· 综述 ·

靶向整合素的放射性药物在肿瘤诊疗中的研究进展

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【摘要】 整合素是一类跨膜糖蛋白，在肿瘤新生血管内皮细胞及多种肿瘤细胞中高表达，而在正常组织低表达或不表达。靶向整合素的放射性诊断或治疗性药物可以无创、在体显示肿瘤特性、评估血管新生情况以及对肿瘤进行放射靶向治疗等，具有较大的临床应用价值。该文就靶向整合素的放射性药物在肿瘤诊断和治疗中的研究进展进行综述。

【关键词】 肿瘤；放射性药物；整合素类；发展趋势
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Research progress of integrin-targeted radiopharmaceuticals in tumor diagnosis and treatment

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【**Abstract**】 Integrin is a kind of transmembrane glycoprotein, which is highly expressed in tumor neovascular endothelial cells and various tumor cells, but lowly or negatively expressed in normal tissues. Integrin-targeted diagnostic or therapeutic radiopharmaceuticals can non-invasively display tumor characteristics *in vivo*, evaluate angiogenesis and perform targeted radiotherapy for tumors, which have great clinical application value. This article reviews the research progress of radiopharmaceuticals targeting integrins in tumor diagnosis and treatment.

【**Key words**】 Neoplasms; Radiopharmaceuticals; Integrins; Trends
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整合素（integrin）是细胞黏附分子家族的重要成员，在肿瘤新生血管内皮细胞及多种肿瘤细胞中高表达，而在正常组织低表达或不表达。整合素由 1 个 α 亚基和 1 个 β 亚基非共价结合形成异二聚体，目前共发现 18 种 α 亚基和 8 种 β 亚基，形成 24 种整合素。不同的整合素亚型在特定的肿瘤类型中表达水平不同，通过对整合素亚型进行核医学显像可以特异性检测肿瘤类型，并且能直观反映整合素的表达水平，进而监测肿瘤生长、指导与整合素相关的治疗方案选择以及评估治疗反应。此外，通过标记不同的治疗性核素（如^{177}Lu、^{225}Ac），可以利用整合素靶向分子实现肿瘤核素治疗。因此，整合素靶向放射性药物的体内显像特性尤为重要。本文主要讨论靶向不同整合素亚型的放射性药物研究现状，以期为整合素相关放射性药物的开发和应用提供参考。

一、整合素 $\alpha_v\beta_3$

整合素 $\alpha_v\beta_3$ 是研究最早、最深入和最多的整合素亚型之一。其在肿瘤新生血管内皮细胞和多种肿瘤细胞上高表达，如肺癌、乳腺癌、胃癌、脑胶质瘤、前列腺癌、胰腺癌和卵巢癌等[1]。环状（cyclo，c）精氨酸-甘氨酸-天冬氨酸（Arg-Gly-Asp，RGD）五肽，如 c（RGD-*D*-苯丙氨酸-缬氨酸）[c（RGD-*D*-Phe-Val），c（RGDfV）]、c（RGD-*D*-苯丙氨酸-赖氨酸）[c（RGD-*D*-Phe-Lys），c（RGDfK）]和 c（RGD-*D*-酪氨酸-赖氨酸）[c（RGD-*D*-Try-Lys），c（RGDyK）]，对整合素 $\alpha_v\beta_3$ 的亲和力和选择性高于其他整合素亚型[2]。目前，每年仍有大量基于 RGD 序列的整合素显像探针被报道[1,3-4]，本节概述一些典型的整合素 $\alpha_v\beta_3$ 显像和治疗药物。

^{18}F-糖基化 RGD（galacto-RGD）是第 1 种用于临床患者整合素显像的药物，患者耐受性良好、无严重不良反应，肿瘤摄取积累快、经肾脏快速清除，具有良好的显像对比度[5]。但该药物的放射合成步骤多、耗时长、产率低，导致其临床推广应用受限。基于 Al^{18}F 标记方法的 Al^{18}F-1，4，7-三氮杂环壬烷-1，4，7-三乙酸（1，4，7-trizacyclononane-1，4，7-triacetic acid，NOTA）-RGD$_2$、Al^{18}F-NOTA-聚乙二醇[poly（ethylene glycol），

