LPR@CHG hydrogel formulation reshapes the immune microenvironment for postsurgical PDAC treatment [43]

图5　LPR@CHG纳米水凝胶重塑PDAC术后免疫微环境 [43]

（a）LPR@CHG纳米水凝胶的构建；（b）纳米水凝胶的作用机制；（c）PDAC组织中CD86的表达变化；（d）PDAC组织中CD206的表达变化；（e）PDAC组织中CD8的表达变化。

用，通过抑制ATP的产生，有效遏制PDAC细胞的生长。胰岛素样生长因子1受体（IGF1R）是一种酪氨酸激酶受体，通常在PDAC细胞与基质细胞中高表达，而在正常胰腺组织中低表达。Liu等[101]合成了一种双层脂质包被的介孔二氧化硅纳米颗粒，表面修饰可与IGF1R特异性结合的硫酸肝素蛋白聚糖Syndecan-1，实现了吉西他滨对PDAC的靶向递送和高效抑制。

综上，纳米药物递送体系独特的理化性质及功能化修饰使其更易穿越致密的肿瘤基质，通过对TME中多种基质细胞的协同调控，显著提高PDAC疗效。值得注意的是，单纯清除PDAC微环境ECM的传统策略具有诱导免疫抑制、促进肿瘤细胞转移的潜在风险[82，102]，而靶向调控PSC静息的纳米策略更有利于促进PDAC微环境平衡。此外，如何通过纳米药物体系对抗肿瘤相关巨噬细胞高度的可塑性、持续诱导其M1表型仍是一个挑战[103]。进一步提高药物递送效率、增强瘤内积累也是靶向PDAC微环境的纳米药物递送策略面临的问题[104-105]。

3 总结与展望

PDAC恶性程度高、早期诊断困难、微环境复杂，其临床治疗是医学领域有待攻克的难题。随着对PDAC分子病理学和TME机制认识的不断深入，在多学科综合治疗基础上，基于纳米生物医学技术，不断发展创新靶向治疗药物和治疗方案，突破肿瘤基质屏障，提高药物生物利用度，有望为改善PDAC患者预后带来更多选择。近年来，包括本团队在内的大量领域研究人员通过功能化纳米递送体系的设计构筑，针对PDAC中的多种细胞及微环境分子靶点，实现了对PDAC细胞或TME特异性的靶向药物递送、对局部病理信号响应性的可控药物释放、对增生基质屏障的高效穿越，以及个性化联合治疗方案的灵活实施，从而在降低传统药物毒副作用的同时，显著提高了PDAC的精准治疗效果。这些阶段性成果展示了纳米前沿技术在以PDAC为代表的一类基质增生肿瘤治疗领域创造的突破契机。

值得注意的是，PDAC的遗传背景复杂且细胞异质性明显，针对药物临床应用局限设置单一靶向和响应模块的初代纳米载体功能化设计，在复杂的PDAC微环境中往往无法充分实现。目前，通过纳米载体靶向富集到肿瘤组织的药物绝对浓度仍十分有限，大量复杂纳米递送体系的体内生物学行为因缺乏有效的监测手段而难以预测和评价，纳米药物的临床实验设计、产业化开发和监管审批也面临众多挑战[106]。虽然已有应用于PDAC治疗的纳米药物上市或处于临床试验阶段（表1），但迄今尚无具有主动靶向功能的纳米药物被批准应用于临

Table 1 Representative nanomedicines for PDAC treatment

表1 代表性抗胰腺癌纳米药物[1)]

