

癌症声动力疗法的研究进展

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摘要: 声动力疗法 (sonodynamic therapy, SDT) 是一种新兴的癌症治疗方法, 具有精确度高、组织穿透力优良、患者依从性高、不良反应少等优点, 临床应用前景广阔。该文介绍了声动力疗法的机制及声敏剂的种类, 阐述了增强声动力疗法的策略, 并总结了声动力联合疗法的研究进展。

关键词: 声动力疗法; 肿瘤; 纳米载体; 肿瘤微环境

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Advance in sonodynamic tumor therapy

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Abstract: Sonodynamic therapy (SDT) is a newly developed therapeutic approach. Due to its high accuracy, deep tissue penetration, high compliance in patients, and rare adverse effects, it has great potential in clinical application. This paper briefly introduced the mechanisms of SDT and different types of sonosensitizers, elaborated various strategies for enhanced SDT, and summarized the advances in the combination of SDT with other therapies.

Key words: sonodynamic therapy; tumor; nanocarriers; tumor microenvironment

癌症是威胁人类健康的重大致命疾病之一^[1-3]。常规的癌症治疗手段主要包括外科手术治疗、放疗和化疗等, 这些治疗手段各有优势的同时也各具其毒副作用。在减轻严重毒副作用的同时改善疗效且低毒、无创的新兴癌症治疗方法受到了研究者越来越多的关注。例如, 光动力疗法 (photodynamic therapy, PDT) 是临床用于皮肤癌等浅表癌症的一种非侵入性治疗技术, 利用光敏剂在激光刺激下产生的单线态氧杀死癌细胞^[4-6]。由于光穿透人体组织的深度有限, 即使是近红外 (near infrared, NIR) 激光也只能穿透组织几毫米, PDT 对深部癌症的治疗效果并不理想。为了克服光动力疗法的

缺点, 自 20 世纪 80 年代末发展起来的低强度超声结合声敏剂的声动力疗法 (sonodynamic therapy, SDT) 成为一种非常有前景的癌症治疗方法^[7-10]。

超声作为一种机械波, 在软组织中具有较高的穿透深度 (可达 10 cm 以上), 已在临床诊断和治疗中得到了广泛应用^[11]。低强度超声波通过触发声敏剂, 激活活性氧 (reactive oxygen species, ROS)、空化、气泡、热疗等物质的产生, 从而杀死恶性肿瘤。相比 PDT 中使用的激光, 超声可以到达深部器官 (例如肝脏和胰腺), 治疗 PDT 难以治疗的深部癌症^[12]。此外, 根据超声的频率可以精确地聚焦于癌症部位, 从而实现声敏

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剂的靶向激活,最终在不损伤周围健康器官的情况下实现对癌细胞的选择性杀伤,对治疗深部恶性肿瘤具有良好的疗效。与PDT相比,SDT具有安全性高、穿透力深、成本低、靶向性良好等优点,有望成为一种有前途的癌症治疗方法。

1 声动力治疗的机制与声敏剂

1989年,Yumita和Umemura首先提出了SDT的概念^[13]。然而,由于SDT的复杂性,其确切机制尚未明了。目前所提出的理论包括ROS的产生、空化效应和热损伤^[14],具体如下:(1)ROS的产生,一般认为SDT的主要机制是超声作用下激活声敏剂产生ROS导致癌细胞死亡。空化效应、热解效应和声光效应都会产生大量ROS,通过破坏癌细胞中的蛋白质、损伤DNA、促进脂质过氧化诱导肿瘤细胞凋亡达到抗癌效果。(2)空化效应,它是一种物理现象,是组织液在超声波的作用下产生大量直径介于1~10 μm 的空化微泡,并发生冲击、膨胀、收缩和内爆的动态过程,分为稳定空化和惯性空化。稳定空化使气泡振荡,加速周围液体的流动,使周围介质混合,惯性空化作用使气泡增长,直到接近共振尺寸,并在塌陷前膨胀到最大尺寸。惯性空化引起能量释放,导致细胞在高温高压下坏死。空化微泡塌陷产生的强烈冲击波导致癌细胞的机械损伤和死亡。(3)热效应,超声机械能的吸收和转化在其传播过程中诱发热能提高组织温度导致癌细胞坏死。

