利用纳米技术靶向肿瘤干细胞的研究进展

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2015-06-16 收稿, 2015-07-30 接受, 2015-09-17 网络版发表

摘要 肿瘤作为一个复杂的组织, 其中的肿瘤干细胞在肿瘤的生长、转移和复发过程中发挥至关重要的作用, 因此靶向肿瘤干细胞治疗为肿瘤治愈提供了新的思路. 新兴的纳米技术为克服传统药物的局限、有效靶向与杀伤肿瘤干细胞创造了可能. 本文概述了肿瘤干细胞的特点, 总结了目前靶向肿瘤干细胞的药物研究进展, 并对靶向肿瘤干细胞纳米技术的应用进行了总结与展望.

关键词

纳米技术
肿瘤干细胞
靶向治疗

癌症已经成为危害人类健康的头号杀手, 全世界因癌症死亡的人数逐年剧增. 随着诊断技术的提高以及一些靶向药物的出现, 很多癌症的死亡率在逐步下降. 但在手术切除治疗、化疗、放疗等传统治疗后出现的肿瘤复发与转移仍然是现今需要面对的严峻问题. 作为一个复杂的组织, 肿瘤内部存在表型与功能多样化的细胞, 其各部分在增殖、迁移以及耐药性方面均存在一定差异^[1]. 虽然产生机理尚不明确^[2,3], 但近年来越来越多的研究发现, 在多种肿瘤中均存在这样一群细胞: 在肿瘤的发生、发展等过程中起着关键作用, 具有强大的自我更新、增殖、迁移以及耐药抗凋亡等能力, 它们被定义为肿瘤干细胞. 传统肿瘤治疗策略往往针对非肿瘤干细胞, 而肿瘤干细胞才是导致癌症复发、转移及放化疗耐药的根源, 靶向肿瘤干细胞为肿瘤的治疗提供了新思路. 同时, 纳米技术作为跨学科的新兴前沿领域, 能够为靶向肿瘤干细胞治疗提供具有独特物理化学性质和生物功能的材料以及工具. 本文将重点介绍肿瘤干细胞的基本特点, 回顾靶向肿瘤干细胞的纳米药物的研究进展, 并简要总结该领域的发展前景.

1 肿瘤干细胞

1.1 肿瘤干细胞的发现

早在 1959 年, Makino^[4]就发现在肿瘤中存在一小群对化疗不敏感的细胞, 它们与其余细胞存在染色质特性差异, 首次引入“肿瘤干细胞”的概念. 之后在 20 世纪 70 年代, 一系列体内外实验验证了 Makino 的发现, 肿瘤中存在极少数的具有自我更新能力的肿瘤干细胞, 很少的数量即可以形成肿瘤^[5,6]. 肿瘤干细胞的起源目前有 2 种猜测: (1) 来源于正常干细胞, 相对于分化的细胞, 干细胞生命周期更长从而更容易积累多基因的突变, 进而破坏了正常分化和增殖的有序性, 使其发生恶性突变, 形成肿瘤干细胞^[7,8]; (2) 某些基因的突变也可能导致任意一个已分化细胞中某些维持干性的信号通路或转录因子发生活化, 从而获得“干细胞”干性, 成为肿瘤干细胞^[9-12]. 如何将少量肿瘤干细胞从大量肿瘤细胞中区分出来, 一直是研究的热点. 近些年的研究发现了多种在不同造血系肿瘤和实体瘤中富集肿瘤干细胞的分子标记物. 1994 年, Dick 课题组^[13]首次证实 CD34⁺CD38⁻细胞是人急性粒细胞白血病干细胞, 随后 Wicha 研究

引用格式: 杜锐凯, 柳素玲. 利用纳米技术靶向肿瘤干细胞的研究进展. 科学通报, 2015, 60: 3417-3423

Du R K, Liu S L. Applications of nanotechnology in targeting cancer stem cells (in Chinese). Chin Sci Bull, 2015, 60: 3417-3423, doi: 10.1360/N972015-00491

<https://engine.scichina.com/doi/10.1360/N972015-00491>

组^[14]从乳腺癌中发现CD44⁺CD24^{-low}标记的肿瘤干细胞,首次证明了实体瘤中肿瘤干细胞的存在.之后又陆续有研究显示CD133⁺是肾癌^[15]、黑色素瘤^[16,17]、肝癌^[18]、肺癌^[19]、直肠癌^[20]等多种实体瘤的肿瘤干细胞标记物.同时,除了这些肿瘤干细胞表面标记物外,乙醛脱氢酶 1(ALDH1)也被报道是乳腺癌^[21]、头颈部鳞状细胞癌^[22]以及视网膜膜癌^[23]等多种肿瘤的肿瘤干细胞标记物.

