用于中子俘获治疗的钆携带剂

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摘要 钆中子俘获治疗(gadolinium neutron capture therapy, Gd-NCT)是硼中子俘获治疗(boron neutron capture therapy, BNCT)的替代和补充方法. 该疗法在杀伤肿瘤细胞的同时, 还可以利用磁共振成像(magnetic resonance imaging, MRI)实现肿瘤的诊疗一体化. Gd-NCT成功的关键因素之一是钆携带剂具有良好的肿瘤靶向性、特异性、亲和性和稳定性. 目前的钆携带剂可分为三类: 钆的小分子螯合物, 螯合剂一般为多胺多羧酸; 纳米携带剂, 包括用脂质体等纳米载体负载的钆小分子螯合物及新型含钆纳米材料; 将Gd-NCT和BNCT结合的Gd-B双携带剂. 本文综述了各种钆携带剂的优缺点, 总结了有望进一步提高Gd-NCT治疗效果的新型钆携带剂的发展方向.

关键词 中子俘获治疗, 钆携带剂, 诊疗一体化, 肿瘤

中子俘获治疗(neutron capture therapy, NCT)是一种可以选择性杀伤肿瘤细胞的放射疗法. 该方法首先将热中子截面大的核素引入亲肿瘤药物并注射到癌症患者体内, 待药物富集于肿瘤组织后, 用中子束照射肿瘤部位引起中子俘获反应, 利用核反应产生的次级辐射及反冲粒子杀伤癌细胞^[1-3].

用于NCT的亲肿瘤药物称为NCT药物或携带剂, 其中所含的热中子俘获截面大的核素称为靶核素. NCT靶核素须有以下特点^[1]: (1) 热中子俘获截面大; (2) 非放射性或半衰期极长, 天然丰度较高; (3) 俘获中子后发生核反应, 发射的次级辐射具有合适的射程和很大的动能. 射程太短不能保证摧毁癌细胞核, 射程太长则可能杀死邻近的正常细胞; (4) 核反应产物最好是非放射性的.

完全符合上述条件的核素很少, 迄今人们考虑过的核素包括¹⁰B、¹⁵⁷Gd、⁶Li和²³⁵U. 目前有关NCT的研

究主要是基于¹⁰B, 硼中子俘获治疗(boron neutron capture therapy, BNCT)的硼携带剂已发展到第三代, 全球几百例临床病例证明硼中子俘获治疗对于多形性胶质母细胞瘤、头颈癌、多灶性肝细胞癌、复发性肺癌、鳞状细胞癌、涎腺癌、肉瘤、复发性恶性脑膜瘤等多种实体肿瘤具有显著可靠的疗效^[4,5]. 钆中子俘获治疗(gadolinium neutron capture therapy, Gd-NCT)设想的提出比硼中子俘获治疗晚了半个世纪, 作为另外一种NCT的靶核素, ¹⁵⁷Gd有其独特的优势: (1) 热中子吸收截面极高, 达 2.54×10^5 b, 而¹⁰B为3837 b; (2) 注射后可用核磁共振成像追踪药物去向, 实现诊疗一体化. 由于缺少肿瘤靶向的钆携带剂等原因, Gd-NCT进展缓慢^[6,7]. 近年来, 随着靶向药物递送系统研究的深入, 新型钆携带剂的研究也日益受到关注.

钆属于稀土元素, 原子序数为64, 核外电子排布为[Xe]4f⁷5d¹6s². 由于其4f轨道有7个未成对电子, 具有良

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好的顺磁性。钆的有机配体螯合物在临床上被广泛用作核磁共振成像造影剂(或称对比剂)。钆有质量数为152、154~158和160的7种稳定同位素,天然丰度分别为0.2%、2.18%、14.8%、20.47%、15.65%、24.84%和21.86%。除 ^{157}Gd 外, ^{155}Gd 的热中子吸收截面也很高,达60900 b。两者与热中子发生(n, γ)反应后的产物为稳定同位素 ^{156}Gd 和 ^{158}Gd 。钆优良的吸收中子的性能使其在核科学技术领域得到广泛应用。在核反应堆中,钆被用作控制材料。最近,掺杂了钆(0.1%)的有机液体闪烁体在中微子物理研究中发挥了关键作用^[8]。

