液气相变型超声分子探针研究进展

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摘要 随着分子成像技术和各种纳米生物材料的迅速发展, 医学影像技术有望对人体疾病实现从器官、组织水平到细胞、分子水平全方位、多层次在体实时观察. 通过基于分子靶标的肿瘤早期诊断、革命性的肿瘤分子分型以及肿瘤边界确定和术中手术导航的全面开展, 实现精准医学. 超声分子影像是分子影像学的一个新的分支, 在近10年发展迅速. 液气相变型超声分子探针凭借其良好的穿透性以及诊疗一体化等优点, 已显示出其优于传统超声分子探针的众多优势, 在基础与临床应用方面展现出巨大潜力. 本文对液气相变型超声分子探针的相变机制以及近几年在生物医学应用领域研究进展进行了综述.

关键词 相变型纳米粒, 分子影像, 超声, 靶向治疗

相比于临床常规使用的其他影像设备, 如X线, CT(computed tomography), MRI(magnetic resonance imaging), PET(positron emission tomography), SPECT(single photon emission computed tomography)等, 超声(ultrasound, US)良好的组织穿透性和高生物安全性^[1-3]显示了低成本、实时、便携、无辐射、无创伤等优点^[4,5]. 然而, 其低对比度的成像能力严重限制了其对各种疾病的早期诊断水平. 随着超声造影剂——微泡(microbubbles, MBs)的出现, 增加了声阻抗差异使超声灰阶成像对比度明显改善, 提高了超声诊断能力^[6-8]. 但由于MBs粒径较大(2~10 μm), 既不能透过血管内皮间隙到达肿瘤组织内部^[9], 又容易被网状内皮系统(reticuloendothelial systems, RES)吞噬、破坏, 不能在病灶处有效聚集^[10,11]. 有学者制备了纳米级气泡(nanobubbles, NBs)($<1 \mu\text{m}$), 理论上可以克服上述缺点, 但由于NBs随着粒径的减小, 其背向散射能力也降低, 并且仍然不能克服所包裹的气体欠稳定的缺点, 从而限制了其在对比超声显像领域的

进一步发展^[10,12].

过去的10多年间, 纳米生物医学技术飞速发展, 已能将多种显像分子、靶向基团和药物与特殊纳米材料连接制备成多功能纳米粒^[5,13-19]. 其中, 液态氟碳纳米粒(perfluorocarbon nanoparticles, PFC NPs)是最具代表性之一. 除具有化学性质稳定、无毒性等多种临床应用必备的优点之外^[20], 最重要的是它理论上可以自由穿过血管内皮间隙到达肿瘤细胞, 并在一定条件下发生液气相转变, 形成微泡以增强超声显像, 从而很好地解决了上述存在的问题^[16,21]. 此外, PFC NPs还有望同时实现肿瘤早期分子显像与治疗的双重作用, 进一步推动个体化治疗的发展^[17,22]. 本文将从以下几个方面综述PFC NPs在医学领域的研究进展.

1 相关机制

热力学中, 物质有3相(固相、液相、气相). 其中, 蒸汽压是固相、液相物质的固有属性. 当蒸汽压

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小于外界周围压时,物质维持原有的固态或液态,然而,在一定条件下,当蒸汽压升高或者周围压降低,致蒸汽压超过周围压时,物质将发生升华或气化,变成气态^[23]。表1为各种液态氟碳物质在1个大气压下的不同沸点和相关参数^[10,11,24~26]。

1.1 声致相变(acoustic droplet vaporization, ADV)

ADV是指在超声波作用下,氟碳液滴转换成气泡的现象,最早见于1998年Apfel^[27]的文献报道。而ADV的概念则是由Kripfgans等人^[28]在2000年提出。声波场中的PFC NPs,在超声波的作用下发生规律的压缩和膨胀。其内部压会随着外在声压的变化而循环变化,如图1所示^[23]。当内部压降低至外部压(水的蒸汽压)以下时,液态的PFC会迅速发生相转变。由于声波的振幅越高,内部压降低越明显,因此,ODV的发生与声波的频率成反比、与振幅成正比^[29,30]。此外,许多有关这一机制的报道还证明:对于球状的小液滴而言,由于拉普拉斯压的存在^[23],PFC NPs通过ODV实现相转变的能力也会与液滴的粒径和表面张力系数有关^[31,32]。