1.2 靶向肿瘤干细胞的药物研发进展

随着对肿瘤干细胞研究的深入,研究者发现许多传统化疗药物,如紫杉醇^[24-26]、顺铂^[27]、来曲唑(letrozole)^[26]、舒尼替尼(sunitinib)及贝伐单抗^[28]等在消灭肿瘤细胞的同时却也富集了肿瘤干细胞,以致增强了肿瘤的转移及复发,甚至联合用药^[29]也出现类似情况.鉴于此,越来越多的研究致力于寻找肿瘤干细胞中的新靶点,随之出现的肿瘤干细胞靶向药物也与日剧增.目前应用于肿瘤干细胞靶向治疗的药物主要包括小分子化疗药和抗体蛋白等.

Wnt, Notch和Hedgehog信号通路在多种肿瘤干细胞中发挥重要作用,因此针对这些信号通路为靶向肿瘤干细胞治疗提供了新的策略^[30,31]. PRI-724 是 β -catenin拮抗剂,可以抑制Wnt信号通路,目前已进入急/慢性骨髓性白血病以及胰腺癌等肿瘤治疗的临床实验^[32]. Vantictumab是另一种靶向Wnt通路Frizzled受体的抗体,前期实验显示其能够抑制肿瘤增殖及复发,并与传统治疗有一定的协同作用^[33]. MK-0752作为 γ secretase抑制剂可抑制Notch通路的活化^[34],而Demiczumab是一种靶向Notch通路配体DLL4的人源化抗体,试验显示其可以抑制肿瘤干细胞的生长以及促进细胞分化^[35,36],这些药物也都在开展临床试验. Hedgehog信号通路小分子抑制剂Vismodegib^[37], BMS-833923^[38]等也在多种肿瘤中显示出肿瘤干细胞清除效果.此外,许多天然化合物如萝卜硫素(sulforaphane)^[39,40]、姜黄素(curcumin)^[41]等也呈现出有效的肿瘤干细胞靶向杀伤的作用.

然而上述抗肿瘤药物多为小分子,包括抗体类药物在内,它们通常存在稳定性差、可溶性低、体内清除快速、半衰期短以及细胞摄入量低等一系列的问题.针对以上难题,纳米技术体现出其独特优势.

纳米药物直径一般小于 200 nm,由于其相对传

统药物尺寸小,因此具有比表面积大、表面反应活性高、吸附能力强等优点.并且可以通过对颗粒表面进行不同修饰来对药物载量、药物动力学特性以及生物相容性等方面进行优化.以上这些特性使得纳米药物具有以下特点:可缓释药物、提高药物稳定性、延长药物半衰期、增加药物体内作用时间;靶向作用;可保证药效前提下减少给药剂量以减轻或避免毒副反应;较好的生物相容性等.因此纳米药物适合以目前较为难以治疗的疾病作为目标,肿瘤便是其中之一.

目前纳米技术靶向肿瘤干细胞治疗的方式主要有以下几类:利用纳米载体对肿瘤干细胞靶向药物进行一定修饰改良,使其能够成功到达肿瘤部位;对纳米载体进行修饰,使载体本身具有靶向输送药物至肿瘤干细胞的能力;纳米材料因其独特的理化性质,直接对肿瘤干细胞具有特异性杀伤能力.下面我们将具体介绍纳米技术靶向肿瘤干细胞治疗的一些代表性研究.

2 纳米技术靶向肿瘤干细胞策略

2.1 纳米载体提升肿瘤干细胞靶向药物的成药性

纳米载体的一大应用便是输送存在溶解性、稳定性差,或具有较强的副作用等问题的“非成药”分子或药物.例如,盐霉素(salinomycin)在肺癌^[42]、乳腺癌^[25,43]以及慢性髓系白血病^[44]中显示出理想的肿瘤干细胞特异性杀伤效果,但是其水溶性较差,并具有较强的毒性,这在一定程度上阻碍了其在临床的应用. Zhao等人^[45]将盐霉素偶联到iTEP(免疫耐受的弹性蛋白样多肽),使其能够自组装为纳米颗粒,并可在内部包裹更多的游离盐霉素.该纳米颗粒使盐霉素能够在肿瘤处更好的富集并具有更长的体内循环时间,从而大幅度提高了药物对肿瘤干细胞的杀伤能力.环巴胺(cyclopamine)是一种Hedgehog通路抑制剂^[46], Zhou等人^[47]将其偶联到羟丙甲丙烯酸甲酯(HPMA)上,很大程度提升了水溶性并降低了系统毒性,使其在前列腺肿瘤中能够有效地清除CD133⁺肿瘤干细胞.另一研究组则使用聚乙丙交酯(PLGA)-PEG纳米颗粒荷载HPI-1,同样是一种Hedgehog通路抑制剂,解决了其水溶性差的难题,使其能够有效消除胰腺癌和肝癌中CD133⁺肿瘤干细胞^[48,49].

