声动力肿瘤疗法:使用光敏剂和低强度超声-非侵入性反复治疗方法

(Sonodynamic Cancer Therapy: A Non-invasive and Repeatable Approach Using Low-intensity Ultrasound with a Sonosensitizer)

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使用低强度超声
用于临床诊断（例如腹部回波检查）的低强度超声是非侵入性治疗，并且比光更深地渗透到身体中。最近，声波动力学治疗（SDT），其使用低强度超声与声敏剂一起，已经开发用于癌症治疗应用这样的性质的超声。到目前为止，已经开发的大多数超声增敏剂对光以及超声敏感，这意味着在光动力学治疗期间使用的光敏剂的缺点，例如皮肤敏感性，仍然需要在SDT中克服。然而，在最近的研究中报道了一些例外，其中敏化剂主要通过超声激活而不是通过光激活。此外，最近的体内研究已经证明，具有声敏剂的SDT作为用于癌症治疗的非侵入性和可重复的治疗具有巨大的潜力。
低强度超声超声波治疗超声波敏化剂审查恶性肿瘤的主要治疗是手术，放射治疗，化疗和这些的组合。虽然联合治疗被认为是具有潜在的附加益处的选项，但是增加的副作用通常使得患者选择停止治疗，例如根治性放射疗法或化学疗法，其限于单一疗程，即使患者具有复发性疾病或在辐射场中的第二原发表现.因此需要新的治疗策略，优选由非侵入性治疗组成。
光的使用是可以考虑用于非侵入性治疗的选项之一。用于治疗目的的光治疗已经进行了数千年，但是最近，已经开发了在光动力疗法（PDT）中使用具有某些化学物质的光来治疗疾病，特别是在肿瘤学中(1-4)。已知PDT需要敏化剂，光能和氧以产生活性氧（ROS），例如单线态氧和自由基，其介导细胞毒性（5-7）.到目前为止，许多化学产品可以作为光敏剂，并且定期发现新的试剂。然而，很少，进行到临床试验，甚至更少成为临床光敏剂。
理想的光敏剂不应是有毒化学品，不能产生新的有毒副产品。 Photofrin具有最长的临床病史和患者记录，是血卟啉衍生物。在临床PDT中，需要红光（50-500J / cm 2）来活化光敏素（8）。一旦敏化剂被从其基态的特定波长的光激活为激发态，在PDT期间发生两种类型的反应：（i）活化的敏化剂可以与底物或分子直接反应，形成氢原子自由基，然后自由基需要与氧产生氧化产物，或（ii）活化的敏化剂可以将能量转移到氧，导致单线态氧形成，然后这种高活性氧物质氧化周围基板。在PDT中，癌细胞死亡直接通过有效诱导凋亡以及通过非凋亡途径发生。最近的证据表明，除了作为非凋亡细胞死亡模式的坏死之外，自噬还由PDT诱导，以允许关键的光损伤细胞器的修复和存活，并且当初始恢复应答失败时可以变成死亡信号(9，10）。这些信号级联在暴露于光动力学应激的癌细胞中被触发，并且根据损伤性ROS或敏化剂的亚细胞定位，将这些信号转导到细胞死亡反应中（11,12）。
如上所述，PDT是用于癌症治疗的有用的非侵入性治疗;然而，存在需要克服的至少两个显着缺点：有限的光穿透进入深的肿瘤组织，这是激活光敏剂所需的，以及某些潜在的严重副作用，例如由于保留在皮肤组织中的光敏剂（13,14）。

当考虑克服PDT的问题的其他非侵入性治疗时，低强度超声与称为声波动力疗法（SDT）的声敏剂一起是有希望的候选者，因为超声的非侵入性和更深的穿透性质。最近的体内研究已经证明，具有声敏剂的SDT作为对于癌症患者的非侵入性和可重复的治疗具有巨大的潜力，即使当肿瘤位置太深而不能使用常规PDT治疗时。

