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综述与论文

动脉粥样硬化分子影像研究进展

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摘 要：急性心脑血管疾病目前位居全球死亡原因首位，其关键病理基础是动脉粥样硬化并导致急性心肌梗死、中风等。由于动脉粥样硬化病情进展隐匿突发，目前的诊断方式不足以筛查出早期高风险病变。如何在急性心脑血管事件发生前准确地识别出斑块破裂风险高的患者并对患者进行有效干预，已成为目前迫切需要解决的问题，同时这也是降低急性心血管事件发生率的关键。近年来，迅速发展的分子影像及纳米医学技术为实现动脉粥样硬化斑块早期诊疗带来了新契机。

关 键 词：动脉粥样硬化斑块；分子影像；分子探针；纳米材料

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动脉粥样硬化主要累及大中型动脉及动脉分叉处，导致动脉管壁增厚变硬、失去弹性、管腔狭窄，其病情进展隐匿突发，一般出现临床病症已是疾病中晚期[1]，临床表现主要以受累器官病变为主，如缺血性脑卒中、急性心肌梗死等已成为人类头号杀手[2]。而现有的诊断方式不足以筛查出早期高风险病变，因此，利用具有高空间分辨率和灵敏度的无创性分子影像技术，对斑块破裂风险高的病人做出及时诊断和监测至关重要[3]。越来越多的科研工作者致力于研究通过靶向斑块不同的分子和细胞结构实现斑块的检测、动态监控和诊疗一体化的分子探针[4]，它已成为一种对斑块进行早期诊疗的新方法。

1 动脉粥样硬化病理过程

动脉粥样硬化是一种脂质沉积于血管壁的慢性炎症性疾病[5]，以血管内皮损伤为基础、血管慢性炎症为特征，具有变质、渗出和增生等炎症的基本特征。病变初期血液中脂质代谢紊造成内皮损伤，单核细胞通过内皮间隙进入到内膜下分化为巨噬细胞，巨噬细胞通过其清道夫受体吞噬大量

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被氧化修饰的氧化低密度脂蛋白(OX-LDL),形成大的液泡脂质小滴贮存在巨噬细胞中[6],最终形成泡沫细胞。泡沫细胞在血管壁上堆积形成脂质斑块,造成血管管腔狭窄[7],最终导致供血脏器因缺血缺氧而出现一系列病变。同时泡沫细胞分泌组织因子、基质金属蛋白酶(Matrix metalloproteinase, MMP)等促炎因子[8],加速降解纤维帽中的基质蛋白和细胞外基质,使纤维帽变薄,导致斑块不稳定易于破裂。斑块一旦发生破裂,将导致一系列如急性心肌梗死、脑卒中等恶性心血管事件,严重影响患者生活质量[9]。

2 分子影像与动脉粥样硬化

2.1 动脉粥样硬化斑块的生物靶标

动脉粥样硬化病理生理发展过程中可作为斑块生物靶标的主要有:

(1) 内皮细胞:由于动脉弯曲和分支点的内皮层始终暴露于血流的不断冲击中,刺激内皮细胞表达促炎因子和粘附分子,使循环于血液中的单核细胞、脂蛋白更容易穿透动脉壁积聚在内膜上[10]。血管细胞粘附分子-1(Vascular cell adhesion molecule-1,VCAM-1)是靶向递送至动脉粥样硬化斑块最常见的生物标志物,其通过促进内皮细胞转录诱导参与炎症细胞向活化内皮表面的募集。已有报道显示噬菌体展示文库技术成功筛选靶向 VCAM-1 的配体多肽[11](如表 1 所示)。

(2) 炎症细胞:巨噬细胞的浸润发生于整个动脉粥样硬化发生发展过程中,鉴于它们在斑块中的丰富程度、可摄取大量纳米颗粒,最终因发生细胞凋亡和继发性坏死而形成脂质核心,使其成为靶向斑块最常见的免疫细胞[12],作为生物标志物最常见的是清道夫受体[13],例如,A 类清道夫受体(MSR-1)和 B 类清道夫受体(SR-BI 或 CD-36)用于识别和内化 OX-LDL;硫酸葡聚糖(MSR-1 的配体)广泛用作 NP 核的涂层材料用于靶向斑块;LDL 模拟肽,如载脂蛋白 A1(ApoA-1)也是靶向斑块巨噬细胞的常见配体(如表 2 所示)。