RNA类药物也同样存在多种局限:组织特异性不足,细胞摄取差以及存在系统毒性风险^[50]. Shi等

人^[51]使用固体脂质纳米颗粒(SLP)输送miRNA-34a(CD44抑制物),能够有效清除肺癌CD44⁺肿瘤干细胞。而Mirna Therapeutics公司则利用一种特殊的脂质体来输送MRX34(miRNA-34a的类似物)靶向肝癌肿瘤干细胞,并已作为首个microRNA类似物药物进入一期临床^[52]。Liu等人^[53]使用脂质复合纳米颗粒搭载靶向多药耐药基因(MDR1)的siRNA,成功抑制结肠癌CD133⁺肿瘤干细胞的化疗耐药性,提高了其对紫杉醇治疗的敏感性。

2.2 纳米载体靶向输送药物至肿瘤干细胞

除了使用纳米载体改善肿瘤干细胞靶向药物外,还可以对纳米颗粒本身进行修饰,使其也具有靶向肿瘤干细胞的能力。同样是荷载盐霉素,Wei等人^[54]使用能够与CD44结合的透明质酸样纳米凝胶作为载体,可以高效率地将药物靶向输送至CD44⁺肿瘤干细胞。该研究组还使用同样的载体荷载姜黄素,同样显示出理想的CD44⁺肿瘤干细胞清除效果^[55]。

纳米颗粒的一项重要特点便是可以同时搭载多种药物,基于这一特点,许多研究组使用单克隆抗体偶联的纳米载体用于靶向输送药物至肿瘤干细胞。Swaminathan研究组^[56]将抗CD133单克隆抗体偶联到PLGA纳米颗粒上,之后荷载紫杉醇药物,结果发现CD133⁺细胞对该颗粒的摄取量是非靶向颗粒的9倍以上。Yang等人^[57,58]将抗ABCG2(ABC转运泵家族成员,多种肿瘤干细胞耐药性与其高表达有一定相关性)单克隆抗体偶联的氧化铁纳米颗粒荷载紫杉醇后,发现其对多发性骨髓瘤肿瘤干细胞的杀伤能力有显著提升^[59]。Gao等人^[60]则使用超顺磁氧化铁纳米颗粒(SPIONs)偶联靶向前列腺干细胞抗原(PSCA)的单克隆抗体后,荷载多西他赛(Docetaxol)用于靶向前列腺癌肿瘤干细胞治疗,与此同时SPIONs在肿瘤部位的富集,也为MRI成像诊断创造了条件。然而,抗体偶联的纳米颗粒的局限在于其潜在的免疫原性,以及针对同一抗原不同位点的抗体效率存在较大差异。最近的研究使用无免疫原性的特异性核酸适配体来代替抗体行使靶向功能。如Shigdar等人^[61]使用15个碱基的RNA适配体来靶向CD133分子,相比抗CD133单克隆抗体具有更好的肿瘤部位渗透及滞留效果。

2.3 新型纳米材料直接靶向杀伤肿瘤干细胞

在前面提到的工作中,纳米材料通过荷载或修

饰某些药物而发挥靶向肿瘤干细胞的杀伤作用,那么纳米材料本身是否也可以作为靶向肿瘤干细胞治疗的制剂呢?答案是肯定的。研究人员合成了一些具有独特的物理或生物特性的新型纳米材料,能够直接作为肿瘤干细胞靶向治疗制剂。

肿瘤干细胞常常处于低氧环境,并且周围具有较低的活性氧(ROS)水平,这与肿瘤干细胞较强的放化疗耐受性有一定的相关性^[62-66]。因此,增加肿瘤干细胞周边的氧化作用,将有可能打破肿瘤干细胞对外界治疗的耐受性。围绕这一想法,许多研究组发现,使用加热疗法可以促进肿瘤的氧化从而增加了其对放化疗的敏感性^[67-70]。然而传统方法无法做到精确在肿瘤部位进行热疗而不伤害周边正常组织,此时新型纳米材料便体现出其价值。

Sadhukha等人^[71]利用SPION材料在交流磁场中产生的热效应,有效地减少甚至清除了肿瘤干细胞。Chen研究组^[72]则提出了热疗-化疗相结合,提高化疗药物治疗效果的优化治疗方式。金纳米棒(AuNRs)介导的光热治疗,能有效地消除MCF-7乳腺癌细胞中的肿瘤干细胞,明显降低乙醛脱氢酶(ALDH)阳性细胞的数量及球囊形成能力。进一步在AuNRs中装载盐霉素,激光触发药物释放的同时进行热疗,发现两者可以协同抑制肿瘤干细胞活力^[73]。