作为Gd-NCT的靶核素, ^{157}Gd 中子俘获反应式为 $^{157}\text{Gd}+n\rightarrow^{158}\text{Gd}+\gamma$, $Q=7.94\text{ MeV}$ 。生成的复合核能量很高,向基态跃迁时,有发射瞬发 γ 射线和发射内转换电子两个相互竞争的过程。一般而言,同质异能跃迁能越小,原子核的核电荷数越大,内转换系数越大,且与跃迁的多极性有关。所以内转换主要发生在重核的低能同质异能跃迁场合。由于发射内转换电子后的核素电子壳层上留下空位,也必将再发射与EC衰变后相似的X射线或俄歇电子。钆-157中子俘获反应生成的复合核首先通过发射瞬发 γ 射线退激, γ 跃迁是级联式的,仅当退激到 10^2 keV 以下时,内转换成为主要的衰变方式。发射内转换电子进一步引发原子核释放5个俄歇和科斯特-克朗尼格(Auger and Coster-Kronig, ACK)电子及特征X射线^[9]。Gd-NCT就是利用高传能线密度(linear energy transfer, LET)的ACK电子杀伤肿瘤细胞。

ACK电子平均LET为 $0.3\text{ MeV}/\mu\text{m}$,俄歇电子平均能量为 4.19 keV ,钆中子俘获的俄歇电子平均射程为 $0.62\text{ }\mu\text{m}$ 。相对于直径约 $10\text{ }\mu\text{m}$ 的哺乳动物细胞核,俄歇电子的射程非常短。相比之下,钆中子俘获反应产生的平均能量为 45.9 keV 的内转换电子,对应的射程为 $38.19\text{ }\mu\text{m}$ 。显然,内转换电子会将能量沉积在细胞外。只有俄歇电子可以将能量沉积在细胞核的尺寸范围内。这表明,钆中子俘获反应将从发射的俄歇电子中产生一个聚集的、高LET的能量沉积事件,由此产生的损伤将高度局部化。用热中子轰击结合在DNA上的 ^{157}Gd 能够有效诱导DNA双链断裂^[10]。

对于钆中子俘获治疗,肿瘤组织中 ^{157}Gd 最佳浓度为 $50\sim 200\text{ }\mu\text{g/g}$ 。过低达不到治疗效果,过高(如高于 $1000\text{ }\mu\text{g/g}$)会因 ^{157}Gd 对中子的高吸收导致组织深度的中子注量迅速减少。Gd-NCT已在许多肿瘤动物模型(小鼠、大鼠、兔、犬)中得到验证,但迄今为止,这种疗法尚未得到临床应用^[6]。

1 钆携带剂

将靶核素特异性地运输到肿瘤细胞,在治疗过程中维持一定的浓度,是实现中子俘获治疗的关键。开发具有高选择性的钆携带剂是目前Gd-NCT研究的首要任务。钆原子独特的核外电子排布使得钆化合物成为核磁共振造影剂的最理想选择,核磁共振造影剂也是钆最重要的临床应用。钆的无机盐如氯化钆、硝酸钆虽能够提高核磁共振成像的对比度,但 Gd^{3+} 进入人体会产生毒副作用。为降低体内游离 Gd^{3+} 的释放,20世纪70年代末,研究人员开始尝试用 Gd^{3+} 与多胺多羧酸类配体形成的螯合物作为核磁共振成像造影剂,如二乙基三胺五乙酸合钆(Gd-DTPA,图1(a))、1,4,7,10-四氮杂环十二烷-1,4,7,10-四羧酸(Gd-DOTA,图1(b))等。到目前为止,已经通过美国食品药品监督管理局(Food and Drug Administration, FDA)批准上市的核磁共振造影剂主要是钆的多胺多羧酸螯合物^[11]。钆基核磁共振造影剂成果被钆携带剂的研究所借鉴。