PEG]$_4$-谷氨酸-c(RGDfK)二聚体{H_2N-Glu-[c(RGDfK)]$_2$,E[c(RGDfK)]$_2$}(^{18}F-Alfatide)和 Al^{18}F-NOTA-E[PEG$_4$-c(RGDfK)]$_2$(^{18}F-Alfatide Ⅱ)可在约 30 min 内完成标记和纯化过程,放化纯大于 95%,使药物临床可用性大大提高[6-8]。这几种探针主要经肾脏排泄,肝脏、脾脏和肠道的摄取与肿瘤中的摄取值相当。^{68}Ga 标记的 RGD 肽也被用于整合素 $\alpha_v\beta_3$ 显像,这些显像剂使用不同的螯合剂如 1,4,7,10-四氮杂环十二烷-1,4,7,10-四乙酸(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTA)[9]、NOTA[10-11]、2-(4,7-二乙酸)-1,4,7-三氮杂环壬烷-1-戊二酸[2-(4,7-bis(carboxymethyl)-1,4,7-triazonan1-yl)pentanedioic acid, NODAGA][12-13]和 1,4,7-三氮杂环壬烷-1,4,7-三亚甲基膦酸[1,4,7-triazacyclononane-1,4,7-tris(methylene(2-carboxyethyl))phosphinic acid, TRAP][14],探针性质也略有差异。为了提高探针在肿瘤的摄取、改善代谢性能,一些临床前研究使用多聚化策略制备 RGD 三聚体(如^{68}Ga-TRAP(RGD)$_3$[14])、四聚体甚至八聚体(如^{64}Cu-DOTA-RGD tetramer、^{64}Cu-DOTA-RGD octamer[15]),结果显示探针的性质并不是随着多聚体数目增加而提升。通过药盒法可制备^{99}Tc^m 标记的 3 个 PEG$_4$ 修饰的 RGD 二聚体探针^{99}Tc^m-3PRGD$_2$,该方法操作简便,产物放化纯高、对整合素 $\alpha_v\beta_3$ 的亲和力较高,在不同类型的肿瘤患者中均取得很好的显像和诊断效果[16-17]。在核医学显像诊断的基础上,Shi 等[18]制备了用于肿瘤治疗的^{177}Lu-3PRGD$_2$,其对小鼠肿瘤模型有一定的抑制效果,但由于多肽代谢清除较快、肿瘤摄取绝对值相对较低,需要较大的给药剂量。Gao 等[19]使用白蛋白结合分子 4-(*P*-碘苯基)-丁酸[4(*P*-iodophenyl)butyryl, IP]修饰^{177}Lu-3PRGD$_2$,成功制备^{177}Lu-AB-3PRGD$_2$,其具有更长的血液半衰期和更高的肿瘤摄取和滞留,只需更小的剂量即可显著抑制小鼠肿瘤生长,与免疫抑制剂联合使用后甚至能清除肿瘤。有研究者则使用伊文思蓝(Evans blue, EB)结构作为白蛋白结合分子,制备一系列 EB 修饰的 RGD 类药物,标记^{64}Cu 或^{177}Lu 后进行肿瘤治疗研究[20-23]。

总之,对于影像诊断,在保持病变与正常器官高对比度的基础上,要求显像剂尽快从血液和正常脏器清除;对于核素治疗,要在保持一定血药浓度和足够治疗作用的基础上,尽量减少对正常脏器的损伤[24]。目前大部分治疗性药物在保持肿瘤摄取较高的同时,其在正常组织器官的摄取也较高,因此可能需要更多的策略以优化分子探针,实现诊断和治疗的不同药代动力学要求。