下一节　超声

超声是一种机械声波，在人类听觉范围（16-20 kHz）内在大于20kHz的频率下在连续介质中具有周期性振动。超声波的变化，例如允许超声波到达物体的散射，反射和吸收等，对于探测物体的内部或界面是有用的。通过超声改变对象的动作被分类为通过声空化或其他的动作。声空化涉及通过辐射超声在液体中气泡的形成，生长和近绝热崩解（15）。当液体中的气泡剧烈崩溃时，温度和压力达到超过10,000K和10,000大气压的值，带有冲击波和微射流。声空化也产生光，称为声致发光的发射。超声介导生物组织中的热和非热效应。超声可以比光更好地渗透到组织中，并且通常其生物效应是强度和频率依赖性的。更高的强度导致有效的热产生，并且更低的频率有助于声空化（15,16）。由于超声波可以使用声透镜，碗形换能器或电子相控阵列像光学和音频波聚焦，已经开发了高强度聚焦超声（HIFU）来介导热效应（17,18）。一旦在焦点处的能量密度足够高，组织就被损坏。在HIFU处理期间，温度变得远远大于80℃。在这种情况下，在1秒钟内立即发生热毒性或凝血性坏死的不可逆细胞死亡。最近，磁共振成像（MRI）或超声引导的HIFU已经不仅用于前列腺癌，而且用于肝癌（19,20）。另一方面，非热生物效应通常与振荡或空化气泡相关，但也包括非空化效应，例如辐射压力，辐射扭矩和声流。

下一节 药物递送系统和基因治疗与超声

由于肿瘤血管系统的高度无组织的性质，肿瘤组织中的高血压和高血液粘度，单独施用药物在肿瘤部位不起作用。为了改善抗癌治疗，在过去二十年中已经尝试了各种策略以将抗癌药物递送至感兴趣的部位并使剂量最小化，例如脂质体，胶束，微/纳米颗粒，聚合物 - 药物缀合物和植入物（21- 23）。

最近，已经建立了使用低强度超声的新策略，以便引入新的药物递送方法并开发用于抗癌剂的有用的载体系统（24-26）。

超声增加膜渗透性和细胞膜上的空化作用的细胞内药物吸收，称为声波穿透，虽然声波穿透的机制仍不清楚。此外，空化和/或非空化效应有助于从胶束释放药物，并且肿瘤部位浓度的增加增强细胞内吸收（27,28）。

在调查超声对基因治疗的效力的第一研究中，在药物递送研究中使用的典型超声频率在20-90kHz的范围内，并且超声的最佳功率密度（强度）在1至5W / cm 2的范围内，取决于对照射时间，在连续超声照射下通常为30-60秒。然而，已经采用使用1-3MHz的频率和0.5-3W / cm 2的脉冲模式的治疗性超声，因为更高频率的组织损伤以及空化。尽管使用高功率超声（包括脉冲HIFU暴露）的实验条件导致在增强药物递送中更高的功效，但是仍然存在关于成功抗癌治疗的标准方案的开发的相当大的争论。最近，研究人员通过将基因和纳米/微泡（气泡脂质体）注射到血流中来开发超声介导的基因递送（29,30）。

根据这些报告，气泡脂质体通过空化迅速地将质粒DNA转导到感兴趣的组织中，即使存在血流。在超声介导的药物和基因递送的体外研究的显着成功之后，最近的体内动物研究表明低频超声显着减少异种移植模型中的肿瘤大小（31-33）。

或者，在使用低强度超声的树突状细胞（DC）基癌症免疫治疗中开发了肿瘤相关抗原和气泡脂质

体的组合（34）。有趣的是，当使用气泡脂质体与超声结合递送到胞质溶胶时，外源抗原被认为是内源抗原，导致将抗原呈递到MHC I类，其对于激活肿瘤特异性细胞毒性T淋巴细胞是必需的。

下一节 超声疗法

暴露于超声和随后的空化崩溃可以通过促进卟啉衍生物（例如光对PDT的作用）产生自由基具有类似的效果（35,36）。此后，SDT连同sonosensitizer开发用于癌症治疗（37）。尽管通过从稳定状态到激发状态的超声照射来激活敏化剂的机制仍然不清楚，但是认为该过程可能与当光投射在PDT上时的过程相同，如上所述。
该假说对于两种声敏剂是可疑的：13,17-双（1-羧乙基）-8- [2-（2,4-二氯苯肼基）亚乙基] -3-乙烯基-7-羟基-2,7,12,18-四甲基二氢卟酚，二钠盐[DCPH-P-Na（I）]，新型卟啉衍生物和二氧化钛（TiO 2），光催化剂。两种敏化剂显示与目前报道的光和超声辐射的那些不同的反应性。与ATX-70（一种强的光敏剂，其显示强的细胞毒性）相比，前者对约6,000lux的可见光具有相当弱的反应性（38）。后者需要60倍更长的UV照射周期（5mW / cm 2），以在超声暴露（1.0W / cm 2）（39）上获得类似的细胞毒性。此外，由UV暴露诱导的TiO 2的细胞毒性被自由基清除剂完全抑制，而通过超声辐射的TiO 2仅部分抑制。
考虑到除了上述结果之外，ATX-70在人胃癌细胞系MKN-45上表现出比DCPH-P-Na（I）更小的神经毒性的事实，可以促进SDT中有希望的sonosensitizer候选物通过在PDT上观察到的不同机制，即空化和塌陷能量，但不是声致发光。对于通过手术，放射治疗和/或多种化疗剂的患者，皮肤超敏反应或30天的阳光光敏性可能是一种小的价格来支付非侵入性或无痛性治疗，而具有没有光敏性的sonosensitizer的SDT可能是理想的治疗在非侵入性和可重复的癌症治疗中。