1.1 钆小分子螯合物

美国密苏里大学哥伦比亚分校的Brugger和Shih^[12]最早提出将已批准临床使用的钆基造影剂试剂用作Gd-NCT钆携带剂。尤其是常用于中枢神经系统疾病诊断的Gd-DTPA,具有高对比增强能力、高稳定性的特点。静脉注射的Gd-DTPA能够快速从血液清除,保证了其安全性。Gd-DTPA能够进入血脑屏障被破坏的肿瘤组织,但不能通过正常的血脑屏障,Gd-DTPA对脑瘤的T/N比很高(~ 10)^[13]。Khokhlov等人^[14]报道了以Gd-DTPA为携带剂,通过NCT治疗大鼠Jensen肉瘤的工作。瘤内注射 13.75 mg/g 肿瘤组织的钆,随后用注量率为 $3.6\times 10^{11}\text{ n/cm}^2$ 的热中子照射。治疗后肿瘤生长抑制率

图1 (网络版彩色)Gd-DTPA(a)和Gd-DOTA(b)的结构
Figure 1 (Color online) Chemical structures of Gd-DTPA (a) and Gd-DOTA (b)

可以达到80%,组织学观察亦证实了对照组和治疗组之间的差异。

由于ACK电子的射程很短, Gd与肿瘤细胞的DNA需尽可能接近以提高高能电子的杀伤力。一般认为包括Gd-DTPA在内的钆多胺多羧酸螯合物无法进入细胞,但随着分析技术的发展,对于这一问题有了新的认识。De Stasio等人^[15]用Gd-DTPA溶液处理原代人胶质母细胞瘤(glioblastoma, GBM)细胞,采用基于同步辐射的光发射电子显微镜磁成像技术和飞行时间二次离子质谱分析了Gd在细胞中的分布。结果发现, Gd-DTPA不仅能穿透细胞膜,而且在细胞核中的浓度高于细胞质中的浓度。随后,他们又利用基于第三代同步辐射光源的软X射线扫描透射显微成像,分析了Gd在体外培养的细胞、荷瘤大鼠鼠脑及胶质母细胞瘤患者肿瘤组织切片中的微区分布^[16]。结果表明,经Gd-DTPA和Gd-DOTA处理,分别在84%和56%的人胶质母细胞瘤细胞的细胞核中发现Gd的富集。大鼠被单次和两次静脉注射Gd-DOTA,在细胞核中发现Gd的比例从47%提高到85%。然而,在GBM患者肿瘤组织中,仅6.1%的细胞核含有Gd-DTPA。De Stasio等人^[16]认为,肿瘤细胞的细胞核Gd摄取量不足决定了以Gd-DTPA和Gd-DOTA为Gd携带剂无法取得较好的治疗效果。

Zhang等人^[17]在Fisher 344大鼠脑中植入脑胶质瘤,静脉注射Gd-DTPA和脑肿瘤选择性造影剂钆贝酸二葡甲胺(Gd-BOPTA),比较了肿瘤组织对Gd-DTPA和Gd-BOPTA的摄取。研究发现,肿瘤组织中Gd-BOPTA的摄取量明显高于瘤周组织和正常大脑,与Gd-DTPA相比, Gd-BOPTA在脑肿瘤中滞留时间更长。随后,他们给在双侧后肢接种了9 L胶质肉瘤的Fisher 344大鼠颅内分别注射相同剂量的Gd-BOPTA和Gd-DTPA,热中子照射后, Gd-BOPTA比DTPA表现出更强的抑制肿瘤生长的能力。他们认为,由于Gd-BOPTA对蛋白的结合亲和力和较Gd-DTPA弱,增加了在肿瘤组织中的滞留。因此, Gd-BOPTA被认为是NCT的有效靶向化合物^[18]。