二、整合素 $\alpha_v\beta_6$

整合素 $\alpha_v\beta_6$ 仅在上皮细胞来源的肿瘤细胞中过表达,如胰腺癌、肺癌、头颈癌、乳腺癌、结肠癌、肝癌和卵巢癌等[1],是有前景的核医学显像或治疗靶点。针对整合素 $\alpha_v\beta_6$ 的核医学显像或治疗探针可直接与肿瘤细胞结合,反映肿瘤细胞的特征或直接杀伤肿瘤细胞。

目前靶向整合素 $\alpha_v\beta_6$ 的大部分放射性药物均基于多肽或小分子。Hausner 等[25]制备了^{18}F-*N*-(4-氟苯甲酰基)[Bz(4-F), FBA]-天冬酰胺-丙氨酸-缬氨酸-脯氨酸-天冬酰胺-亮氨酸-精氨酸-甘氨酸-α-天冬氨酸-亮氨酸-谷氨酸-缬氨酸-亮氨酸-丙氨酸-谷氨酸-赖氨酸-缬氨酸-丙氨酸-精氨酸-苏氨酸(Asn-Ala-Val-Pro-Asn-Leu-Arg-Gly-Asp-α-Leu-Gln-Val-Leu-Ala-Gln-Lys-Val-Ala-Arg-Thr-NH_2, A20FMDV2),通过 PET/CT 显像验证了整合素 $\alpha_v\beta_6$ 阳性肿瘤 PET 显像的可行性。为增加探针的体内代谢稳定性,Hausner 等[26]使用 PEG$_{28}$ 修饰^{18}F-FBA-A20FMDV2,得到^{18}F-$\alpha_v\beta_6$-结合肽(binding peptide, BP),该探针在转移性肺癌、结肠癌、乳腺癌和胰腺癌患者中的 PET/CT 显像结果显示其可以特异性检出肿瘤原发灶和转移灶(包括脑、骨、肝和肺转移灶),表明其在多种整合素 $\alpha_v\beta_6$ 阳性肿瘤的检测中有较大潜力。为延长药物体内生物半衰期、增加肿瘤摄取、改善药代动力学,多项研究引入白蛋白结合结构(albumin binding moiety, ABM),分别制备 Al^{18}F-NOTA-K(ABM)-$\alpha_v\beta_6$-BP(K 代表赖氨酸)[27]、^{64}Cu-DOTA-K(ABM)-$\alpha_v\beta_6$-BP[28]、^{64}Cu-DOTA-IP/EB-$\alpha_v\beta_6$-BP[29],这些探针在肿瘤的摄取都有所增加,但正常组织摄取也有所升高,目前仍处于临床前研究阶段。Ganguly 等[30]和 Davis 等[31]基于 $\alpha_v\beta_6$-BP 制备^{68}Ga-DOTA-5G 和^{177}Lu-DOTA-ABM-5G,并在胰腺癌患者中进行显像和治疗研究;结果显示^{68}Ga-DOTA-5G 主要经肾排泄,能够检出骨、肺和肝转移灶;^{177}Lu-DOTA-ABM-5G 主要经肾排泄,且能被^{68}Ga-DOTA-5G 检出的病灶所摄取,在治疗剂量(最大为 5.55 GBq)下具有良好的安全性和耐受性,未观察到药物相关严重不良事件。总之,在靶向整合素 $\alpha_v\beta_6$ 的放射性药物开发过程中,基于 A20FMDV2 序列的多肽类药物具有较大的临床应用前景,尤其是对于胰腺癌的早期诊断和治疗。