虽然对SDT的机制尚有争论,但毫无疑问,SDT对癌细胞有明显的杀伤作用。一般来说,SDT以超声为激励源,通过声敏剂介导引起细胞凋亡。因此,它被认为是SDT的另一个关键因素,在过去几十年中得到了迅速发展。选择合适的声敏剂用于SDT也是当前研究中的一个热点问题。声敏剂主要可分为有机声敏剂和无机声敏剂^[15]。有机声敏剂主要包括卟啉衍生物、玫瑰红(RB)、菁、天然产物等,早期主要是第一代光敏剂,多数是脂溶性小分子,因其良好的生物安全性和潜在临床转化前景而被广泛研究,但也存在水溶性差、循环时间短、肿瘤富集率低等问题,限制了它们的进一步应用。无机声敏剂主要包括二氧化钛(TiO_2),氧化锌(ZnO)、四氧化三铁(Fe_3O_4)和黑磷(black phosphorus, BP)等。与有机声敏剂相比,无机声敏剂具有更好的稳定性、低光毒性和某些独特的理化性质,使其在血液中更容易循环,但其缺点是自身毒性较大和较低的超声吸收效率。为了克服这些缺陷,研究者采取了将声敏剂(有机/无机)与纳米技术结合的策略,从而使其具有

巨大的潜力。例如, Ma等^[16]合成了3种金属-4-甲基苯基卟啉(TTP)配合物(MnTTP 、 ZnTTP 和 TiOTTP),并用人血清白蛋白(HSA)包封形成纳米声敏剂,这些合成物表现出良好的生物相容性、肿瘤靶向性、光稳定性、组织穿透性和抗肿瘤效果。基于铁转运血清糖蛋白转铁蛋白(Tf)结合肿瘤细胞的能力,Zhang等^[17]通过直接酰胺化原卟啉(PpIX)的羧基和铁饱和转铁蛋白(Tf)的氨基制备了自组装纳米声敏剂(Tf-P NPs),它具有良好的生物安全性,在4 $^{\circ}\text{C}$ 下可长期稳定存在2个月。由于HeLa肿瘤细胞高表达转铁蛋白受体(TfR),纳米声敏剂通过TfR介导的内吞作用递送到肿瘤深部,能显著增强其SDT疗效。为了进一步提高 TiO_2 纳米粒子的稳定性和生物相容性, You等^[18]将羧甲基葡聚糖(CMD)化学键合在 TiO_2 纳米粒子表面制备得到亲水的HTIO₂纳米声敏剂,在PBS中5 d内没有观察到明显的聚集现象,从而表现出良好的稳定性,并且在超声作用下HTIO₂纳米声敏剂产生的ROS可显著抑制浅表肿瘤和深部肝脏肿瘤的生长。

2 增强声动力治疗的策略

声敏剂自身效率较低,加上乏氧、还原性较强的肿瘤微环境(TME),严重限制了SDT的治疗效果^[19]。因此,改善肿瘤微环境可以显著提高SDT对癌症的杀伤效率。根据SDT的机理和肿瘤微环境的特点,利用声敏剂增强SDT效率的策略主要包括增强空化作用、缓解乏氧与消耗谷胱甘肽。

2.1 增强空化效应

超声作用下,声敏剂介导产生的空化效应是保障SDT良好治疗效果的重要因素之一。因此,有效提高声敏剂在肿瘤部位的空化效应可以显著改善SDT疗效^[20-23]。首先,可通过开发具有独特结构的声敏剂提高空化效应改善SDT疗效。例如,有研究者成功合成了具有很高SDT疗效的纳米声敏剂PMCS,在超声作用下,PMCS可高效产生单线态氧和羟基自由基;同时,高速摄像机首次捕捉到纳米颗粒辅助的空化过程,利用PMCS特殊的多孔结构和高比表面积增强空化效应,大大提高了SDT的效率,进而有效地消灭肿瘤细胞及显著抑制肿瘤的生长^[24]。其次,可通过在肿瘤部位原位生成气体大大增强空化效应改善SDT疗效。例如,Feng等^[25]制备了基于介孔碳酸钙纳米粒子装载血卟啉单甲醚(HMME)并修饰透明质酸(HA)的纳米声敏剂HMME/MCC-HA增强SDT疗效,通过CD44受体介导的内吞作用定位到肿瘤区域后,在超声作用