铂复合物例如顺铂(cisplatin)能够穿过细胞膜进入细胞核,与DNA结合从而阻止癌细胞生长,是一种重要的抗癌药物。Crossley等人^[19]提出制备Pt-Gd复合物,将Gd输送到肿瘤细胞核的方案。该复合物通过将DTPA连接到两个具有以插入方式结合DNA能力的{Pt^{II}(2,2':6',2'':三吡啶)}基团,有效地靶向肿瘤细胞的细胞核。同步辐射X射线荧光分析的结果证明在细胞中, Gd和Pt均在细胞核中富集。他们推断,相关的Pt-Gd物种PtDTPA将

有能力将Gd传递到DNA,以便充分利用俄歇电子的毒性作用。

苯并噻唑衍生物广泛用于抗肿瘤尤其是具有分子靶向性抗肿瘤药物的研发。Kim等人^[20]将1,4,7,10-四氮杂环十二烷-1,4,7-三乙酸(DO3A)与苯并噻唑苯胺(BTA)共价连接,再螯合上Gd³⁺,制备出具有高抗肿瘤活性的诊疗剂Gd-DO3A-BTA。该螯合物具有肿瘤靶向性,能够在细胞核中富集。荷瘤裸鼠尾静脉注射0.1 mmol/kg Gd-DO3A-BTA, 24 h后肿瘤部位累积Gd为40~220 μg/g肿瘤,在Gd-NCT的最佳量(50~200 μg/g肿瘤)范围内。

磷(膦)类配体(配合物)有较强的趋骨性。20世纪80年代,人们合成了EDTA的膦酸衍生物乙二胺四甲基膦酸(EDTMP),并用稀土元素放射性同位素标记物¹⁵³Sm-EDTMP、⁹⁰Y-EDPMP治疗骨肿瘤^[21]。Gd-EDTMP在骨肿瘤中富集,浓度可达800 μg/g,有望作为治疗骨肿瘤的Gd-NCT携带剂。

1.2 纳米Gd携带剂

近年来随着纳米技术的蓬勃发展,新型纳米材料不断涌现,为重大疾病治疗提供了新的思路。纳米递药系统一方面可以通过高渗透长滞留(enhanced permeation retention, EPR)效应被动靶向肿瘤部位;另一方面,还可以通过对材料靶向修饰,从而主动靶向肿瘤血管和细胞,促进药物在肿瘤部位的富集,提高化疗药物安全性,降低其毒副作用^[22]。将靶向递送、诊断和治疗功能结合在同一个纳米载体上,实现多种成像模式联合诊断、多种治疗方法协同治疗的诊疗一体化是未来医学发展的趋势^[23]。钆基纳米造影剂是纳米医学和分子影像学的研究热点,涉及的纳米材料包括脂质体、树形分子、碳纳米材料、金属氧化物纳米材料等^[24]。这些纳米载体的设计同样可以为用于Gd-NCT的钆纳米携带剂的研发提供借鉴^[25,26]。

20世纪90年代,北京大学王祥云课题组^[27]开展了脂质体包埋钆螯合物的研究,制备了水动力学直径约为610 nm的Gd-EDTA@脂质体。研究发现,SP_{2.0}骨髓瘤细胞摄入Gd-EDTA@脂质体速率是Gd-EDTA的8倍,而对于释放速率, Gd-EDTA@脂质体远低于Gd-EDTA。这些结果提示Gd-EDTA@脂质体有望作为GdNCT的钆携带剂。表1列出了近期报道的Gd-NCT纳米携带剂,多数采用的设计方案是用纳米载体负载临床钆基造影剂(尤其是Gd-DTPA)。利用这些纳米载体将Gd化合物输