胱氨酸结肽(cys-knot peptide, knottin)是相对分子质量为(3~4)×10^3 的多肽,具有稳定性强、血液清除快、序列可变性强等特点,适合作为核医学显像探针。Kimura 等[32]制备^{68}Ga-NODAGA-R01-MG、^{18}F-FP-R01-MG-F2、^{64}Cu-DOTA-R01-MG,并在肺癌、胰腺癌和宫颈癌患者中进行临床显像研究;结果表明,knottin PET 探针能特异性对肺癌、胰腺癌和宫颈癌病灶进行检测,在整合素 $\alpha_v\beta_6$ 阳性肿瘤病灶中迅速积聚且持续增加,在大多数正常器官中的摄取通常很低,但垂体摄取较高,可能与整合素 $\alpha_v\beta_6$ 的表达有关。线性肽 H2009.1 能特异性靶向整合素 $\alpha_v\beta_6$,基于此序列的^{99}Tc^m-精氨酸-甘氨酸-天冬氨酸-亮氨酸-丙氨酸-苏氨酸-亮氨酸-精氨酸-谷氨酰胺-亮氨酸-丙氨酸-谷氨酰胺-谷氨酸-天冬氨酸-甘氨酸-缬氨酸-缬氨酸-甘氨酸-缬氨酸-精氨酸-赖氨酸-联肼尼克酰胺(HOOC-Arg-Gly-Asp-Leu-Ala-Thr-Leu-Arg-Gln-Leu-Ala-Gln-Glu-Asp-Gly-Val-Val-Gly-Val-Arg-Lys-6-hydrazinonicotinyl, RGDLATLRQL-AQEDGVVGVRK-HYNIC; HKK)[33]或^{68}Ga-DOTA-环(精氨酸-甘氨酸-天冬氨酸-亮氨酸-丙氨酸-苏氨酸-亮氨酸-赖氨酸)[DOTA-cyclo(Arg-Gly-Asp-Leu-Ala-Thr-Leu-Lys), DOTA-cyclo(RGDLATLK); cycratide][34]标记的探针已被报道。^{68}Ga-cycratide 被用于临床显像,健康志愿者对该药的耐受性良好,胰腺癌患者 PET/CT 显像结果表明该药在诊断显像和术后肿瘤复发监测方面与^{18}F-FDG 的效果相当[34]。有研究制备了三聚体探针^{68}Ga-TRAP-(酪氨酸-精氨酸-甘氨酸-天冬氨酸-亮氨酸-丙氨酸-酪氨酸-*N*-甲基赖氨酸)环肽三聚体[TRAP-cyclo(Tyr-Arg-Gly-Asp-Leu-Ala-Tyr-*p*(NMe)Lys)$_3$, Trivehexin][35-36],其对头颈癌、胰腺癌患者中的肿瘤原发灶和转移灶具有较高的检测灵敏度,显示出诊断潜力。研究表明,^{68}Ga-DOTA-甘氨酸-精氨酸-半胱氨酸-苏氨酸-苯丙氨酸-

精氨酸-甘氨酸-天冬氨酸-亮氨酸-甲硫氨酸-谷氨酰胺-亮氨酸-半胱氨酸-酪氨酸-脯氨酸-天冬氨酸(Gly-Arg-Cys-Thr-Phe-Arg-Gly-Asp-Leu-Met-Gln-Leu-Cys-Tyr-Pro-Asp, GRCTFRGDL-MQLCYPD; SFITGv6)和^{68}Ga-DOTA-甘氨酸-精氨酸-半胱氨酸-苏氨酸-甘氨酸-精氨酸-甘氨酸-天冬氨酸-亮氨酸-甘氨酸-精氨酸-亮氨酸-半胱氨酸-酪氨酸-脯氨酸-天冬氨酸(Gly-Arg-Cys-Thr-Gly-Arg-Gly-Asp-Leu-Gly-Arg-Leu-Cys-Tyr-Pro-Asp, GRCTGRGDLGRLCYPD; SFLAP3)对整合素 $\alpha_v\beta_6$ 均具有较高的亲和力,且在非小细胞肺癌和头颈癌患者中表现出特异性摄取,但这 2 种探针在肿瘤摄取绝对值不高、肾脏和肠道排泄较多而使得肾脏和肠道摄取较高,在一定程度上影响了腹部病灶的检出,因此仍需要优化和改善多肽的药代动力学性质[37-39]。有学者制备了^{68}Ga-NOTA-c(精氨酸-甘氨酸-天冬氨酸-*L*-环己基甘氨酸-谷氨酸)-酰胺[c(Arg-Gly-Asp-(*L*-cyclohexylglycine)-Glu)-$CONH_2$, SDM17],该探针主要经肾脏排泄、在正常组织中的摄取较低,在肿瘤模型中均有特异性摄取[40]。为了增强探针对整合素 $\alpha_v\beta_6$ 的亲和力、提高肿瘤摄取水平,该研究组又制备了三聚体探针^{68}Ga-TRAP-$(SDM17)_3$,此探针在 $\alpha_v\beta_6$ 阳性的小鼠 H2009 肿瘤模型中有更高的摄取、更长时间的保留、更优的图像对比度,显示出较强的临床转化潜力[41]。

