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Research progress on reactive oxygen species production mechanisms in tumor sonodynamic therapy

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Abstract

In recent years, because of the growing desire to improve the noninvasiveness and safety of tumor treatments, sonodynamic therapy has gradually become a popular research topic. However, due to the complexity of the therapeutic process, the relevant mechanisms have not yet been fully elucidated. One of the widely accepted possibilities involves the effect of reactive oxygen species. In this review, the mechanism of reactive oxygen species production by SDT and ways to enhance the sonodynamic production of reactive oxygen species are reviewed. Then, the clinical application and limitations of SDT are discussed. In conclusion, current research on sonodynamic therapy should focus on the development of sonosensitizers that efficiently produce active oxygen, exhibit biological safety, and promote the clinical transformation of sonodynamic therapy.

INTRODUCTION

According to the latest statistics from Cancer Statistics, 2023, it is estimated that there will be 1,958,310 new cancer cases and 609,820 cancer deaths in the United States in 2023[1]. Likewise, the cancer situation in China remains critical, with 4.064 million new cases and approximately 2.41 million deaths, according to data released by the National Cancer Centre in 2023[2]. Thus, cancer has become one of the major global threats to human health. Surgery, radiotherapy and chemotherapy are still the main treatment

modalities for most malignancies. For example, the standard treatment for ovarian cancer, a common malignancy in women, is extensive tumor reduction surgery in combination with platinum or paclitaxel-based drugs, with or without angiogenesis inhibitors such as bevacizumab[3, 4]. Despite the clinical benefits of combining multiple modalities for cancer, the mortality rate of cancer patients unfortunately continues to rise each year: late detection because early symptoms of malignant tumors are atypical, tumor recurrence and metastasis, resistance to therapeutic agents, and the systemic toxicity of treatment are important causes of failure of cancer treatment[5-8]. Therefore, exploring novel cancer therapeutics with higher efficacy, lower toxicity and fewer adverse reactions has become an urgent challenge.

Noninvasive therapies such as high-intensity focused ultrasound (HIFU)[9], photodynamic therapy (PDT)[10], sonodynamic therapy (SDT)[11], and photothermal therapy (PTT)[12] have been widely used in clinical practice and have achieved good therapeutic effects. PDT is a treatment based on reactive oxygen species (ROS) that utilizes a photosensitizer (PS) combined with a specific light source to exert cytotoxic activity on tumor cells[13]. The PS, light and oxygen are the three key factors in PDT, and the combination of the three factors can generate ROS. The antitumor effect of PDT comes from three interrelated mechanisms—the direct cytotoxic effect on tumor cells; the destruction of tumor blood vessels, resulting in the deprivation of nutrients needed for tumors to survive[14]; and the release of cytokines and exosomes by tumor cells, which stimulate the recruitment of immune cells into tumor tissues and promote the antitumor immune response, reducing the mobility and invasion ability of tumor cells[10, 15, 16]. However, due to adverse factors such as the phototoxicity of PSs, the lack of specific accumulation in malignant tissues, the lack of endogenous oxygen in tumors, and limited light penetration depth (depth < 0.5 cm), PDT has unsatisfactory therapeutic effects on deep tumors, impeding its practical application[17]. Ultrasound has great preclinical and clinical potential due to its noninvasive nature, low energy attenuation and deep tissue penetration[18]. Yumita *et al* overcame the disadvantages of, such as shallow tissue penetration (depth＜0.5 cm) and phototoxicity, by first proposing

SDT to treat solid tumors[19]. SDT is a noninvasive therapeutic modality that synergizes low-intensity and low-frequency ultrasound (0.5-3 W/cm^2, 1.0-2.0 MHz) with a sonosensitizer. Its main principle is to irradiate tumor sites with ultrasound under aerobic conditions to achieve the directional activation of sensitizers and a series of sonochemical reactions to kill tumor cells and achieve a therapeutic effect[20]. As an advanced treatment method of low-intensity ultrasound combined with an acoustic sensitizer, SDT has the advantages of high tissue penetration (>10 cm), high long-range space-time selectivity, and noninvasiveness. It can treat deep lesions that are difficult to access by photodynamic therapy (PDT) and therefore has broad clinical application prospects[18, 21].

The therapeutic effect of SDT depends on ROS-mediated oxidative stress. However, the production of ROS is low, and the overexpression of the antioxidant glutathione in tumor tissues leads to high ROS consumption, which significantly reduces the therapeutic effect of SDT[22, 23]. Therefore, improving the production capacity of ROS and reducing their consumption are the main strategies to improve the therapeutic effect of SDT[24].

CONCLUSION

SDT, which relies on the strong penetration of ultrasound and the tumor-specific accumulation of sonosensitizers, has been proven to be an effective, low-cost and safe antitumor treatment technique with good clinical application prospects[80]. SDT mainly relies on the research and development of sonosensitizers and the alleviation of the tumor hypoxic microenvironment to promote the efficient production of reactive oxygen species by sonosensitizers. Therefore, the development of sonosensitizers with strong ROS generation ability and good biodegradability will help SDT to obtain better clinical application prospects. In short, SDT has been proven to have good therapeutic effects on tumors, but most of these effects are based on preclinical research. In the future, more research efforts are needed to promote the clinical transformation of SDT[21, 32].

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1	www.ncbi.nlm.nih.gov Internet	34 words — 4%
2	Linjie Shao, Taishun Hu, Xingyu Fan, Xiaozan Wu et al. "Intelligent Nanoplatform with Multi Therapeutic Modalities for Synergistic Cancer Therapy", ACS Applied Materials & Interfaces, 2022 Crossref	16 words — 2%

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