下一节 体内动物模型中的SDT上的Sonosensitizer

除了在细胞培养物中，很少有最近的超声介导的抗肿瘤效应的研究结合对动物模型进行声音致敏剂，如表1所概述的。对SDT中声波穿透机制的了解仍然非常有限，并且构成主要障碍在确定影响声学触发的敏化剂的激活的因素和在成功的抗癌治疗的标准协议的发展。在体内动物模型中迄今最常用作声增敏剂的卟啉衍生物是光敏素，原卟啉IX（PPIX），ATX-70和DCPH-P-Na（I）（38,40-42）。虽然卟啉衍生物选择性地累积在肿瘤中的机制是复杂的并且未完全理解，但是可能是因为试剂的高血管通透性以及它们对增殖性内皮的亲和力和在肿瘤中缺乏淋巴引流。研究这些衍生物的药代动力学参数，除了DCPH-P-Na（I），并且在肿瘤，皮肤和肌肉中显示类似的模式，支持这种假设。此外，DCPH-P-Na（I）在SDT中的抗肿瘤作用表明静脉内施用后6至24小时更高的预防肿瘤生长的功效（未发表的数据）。SDT使用5-氨基乙酰丙酸（5-ALA）也报告在这个问题与低强度但聚焦超声在深部胶质瘤模型（43）。 5-ALA诱导的荧光已被用于恶性胶质瘤，以便在手术中更完全切除（44）。肿瘤细胞在施用5-ALA后合成丰富的细胞内PPIX。因此，5-ALA的施用可以与在SDT中与PPIX的机制类似的机制起作用。在SDT中恶性胶质瘤中使用5-ALA的另一个优点是它可以口服给予患者。
最近报道了使用C32黑素瘤肿瘤细胞在体内的TiO 2纳米颗粒作为新的超声波致敏剂的潜力（45）。在化学工业和环境处理中，TiO 2作为光催化剂是众所周知的，其具有强氧化活性并且通过照射UV光或超声波产生氧化自由基（46,47）。这些性质不仅用于PDT中的光敏剂，而且用于SDT中的声敏剂。在肿瘤块中缺乏颗粒的选择性积聚导致选择性不足和低效率是临床环境中的缺点之一。

下一节 结论

理论上，使用低强度超声与声敏剂的SDT在所有类型的癌症中可能是有效的，而不需要选择靶分子，蛋白质和/或基因。最近在体内和体外研究中进行的报道支持这一假设，因此，SDT是非侵入性和可重复的癌症治疗的有希望的候选物。迄今为止报道的大多数声波敏化剂，包括最近的一种，单-1-天冬氨酰二氢卟酚e6（NPe6），叶绿素样底物，也被称为光敏剂，意味着皮肤敏感性，这种声敏剂在PDT中的严重不良作用，仍然是一个需要在SDT（48）中克服的问题。然而，预期越来越多的实验数据和敏化剂的数量将导致SDT在不久的将来在体内的各种癌症模型中的广泛应用。

Sonodynamic Cancer Therapy: A Non-invasive and Repeatable Approach Using Low-intensity Ultrasound with a Sonosensitizer

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Next Section

Abstract

The low-intensity ultrasound that is used in clinical diagnoses, such as abdomen echo inspection, is a non-invasive treatment, and penetrates deeper into the body than light. Recently, sonodynamic therapy (SDT), which uses low-intensity ultrasound together with a sonosensitizer, has been developed for cancer therapy in applying such properties of ultrasound. So far, most sonosensitizers that have been developed are sensitive to light as well as ultrasound, implying that the shortcomings of photosensitizers used during photodynamic therapy, such as skin sensitivity, still need to be overcome in SDT. Some exceptions were, however, reported in recent studies in which sensitizers were activated mainly by ultrasound but not by light. Furthermore, recent in vivo studies have demonstrated that SDT with a sonosensitizer has a great potential as a non-invasive and repeatable treatment for cancer therapy.

