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Research progress on the anti-tumor effect of deuterium-depleted water and its possible mechanism

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[Abstract] Drinking deuterium-depleted water can prevent diseases, delay aging, and activate the body's immune cells, especially as an auxiliary treatment for certain cancers and other diseases. It is a major breakthrough in the research on deuterium-depleted water in the fields of nuclear medicine and water physiology abroad in recent years. At present, anti-cancer chemotherapy drugs are still an important treatment for tumors, but they have strong toxic side effects and can easily lead to multidrug resistance. Deuterium-depleted water is easy to use, has no toxic side effects, and may have a huge effect on reversing the multidrug resistance of tumors. Its anti-cancer mechanism is extremely complex, so this article reviews the research progress of the anti-tumor effect of deuterium-depleted water and its possible mechanism.

[Keywords] Deuterium-depleted water; anti-tumor;

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Research progress and the possible mechanisms of the inhibitory effect of deuterium-depleted water on cancers CHEN

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ZHU Baohua2ÿ 1.Department of Hepatobiliary Surgery, Affiliated Hospital of Guangdong Medical College, Guangdong Province, Zhan-jiang 524023, China; 2.China and America Cancer Research Institute, Guangdong Medical College, Guangdong Province, Dongguan 523808, China [Abstract] Drinking deuterium-depleted water can conduce to disease prevention, senility delay and activation of im-mune cells, especially for certain types of cancer and other diseases, its effect of adjunctive therapy has been a signifi-cant breakthrough in the field of nuclear medicine and water -physiology in recent years. Currently, anticancer chemotherapeutic agents remain an important treatment; nevertheless, toxic and side effects of them are quite common. Moreover, multidrug resistance will be easily led by chemotherapeutic agents. Deuterium-depleted water, by contrast, has little toxic and side effects, and may play a significant role in reversing multidrug resistance of tumor. The anti-cancer mechanism of deuterium-depleted water is complex and intricate, and therefore this paper reviews the research progress and possible mechanism of its anticancer effect.

[Key words] Deuterium-depleted water; Anti-tumor; Mechanisms

Water in nature is composed of 2 hydrogen atoms and 1 oxygen atom. Hydrogen atoms are divided into 3 isotopes according to their mass , namely hydrogen (H), deuterium (D), and tritium (T). The content of heavy hydrogen is about 0.015%. Water with D replacing H is heavy water. The ratio of deuterium to protium in natural water (D/H) is 1:6600. Water with a deuterium volume fraction of less than 0.015% (150× 10-6) is usually called deuterium-depleted water or deuterium-depleted water (DDW) [1-5]. The physical and chemical effects of deuterium-depleted water were first discovered. Due to its special properties, it is widely used in the chemical industry, nuclear energy and other industries. With the discovery of its effects in preventing and treating diseases, enhancing the body's antioxidant capacity and immunity, and delaying aging, deuterium-depleted water has been commercialized as drinking water abroad. In early studies, it was found that reducing the deuterium content in water can enhance the body's antioxidant capacity. As the research progressed, it was found that deuterium-depleted water also has It has the functions of enhancing vascular reactivity[6], radiation protection and activating immunity[7], promoting the growth of cultured cells[8], improving the body's basal metabolic level, resisting cell mutation and delaying aging[9]. It is a major breakthrough in the application of deuterium-depleted water in the fields of nuclear medicine and water physiology in foreign countries in recent years[6-7]. At the same time, studies have found that deuterium-depleted water can induce tumor cell apoptosis, inhibit the proliferation of various tumor cells, and cause tumor tissue regression in transplanted tumor mice[10-12]. With the deepening of research on deuterium-depleted water, research on deuterium-depleted water has now involved multiple fields including medicine, food, beauty care, agriculture, etc., and has achieved remarkable success. Due to the unique properties and functions of deuterium-depleted water, it has become a hot topic of research, and its products have been put into the fields of drinking water and cosmetics.