综上,目前已有多种靶向整合素 $\alpha_v\beta_6$ 的放射性药物在临床患者(主要是胰腺癌、头颈癌和肺癌患者)中进行了初步验证,其中最有希望的应用领域是胰腺癌诊断显像[42]。目前^{18}F-FDG 尚不能可靠地对胰腺癌进行显像,且胰腺癌是预后最差的癌症之一,治疗方案有限。通过不断优化靶向整合素 $\alpha_v\beta_6$ 放射性药物的药代动力学性质,使其标记不同的诊断或治疗性核素,则可以对胰腺癌进行精准的核医学显像以及靶向放射治疗,将为胰腺癌的诊疗手段提供新的范式。

三、其余整合素亚型

也有部分研究聚焦于其他整合素亚型,并在特定肿瘤类型中进行了核医学显像研究。靶向整合素 $\alpha_2\beta_1$ 的核医学探针有^{68}Ga-DOTA-6-氨基己酸-半胱氨酸-6-氨基己酸-(甘氨酸-天冬氨酸-甘氨酸-谷氨酸-丙氨酸-*D*-酪氨酸-赖氨酸)环肽[Ahx-Cys-Ahx-cyclo(Gly-Asp-Gly-Glu-Ala-*D*-Tyr-Lys), A2B1]、^{68}Ga-DOTA-四乙酸-甘氨酸-赖氨酸-甘氨酸-丙氨酸-谷氨酸-甘氨酸-天冬氨酸-赖氨酸-(精氨酸四聚体)[DOTA-Gly-Lys-Gly-Ala-Glu-Gly-Asp-Lys(Lys(Arg)$_2$)$_2$, IABtP]等[43-45],多基于多肽序列天冬氨酸-甘氨酸-谷氨酸-丙氨酸(HOOC-Gly-Asp-Gly-Glu-NH_2, DGEA)。在部分前列腺特异膜抗原(prostate specific membrane antigen, PSMA)低表达的前列腺癌中,DGEA 探针显像有潜力作为 PSMA 显像的补充[44]。整合素 $\alpha_4\beta_1$ 是跨膜非共价异二聚体,广泛表达于黑色素瘤和多发性骨髓瘤等。*N*-[[4-[[[(2-乙基苯基)氨基]羰基]氨基]苯基]乙酰基]-N^{ε}-6-[(2E)-1-氧代-3-(3-吡啶基-2-丙烯基)]-*L*-赖氨酰基-*L*-2-氨基己二酰基-(1-氨基-1-环己烷)甲酰胺[*N*-((4-((((2-ethylphenyl)amino)carbonyl)amino)phenyl)acetyl) N^{ε}-6-((2E)-1-oxo-3-(3-pyridinyl-2-propenyl))-*L*-lysyl-*L*-2-aminohexanedioyl-(1-amino-1-cyclohexane) carboxamide, LLP2A]是靶向整合素 $\alpha_4\beta_1$ 的多肽,多项研究以 LLP2A 为靶向分子制备^{64}Cu、^{68}Ga 或^{177}Lu 标记的放射性药物,并用于多发性骨髓瘤和黑色素瘤的核医学显像[46-47]。