(3) 非细胞成分:斑块非细胞成分作为生物靶标最常见的是胶原蛋白[14],作为细胞外基质的关键部分,胶原调节细胞反应有助于纤维帽的强度和完整性[15],噬菌体展示文库筛选鉴定的肽,可用于靶向血管基底膜上大量存在的胶原蛋白Ⅳ(由于血管损伤期间渗透性增加而暴露),并且可构建含有肽的聚合物,金和脂蛋白 NP[16],用于靶向动脉粥样硬化斑块内的胶原蛋白(如表 3 所示)。

表 1 靶向斑块血管细胞成分

Targeting the blood vasculature of plaques

生物靶标	配体	纳米材料类型	动物模型	引用文献
内皮细胞				
VCAM-1	VCAM-1 靶向多肽(VHPKQHR)	脂质	$ApoE^{-/-}$ mice	[17]
	VCAM-1 靶向多肽(VHPKQHR)	氧化铁纳米颗粒	$ApoE^{-/-}$ mice	[18]
	VCAM-1 靶向多肽(VHPKQHR)	聚合物	$ApoE^{-/-}$ mice	[11]
	VCAM-1 靶向多肽(V_P-TSL-T_J)	脂质体	$ApoE^{-/-}$ mice	[19]
	VCAM-1 靶向多肽(CVHSPNKKCGGSK)	蛋白	$ApoE^{-/-}$ mice	[20]
IL-4 受体	靶向多肽(CRKRLDRNC)	聚合物	$Ldlr^{-/-}$ mice	[21]
$\alpha_v\beta_3$ 整合素	卵磷脂	脂质	新西兰动脉粥样硬化白兔	[22]
血管平滑肌细胞				
肌动蛋白	肌动蛋白-1 抗体	氧化铁纳米颗粒	$ApoE^{-/-}$ mice	[23]
TRPV-1 信号通路	TRPV-1 抗体	硫化铜纳米颗粒	$ApoE^{-/-}$ mice	[24]

表 2　靶向斑块炎症细胞

Targeting inflammatory cell types inside plaques

生物靶标	配体	纳米材料类型	动物模型	引用文献
炎症细胞				
巨噬细胞	低密度脂蛋白(LDL)	聚合物	$ApoE^{-/-}$ mice	[25]
	ApoA-I 模拟肽	脂质	$Ldlr^{-/-}$ mice	[26]
	ApoA-I 模拟肽	脂质	$ApoE^{-/-}$ mice	[27]
	高密度脂蛋白(HDL)模拟肽	脂质	$ApoE^{-/-}$ mice	[28]
	高密度脂蛋白(HDL)和卵磷脂	脂质	$ApoE^{-/-}$ mice/新西兰白兔	[29]
	高密度脂蛋白(HDL)	脂质	$ApoE^{-/-}$ mice	[30]
	葡聚糖	氧化铁纳米颗粒	新西兰动脉粥样硬化白兔	[31]
巨噬细胞趋化因子受体	病毒巨噬细胞炎症蛋白-Ⅱ	聚合物	$ApoE^{-/-}$ mice	[32]
M1 型巨噬细胞	磷脂酰丝氨酸、氧化胆固醇酯衍生物胆固醇-9-羧酸壬酯	脂质	$ApoE^{-/-}$ mice	[33]
泡沫巨噬细胞骨皮蛋白(Osteopontin)	Osteopontin 抗体	$NaGDF_4$	$ApoE^{-/-}$ mice	[34]
巨噬细胞 P32/gC1qR/HABP1 受体	LyP-1 多肽	氧化铁纳米颗粒	$ApoE^{-/-}$ mice	[35]
巨噬细胞 A 类清道夫受体(MSR-1)	油酸 -葡聚糖	氧化铁纳米颗粒	$ApoE^{-/-}$ mice	[36]
巨噬细胞透明质酸受体	透明质酸	聚合物	$ApoE^{-/-}$ mice	[37]
单核细胞趋化因子受体	单核细胞趋化蛋白-1(YNFTNRKISVQRLASYRRITSSK)	聚合物	$ApoE^{-/-}$ mice	[38]