和肿瘤固有的酸性条件共同作用下释放HMME并产生二氧化碳,一方面超声激发的二氧化碳的气泡和爆裂效应导致癌细胞坏死及血管损伤,进一步阻断了血液供应,另一方面,超声激发HMME产生大量的ROS进一步诱导癌细胞凋亡,从而细胞凋亡/坏死和多种机制的结合产生明显的抗肿瘤效果,同时减少了对正常组织的毒副作用。总之,通过增强空化效应可以显著提高SDT抗肿瘤的疗效。

2.2 改善乏氧

氧气是SDT过程中ROS的主要来源之一,SDT的治疗效果受肿瘤内氧气浓度的影响。然而,肿瘤缺氧是实体瘤的恶性特征之一,将严重削弱SDT的治疗效果。且SDT治疗过程中的氧气消耗会进一步加重肿瘤内的缺氧程度,诱导癌细胞的再生,使治疗过程更加困难。因此,靶向递送或肿瘤部位原位生成氧气以高效提高肿瘤局部的氧气浓度是提高SDT疗效的有效策略^[26-30]。为了缓解肿瘤微环境的乏氧状态,提高SDT的抗癌效果,Zhang等^[31]合成了中空普鲁士蓝纳米粒子同时包载声敏剂和携带氧气的全氟己烷,在超声作用下,全氟己烷由液滴变为微泡,同时释放声敏剂和氧气高效地产生ROS。实验结果表明,该纳米声敏剂能显著提升肿瘤内活性氧浓度,提高SDT疗效。除靶向递送氧气到肿瘤部位外,还可直接在肿瘤中原位产生氧气以解决缺氧问题。例如,Zhu等^[32]通过氧化还原反应在介孔硅的通道中合成了MnOx纳米粒子,同时将原卟啉负载到介孔硅中,并进一步用肿瘤靶向的环精氨酸-甘氨酸-天冬氨酸(RGD)多肽修饰其表面得到最终的纳米声敏剂。首先RGD多肽作用使纳米声敏剂肿瘤中高度聚集,利用MnOx分解肿瘤中过表达的过氧化氢(H₂O₂)使之生成氧气,最终通过增加肿瘤内氧气水平提高SDT的疗效。同样,MnO₂纳米结构本身可以作为声敏剂载体,Zhang等^[33]利用中空MnO₂纳米粒子作为载体,将葡萄糖氧化酶(GOx)修饰在其表面,内载声敏剂血卟啉甲醚(HMME)。利用葡萄糖氧化酶消耗肿瘤部位葡萄糖生成高浓度过氧化氢和葡萄糖酸进行肿瘤饥饿治疗,同时中空MnO₂纳米粒子催化高浓度过氧化氢原位产生氧气显著提高SDT的效率。在另一例子中,Liang等^[34]制备了纳米声敏剂H-Pt-TiO₂,由于其特殊的中空结构,H-Pt-TiO₂纳米声敏剂可装载药物Doxorubicin(DOX)。在这个体系中,DOX不仅是化疗药物,而且是良好的声敏剂。同时,Pt纳米粒子在纳米声敏剂表面的不均匀分布不仅促进了电子转移,而且作为纳米酶催化肿瘤部位内源性过氧化氢的分解生成氧气缓解肿瘤缺氧,大大增强

了SDT的效果。综上,SDT治疗需要大量氧气,通过不同的方式缓解肿瘤的乏氧状态可以显著提高ROS的生成效率,从而提高SDT抗肿瘤效果。

2.3 消耗谷胱甘肽(GSH)