而另一种新型纳米材料金属富勒醇Gd@C82(OH)₂₂本身可以对多种肿瘤有抑制作用^[74-76]。Liu等人^[77]发现该材料还是三阴性乳腺癌肿瘤干细胞的特异性抑制剂,在对正常的细胞及机体未见明显毒性的同时,能够抑制上皮间充质转化过程及乳腺肿瘤干细胞的自我更新及复制,并且在免疫缺陷小鼠模型中显著抑制了肿瘤的发生与转移。普朗尼克(Pluronic)作为一种两亲性的三嵌段共聚物,能够在水溶液中自组装形成胶束,内部的疏水核心可以较大载量地输送多种化疗药物,在药物传递系统中具有一定的应用价值。近些年来研究显示除了输送药物外,该材料还能够降低肿瘤细胞内的ATP水平从而在一定程度上减弱肿瘤干细胞的耐药性^[78,79],此外还可以降低热休克蛋白70(HSP70)的表达,增加了肿瘤干细胞对加热疗法的敏感性^[80,81],从而增强抗肿瘤干细胞治疗的疗效。

3 展望

目前来说由于缺乏有效的治疗手段,肿瘤在世

界范围内仍是人类健康的巨大威胁. 肿瘤干细胞理论的提出使人们对肿瘤的理解更进一步, 然而对肿瘤干细胞的研究还并不充分, 在寻找新的肿瘤干细胞标记物, 以及深入详细了解肿瘤干细胞完整的代谢及信号转导通路等方面, 都还有较长的一段路要走. 此外, 肿瘤干细胞的发现也使我们逐渐意识到肿瘤的复杂性, 提示我们每种肿瘤都是不同的, 每位患者都是不同的, 甚至同一患者不同时期的肿瘤也是不同的, 因此个性化治疗显得愈发的重要. 这意味着在普通化疗的基础上联合使用针对癌症干细胞的有效的药物的同时, 还需要考虑肿瘤干细胞的异质性, 从而更有效的清除肿瘤细胞及肿瘤干细胞, 抑制复发, 提高患者生存率. 在这一过程中, 纳米材料的独特性质将发挥巨大的作用. 此外, 将纳米靶向技术用于追踪循环肿瘤细胞(CTC)^[82], 将使我们对肿瘤转移过程有更为深入的了解; 同时, 近些年研究表明, 肿瘤微

环境中各组分的理化性质与正常组织之间存在生物学特性差异, 并且肿瘤微环境在肿瘤发生发展过程中发挥了巨大的作用, 这使得肿瘤微环境也成为纳米材料靶向治疗的重要靶点^[83]. 然而尽管在实验室研究中, 纳米材料在肿瘤的诊断与治疗方面的应用已经有了较大的进展, 但对于如何在临床上有效应用仍存在较大挑战. 其中最重要的便是生物安全性问题, 目前还尚未有明确证据显示纳米材料可以在体内有效代谢而不会积累从而引起毒副作用. 此外, 纳米药物的安全使用剂量因无明确评价标准也较难以确定.

虽然纳米材料在临床上广泛应用还存在若干困难, 但其在前期展现出的强大能力有理由使我们相信, 随着纳米技术的进步以及对肿瘤研究的深入, 纳米技术的独特优势会为肿瘤患者个性化治疗的发展创造良好的条件, 最终实现攻克癌症的美好前景.

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Applications of nanotechnology in targeting cancer stem cells

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Previous studies have suggested that many cancers are consisted of both non-cancer stem cells and cancer stem cells (CSCs), a small population with high tumorigenicity and intrinsic drug resistance. CSCs have some characteristics similar to normal stem cells, such as self-renewing and differentiating to other cell types. CSCs are responsible to tumor recurrence and metastasis. Targeting CSCs is a promising approach to cure cancers. However, CSCs usually overexpress the multidrug resistance (MDR) gene and quiescent in G0 state which make traditional chemotherapies have less effect on CSCs. With nanotechnologies developed, new nanocarrier-based medicines show unique advantages in circulation times, stability and bioavailability compared to traditional drugs. So, more and more researchers develop new strategies based on nanotechnology to target CSCs and reduce cancer relapse and metastasis. Those strategies include (1) nanocarriers deliver CSC-targeting drugs (small molecules, siRNA) to tumor tissues which inhibit signaling pathways essential for CSCs, (2) modified nanocarriers deliver drugs to CSCs to improve killing efficiency of drugs to CSCs, (3) physical methods, such as heat or magnetic, directly kill CSCs based on the characteristic features of nano-particles. Despite of these remarkable advances in targeting CSCs with nanotechnology recently, there are still a lot to do to move these to the clinic. This review summarized the research progress about CSCs, traditional drugs on CSC-targeting therapies, and the new approaches to target CSCs with nanotechnologies. In the end, we discussed the prospect of applications of nanotechnology in clinic.

Nanotechnology, cancer stem cells, targeted therapy

doi: 10.1360/N972015-00491