表 1 用于Gd-NCT的纳米携带剂

Table 1 Nano-delivery agents for Gd-NCT

纳米材料	Gd络合物	粒径(nm)	主动/被动靶向	肿瘤模型(在体内/ 体外研究)	注射方式	NCT	瘤内浓度	文献
壳聚糖	Gd-DTPA	391, 214	表面带正电荷	B16F10 C57荷瘤鼠	瘤内	是	500 $\mu\text{g/g}$ (391 nm) 1500 $\mu\text{g/g}$ (214 nm)	[28]
壳聚糖	Gd-DTPA	430	表面带正电荷	B16F10 C57荷瘤鼠	瘤内	是	1800 $\mu\text{g/g}$ (两次注射)	[29]
Ca/P	Gd-DTPA	60	被动	Colon-26荷瘤鼠	尾静脉	是	8 $\mu\text{g/g}$ (单次注射)/16 $\mu\text{g/g}$ (两次注射); 4% ID/g肿瘤	[30~32]
Gd@C ₈₂ -PEG-b-PAMA	Gd	15~25	被动	Colon-26细胞	无	是	无	[33]
GdFeO ₃ /Fe ₃ O ₄ /SiO ₂	GdFeO ₃	60	被动	无	无	否	无	[34]
RGD-PAA-UGNPs	Gd ₂ O ₃	1.8	主动	人脑恶性胶质瘤荷瘤鼠	尾静脉	是	2.3 $\mu\text{g/g}$	[35~37]
GdCo@CNP	Gd ₂ C ₃	20~50	主动(叶酸)	HeLa细胞	无	是	无	[38]
微乳液	Gd-乙酰丙酮	85	主动(叶酸)	KB荷瘤鼠	尾静脉	否	33 $\mu\text{g/g}$	[39]
脂质体	Gd-DTPA	136~152	主动(叶酸或DOTAP)	F98鼠神经胶质瘤和LN229人神经胶质瘤细胞	无	是	F98(叶酸: 250 ng/106细胞; DOTAP: 3000 ng/106); LN229(叶酸: 200 ng/106细胞; DOTAP: 2000 ng/106)	[40]
壳聚糖	Gd-DTPA	未给出	表面带正电荷	恶性纤维组织细胞瘤细胞	无	否	一个细胞培养瓶30.5 mg	[41]
壳聚糖	Gd-DTPA	426	表面带正电荷	L929纤维原细胞, B16F10和SCCVII细胞株	无	否	18.0(L929纤维原细胞), 27.1 (B16F10细胞), 59.8 (SCC-VII 细胞)mg Gd/10 ⁶ 细胞	[42]
树状大分子	Gd-DTPA	未给出	主动(亲和素)	SHIN3人卵巢癌荷瘤鼠	尾静脉	否	162 $\mu\text{g/g}$	[43]
脂质体	GdHPDO3A	100~300	被动	Colon-26荷瘤鼠	尾静脉	是	40.3 $\mu\text{g/g}$	[44]
脂质体	Gd-DTPA	<150	被动	TC-1肺癌荷瘤鼠	尾静脉	否	158.8 $\mu\text{g/g}$	[45]
聚天冬氨酸	Gd-DOTA	8.3, 9.8	被动	小鼠结肠腺癌荷瘤鼠	尾静脉	是	19.4 $\mu\text{g/g}$	[46]
乳糜微粒	Gd-乙酰丙酮	100	被动	野生型Balb/C鼠	尾静脉	否	无	[47]
G6聚合物	Gd-DTPA	9	被动	前哨淋巴结和PT-18(小鼠肥大细胞系)微转移模型	瘤周皮下注射	否	466 $\mu\text{g/g}$	[48]

送到肿瘤组织, 实现MRI精确成像引导的中子治疗, 其中部分研究已在动物实验中取得了较好疗效。日本神户学院大学Ichikawa课题组^[28,29]给荷瘤小鼠瘤内注射壳聚糖负载Gd-DTPA, 热中子照射后, 肿瘤生长被显著抑制; 而注射等量的游离Gd-DTPA, 由于其肿瘤滞留率较低, 没有观察到抑制效果。这一结果说明, 将Gd-DTPA掺入纳米颗粒能显著增加其在肿瘤组织中的滞留时间, 同时壳聚糖外表面的正电荷增强了与细胞膜的作用, 提高了摄取率。Mi等人^[30]采用水热法合成了负载Gd-DTPA的磷酸钙纳米胶束(Gd-DTPA/CaP), 动物实验的结果与Ichikawa课题组^[28,29]的研究结果类似,

