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Ultrasound-Mediated Cancer Therapy as a Noninvasive and Repeatable Treatment Strategy

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Introduction

There is still a great challenge to develop an effective treatment modality against cancer diseases through the numerous disadvantages of conventional methods such as systemic toxicity, drug resistance, low selectivity and potential long-term side effects [1,2]. Researchers, therefore, have been focused on the minimal-invasive and more efficient strategies such as Photodynamic Therapy (PDT) that is a promising treatment modality based on the synergic interactions of a nontoxic photosensitizer, low-energy and non-thermal visible light, and tissue oxygen to destroy the target cells and tissues by producing singlet oxygen and reactive oxygen species [3,4]. Despite the great success and wide utilization of this alternative treatment modality in clinical settings, PDT has also some limitation. For instance, visible light (near-infrared wavelength) employed in PDT could not penetrate into deep tumor tissues and the long term retention of certain photosensitizers in cutaneous tissues leads to potential long-lasting skin toxicity [2,5,6]. Yumita and Umemura had firstly employed low-intensity ultrasound instead of visible light to sonochemically activate the photochemical materials to produce reactive oxygen species (ROS) and destroy target cancer cells [7,8]. Thus, the problem about low-penetration ability of the light into deep tissues was surpassed by the discovery of Sonodynamic Therapy (SDT) because ultrasound is a type of mechanical wave with frequencies greater than 20 kHz that can exert a specifically localized effect from the surface of the skin up to 15-20 cm into the body to reach a cancer target immersed deep within human tissues [9,10]. Since the discovery of SDT, low-intensity ultrasound has been performed in four major fields of cancer therapy, including SDT, ultrasound-mediated chemotherapy, ultrasound-mediated gene delivery and ultrasound-mediated anti-vascular therapy [11]. Although the underlying activity mechanisms of ultrasound-mediated therapies are depended on certain exposure parameters such as intensity, duty factor, ultrasound frequency and pulse repetition frequency, it is well established that non-thermal ultrasound waves may induce the production of ultrasonic cavitation, free radicals, singlet oxygen, reactive oxygen species and ultrasound-mediated apoptosis [12]. Due to the mechanical characteristics of ultrasound waves, changing pressure gradients in liquid leads to the growth, oscillation, and/or collapse of gaseous cavities (bubbles) [13]. Cavitation can be typically observed into two types as stable and inertial, which are regulated by the oscillatory behavior of bubbles under acoustic field [13-16]. Stable cavitation could be identified with the periodic oscillations of gas bubbles that have already existed in the tissue and that could be observed as the waxing bubble during the negative pressure half cycle and the shrinking bubble during the positive pressure half cycle as response to an ultrasound wave field [9,13,17,18]. Although stable cavitation do not collapse violently at any point of the pressure cycles, inertial cavitation or transient cavitation collapses violently after rapid bubble growth during the negative pressure half cycle and the collapse of cavitation at high-pressure amplitudes leads to instantaneously discharge of highly condensed energy at collapse center that induces localized increase in temperature (104 – 106 K) and pressure (81 MPa) in surrounding microenvironment [9,15,19]. The sonomechanical influences of cavitation collapse near solid boundaries (such as a tissue interface) can be observed as shock waves propagation and micro-jets travelling at high speed (~ 100 m/s) towards the rigid surface [15,20]. Ultrasound-mediated chemotherapy, sonoporation, drug delivery, gene delivery etc. principally use these sonomechanical effects to disrupt the normal functions of the cellular membranes [21]. The sonochemical effects of the bubble collapse can be monitored as the generation of free radicals, singlet oxygen and reactive oxygen species, and / or the occurring of sonoluminescence that can activate the sonosensitizer molecules [19]. Although it is not a surprise to expect light emission due to the high temperature releasing by transiently cavitating bubbles collapse, the precise mechanism of light production is still unclear. Sonoluminescence may be occurred due to the blackbody radiation, bremsstrahlung radiation, recombination radiation, or combinations thereof [19,22-25].

Consequently, ultrasound seem to be a promising technology with non-toxic and tolerable behavior besides the requiring inexpensive equipment and easy implementation in SDT, drug delivery, gene delivery and the other cancer therapies, as well as its conventional usage for diagnostic purposes. Due to the encouraging results of a significant number of in vitro and in vivo experiments, we think that more scientific effort should be attracted along the ultrasound-mediated therapies by planning the researches in naturally occurring cancers and in larger mammals for the promptly application in a clinical trial.

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