整合素 $\alpha_5\beta_1$ 在静息内皮细胞中的表达水平非常低,但在肿瘤新生血管中显著上调,与肿瘤血管生成密切相关,是潜在的肿瘤治疗预测靶标[48]。多种基于 $\alpha_5\beta_1$ 拮抗剂[49]或 c(*D*-苯丙氨酸-异天冬氨酸-甘氨酸-精氨酸-*D*-赖氨酸)[c(*D*-Phg-isoAsp-Gly-Arg-*D*-Lys), c(phg-isoDGR-k)]多肽[50-52]的探针被用于肿瘤新生血管显像。整合素 $\alpha_v\beta_8$ 主要参与细胞发育和分化过程。在许多不同类型的癌症中,$\alpha_v\beta_8$ 表达升高与患者预后不良相关。文献报道了整合素 $\alpha_v\beta_8$ 靶向探针^{68}Ga-TRAP-2a[53]和^{68}Ga-TRAP-c(甘氨酸-亮氨酸-精氨酸-甘氨酸-天冬氨酸-亮氨酸-*N*-甲基赖氨酸)肽三聚体[TRAP-c(Gly-Leu-Arg-Gly-Asp-Leu-p(NMe)Lys)$_3$, Triveoctin][54];其中,人类受试者^{68}Ga-Triveoctin PET/CT 显像表明该探针可用于整合素 $\alpha_v\beta_8$ 表达水平的检测,以及整合素 $\alpha_v\beta_8$ 相关治疗前的患者筛选和疗效监测[54]。α_6 与 β_1 或 β_4 亚基结合分别形成整合素 $\alpha_6\beta_1$ 或 $\alpha_6\beta_4$,其作用是促进肿瘤细胞的迁移、侵袭和存活,导致转移增加、预后不良和生存率降低[55]。整合素 α_6 显像在肝细胞癌、乳腺癌、肺癌、结直肠癌和胰腺癌等肿瘤中有潜在的预后预测价值;多种基于整合素 α_6 靶向 c(半胱氨酸-精氨酸-色氨酸-酪氨酸-天冬氨酸-谷氨酸-谷氨酰胺-丙氨酸-半胱氨酸)肽[c(Cys-Arg-Trp-Tyr-Asp-Glu-Asn-Ala-Cys), c(CRWYDENAC); RWY]的探针被报道,研究者通过标记不同核素、使用二聚化策略、引入非天然氨基酸等对 RWY 多肽进行优化改造,增加其亲和力和体内稳定性,以期改善显像效果[56-59]。

四、靶向整合素及其他靶蛋白的双靶向探针

除针对整合素开发探针外,一些研究还开发了靶向整合素和不同靶蛋白的异源二聚体探针并用于肿瘤显像或治疗。异源二聚体能以单一药物靶向多种肿瘤标志物,克服不同肿瘤类型中靶蛋白表达的异质性问题,实现表达任一靶点或 2 种靶点的肿瘤靶向。目前,多数异源二聚体探针靶向的整合素亚型为 $\alpha_v\beta_3$,其余的靶蛋白则呈现出多样化。

