MINI-REVIEW

Current Status and Future Perspectives of Sonodynamic Therapy and Sonosensitiers

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Abstract

The precaution and treatment for cancer become inevitable with the rising of morbidity and mortality. In this article, a promising new methodology for cancer treatment, sono-dynamic therapy (SDT) was introduced. In addition, we extensively reviewed the molec-ular mechanisms of SDT killing cancer and summarized the classification of sonosensi-tizers. At the same time, research progress of SDT indicates that it is possible to become a developing field for cancer treatment in clinical application.

Keywords: Cancer - sonodynamic therapy - sonosensitizer

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Introduction

Cancer is characterized by the dysregulation of cell signaling pathways at several steps, which is a collection of over 100 diseases affecting all body organs (Sadanala et al., 2014). No matter in developed or developing countries, cancers are still the leading cause of death and disability. The Union for International Cancer Control (UICC) World Cancer Congress 2014 in Melbourne, Australia discussed a theme " Looking Toward the Realization of Universal Health Care (UHC) for Cancer in Asia", which is aimed to decrease the global cancer burden and promote health services quality (Hideyuki et al., 2015). In recent years, significant advancements have been achieved in the treatments of all kinds of cancer, especially, the availability of new agents to treat cancers has greatly increased (Mitchison 2012). Generally speaking, the traditional therapies include surgery, chemotherapy and radiation therapy. However, there are numerous disadvantages for conventional treatments such as systemic toxicity, low selectivity, drug resistance and potential long-term side effects (Chen et al., 2014), which may seriously influence life quality of patients. Accordingly, researches on noninvasive therapeutic strategies are urgently required.

The mechanism of SDT

Ultrasound is a mechanical wave at a frequency beyond human hearing. Low not high frequency of ultrasound wave is harmless (Milowska 2007). SDT involves the synergistic interaction of ultrasound and some chemical compounds termed as sonosensitizers. SDT could markedly inhibit proliferation of cancer tissues and be desirable to kill cancer cells and be useful in the treament of atherosclerosis (Li et al., 2015), pancreatic cancer (Li et al., 2014) and so on. Not only depending on cell size and type, but also using cytoskeletal directed agents and cell cycle growth control parameters, ultrasound could induced a higher rate of lysis for cells of a given size (Trendowski et al., 2015). However, the detailed mechanism remains unclear.

Apoptosis

Apoptosis, the process of deliberate cell death within a multicellular organism, has been linked to both the development and the demise of cancer causing cells (Bhatia et al., 2010). However, it is different from necrosis, which refers to uncontrolled cell death, apoptosis, which is carried out in a programmed process, is also important to be develop and remove useless tissue. Song et al. (2011) confirmed the apoptosis on SAS cells by 5-Aminolevulinic acid (ALA)-mediated SDT, which was mainly related to the excessive intracellular ROS production followed by lipid peroxidation (LPO) increase and mitochondrial membrane potential (MPP) decrease.

Collectively, calcium overload (Dai et al., 2014), increased intracellular reactive oxygen species (ROS) generation (Su et al., 2013), activation of p53 protein (Tang et al., 2011) may play potential roles in the process of apoptosis.

Autophagy

Autophagic vacuoles formation clearly occurred after murine leukemia L1210 cells treated by SDT and simultaneously accompanied by obvious LC3 processing and increased Atg5 expression levels in vitro experiments. This suggested autophagy was involved in cell damage induced by SDT treatment at the experimental conditions

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(Zhao et al., 2011). As well, some researchers received the similar results, which investigated the combination of SDT with autophagy inhibitors, especially preventing autophagy at the early stage by 3-methyladenine (MA), could significantly enhance the antitumor effect of SDT through induction of apoptosis and necrosis (Wang et al., 2010).

The mechanism of SDT is not apart, apoptosis and autophagy occurred at the same time after treated by protoporphyrin IX (PpIX)-mediated SDT (PpIX-SDT) on human leukemia K562 cells, and them depended on intracellular reactive oxygen species (ROS) production (Su et al., 2015).

DNA damage

Under low frequency ultrasonic irradiation in the presence of hematoporphyrin-gallium(HP-Ga) complex and a certain condition, the damage degree of DNA was enhanced with increasing ultrasonic irradiation time, HP-Ga complex concentration and ionic strength. Whether the PH value was too high or too low, it would be disadvantage to the damage of DNA. These results would be significant for driving SDT to the clinical application in the future (Wang et al., 2008).