Low-intensity ultrasound sonodynamic therapy sonosensitizers review

Major treatments for malignant tumors are surgery, radiotherapy, chemotherapy and a combination of these. Although combination therapy is considered to be an option with potential

additive benefits, the increasing side-effects often cause patients to elect to discontinue treatment, such as radical radiotherapy or chemotherapy, which are limited to a single course even if patients have recurrent disease or a second primary manifestation in the irradiated field. Novel therapeutic strategies, preferably consisting of non-invasive treatments, are therefore required.

The use of light is one of the options that could be considered for non-invasive treatments. Light treatment for therapeutic purposes has been performed for thousands of years but more recently, the use of light with certain chemicals in photodynamic therapy (PDT) has been developed to treat diseases, especially in oncology (1-4). It is known that PDT requires a sensitizing agent, light energy and oxygen to generate reactive oxygen species (ROS), such as singlet oxygen and free radicals, which mediate cellular toxicity (5-7). Thus far, many chemical products can act as photosensitizers and new agents are regularly discovered. Very few, however, are carried through to clinical trials, and even fewer become clinical photosensitizers. Ideal photosensitizers should not be toxic chemicals and not create new toxic byproducts. Photofrin, which has the longest clinical history and patient track record, is a hematoporphyrin derivative. In clinical PDT, red light (50-500 J/cm2) is needed to activate photofrin (8). Once a sensitizer is activated by specific wavelengths of light from its ground state into an excited state, there are two types of reactions that occur during PDT: (i) the activated sensitizer can react directly with substrates or molecules, transforming a hydrogen atom to form radicals, and then the radicals need with oxygen produce oxygenated products, or (ii) the activated sensitizer can transfer the energy to oxygen resulting in singlet oxygen formation, and then this highly reactive oxygen species oxidizes surrounding substrates. In PDT, cancer cell death occurs directly by the efficient induction of apoptosis, as well as through a non-apoptotic pathway. Recent evidence indicates that autophagy, in addition to necrosis as a mode of non-apoptotic cell death, is induced by PDT in order to allow repair and survival of key photodamaged organelles and can be turned into a death signal when the initial recovery response fails (9, 10). These signaling cascades are triggered in cancer cells exposed to photodynamic stress and, depending on the subcellular localization of the damaging ROS or sensitizers, transduce these signals into a cell death response (11, 12). As mentioned above, PDT is a useful non-invasive treatment for cancer therapy; however, there are at least two notable shortcomings that need to be overcome: limited penetration of light into deep tumor tissue, which is required to activate the photosensitizer, and certain potentially serious side-effects, such as long-lasting skin sensitivity due to the retention of the photosensitizer in cutaneous tissues (13, 14).

When considering the other non-invasive therapy that overcomes the problems of PDT, low-intensity ultrasound together with a sonosensitizer, termed sonodynamic therapy (SDT), is a promising candidate because of the non-invasive and deeper penetrating properties of ultrasound. Recent in vivo studies have demonstrated that SDT with a sonosensitizer has great potential as a non-invasive and repeatable treatment for cancer patients, even when tumors are located too deep to be treated using regular PDT.

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Ultrasound

Ultrasound is a type of mechanical sound wave with periodic vibrations in a continuous medium at frequencies greater than 20 kHz over the range of human hearing (16-20 kHz). Changes in ultrasound, such as scattering, reflection and absorption, among others, which allow ultrasound to reach the object, are useful to explore the object's inside or interface. The actions changing an object by ultrasound are classified as either actions by acoustic cavitation or others. Acoustic cavitation involves the formation, growth and near-adiabatic collapse of gas bubbles in liquids by irradiating ultrasound (15). When gas bubbles in liquid violently collapse temperature and pressure reach values in excess of 10,000 K and 10,000 atm with shockwaves and microjets. Acoustic cavitation also generates light, an emission known as sonoluminescence.