纳米药物名称	纳米载体	药物成分	适应症	临床阶段	批准号
Abraxane	人血清白蛋白	紫杉醇	转移性胰腺癌	批准（2005年）	–
Aldoxorubicin（INNO-206）	人血清白蛋白	多柔比星	晚期胰腺癌	II	NCT01580397
Onivyde	脂质体	伊利替康	转移性胰腺癌	批准（2015年）	–
脂质体多柔比星	脂质体	多柔比星	晚期胰腺癌	II	NCT00426127
脂质体伊立替康	脂质体	伊立替康	局部晚期胰腺癌	II	NCT03861702
盐酸米托蒽醌脂质体	脂质体	米托蒽醌	晚期胰腺癌	II	NCT05100329
脂质体多烯紫杉醇	脂质体	多烯紫杉醇	晚期胰腺癌	I	NCT01041235
BP-C1	聚合物	顺式二氨合铂（II）与木质素衍生的苯多羧酸聚合物的络合物	转移性胰腺癌	II	NCT03627390
NBTXR3	氧化铪纳米颗粒	–	局部晚期或临界可切除胰腺癌	I	NCT04484909
AGuIX	钆纳米颗粒	–	局部晚期不可切除胰腺癌	I/II	NCT04789486
TKM-080301	脂质体	Polo样激酶-1 siRNA	伴有肝转移的胰腺癌	I	NCT01437007
iExosomes	间充质基质细胞来源的外泌体	KrasG12D siRNA	携带KrasG12D突变的转移性胰腺癌	I	NCT03608631
siG12D LODER	聚合物	KrasG12D siRNA	局部晚期胰腺癌	I	NCT01188785

[1)]https://www.clinicaltrials.gov

床[107]。因此，理性设计具有更高生物安全性、体内行为高度可控、能够执行复杂任务的智能纳米机器，正在引领抗肿瘤纳米药物研究领域新的发展方向。基于核酸、蛋白质、生物膜等生物分子来源的纳米材料，本团队发展了一系列自组装智能纳米机器和免疫调节药物，并在胰腺癌等多种肿瘤模型中进行了治疗新方案的初步探索[40，108-110]。同时，基于纳米递送系统的mRNA疫苗等临床纳米药物已经展现了纳米技术在应对人类重大健康问题方面的巨大潜力，新一代智能纳米药物终将为PDAC等恶性肿瘤的精准治疗带来变革与突破。

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Nanodrug Delivery System: a Promising Targeting Strategy for Treatment of Pancreatic Ductal Adenocarcinoma*

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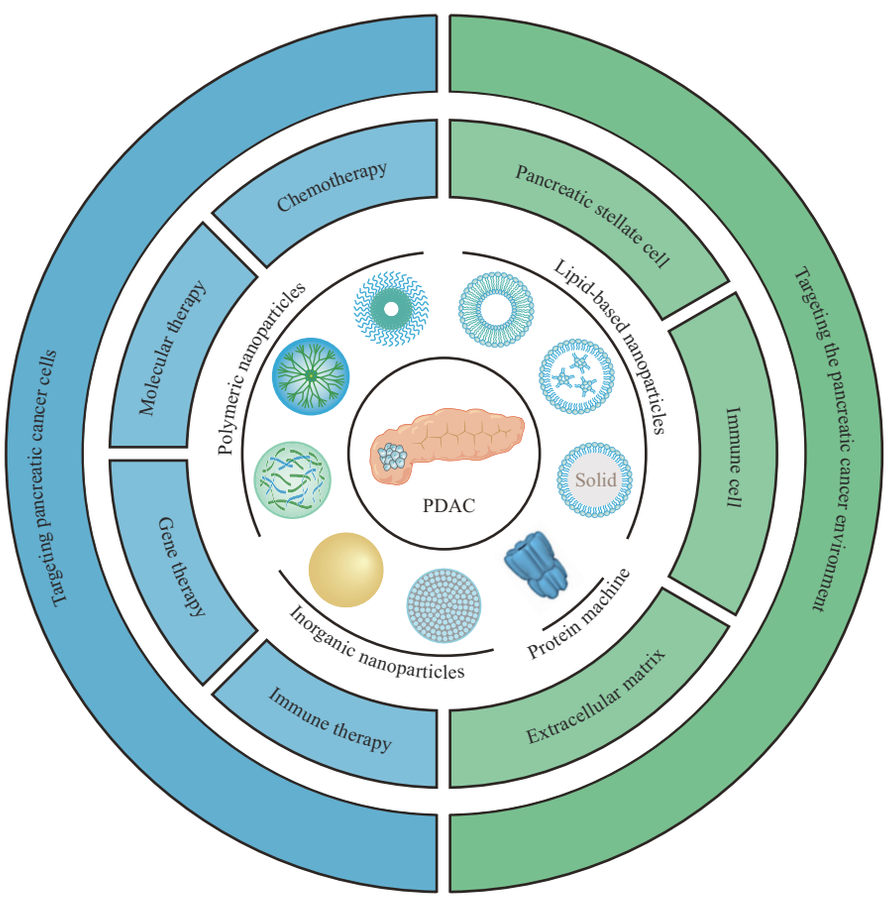
Graphical abstract