Besides the mechanism above, other studies also confirmed ERK signal pathway delivered a survival signal which counteracted SDT-induced cell death, while combination with ERK inhibitor U0126 could significantly potentiate the SDT-induced cytotoxic effect in U937 cells (Su et al., 2014).

Sonosensitizers

Porphyrin and its derivatives

Sonosensitizers are developed on the basis of photosensitizers such as porphyrin and its derivatives. Porphyrins especially hemoporphyrin derivatives (HpD) can preferentially accumulate in malignant cells and be eliminated slowly (Li et al., 2009), becoming the common sonosensitizers. In the presence of ultrasound, protoporphyrin IX (PpIX) induced decrease of cell viability, intracellular ROS generation, and DNA damage in a concentration-dependent (Li et al., 2014). At the same condition, hematoporphyrin monomethyl ether (HMME) could effectively inhibit the expansion of intracranial gliomas in vivo, and that the corresponding mechanism was closely related to mechanical injury and the induction of apoptosis (Song et al., 2014).

However, the component of the first generation of sonosensitizers is complex and the active ingredient is unclear, so that its stability and tissue selectivity are limited. Hematoporphyrin (Hp) and its derivatives (HpD), which have photoxicity and long-lasting skin sensitivity markedly prevent their clinical application. The second generation of sonosensitizers, such as chlorine e6, is a monomer compound, with consisting of single chemical structure. Thereby, its tumor selectivity is improved obviously. Li Y et al. (Li et al., 2014) discussed the effect of chlorine e6 (Ce6) mediated SDT on human chronic myelogenous leukemia K562 cells. Loss of mitochondria and activation of caspase 9 were observed. These findings revealed that Ce6-mediated SDT triggered mitochondria and caspase-dependent apoptosis, oxdative injury might play a vital role in apoptotic signaling cascades.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) was used in the treatment of fever and pain and the prevention of cardiovascular and cerebrovascular diseases. Recently they was discovered to have the theraputic effects on cancer (Liu et al., 2011).The antitumor effects of non-steroidal anti-inflammatory drugs, tenoxicam and piroxicam, was examined in vitro under ultrasonic irradiation against sarcoma 180 cells. The survival rate of tumor cells when tenoxicam or piroxicam was added was significantly lower than that when ultrasound alone was applied. Furthermore, when L-histidine, a scavenger of singlet oxygen and hydroxyl radical was used concurrently, the survival rate of tumor cells was significantly higher with L-histidine. These showed tenoxicam and piroxicam increase the antitumor effects of ultrasound by increasing the production of singlet oxygen and other active oxygen species (Sakusabe et al., 1999; Okada et al., 2002).

Other sonosensitizers

Besides the common sonosensitizers, some novel ones are brought up in recently, such as pyropheophorbide-a methyl ester (MPPa) (Xu et al., 2011), SF1 (Wang et al., 2008), phthalocyanines (Kolarova et al., 2009) , cytochalasin B (Trendowsski et al., 2014) and Thymol Blue (TB) derivants (Wang et al., 2014) are respectively manifested to be the latent sonosensitizers for treatment of a specific type of cancers as well as some traditional Chinese medicines such as emodin (Gao et al., 2011).

A water-soluble phthalocyanine, namely tetra-a-(3-carboxyphenoxyl) zinc (II) phthalocy-anine (ZnPcC4) and a non-covalent BSA (bovine serum albumin) wereprepared. Compared with ZnPcC4, conjugate ZnPcC4-BSA showed a higher sonodynamic activity with an IC50 value of 7.5uM. Upon illumination with ultrasound, ZnPcC4-BSA can induce an increase of ROS level, resulting in cellular apoptosis. The results suggested that the albumin conjugates of zinc (II) phthalocyanines functionalized with carboxyls can serve as promising sonosensitizers for SDT (Xu et al., 2015).

By comparing the influence of ultrasound, methylene blue alone and together to ovarian cancer cells, we observed more seriously damaged mitochondria, even with almost complete disappearance of cristae in the cells treated by ultrasound sonication in the presence of methylene blue than others (Xiang et al., 2014). So methylene blue may be a potential sonosensitizer.