Ultrasound mediates both thermal and non-thermal effects in biological tissues. Ultrasound can penetrate into tissue better than light, and generally its bioeffects are intensity- and frequency-dependent. A higher intensity results in efficient heat production, and a lower frequency facilitates acoustic cavitation (15, 16). Because ultrasonic waves can be focused like optical and audio waves using an acoustic lens, a bowl-shaped transducer or electronic phased array, high-intensity focused ultrasound (HIFU) has been developed to mediate thermal effects (17, 18). Once the energy density at the focus point is high enough, tissue is damaged. During HIFU treatment, the temperatures become much greater than 80°C. In such a case, thermal toxicity or irreversible cell death from coagulative necrosis occurs immediately within one second. Recently, magnetic resonance imaging (MRI)- or ultrasound-guided HIFU has been developed not only for prostate cancer but also for liver cancer (19, 20). Non-thermal bioeffects, on the other hand, are generally associated with oscillating or cavitating bubbles, but also include non-cavitating effects, such as radiation pressure, radiation torque, and acoustic streaming.

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Drug Delivery System and Gene Therapy with Ultrasound

Due to the highly disorganized nature of tumor vasculature, high blood pressure in the tumor tissue and high blood viscosity, the administration of drugs alone does not work at the site of tumor mass. In order to improve anticancer therapy, various strategies have been attempted in the last two decades to deliver anticancer drugs to the site of interest and minimize the dose, such as liposomes, micelles, micro/nanoparticles, polymer-drug conjugates and implants (21-23). Recently, new strategies using low-intensity ultrasound have been established in order to introduce new methods of drug delivery and to develop useful carrier systems for anticancer agents (24-26). Ultrasound increases membrane permeability and intracellular drug uptake by cavitation on the cell membrane, called sonoporation, although the mechanism of sonoporation is still unclear. Furthermore, cavitating and/or non-cavitating effects help to release a drug from micelles and the increase in concentration at tumor site enhances intracellular uptake (27, 28).

In the first studies investigating the efficacy of ultrasound for gene therapy, typical ultrasound frequencies employed in drug delivery studies are in the range of 20-90 kHz and the optimal power density (intensity) of ultrasound ranges from 1 to 5 W/cm2, depending on the irradiation time, which is usually 30-60 s at continuous ultrasound irradiation. However, therapeutic ultrasound that uses frequencies of 1-3 MHz and intensities of 0.5-3 W/cm2 with pulse-mode has been employed because of tissue damage with higher frequencies along with cavitation. Although experimental conditions with high power ultrasound, including pulsed HIFU exposure, led to higher efficacy in enhancing drug delivery, there is still considerable debate regarding the development of standard protocols for successful anticancer therapy. More recently, researchers developed ultrasound-mediated gene delivery by injecting gene and nano/microbubbles (bubble liposomes) into blood flow (29, 30). According to these reports, bubble liposomes quickly transduced plasmid DNA into the tissue of interest by cavitation, even with the existence of a blood stream. After significant successes of in vitro studies of ultrasound-mediated drug and gene delivery, a recent in vivo animal study indicated that low-frequency ultrasound significantly reduced tumor size in xenograft models (31-33). Alternatively, a combination of tumor-associated antigens and bubble liposomes was developed in dendritic cell (DC)-based cancer immunotherapy with low-intensity ultrasound (34). The exogenous antigens, interestingly, were recognized as endogenous antigens when delivered to the cytosol using bubble liposomes in combination with ultrasound, resulting in presenting antigens to MHC class I, which is essential for activating tumor-specific cytotoxic T lymphocytes.

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Table I.
Sonosensitizers used in SDT in an in vivo animal model and SDT conditions.

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Sonodynamic Therapy

Exposure to ultrasound and subsequent cavitation collapse can have similar effects in producing free radicals by facilitating porphyrin derivatives, such as the effect of light on PDT (35, 36). Thereafter, SDT together with a sonosensitizer was developed for cancer therapy (37). Although the mechanisms for activating sensitizers by ultrasound irradiation from a steady state to an exited state are still unclear, it is thought that the process is likely to be identical to that when light is cast on PDT, as mentioned above. This hypothesis is doubtful for two sonosensitizers:
13,17-bis(1-carboxyethyl)-8-[2-(2,4-dichlorophenylhydrazono)ethylidene]-3-ethenyl-7-hydroxy-2,7,12,18-tetramethylchlorin, disodium salt [DCPH-P-Na(I)], a novel porphyrin derivative, and titanium deoxide (TiO2), a photocatalyst. Both sensitizers showed different reactivity from those so far reported to light and ultrasound irradiation. The former had quite weak reactivity to visible light of approximately 6,000 lux for 10 min compared to ATX-70, a strong photosensitizer, which showed potent cytotoxicity (38). The latter required 60-fold longer periods of UV irradiation (5