只有纳米形式的Gd-DTPA能够有效抑制肿瘤生长且不影响体重, 表明Gd-DTPA/CaP具有安全治疗肿瘤的潜力。此外, 由于Gd-DTPA在肿瘤中的积聚增加, 利用MRI可观察到肿瘤组织的选择性对比增强, 实现了肿瘤精确定位^[31,32]。

除了在纳米载体上负载钆基核磁共振造影剂的方案以外, Gd-NCT纳米携带剂的另一个方案是制备新型含钆纳米材料, 如Gd@C₈₂^[33]、GdFeO₃^[34]、Gd₂O₃^[35]等, 并对其表面进行功能化修饰。Horiguchi等人^[33]用对聚乙二醇-嵌段-聚甲基丙烯酸N,N-二甲氨基乙酯(PEG-b-PAMA)修饰金属富勒烯Gd@C₈₂使之具有良好的水溶

性和生物相容性。Colon-26腺癌细胞经浓度为317 $\mu\text{mol/L}$ 的Gd@C₈₂-PEG-b-PAMA处理后再用热中子照射,细胞存活率下降约20%。Bridot等人^[36]将Gd₂O₃纳米颗粒封装在携带有机荧光团聚硅氧烷壳中,表面用羧基化PEG修饰,得到水合粒径为10~20 nm的多功能纳米复合物。用50 $\mu\text{mol/L}$ 复合物处理小鼠淋巴瘤细胞,随后用热中子照射。当中子剂量为2 Gy时,细胞增殖受到抑制;剂量为3 Gy时细胞全部被杀死。利用该纳米复合物的荧光和顺磁特性,可以通过荧光成像和MRI跟踪细胞的摄取情况。

Ho等人^[37]设计合成了一种可用于MRI、Gd-NCT和肿瘤细胞检测的超小多功能钆基纳米复合物Rho-PAA-UGNPs。聚丙烯酸(PAA)表面包覆以确保稳定和生物相容性,并修饰上罗丹明(RhO)作为检测肿瘤细胞的pH敏感荧光探针。该复合物被成功地应用于人脑恶性胶质瘤细胞U87MG的体外Gd-NCT,癌细胞死亡率比使用商业核磁共振造影剂钆布醇高1.75倍。随后,他们又合成了靶向小肽Arg-Gly-Asp(RGD)修饰,具有肿瘤靶向能力的超小钆基纳米复合物RGD-PAA-UGNPs。将该复合物尾静脉注射到荷人脑恶性胶质瘤的裸鼠体内,利用核磁共振成像监测肿瘤部位复合物的累积情况,同时使用热中子照射,肿瘤生长被显著抑制。

将纳米Gd携带剂表面修饰叶酸^[38~40]、正电荷基团^[28,29,39,41,42]或抗生物素^[43],可以使其具有肿瘤靶向性,解决通过静脉注射的纳米颗粒瘤内浓度较低的问题^[44~47]。而采用瘤内或瘤周皮下注射Gd-NCT纳米携带剂,可获得很高的瘤内Gd浓度^[29,48]。

1.3 Gd-B双携带剂

体外实验发现,用40 ppm的对-二羟基硼酰苯丙氨酸(BPA)和5 ppm的Gd-DTPA混合溶液处理肿瘤细胞,热中子照射后,细胞存活率比仅用BPA处理的细胞下降了1/10^[49]。但如果Gd的浓度过高,由于¹⁵⁷Gd的热中子截面远大于¹⁰B,反而降低治疗效果^[50]。发展能够同时负载Gd和B的Gd-B双携带剂,一方面能够利用BNCT和Gd-NCT的协同作用提高疗效;另一方面,还可以通过MRI实时检测B的分布,实现诊疗一体化。