肿瘤微环境的另一个特点是大量存在的还原性谷胱甘肽(GSH),可以保护癌细胞免受游离ROS引起的氧化损伤。为了削弱和适应SDT引起的高水平的胞内ROS,癌细胞也会产生高浓度的抗氧化剂谷胱甘肽(GSH)以维持细胞生存所需的氧化还原平衡。如果GSH不能及时大量被消耗,SDT的疗效将大大减弱。因此,促进ROS的产生和/或通过消耗谷胱甘肽减少ROS的清除以破坏细胞内氧化还原的平衡,可以显著放大细胞内的氧化应激提升SDT抗肿瘤效果。基于此,可通过开发具有谷胱甘肽消耗特性的纳米声敏剂增强SDT^[35-39]。例如,Gong等^[40]制备了缺氧双金属氧化物MnWOx-PEG纳米声敏剂用于多模态成像引导的SDT抗癌,聚乙二醇的修饰使其在水、PBS和细胞培养基中表现出良好的稳定性,且在超声作用下可高效产生单线态氧和羟基自由基进行抗癌。此外,该纳米声敏剂表现出高效的谷胱甘肽清除能力,通过抑制谷胱甘肽介导的活性氧清除进一步提高SDT的效率。最终,MnWOx-PEG纳米声敏剂在尾静脉注射后可以迅速代谢并从小鼠体内排出,减轻了长期滞留造成的毒性。因此,可以作为安全高效的纳米声敏剂用于提升肿瘤SDT疗效。除了具有清除谷胱甘肽特性的无机纳米粒子外,一些小分子药物也被用来消耗谷胱甘肽以提高SDT的治疗效果。g-谷氨酰半胱氨酸合成酶(g-GCS)对于细胞中谷胱甘肽合成至关重要,而L-丁硫氨酸亚磺酰亚胺(BSO)能够有效抑制g-谷氨酰半胱氨酸合成酶。Dong等^[41]以无定形碳酸钙(CaCO₃)为模板制备了具有pH响应型解离特性的空心BSO-TCPP/Fe@CaCO₃-PEG纳米声敏剂,他们通过引入L-丁硫氨酸亚磺酰亚胺抑制谷胱甘肽合成,BSO-TCPP/Fe@CaCO₃-PEG纳米声敏剂表现出pH响应型释放L-丁硫氨酸亚磺酰亚胺和Ca²⁺的特性,放大了肿瘤细胞的氧化压力。由于其出色的声动力学性能,BSO-TCPP/Fe@CaCO₃-PEG纳米声敏剂可以有效地抑制肿瘤的生长。总之,在肿瘤部位可以通过有效地消耗谷胱甘肽降低ROS的清除效率来显著提高声敏剂的声动力性能,从而提高SDT的治疗效率。

3 声动力联合疗法

除了SDT,光动力疗法^[42-47]、光热疗法^[48-52]、化疗^[53-57]、免疫治疗^[58-62]、化学动力学疗法^[63-67]和气体疗

法^[68-72]等也是常见的肿瘤治疗方式,并且已发展了多年。考虑到肿瘤固有的异质性和肿瘤生长过程中多种途径的参与,单一的治疗方法很难取得满意的疗效。针对这一问题,很多研究将其他疗法与SDT互补进行联合治疗,以提升肿瘤治疗效果。

3.1 声动力/光动力联合治疗

由于光穿透组织的深度非常有限(0.5~2.0 mm),使用紫外或可见光的光动力疗法前景较差。SDT和光动力疗法联合使用会产生更多的ROS,降低声敏剂/光敏剂剂量,增强细胞毒性^[73-77]。到目前为止,已经研究了许多同时可作为声敏剂的光敏剂,如卟啉衍生物和玫瑰红等。例如,同时可作为光敏剂和声敏剂的血卟啉(HP)由于其水溶性差,临床应用受到限制。Nomikou等^[78]制备了基于聚乳酸-羟基乙酸共聚物[poly(lactic-co-glycolic acid), PLGA]的多功能可生物降解的纳米载体包载血卟啉和吲哚菁绿(ICG),其中PLGA是一种被FDA批准可用于临床的可生物降解生物相容性聚合物,且吲哚菁绿也是已批准的可临床应用的近红外荧光探针,其实验显示,在光和超声单独或联合作用下,肿瘤生长均明显受到抑制,表明该纳米药物可以用于声动力和光动力联合治疗。同时,玫瑰红(RB)是一种水溶性的红光荧光染料,也被用作光敏剂和声敏剂。针对其水溶性和生物利用度都很差的问题,Chen等^[79]合成6种玫瑰红的衍生物,极大改善了两亲性和细胞摄取能力,其中的甲氧基聚乙二醇修饰的玫瑰红衍生物更是被HepG2细胞高效摄取后,经光照和超声激发产生大量的ROS实现了良好的声动力/光动力联合治疗效果。在另一例子中,Zhang等^[80]利用叶绿素衍生物作为光敏剂和声敏剂,在光动力治疗的同时,对12例乳腺癌患者进行声动力联合小剂量化疗,结果显示75%的患者在第1周期治疗后显示出治疗效果,尤其针对一位同时转移到内脏和大脑的患者有良好的治疗效果,提示声动力/光动力联合治疗不良反应较小,以及其在提高晚期乳腺癌小剂量化疗疗效方面的潜力。