表 3　靶向斑块非细胞成分

Targeting non-cellular components inside plaques

生物靶标	配体	纳米材料类型	动物模型	引用文献
斑块非细胞成分				
活化血小板	IGF_4 抗体	氧化铁纳米颗粒	$ApoE^{-/-}$ mice	[39]
胶原	EP3533 靶向多肽(CTTKFPHHYC)	脂质	$ApoE^{-/-}$ mice	[16]
胶原蛋白Ⅳ	胶原蛋白Ⅳ靶向多肽(CGGGKPLVWLK)	聚合物	$Ldlr^{-/-}$ mice	[40]
弹性蛋白	弹性蛋白抗体	聚合物	$ApoE^{-/-}$ mice	[41]
富含纤维血栓	血栓结合肽(CREKA)	聚合物	$ApoE^{-/-}$ mice	[42]
氧化低密度脂蛋白(OX-LDL)	抗小鼠 OX-LDL 多克隆抗体	氧化铁纳米颗粒	$ApoE^{-/-}$ mice	[43]

2.2　生物纳米材料与动脉粥样硬化

近年来,随着分子影像技术的发展,心血管分子影像技术在动脉粥样硬化斑块成像等方面的研究中取得了较大进展(如表 4 所示)[28],越来越多的科研工作者致力于将生物纳米材料作为靶向动脉粥样硬化斑块特异性载体的研究[44],主要有三方面的原因:

(1) 生物纳米材料特殊的理化性质及其纳米结构在斑块巨噬细胞成像中优势明显[45]。如近红外荧光成像(Near infrared fluorescence imaging,

NIRF)的量子点、X 射线计算机断层扫描(Computed tomography imaging,CT)的金纳米粒子、磁共振成像(Magnetic resonance imaging,MRI)的氧化铁纳米颗粒和含钆(Gd^{3+})的纳米颗粒、单光子发射计算机体层显像(Single photon emission computed tomography,SPECT)的放射性示踪剂标记的聚合物纳米颗粒等。

(2) 生物纳米材料可修饰多种特异性靶向斑块组织或细胞的生物分子[46]。如 Nahrendorf 等[18]研发了肽聚合的磁性纳米颗粒,它能靶向由内皮细胞和巨噬细胞表达的 VCAM-1,实现近红外荧光成像和磁共振成像,尾静脉注射到 $ApoE^{-/-}$ 小鼠体内,观察到主动脉根部的斑块内有 NP 升高的信号; TRPV1 抗体偶联的硫化铜(CuS)NP 尾静脉注射到 $ApoE^{-/-}$ 小鼠体内[24],靶向血管平滑肌细胞上的 TRPV1,引起温度敏感的 TRPV1 信号通路打开,从而达到抗动脉粥样硬化的效果。

(3) 生物纳米材料可装载大剂量造影剂或治疗药物[47],利用其在体内长效循环和主动靶向斑块的优势,将药物高效递送至斑块部位[48]。如 Mishra 等[49]将 d-苏氨酸-1-苯基-2-癸酰氨基-3-吗啉代-1-丙醇(一种糖鞘脂合成抑制剂)装载进聚合物 NP 中,注射到 $ApoE^{-/-}$ 小鼠体内可使其血液循环量提高 50 倍;帅心涛等[50]制备了由聚乙二醇和聚丙烯硫化物(PEG-PPS)的嵌段共聚物组装的纳米胶束装载穿心莲内酯,由于 PEG-PPS 的活性氧(Reactive oxygen species,ROS)响应性质,胶束可快速释放包封的药物穿心莲内酯,并且在斑块处消耗 ROS,有效抑制促炎因子的表达,减轻斑块处的氧化应激,从而降低炎症反应以达到治疗效果。

表 4 动脉粥样硬化成像技术的总结

Summary of imaging techniques used in atherosclerosis

成像方式	造影剂	优点	缺点	成本
磁共振成像(MRI)	氧化铁纳米颗粒、含钆脂质/纳米颗粒	安全无电离辐射、空间分辨率高、可辨别深层的软组织,无须借助成像探针便可实现功能成像	扫描时间长、体内装置金属器械的患者无法实现	高
近红外荧光成像(NIRF)	近红外光吸收的染料和聚合物纳米颗粒	灵敏度高、方便快捷	空间分辨率低、组织穿透深度有限	低
X 射线计算机断层扫描(CT)	碘化分子、X 射线吸收的纳米粒子	空间分辨率高、方便快捷	暴露于电离辐射、不适合连续监测	低/中等
正电子发射型计算机断层成像(PET)	放射性核素标记的纳米颗粒	灵敏度高、探针的示踪剂量小、成熟的分子成像技术	暴露于放射性、价格昂贵	高
单光子发射计算机体层显像(SPECT)	放射性核素标记的纳米颗粒	灵敏度高、探针的示踪剂量小、成熟的分子成像技术	暴露于放射性、价格昂贵	高
超声(US)	微泡纳米粒子	灵敏度高、方便快捷	只能进行局部成像	低