拉普拉斯压力公式如下:

$$\Delta P = P_{\text{in}} - P_{\text{out}} = 2\gamma/R, \quad (1)$$

其中, γ 是表面张力系数, R 是曲率半径, P_{in} 是内部压力, P_{out} 是外部压力。如图2所示。

1.2 光致相变(optical droplet vaporization, ODV)

随着对相变型PFC NPs研究得逐步深入, ODV的概念被提出。即通过一定能量的激光辐照, PFC NPs可以发生液气相变, 增加背向散射信号, 用来超声显像。但是有关ODV的机制目前尚不明确, 有待进一步研究探讨。一种假设认为: 当激光辐照PFC NPs后,

表1 常用氟碳化合物

Table 1 Properties of perfluorocarbons

英文缩写	结构式	通用名	沸点(°C)	文献
OFP	C ₃ F ₈	全氟丙烷	-37	[24]
PFB	C ₄ F ₁₀	全氟丁烷	-2	[24]
PFP	C ₅ F ₁₂	全氟戊烷	29	[10]
PFH	C ₆ F ₁₄	全氟己烷	56	[11]
PFHB	C ₆ F ₁₃ Br	全氟溴己烷	97	[25]
PFOB	C ₈ F ₁₇ Br	全氟溴戊烷	142	[26]
PFCE	C ₁₀ F ₂₀ O ₅	全氟-15-冠-5	146	[10]

图1 (网络版彩色)上方的正弦曲线表示直径1 μm的PFC液滴内部压力,下方的正弦曲线表示PFC液滴外部压力。两者的差值即拉普拉斯压。图中另外3条水平线分别表示37°C, 1个大气压下PFC5(PFP), PFC6(PFH)和水的蒸汽压(vapor pressure, V.P.)^[23]

Figure 1 (Color online) Upper sinusoidal line represents the internal pressure of a PFC droplet with 1 μm in diameter. Lower sinusoidal line represents the surrounding pressure of the fluid under the ultrasound irradiation. The deviation is the Laplace pressure. The vapor pressures (V.P.) of PFP, PFH, and water are indicated at 1 atmosphere pressure^[23]

PFC NPs中的吸光物质吸收光的能量转化为热能,使纳米粒中的氟碳物质温度升高,发生相变^[33]。另一种假设认为: ODV可能与ADV有关。有研究报道纳米粒极小的粒径和众多的数量可以作为优质的声源,在受到激光辐照时,能够产生确切的光声信号,有可能改变氟碳液体的蒸汽压发生相变^[28,33]。

1.3 磁致相变(magnetic droplet vaporization, MDV)

针对ADV与ODV存在的一些缺点,如ADV受骨骼、气体等影响, ODV受制于光的穿透深度不足,并且更重要的是当ADV与ODV必须要事先明确拟触发部位,这限制了其在不知道确切位置的肿瘤早期诊断中的应用。在磁热研究的基础上,我们提出了MDV的概念。通过制备一种空心或者铃铛结构的磁性纳米粒,并将PFH或PFP导入纳米粒内部。在外加交变磁场的作用下,磁性成分产热导致纳米粒内部的PFH或PFP发生液气相转变形成微泡,从而增强超声显像。进一步,利用磁性纳米粒产生的磁热效应对

图2 (网络版彩色)拉普拉斯压力

Figure 2 (Color online) Schematic illustration of Laplace pressure

肿瘤进行治疗. MDV理论上克服了ADV与ODV存在的缺点,有望在肿瘤早期诊疗方面得到广泛应用.

2 医学应用

2.1 多模态成像与增效研究

临床上各种医学成像模式都有其内在的优势和劣势,医生往往需要结合多种影像检查诊断、治疗疾病以及评估疗效.然而,多种影像对比剂的使用不仅会增加经济负担,还要面对药物间相互作用后潜在的医疗风险.因此,研究一种可实现多种影像设备同时成像的多模态对比剂成为临床迫切的需求.多模态成像不仅可结合多种医学成像模式各自不同的优点,还可弥补各自的不足,实现真正意义上的优势互补^[34].