3.2 声动力/光热联合治疗

光热疗法(PTT)是在光照射下利用光热转换剂将光能转化为热能,提高肿瘤组织周围环境的温度从而导致肿瘤细胞的损伤的治疗方法,是一种被广泛研究的抗肿瘤疗法。常见的光热转换剂包括金纳米粒子、还原氧化石墨烯、超薄氧化石墨烯和黑色二氧化钛(TiO_2)等^[81-84]。作为最具代表性的无机纳米声敏剂,黑色二氧化钛能在超声作用下产生ROS,然而ROS产生量较低。为了提高SDT和光热治疗的协同抗肿瘤性能,研

究人员将黑色二氧化钛直接生长在还原型氧化石墨烯(GR)纳米片表面,还原型氧化石墨烯不仅提高了黑色二氧化钛的SDT效果,还其高效的光热转换特性实现了协同PTT抗肿瘤^[85-90]。最近,还有研究人员研制了一种可用于声动力/光热联合治疗的 TiO_2 涂层金纳米粒子,金纳米粒子自身在近红外一区(NIR-I)具有良好的光热转换效应,但经 TiO_2 修饰后在近红外二区(NIR-II)表现出较强光热转换率(1 064 nm处 $\eta=42.05\%$),体外和体内的实验结果证实了它具有显著的协同治疗效果^[91]。此外,有文献报道了一种新型的Pt-Cu Janus纳米粒子(PCPT),其中具有较大内腔的空心半导体硫化铜(CuS)可高效负载声敏剂四(4-氨基苯基)卟啉(TAPP, 18.5wt%),动态光散射实验证实其在PBS和培养基中具有良好的稳定性,更是在808 nm激光辐照下表现出良好的光热转换性能。Pt-Cu Janus纳米粒子还可以催化肿瘤微环境中高浓度的过氧化氢产生氧气克服肿瘤缺氧,从而促进SDT抗肿瘤效率,CT26荷瘤小鼠动物实验证实,基于Pt-Cu Janus纳米粒子的声动力/光热联合治疗组对CT26荷瘤小鼠的肿瘤生长有明显的抑制作用,且具有较高的疗效和安全性^[92]。

3.3 声动力/药物联合治疗

化疗是临床上治疗癌症的一种常见而高效的方法,提高肿瘤对化疗药物的敏感性及克服耐药性一直是热点。有研究表明,超声作用可以选择性地增加肿瘤细胞对化疗药物的摄取,从而缓解耐药并减少对正常细胞和组织的毒副作用。同时,SDT还可以通过激活线粒体Caspase信号通路提高肿瘤细胞对化疗药物的敏感性。此外,SDT不仅能直接导致肿瘤细胞死亡还能促进肿瘤部位药物释放。超声诱导的细胞内药物释放可逆转多药耐药(MDR)从而增强药物治疗效果。因此,SDT与化疗的结合可以达到协同治疗效果。低剂量的SDT能诱导自噬,可通过调节自噬来增强SDT的效率^[93-98]。Feng等^[99]开发了可通过调节自噬来优化乳腺癌SDT疗效的纳米仿生系统,他们将自噬抑制剂硫酸羟氯喹(HCQ)负载于中空介孔 TiO_2 纳米颗粒(HMTNPs)并包裹癌细胞膜后,得到了一种仿生纳米系统CCM-HMTNPs/HCQ。该仿生纳米系统稳定性良好,能避免巨噬细胞吞噬并通过同源靶向主动识别和定位肿瘤。随后,在超声作用下释放的硫酸羟氯喹抑制自噬切断受损细胞器的营养供应,从而消除了癌细胞对SDT的抗性。体内研究证实显著的协同抗肿瘤作用。同时,Wu等^[100]报道了由透明质酸(HA)、端羧基聚酰胺胺树状分子(PCH)、ICG和DOX组成