2.3 核磁共振成像(Magnetic resonance imaging, MRI)

MRI 具有分辨率高、软组织对比度和信噪比高的优点,患者无需暴露在电离辐射中,适用于易损斑块的诊断和斑块稳定性的评估[51]。最常见的 MRI 造影剂是基于氧化铁 NP[52](T1、T2 加权成像)和含钆(Gd)的 NP(T1 加权成像),为了更好地利用其超顺磁性,氧化铁 NP 的尺寸保持在 20 nm 以下[53]。这种超顺磁氧化铁纳米颗粒(SPIONs)[39],表面经葡聚糖包被可展示靶向斑块各种成分的多肽、抗体、蛋白质等。使用 CD81 靶向的氧化铁微粒(CD81-microparticles of iron oxide,

CD81-MPIO)用于小鼠动脉粥样硬化的 MRI 成像显示在 $ApoE^{-/-}$小鼠主动脉根部 T2 弛豫时间明显缩短[54];单核细胞靶向的氧化铁磁性纳米颗粒(MNPs),其来源于趋化因子受体 2(CCR2)可结合单核细胞趋化蛋白-1(MCP-1)的基序肽,通过 MRI 成像实现对动脉粥样硬化斑块的诊断[55]。

2.4　CT 成像(Computed tomography imaging)

CT 成像可实现整个心脏,冠状动脉和钙化斑块的快速、高分辨率图像采集[56]。碘化聚合物胶束是用于脉管系统可视化的主流造影剂,它比自由分子在体内循环时间长[57]。近年来报道的金纳米颗粒靶向动脉粥样硬化斑块中,Chhour 等[58]并没有将 AuNPs 直接注入血液中,而是用金 NP 标记原代单核细胞,然后将这些 AuNP 标记的单核细胞转移到 $ApoE^{-/-}$小鼠中追踪它们向斑块的迁移,结果显示金标记的单核细胞募集到斑块中,实现了将纳米颗粒注射到 $ApoE^{-/-}$小鼠中完成的 CT 成像;Damiano 等[59]研发的金聚合高密度脂蛋白(Au-HDL)造影剂,可通过光谱 CT 系统检测 $ApoE^{-/-}$小鼠斑块的巨噬细胞负荷,斑块的钙化和狭窄。

2.5　近红外荧光成像(Near infrared fluorescence imaging)

NIRF 成像灵敏度高,具有近红外荧光发射的 NP 或染料分子经过修饰可靶向斑块,是可用于荧光成像的双功能生物纳米材料[60]。如用 Cy5.5 标记的靶向内皮细胞的肽缀合壳聚糖 NP[21]、靶向巨噬细胞抗体标记的 $NaGdF_4$: Yb/Er @ $NaGdF_4$ 上转换 NP[61]等;Marrache 和 Dhar[62]制备了含有载脂蛋白模拟肽的 HDL 合成 NP,装载近红外量子点,用于 NIRF 成像;Sun 等[63]制备的基于猿猴病毒 40(SV40)的 NPs,融合表达纤维蛋白靶向肽,通过将量子点封装在 SV40 的 NP 中,在深层组织中实现了量子点更高、光稳定性和检测灵敏度更好的近红外荧光成像;滕皋军等[64]将抗小鼠 ox-LDL多克隆抗体与 NIR797 染料缀合生成 ox-LDL靶向的 NIRF 探针,实现了基于 ox-LDL 的斑块分子成像,并且提供了表征易损斑块和监测动脉粥样硬化治疗干预的重要方法。

2.6　正电子发射断层扫描(Positron-emission tomography,PET)和单光子发射 CT(Single photon emission CT,SPECT)