Anufriev等人^[51]提出了设计Gd-B双携带剂的两个方案:一是修饰多胺多羧酸类配体,一端螯合钆,一端连接含硼基团,并增加与各种生物大分子结合的官能团;二是在碳硼烷上连接可与钆螯合的基团。Matsumura等人^[52]最早开展了Gd-B双携带剂的研究。他们开

发了一种新的卟啉衍生物,同时与硼和钆偶联,再利用卟啉衍生物对肿瘤的亲和作用靶向肿瘤细胞。随后,他们合成了BPA共轭Gd-DTPA复合物(BPA-Gd-DTPA)。利用瞬发 γ 射线分析和放射自显影确定了尾静脉注射BPA-Gd-DTPA后,该Gd-B双携带剂在背部植入AH109A肿瘤的大鼠体内分布^[53]。注射后20和60 min时,肿瘤内%ID值分别为0.010和0.0025。由于BPA转运蛋白在肿瘤细胞上的高表达,与碳硼烷Gd-DTPA复合物相比,在肿瘤组织中积累量更高。然而,Gd-DTPA单元(M.W.=590)与BPA(M.W.=209)的结合导致BPA-Gd-DTPA中B原子的生物分布和瘤内浓度相对于BPA本身发生了显著变化。

肿瘤细胞在快速增殖过程中需要大量的胆固醇。低密度脂蛋白(low-density lipoprotein, LDL)是一种在血浆中大量存在的天然纳米颗粒(粒径为22~27 nm),能将脂质、胆固醇、蛋白及疏水性药物通过体循环转运至肝外组织。意大利都灵大学Geninatti-Crich课题组^[54]将碳硼烷基团通过酰胺键连接到脂肪链和Gd-DOTA螯合物,构建了用于Gd-BNCT的Gd-B双携带剂Gd/B/L(L为配体)。再将Gd/B/L载入LDL以获得靶向肿瘤的能力并增强生物相容性,每个LDL颗粒最多装载190个Gd/B/L。细胞实验发现,该双携带剂没有明显的细胞毒性,30 mg/mL处理人肝癌(HepG2)、小鼠黑色素瘤(B16)和人胶质母细胞瘤(U87)细胞16 h,细胞内探针浓度分别为34、20和16 $\mu\text{g/g}$ 。给颈部接种了黑色素瘤的小鼠皮下注射Gd/B/L-LDL,在4~6 h后,肿瘤中的硼含量(30 $\pm$ 5 ppm)高于NCT治疗所需的阈值。热中子照射后,通过MRI来观察肿瘤的生长情况。与对照组相比,治疗组小鼠的肿瘤生长速度明显降低。随后,Geninatti-Crich课题组^[55]又用上述Gd-B双携带剂Gd-BNCT治疗小鼠的肺转移瘤和转基因EML4-ALK小鼠的原发性肺部肿瘤。与对照组相比,治疗组小鼠肿瘤体积的增加明显慢于对照组。但治疗后25~30 d,两种小鼠模型均观察到肿瘤复发,这可能与注入肺部肿瘤的中子剂量不足,无法杀死所有癌细胞有关;或肿瘤中存在静止期细胞,相对于高度增殖的细胞,静止期细胞靶受体低表达,对靶向治疗抵抗力更高。此外,Geninatti-Crich课题组^[56]还制备了另一种Gd-BNCT双携带剂——Gd-B-AC01。该双携带剂一侧带有胆固醇单元(以插入脂质体双层膜)的碳硼烷单元,另一侧为Gd螯合物Gd-DOTA。为使Gd-B-AC01具有肿瘤靶向性,将嵌入碳硼烷和Gd-DOTA的脂质体与叶酸偶联。体外实验表明,负载Gd-B-AC01的脂

质体能在人卵巢癌细胞IGROV-1中蓄积。热中子照射后,经双携带剂处理的细胞存活率显著降低。

2 总结与展望

钆中子俘获治疗作为BNCT的补充和替代性手段,有其独特的优势。为进一步提高Gd-NCT相对于其他常规肿瘤治疗方案的竞争力,最终实现临床应用,新型钆携带剂的研发是面临的最大挑战。亟待开展的研究工作包括: (1) 进一步提高钆携带剂的肿瘤靶向性,降低对肿瘤组织周围正常组织的损伤; (2) 设计、合成能够