的纳米复合材料(ICG@PCH@DOX@HA, HPCID)用于声动力/药物联合治疗。HPCID被CD-44过度表达的4T1癌细胞吸收后透明质酸酶响应型释放DOX,联合超声介导ROS生成诱导癌细胞凋亡。在4T1小鼠肿瘤模型中,HPCID介导的声动力/药物联合治疗对肿瘤生长和肿瘤肺转移有明显的抑制作用,此研究为世人提供了一种治疗乳腺癌的新策略。

3.4 声动力/免疫联合治疗

与其他癌症治疗方式不同,免疫治疗主要利用免疫系统来特异性识别和摧毁肿瘤,因此不会对正常组织造成任何损害。此外,免疫治疗具有持久的抗肿瘤作用,可产生免疫记忆,防止肿瘤复发和转移。因此,免疫治疗是一种非常具有前途的肿瘤治疗方法。免疫治疗虽有诸多益处,但在实际应用中仍有许多缺点和局限性。例如,免疫疗法对治疗晚期实体瘤的效果较差。通过免疫治疗与其他治疗方法的结合可以提高治疗效果并预防癌症的复发和转移。另一方面,SDT并不能有效地根除远端转移瘤,利用免疫疗法,特别是免疫检查点阻断(ICB),可以通过激发人体的免疫系统来识别和攻击肿瘤细胞和组织来解决这个问题。但是,ICB只对一部分患者有效,但大多数患者只有短暂的反应或根本没有效果,严重阻碍了其在临床上的广泛应用。SDT具有优越的组织渗透性和安全性,可以结合免疫治疗联合抗癌。利用SDT可以有效地抑制原发肿瘤,在此过程中释放的免疫原性因子可以激活宿主的免疫反应,从而防止肿瘤的转移并长期抑制肿瘤的复发。因此,SDT联合免疫治疗,不仅能有效治疗原发癌,还能抑制癌症复发^[101-105]。例如,为提高ICB的治疗效果,研究人员利用低强度超声刺激微泡(USMB)介导的SDT与抗免疫检查点抑制剂(抗PD-1, aPD-1)相结合协同抑制肿瘤,在超声作用下,USMB的治疗不仅阻断了肿瘤的血供,而且还诱发了剧烈的空化效应。aPD-1抗体可阻断PD-L1和T细胞上的受体PD-1之间的结合以释放抗肿瘤免疫反应物质,通过USMB介导的SDT和aPD-1抗体介导的ICB联合治疗显著抑制了肿瘤生长,相比单一治疗大大延长了动物生存期。同时,一种基于声敏剂增强的无创SDT与抗PD-L1检查点阻断免疫治疗相结合的联合肿瘤治疗纳米药物(HMM/R837@Lip)也被设计出来,研究所用的声敏剂血卟啉单甲醚(HMME)、Toll样受体激动剂咪喹莫特(R837)和药物载体脂质体均获得FDA临床批准,具有良好的生物安全性。4T1和CT26荷瘤小鼠动物实验证明了HMM/R837@Lip的高肿瘤蓄积和延迟肿瘤滞留特性。联合治疗结果证实抗

PD-L1免疫治疗防止了肺转移。此外,声动力/免疫联合治疗提供了长期的免疫记忆功能,可以有效防止复发^[106]。总之,利用SDT的深层穿透性、非侵入性、局部治疗安全性和诱导免疫反应的优势,通过与ICB的结合可以进一步提高治疗效果,