生长抑素受体 2(somatostatin receptor 2, SSTR2)在大部分神经内分泌肿瘤中过表达,针对 SSTR2 的多种放射性诊断和治疗性药物已获得美国食品和药品监督管理局(Food and Drug Administration, FDA)批准。^{68}Ga-NOTA-3PEG-奥曲肽-RGD 环肽异二聚体(3PEG-octreotide-RGD, 3PTATE-RGD)可特异性靶向 SSTR2 和整合素 $\alpha_v\beta_3$[60],在肺癌、(胃肠胰)神经内分泌肿瘤患者中显示出优于^{68}Ga-DOTA-*D*-苯丙氨酸 1-酪氨酸 3-苏氨酸 8-奥曲肽(*D*-Phe1-Tyr3-Thr8-octreotide, TATE)的肿瘤/本底比值和肝转移癌检出率[61-63],表明其在神经内分泌肿瘤中可能拥有更好的诊断效果。成纤维细胞激活蛋白(fibroblast activation protein, FAP)在 90%以上的上皮肿瘤中过表达,如乳腺癌、结直肠癌、胰腺癌、胃癌和肺癌等[64]。多种基于 FAP 抑制剂(FAP inhibitor, FAPI)02/04 和 RGD 的异源二聚体探针已被成功开发,其中^{68}Ga-FAPI-RGD(^{68}Ga-LNC1007)已在肺癌、鼻咽癌、乳腺癌等不同类型的肿瘤患者中进行 PET 显像评估[65-69]。与^{18}F-FDG 和^{68}Ga-FAPI PET/CT 相比,^{68}Ga-FAPI-RGD 显示出更好的肿瘤摄取和肿瘤/本底比值,具有安全性和临床可行性。同时,^{68}Ga-FAPI-RGD 在肿瘤部位的摄取和滞留时间均有所延长,这使其拥有更大的潜力用于^{177}Lu/^{90}Y/^{225}Ac 标记的肿瘤核素治

疗。除研究较多的靶点外,亦有关于氨基肽酶[70]、胃泌素释放肽受体[71-72]、神经纤毛蛋白 1[73]等靶点的研究,但目前仍处于临床前研究阶段、研究数量较少。

五、总结与展望

在过去的 20 年,关于整合素的放射性药物多为靶向整合素 $\alpha_v\beta_3$ 的 cRGD 肽类药物,目前仍有大量研究在探索这类药物的临床价值与应用场景。近几年,研究重点也逐步转向整合素 $\alpha_v\beta_6$、$\alpha_v\beta_8$、$\alpha_2\beta_1$ 等其他亚型,靶向分子也不再局限于多肽,小分子、胱氨酸结蛋白等种类逐渐多样化,同时探针在临床肿瘤患者中的应用也更加精准。其中,靶向整合素 $\alpha_v\beta_6$ 最受关注。此外,越来越多的研究不仅聚焦于诊断性显像探针的开发,也在不断探索靶向放射性治疗药物的研发,最终达到诊疗一体化的目的。

靶向整合素放射性药物发展迅猛,在药物研发以及临床转化过程中,仍需关注以下几点:(1)大部分探针的体内性质欠佳,仍需要优化。文献报道的多数探针仅在临床前小鼠模型中做了验证,且体内性质欠佳(如肿瘤摄取低、正常组织摄取较高等),因此仍需要改造、优化探针,从靶向分子的结构本身出发,通过改造、修饰来改善探针性质,获得更优的药代动力学特征。(2)大部分探针还局限在临床前研究或仅在小队列中进行临床研究,缺乏大队列的研究来验证探针的有效性和可靠性。(3)仍需进一步寻找靶向整合素放射性药物的临床价值所在。比如针对不同整合素亚型在不同肿瘤中的表达特点,开发相应的放射性药物,以实现对特定肿瘤类型的精准诊断和治疗。对于异源二聚体探针,需要分析 2 种靶蛋白的表达是否有相关性、互补性或者在疾病不同阶段的表达变化,以此为突破口构建探针。(4)靶向放射治疗药物仍需进一步优化。目前的多聚化或修饰白蛋白结合分子策略在增加肿瘤对治疗性药物摄取的同时,也会增加药物在肾脏等正常器官中的摄取,并未很好地达到“增效减毒”的目标,因此有必要进一步思考优化策略、分析药物体内代谢特点,争取做到保证最好治疗效果的同时,尽量减少毒性。

利益冲突　所有作者声明无利益冲突

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