目前,从事生物医学领域的学者们,正在基于各种医学成像模式,包括US, MRI, PET, SPECT等,不断探索、研发能够实现多模态显像、影像融合的新技术、新方法和新材料,并已取得令人鼓舞的阶段性成果.通过MBs或NBs携带各种光敏剂,核磁对比剂不仅能够实现US, MRI, 光声(photoacoustic imaging, PAI)双模态^[35]、三模态成像^[36],还能增加高强度聚焦超声(high intensity focused ultrasound, HIFU)治疗肿瘤的疗效^[37].

但是,MBs(不能透过血管壁)和NBs(背向散射作用较弱)的缺点限制了其进一步的临床应用. PFC NPs通过液-气相转变的特性可以很好地解决MBs/NBs的困境,展现出诱人的应用前景. Jian等人^[38]制备的载印度墨水的相变纳米乳剂,通过使用较低能量的脉冲激光辐照,液态PFC NPs相转变为气态,体外、体内实验均成功实现了光声/超声双模态显像.进一步

使用较高能量的激光辐照相变后的PFC MBs,产生的冲击波、微射流等形成光声效应,可对肿瘤细胞产生明显的杀伤作用. Kopechek等人^[39]将载钆的PFC NPs用于MRI引导下HIFU治疗肿瘤的动物实验,发现不仅能增强US/MRI双模态显像,还能增加HIFU的治疗效果,明显缩短HIFU治疗时间. Ma等人^[26]用高分子材料包裹PFOB并载以喜树碱药物,制备成的新型PFC NPs,在超声作用下产生空化效应,释放药物,同时实现化疗、HIFU的双重增效,有望解决局部治疗后肿瘤残留的问题.

基于学者们前期在声致相变ADV, ODV的研究工作^[30,40,41],我们通过溶胶-凝胶涂布表面活性组件技术及其在自身基础上发生相转变过程制备了一种壳-核式磁球体纳米粒,之后,将PFH通过毛细血管虹吸作用充入这种壳-核式磁球体内.这种磁性PFC NPs不仅可增强MRI成像,置于磁场中还能将磁能转换成热能,受热的PFH小液滴相转变并从外壳的孔洞中穿出.这些释放到球体外的微小气泡不仅能增强局部组织的回声特性实现超声显像,由于其本身固有的高热能、高动能状态还能加速超声作用下的热效应、空化效应、机械效应,引起细胞膜可逆性穿孔、氧自由基释放等一系列生物学效应,促进超声介导下对局部肿瘤组织的磁热治疗.

2.2 载基因和药物治疗

化疗是对临床不能手术切除的肿瘤最重要的治疗措施,但是如何减少其伴随的严重全身副反应是目前医学领域的一个重大挑战.超声靶向微泡破坏系统(ultrasound targeted microbubble destruction, UTMD)可载药物和基因靶向病变部位并精确释放,大大减少了全身毒副反应,在疾病治疗领域,尤其是肿瘤治疗方向展现出诱人的应用前景^[42-44].

近几年,相变型纳米粒用于超声造影剂和药物转运的研究成为热点.相比于传统的微泡载体,相变型纳米粒更加稳定、更有效的长循环和更优良的穿透性能,展现出作为新型药物递送系统用于肿瘤治疗的强大优势. Rapoport等人^[45]通过升温、超声辐照等方式,使纳米尺度的PFC NPs相变形成气泡,实现超声显像和介导药物治疗.在这篇报道中, PFP NPs成功地将阿霉素传递至肿瘤内部,取得显著的肿瘤治疗作用.病理等间接证据显示PFP NPs可以穿过血管内皮间隙到达血管外区域.此后,他们在这个领域又