核素成像中,PET 和 SPECT 与 CT 相比,可用更少量的造影剂实现更高灵敏度的成像[65],因此,放射性 NP 造影剂的设计应具有循环周期长、灵敏度高的特点,可提高多模态成像分辨率。PET/MRI 是表征易损斑块的常用方法,通常需要用 ^{64}Cu[66] 或 ^{89}Zr 标记的葡聚糖包裹氧化铁 NP[67],例如,Beldman 等[68]用 ^{89}Zr 标记的乙酰透明质酸 NPs(^{89}Zr-HA NPs)代替葡聚糖 NPs 作为载体,PET 和 MRI 结合可检测新西兰白兔动脉粥样硬化斑块,由于 HA-NPs 可富集于斑块巨噬细胞中,在注射 12 h 后,^{89}Zr-HA NPs 在斑块处可产生信号,注射后 24 h 主动脉中的最大摄取量比骨骼肌高 6 倍;锝-99m(^{99m}Tc-HFn)放射性标记的天然 H-铁蛋白纳米笼[69]可通过 SPECT 和 CT 结合准确鉴定 $ApoE^{-/-}$小鼠中富含巨噬细胞的斑块;单光子发射计算机体层显像(SPECT)的放射性示踪剂标记的聚合物纳米颗粒,可与心房利钠肽(CANF)结合,并用 ^{64}Cu 标记生物相容的 PEG 甲基丙烯酸酯(PEGMA)共聚物梳状纳米颗粒,检测 $ApoE^{-/-}$小鼠中的斑块[70];由于叶酸受体 β(FR-β)在巨噬细胞上选择性表达,FR 靶向成像剂可用于评估动脉粥样硬化炎症,用氟化铝-18 标记的 1,4,7-三氮杂环壬烷-1,4,7-三乙酸共轭叶酸(^{18}F-FOL),通过 PET/CT 靶向检测 FR-β 阳性巨噬细胞,用于检测动脉粥样硬化斑块炎症[71]。

2.7　超声成像(Ultrasound imaging)

传统的二维超声检查可快速测量颈动脉斑块的大小、内中膜厚度,甚至斑块表面的溃疡和出血,但仍缺乏对斑块成分定性和定量的分析,并且检查结果易受到操作者经验及熟练度等因素影响[72]。由于超声造影剂微泡的大小类似于人体红细胞,具有红细胞的血流动力学特征[73],它可顺利

进入颈动脉斑块微血管内使其快速显像[74]。超声分子成像的目的是将这些微泡特异性附着到相关靶标上，从而实现分子水平的超声成像[75]。全氟化碳暴露的超声波葡萄糖白蛋白(PESDA)微泡在猪动脉粥样硬化模型中附着于发炎、功能失调的内皮细胞，同样在早期主动脉粥样硬化大鼠模型中 PESDA 微泡的信号增加[76]，而 PESDA 微泡的附着是补体介导的，补体耗尽会减少靶向信号[77]；在 $ApoE^{-/-}$ 小鼠早期病变中证实了 P-选择素依赖性单核细胞的富集，并且有 P-选择素表达的超声分子成像也在早期斑块的检测中得到了验证[78]。

3 展望

分子影像及纳米技术为动脉粥样硬化的早期无创诊疗带来了新的可能性，它能够在分子和细胞水平上对斑块进行定性和定量的研究，是传统影像学的进阶发展。然而，想要进一步提高分子影像早期诊断的灵敏度、特异性，生物相容性好的探针必不可少。理想的探针应具有以下几个特点：(1) 灵敏度高，能够产生较强的信号；(2) 对于靶点有高的亲和力和特异性；(3) 生物相容性好，可通过肝肾代谢途径能在体内彻底清除[79]。这些特征与纳米颗粒的尺寸、理化性质、稳定性等诸多因素都密切相关[80]，因此，这类探针在应用于临床前，需要经过严格的标准检验保证其安全性和实用性。

随着纳米探针的设计和成像技术的不断进步，分子影像技术在心血管疾病的诊断与精准治疗方面展现出巨大的发展潜力，定能为心血管病的诊断与治疗开辟新的领域。各种无创影像技术成像原理不同、成像方法不同、每种技术敏感性和特异性不同，因此，多种方法可以灵活地加以联合应用，这将大大提高对斑块诊断的准确率，具有很好的发展前景。

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Recent Advances in Molecular Imaging of Atherosclerotic Plaque

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Abstract: Atherosclerosis-related cardiovascular diseases (e. g., acute myocardial infarction and stroke) are the leading causes of morbidity and mortality in the world today. The rupture of atherosclerotic plaques is the main pathological basis of acute cardiovascular disease events with no obvious clinical symptoms in the early stage of atherosclerosis. How to accurately identify vulnerable plaques and effective treatments in patients before acute cardiovascular and cerebrovascular events has become an urgent problem to solve, it is also the key to reduce the incidence of acute cardiovascular events. The rapid development of non-invasive molecular imaging technology in recent years has brought new opportunities for the diagnosis and treatment of atherosclerotic plaque.

Key words: atherosclerosis plaque; molecular imaging; molecular probe; nanomaterials

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