3.5 声动力/化学动力学联合治疗

化学动力学疗法利用具有芬顿或类芬顿特性的纳米材料催化肿瘤部位高浓度的过氧化氢产生大量的羟基自由基,从而引起肿瘤细胞的凋亡和损伤。它巧妙地利用了肿瘤微环境中的酸性和高水平的过氧化氢原位生成剧毒的羟基自由基,无需任何外界刺激,从而避免了对健康组织/器官的渗透限制和不良反应的问题。通过超声作用产生活性氧的SDT则高度依赖于氧气浓度,而氧气浓度会受到肿瘤缺氧条件的干扰。因此,SDT和化学动力学疗法联合治疗将具有更深的组织渗透和增加活性氧生成的优势,具有协同效果。此外,研究发现许多芬顿或类芬顿材料同时可作为声敏剂,使用这种材料可以大大增强对肿瘤的杀伤效率^[107-111]。例如,最近报道的具有类芬顿催化活性的超细PEG-TiO_{1+x}纳米棒同时可显著提高声动力效果,用于化学动力学增强的SDT。与商业化TiO₂纳米粒子相比,PEG-TiO_{1+x}纳米棒在超声作用下更加高效地产生ROS,且表现出良好的类芬顿催化活性,可催化肿瘤内源性过氧化氢生成大量羟基自由基进行化学动力学疗法。细胞实验和动物实验证实了其声动力/化学动力学联合治疗效果^[112]。同时,肿瘤部位高浓度的谷胱甘肽严重削弱了基于ROS的治疗方法的杀伤力(包括化学动力学疗法和SDT),因此可通过消耗谷胱甘肽来提高化学动力学疗法和SDT的效果。例如,有研究者制备了一种铜基PTCu₃-PEG纳米笼,它既能产生活性氧,又能作为类芬顿材料。经聚乙二醇化在生理介质(H₂O、PBS、0.9% NaCl、FBS)中稳定性良好。此外,PTCu₃-PEG纳米笼可加速GSH的耗竭。实验证实,在加入外源性过氧化氢和超声共同作用下,PTCu₃-PEG纳米笼比单独使用无超声作用时诱导更多的谷胱甘肽耗尽和ROS生成。随着PTCu₃-PEG浓度的增加,4T1细胞的活力明显降低,而在加入外源性过氧化氢和超声作用下则进一步增强化学动力学疗法和SDT疗效。4T1荷瘤小鼠的体内实验表明,PTCu₃-PEG纳米笼介导的声动力/化学动力学联合治疗效果显著^[113]。

3.6 声动力/气体联合治疗

气体疗法是利用一氧化氮(NO)、二氧化碳(CO₂)或氮气(N₂)的微泡进行治疗。然而,由于特定部位的

气体释放和传递是不可控的,因此微泡在体内的应用非常困难。为了克服这些限制,可将气体治疗和SDT结合实现通过提供及时和局部可控的气泡来获得更好的治疗效果^[114-119],原理是利用SDT实现气体可控释放,进而利用所释放气体增强空化效应改善SDT疗效。例如, Lin等^[120]构建了100 nm左右的2, 2'-偶氮-双[2-(2-咪唑啉-2-基)丙烷]二盐酸盐(AIPH)脂质体(LIP-AIPH),其在细胞培养基中稳定性良好,在超声作用下, LIP-AIPH同时产生氮气微泡和高浓度的自由基,可诱导氧化应激和SDT介导的抗肿瘤效果。体外实验证实,在超声作用下经LIP-AIPH处理的MCF-7细胞活力显著降低,呈浓度依赖性。没有超声作用时,细胞毒性很小。此外,经LIP-AIPH超声作用下治疗的MCF-7荷瘤小鼠肿瘤体积显著缩小,且无明显不良反应。

4 结语

SDT无创性和高靶向性等独特优势为肿瘤治疗方案提供新的选择。近年来,SDT已成为癌症治疗的重要选择之一。SDT由声敏剂、氧气分子和超声波等组成。SDT力图将低强度超声和声敏剂结合在一起,从而达到满意的治疗效果,同时最大程度地减少对健康组织的损害。在本文中,笔者总结了SDT的机制、常见声敏剂种类和改善SDT性能的不同策略,包括增强空化效应,缓解乏氧和消耗谷胱甘肽,并介绍了基于SDT的联合治疗,展示了其广阔的应用前景。尽管人们已经做出了很大努力开发新型高效的声敏剂用于SDT,但仍存在一些问题需要解决。首先,如何高效提升声敏剂的声动力学效率仍是当前的研究热点之一;其次,如何避免超声散射和衍射造成的正常组织的损伤,从而广泛应用于临床,这也是SDT面临的问题之一;再次,SDT研究的模型仍主要局限于小鼠皮下实体瘤模型,未能体现SDT组织穿透深度的优势;最后,SDT的效能与超声的强度和频率密切相关,统一的参考声敏剂测量标准和统一的仪器参数仍未得到确定,不利于以后SDT的临床发展。再有的是,如何避免高频超声的不良反应有待进一步研究。SDT的明确机制也存在一定争议,需要更为深入的研究来阐明。

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