The future of SDT

The novel sonosensitizers

At present, most of sonosensitizers possessed photosensitivity, thus seeking a preferential and minimal side-effect sonosensitizer is a hot point in the current medicine research. On the other hand, many methods are used to decrease these toxic effects. One of the common methods is the use of a drug carrier to increase drug

concentration and induce oxidative stress in certain tumor cells (Daniele et al., 2014).

Because of the water-soluble property, most sensitizers are restricted to the clinical applications. Poly (lactic-glycolic acid) (PLGA), an effective biodegradable polymeric nano-particles (NPs) which has been used in drug delivery system, has the controlled and sustained-release properties (Sadat et al., 2014). Meng et al. (Meng et al., 2010) present a water-soluble nanocarrier to load the SDT sensitizer SL052. SL052-NPs greatly improved the physicochemical properties of SL052, and the deepsite cancer drug delivery and imaging for diagnosis. Polymeric microbubbles offered a more stable alternative to lipid microbubbles for the delivery of sensitizers in SDT (McEwan et al., 2014).

Osminkina et al. (2014) investigated the cytotoxicity, bioimaging and sonosensitizing properties about Silicon nanoparticles (SiNPs) prepared by ultrasound grinding of porous silicon nanowires (SiNWs). The prepared SiNPs are character-ized by low cytotoxicity in vitro and can be used for bioimaging of cancer cells. The combined action of ultrasound and SiNPs led to substantially decrease in the number of cancer cells. The obtained results open a new perspective for the usage of biocompatible porous SiNPs in the sonodynamic therapy of cancer. Gold nanoparticles Protoporphyrin IX conjugated to gold nanoparticles also can act as an efficient sonoluminescence agent and could be introduced as a novel sonosensitizer for sonodynamic therapy (Sazqamia et al., 2013).

The combination of SDT and chemotherapy

Platinum is an important component of some anticancer drugs, including cisplatin (DDP), and it's the firstline chemotherapeutic regime for ovarian cancer (Yang et al., 2014). Unfortunately, 5-year survival rate of ovarian cancer patients is only about 30%. Drug resistance is considered one of the main reasons causing the low survival rate. So it is urgently needed a new way to overcome this problem.According to the result of some trials, SDT with increased DNA damage attributed to DDP in chemoresistant human ovarian cancer cells, and might sensitize CsA, decreasing the minimal effective concentration (Yu et al., 2009). Adriamycin (ADM) could enhance the sonodynamic effect of chlorin e6 against the proliferation of MDA-MB-231 cells in vitro, and the effect was schedule-dependent, which became greater when ADM was added after SDT (Gao et al., 2010).

The combination of SDT with gene therapy

Gene therapy is a potential medical way to treat human disease.But human body developed a series of defensive system to detect and silence foreign DNA, which restricted its application (Wong et al., 2015). Triplex helix oligonucleotides modified by a sonosensitizer can overcome its weakness and give the tumor cells DNA targeting to sonosensitizers. Meanwhile, sonosensitizers can modify and strengthen themselves by the selectivity and specifity of helix oligonucleotides (Xu et al., 2005).

Diagnose cancer by SDT

Ultrasound is often used for non-invasive diagnostic use in a clinical setting. Sonosensitizers can selectively distribute in the tumor organization, generating free active oxygen radicals to photons in real time, and release them. After that we can get a very clear image using the photon detection technology (Tachibana et al., 2013).

The prospect of SDT

SDT has a tissue attenuation coefficient that allows it to penetrate intervening tissues and reach internal targets without endoscopy. As well, SDT, as a targeted cancer therapy, it has more limited non-specific toxicities because of directing against cancer-specific molecules and signaling pathways. In addition, the apparatus for ultrasonic exposure is simple and low cost. Thus SDT therapy has broad application prospects with variable success. But at present, sonosensitizer research is inadequate, as well as the lack of technology leads to many limitations of clinical application about SDT. Thus, inventing the novel sonosensitizers and combination of SDT with other therapies (gene therapy, immunotherapy, chemotherapy) become the focus of future research. Although it has just begun, but I believe that, there will be a series new methods about SDT to cancer treatment in the near future.

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