在细胞DNA或关键细胞结构(线粒体和溶酶体)中积聚的新型Gd携带剂,以便充分利用射程极短的俄歇电子产生的毒性效应; (3) 使用 ^{157}Gd 富集稳定同位素或小分子量钆携带剂。 ^{157}Gd 的天然丰度仅为15.7%,富集后可达到98%。使用 ^{157}Gd 富集同位素将降低获得显著治疗效果所需的最低Gd浓度; (4) 发展Gd-B双携带剂以提高治疗效果; (5) 与其他治疗方法结合,利用协同策略提高疗效,彻底杀死肿瘤细胞,避免肿瘤复发。例如,NCT可以与阿霉素或培美曲塞等通常用于癌症治疗的药物联合使用。

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Summary for “用于中子俘获治疗的钆携带剂”

Gadolinium delivery agents for neutron capture therapy

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Neutron capture therapy (NCT) is a binary form of radiation therapy that combines neutron irradiation with a tumor targeting agent labeled with a stable isotope having a high thermal neutron capture cross section and yielding charged particle reaction products after neutron capture. At present, NCT has largely, but not exclusively, focused on the use of boron-10 as the target nuclide. Gadolinium neutron capture therapy (Gd-NCT) is an alternative and supplementary method of boron neutron capture therapy (BNCT). Gd-157, which has the largest cross-section (254000 barns) of thermal neutrons of all stable isotopes, is the most effective isotope in terms of neutron capture. The Gd neutron capture reaction, $^{157}\text{Gd}(n, \gamma)^{158}\text{Gd}$, provokes complicated nuclear decay transitions that generate low linear energy transfer (LET) gamma photons and the emission of high LET conversion electrons and Auger electrons. Therefore, Gd is considered to be highly suitable for the absorption of thermal neutrons in the NCT reaction. Another advantage of Gd-NCT is Gd^{3+} has a longer retention time and can thus be tracked by means of magnetic resonance imaging (MRI) methods. Currently, Gd(III) based MRI contrast agents are most commonly used in clinical practice. However, due to lack of appropriate tumor-selective Gd agents, the Gd-NCT concept has not yet been clinically tested.

For a successful neutron capture therapy, a target nuclide delivery system with high therapeutic efficiency and low adverse effects is crucial. Three major classes Gd delivery agents have been developed so far, small molecule chelates of Gd, nano-delivery agents, and Gd-B dual delivery agents. In the first trial of Gd-NCT, commercially available MRI contrast agents composed of Gd-chelating compounds were used as Gd delivery agents. However, due to the insufficient number of tumor cell nuclei incorporating Gd, efficacy of small molecule chelates of Gd as Gd-NCT delivery agents is generally low. In recent years, with the rapid development of nanotechnology, nanomaterials have been widely employed as carriers for cancer theranostics. A variety of Gd-based nanomaterials have been developed for pre-clinical trials of NCT. The majority of them are constructed by incorporating commercially available MRI contrast agents in biocompatible nanomaterials (liposomes, albumin, and micelles), or employing Gd based nanoparticles with their unique physiochemical properties. While nano-Gd delivery agents have proved to be a promising strategy in Gd-NCT, it is also possible to integrate of both Gd and B in one delivery agent. The design of many Gd-NCT agents to date has focused on combined BNCT and Gd-NCT agents in order to maximise cytotoxicity from the combined effects or to use the B component for NCT and the Gd component as a MRI imaging agent.

This paper highlights the recent advances in Gd selective and efficient delivery methods and the preclinical outcome of Gd-NCT, both advantages and disadvantages of various Gd delivery agents were addressed. Finally, we offered our perspectives on the challenges and future development of Gd delivery agents for Gd-NCT.

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