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Abstract Pancreatic ductal adenocarcinoma (PDAC) is a highly malignant solid tumor of the digestive system, characterized by rapid progression and difficulties of early diagnosis. Five-year survival rate of the patients is less than 9%. With the acceleration of global population aging and lifestyle change, the incidence of PDAC has been increasing annually. Currently, surgical treatment and chemotherapy remain the standard treatment options for PDAC patients. Early symptoms of PDAC are so undetectable that most patients miss the optimal opportunity for radical surgical resection. Even among those who undergo surgery, the high recurrence rate remains a major problem. PDAC is known for its unique tumor microenvironment. The cellular and non-cellular components in the tumor microenvironment account for as much as 90% of the tumor stroma, presenting many potential targets for PDAC therapy. Activated pancreatic stellate cells within PDAC tissue express specific proteins and secrete various cytokines and metabolites, which directly contribute to the proliferation, invasion, and metastasis of PDAC cells. These elements are critical in extracellular matrix production, connective tissue hyperplasia, immune tolerance, and drug resistance. Immune cells, such as macrophages and neutrophils, exert immunosuppressive and tumor-promoting roles in PDAC progression. The extracellular matrix, which serve as a natural physical barrier, induces interstitial hypertension and reduces blood supply, thereby hindering the delivery of drugs to the tumor. Additionally, it helps the metastasis and differentiation of PDAC cells, reducing the efficacy of clinical chemotherapy and immunotherapy. Although chemotherapeutic agents like gemcitabine have been used in the clinical treatment of PDAC for more than 20 years, the curative effect is obstructed by their poor stability in the bloodstream, low cellular uptake, and poor targeting. While small-molecule inhibitors targeting mutations such as *KRAS*^{G12C}, *BRCA*, and *NTRK* fusion have shown great potential for molecular targeted treatments and gene therapies of PDAC, their broader application is limited by side effects and restricted scope of patients. The advancement of nanotechnology brings new strategies for PDAC treatment. By virtue of unique size characteristics and actual versatility, different drug-delivery nanosystems contribute to overcome the dense stromal barrier, prolong the circulation time of therapeutics and realize precise PDAC treatment by targeted drug delivery. Clinical nanodrugs such as albumin-bound paclitaxel (nab-paclitaxel) and irinotecan liposome greatly improve the pharmacokinetics of conventional chemotherapeutics and promote drug accumulation inside the tumor, thereby are applying to the first-line treatment of PDAC. It is noteworthy that none nanodrugs with active targeting design have been approved for clinical treatment yet, though many are in clinical trials. In this review, we discuss promising targeting strategies based on different nanodrug delivery systems for treatment of PDAC. One major nanostrategy focuses on the tumor cell targeting and its applications in chemotherapy, molecular targeting therapy, gene therapy, and immunotherapy of PDAC. Another nanostrategy targets the tumor microenvironment, which highlights the nanosystems specifically regulating pancreatic stellate cells, immune cells and the extracellular matrix. Recent progress of developing new nanotheraputics for breakthrough in the fight of PDAC are elaborated in this review. We also provide our perspectives on the challenges and opportunities in the field.

Key words pancreatic ductal adenocarcinoma, nanodrug delivery system, tumor microenvironment, targeted therapy

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