mW/cm2) to obtain similar cytotoxicity on ultrasound exposure (1.0 W/cm2) (39). Furthermore, the cytotoxicity of TiO2 induced by UV exposure was completely inhibited by a radical scavenger while that by ultrasound irradiation was only partly inhibited. Taking into consideration the fact that ATX-70 demonstrated less sonotoxicity than DCPH-P-Na(I) on a human gastric cancer cell line, MKN-45, in addition to the results mentioned above, a promising sonosensitizer candidate in SDT might be facilitated by different mechanisms observed on PDT, namely cavitation and collapsing energy, but not sonoluminescence. Skin hypersensitivity or 30 days of sunlight photosensitivity might be a small price to pay for non-invasive or painless treatment for patients who have been through surgery, radiotherapy and/or multiple chemotherapy agents, whereas SDT with a sonosensitizer without photosensitivity may be an ideal treatment in non-invasive and repeatable cancer therapy.

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Sonosensitizer on SDT in an In Vivo Animal Model

Except in cell cultures, there are very few recent studies of ultrasound-mediated antitumor effects in combination with a sonosensitizer performed on animal models, as summarized in Table I. Knowledge of the mechanism of sonoporation in SDT is still very limited, and constitutes a major obstacle in determining the factors affecting acoustically triggered activation of sensitizers and in the development of standard protocols for successful anticancer therapy.

Porphyrin derivatives thus far used most often as a sonosensitizer in in vivo animal models are photofrin, protoporphyrin IX (PPIX), ATX-70 and DCPH-P-Na(I) (38, 40-42). Although the mechanisms by which porphyrin derivatives selectively accumulate in tumors are complex and not fully understood, it is presumably because of the high vascular permeability of the agents, as well as their affinity for proliferating endothelium and the lack of lymphatic drainage in tumors. Pharmacokinetic parameters of these derivatives were investigated except for DCPH-P-Na(I), and showed similar patterns in tumor, skin and muscle, supporting this hypothesis. Furthermore, the antitumor effect of DCPH-P-Na(I) in SDT indicated a higher efficacy for preventing tumor growth from 6 up to 24 h after intravenous administration (unpublished data).

SDT using 5-aminolevulinic acid (5-ALA) was also reported in this issue with low-intensity but focused ultrasound in deep-seated glioma model (43). 5-ALA-induced fluorescence has been used in malignant glioma in order to render more complete resection in surgical operations (44). Neoplastic cells synthesize abundant intracellular PPIX after administration of 5-ALA. Therefore, the administration of 5-ALA may work with mechanisms similar to that of PPIX in SDT. The other advantage of using 5-ALA in malignant glioma in SDT is that it can be orally administered to patients.

The potential of TiO2 nanoparticle as a novel sonosensitizer was reported recently using C32 melanoma tumor cells in vivo (45). In the chemical industry and environmental treatment, TiO2

is well known as a photocatalyst that has a strong oxidizing activity and produces oxidative radicals with irradiating UV light or ultrasound (46, 47). These properties are useful not only for photosensitizers in PDT, but also for sonosensitizers in SDT. The lack of selective accumulation of particles in a tumor mass resulting in insufficient selectivity and low efficiency is one of the shortcomings in a clinical setting.

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Conclusion

Theoretically, SDT using low-intensity ultrasound in combination with a sonosensitizer might be effective in all types of cancer without a need for choosing the target molecules, proteins and/or genes. Recent reports performed in both in vivo and in vitro studies support this hypothesis, and thus, SDT is a promising candidate for non-invasive and repeatable cancer therapy. Most sonosensitizers reported thus far, including a very recent one, mono-l-aspartyl chlorin e6 (NPe6), a chlorophyll-like substrate, are also known as photosensitizers, implying that skin sensitivity, a serious adverse effect of such sonosensitizers in PDT, still remains a problem that needs to be to overcome in SDT (48). It is expected, however, that a growing amount of experimental data and number of sensitizers would lead to the extensive application of SDT in various cancer models in vivo in the near future.

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