做了更深入的研究^[10,16,21,46]。以PFP为核心、PLGA为外壳制备的载紫杉醇的PFC NPs可以显著缩小裸鼠卵巢癌、乳腺癌、胰腺癌的肿瘤体积^[46]。以PFCE为核心, 携载紫杉醇的PFC NPs不仅可以有效延长在体循环时间, 还能显著地缩小肿瘤、抑制转移, 增强对胰腺癌、乳腺癌的超声显像能力和治疗效果^[21]。

2.3 血栓成像

在临床超声应用中, 纤维斑块因为缺乏回声特异性而很难被检测到。有学者将PFC NPs连接特异性靶标有选择性地靶向纤维斑块, 在活体实验中取得良好的成像效果^[14,47,48], 这将有助于急性肾衰竭、败血症、动脉粥样硬化等血栓性疾病的检测。此外, 利用靶向的PFC NPs的超声分子成像还可以探测血栓性疾病的某些特定组织成分。例如, 组织因子是斑块破裂血栓形成过程中的直接因素, 并且与弥漫性血管内凝血(disseminated intravascular coagulation, DIC)息息相关, 通过连接靶向组织因子的单克隆抗体, PFC NPs超声对比剂可以有效地探测到血管的损伤部位^[49,50]。

2.4 血管闭塞

栓塞治疗是一种利用各种栓塞剂(包括微泡)阻塞血管腔以治疗肿瘤和血管畸形等疾病的方法。目前, 有学者将PFC NPs用于栓塞治疗并取得令人鼓舞的成果。Zhang等人^[51]将PFC NPs静脉注入犬的肾动脉中, 通过相变成的气泡可形成局部组织区域的大

量闭塞。Samuel等人^[52]的研究认为, PFC NPs通过声致相变产生的气泡可以有效闭塞SD大鼠内4~7 μm 的毛细血管床和平均直径在125 μm 的动脉血管。这些研究结果为PFC NPs用于栓塞治疗提供了理论基础。

3 展望

PFC NPs作为一种潜在的超声分子成像对比剂, 因其良好生物相容性、独特相变能力、低溶解度、低扩散性等固有的优势在临床疾病的诊断与治疗方面展现出空前的应用前景, 必将推动超声分子影像医学的进步。尤其是在多模态分子显像和肿瘤的早期诊断与治疗等领域, 有望实现对人体疾病从器官水平、组织水平、细胞水平、分子水平的全方位、多层次在体影像观察, 促进精准医学的发展。

但是, PFC NPs也同时面临一些问题, 例如: 目前尚未有直接证据证实PFC NPs能够穿过肿瘤血管内皮细胞间隙, PFC NPs的靶向聚集的浓度仍然有待提高, PFC NPs特别是包裹PFP的PFC NPs, 其稳定性仍然需要进一步加强; 组成PFC NPs的多种成分, 如相变材料、壳膜材料、荧光材料、核磁材料以及化疗药物等仍需进一步筛选、制备工艺仍需进一步优化; 有关ADV, ODV以及MDV的相关机制仍需进一步阐明; 目前的实验研究仅限于小动物, 但仍缺乏在大动物模型上的研究资料, 临床转化仍然面临众多困难。所有这些亟待解决的问题既是一种艰巨的挑战, 也为我们今后的研究指明了方向。

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Advancement in phase-transitional ultrasound molecular probe

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With the rapid development of molecular imaging technology and materials science, it is very possible for the medical imaging techniques to enable the real-time and multi-modality visualization, characterization, and quantification of biologic processes taking place at the organ, tissue, cellular and molecular levels within intact living subjects. Via the comprehensive progress in terms of tumor early diagnosis based on molecular targets, a revolutionary tumor molecular classification, tumor boundary determination, and surgical navigation, the precision medicine will be achieved. Ultrasound (US) molecular imaging, which is a new branch of molecular imaging, has developed rapidly in the latest decades. The phase-transitional molecular probe has shown significantly more superiority than the traditional US contrast agents owing to its good penetration, stability and the ability for theranostical integration, which indicates a better potential in the basic researches and the clinical applications. In this paper, we reviewed the progress in the studies of the phase-transitional ultrasound molecular imaging probe and its applications in biomedicine.

phase-transitional nanoparticles, molecular imaging, ultrasound, targeted therapy

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