1. The anti-tumor effect of deuterium-depleted water In addition to producing deuterium-depleted water through special preparation processes, there is also water with low deuterium content in nature, such as glacier water and snow water, whose deuterium content is generally 0.0125% to 0.0135%. Investigations have found that animals living on icebergs and cold areas are larger in size, and fish and plankton are more likely to reproduce, because in the cold polar regions or in the polar regions of The deuterium content in water is less than that in tropical and subtropical regions, especially in the ice and snow of Antarctica. The content of heavy water is very small, making the density of Antarctic snow water the smallest and the lightest water on Earth. Regarding the study of deuterium-depleted water, Hughes et al. [10] first discovered that by giving ascites tumor mice 0.0025% to 0.003% deuterium-depleted water to drink , their survival time could be effectively prolonged. Subsequently , Somlyai et al. [11] further discovered that deuterium-depleted water containing 0.003% to 0.01%) can cause a certain change in the D/H ratio in the body, thereby inhibiting the growth of HT-29 colon cancer cells, The proliferation of various tumor cells such as MCF-7 breast cancer cells, PC-3 prostate cancer cells and M19 melanoma cells; subsequently, deuterium-depleted water gradually became a hot topic of research. Studies have found that when the deuterium content in ordinary water is reduced by 65%, it can show a certain anti-tumor effect [12]. In addition, new studies have confirmed that deuterium-depleted water has no toxic side effects and also show that deuterium-

depleted water has an inhibitory effect on various tumor cells, such as lung cancer [13], pancreatic cancer [14], prostate cancer, etc. Krempels et al. [13] conducted a retrospective study on 4 patients with lung cancer and brain metastasis. The results showed that the survival time of patients with lung cancer and brain metastasis who drank deuterium-depleted water (0.001% to 0.002%) for 3 months was 5 to 10 times that of patients treated with other anti-cancer treatments . Cong et al. [15] showed that deuterium-depleted water can inhibit the growth of lung cancer by inducing tumor cell apoptosis. In addition, our research group reported for the first time that deuterium-depleted water can inhibit the proliferation and migration of nasopharyngeal carcinoma cells and cervical cancer cells[16-18], suggesting that deuterium-depleted water has the effect of inhibiting nasopharyngeal carcinoma cells and cervical cancer cells.

In recent years, a double-blind, randomized phase II clinical trial involving more than 1,500 prostate cancer patients was conducted under the approval of the Hungarian Drug Administration . According to the Good Clinical Practice (GCP) standards, the results showed that the survival and quality of life of prostate cancer patients who drank deuterium-depleted water were significantly improved compared with those in the control group who drank ordinary drinking water. This suggests that by reducing the concentration of deuterium in the body, the growth of cancer cells in the body can be inhibited and apoptosis of cancer cells can be induced, which is of great significance for the prevention, recurrence and metastasis of tumors. 2 Possible mechanisms of the anti-tumor effect of deuterium-depleted water 2.1 Regulation of the tumor cell cycle by deuterium-depleted water In the 1990s , researchers found that when L929 cells were cultured in a deuterium-depleted water medium with a volume fraction of 0.003% , the hysteresis period of cell division was extended by 5 to 10 hours compared with L929 cells cultured in normal culture medium [19]. In an experiment to observe the effect of deuterium-depleted water on plant cells in the thallus of seaweed, it was found that after the thallus was placed in a culture medium containing deuterium-depleted water, the plants showed active cellular respiration, stopped photosynthesis, and the intracellular pH was alkaline while the extracellular pH was acidic [20]. Studies have confirmed that changes in intracellular pH are an important mechanism for cell division [21]. Decoursey et al. [22] found through their research on heavy water that only when the deuterium volume fraction is reduced to a certain level can water pass through the cell membrane and proton channel, change the acid-base balance of the cell, affect intracellular proton transport, and thus affect cell division. Cells absorb water The process is achieved by water molecules passing through the cell membrane and proton channels. Since deuterium and oxygen molecules are more likely to form smaller and more stable water molecule structures, they are more likely to penetrate the cell membrane and enter the cell. Studies have shown that a stable deuterium/hydrogen ratio (D/H) in cells is an important condition for maintaining cell signal transduction and tumor cell division and proliferation. When the D/H ratio in cells reaches a certain threshold, the cell cycle regulatory system is triggered, causing cell division. Therefore, by changing or reducing the D/H ratio in cells, the conditions required for tumor cell mitosis disappear, and tumor growth is blocked. In the example of the algae experiment, algae cells cultured in low-deuterium water activated the H+ -ATPase on the cell membrane, expelled H+ from the cell , changed the D/H ratio in the cell, and affected cell growth[20]. In addition, Wang Hongqiang et al.[16-17] and Zhang Li et

al.[18] found through experiments that after tumor cells were cultured in low-deuterium water culture medium, the PCNA protein and P21 protein of the cells were regulated. P21 was originally discovered as a downstream gene of P53 . It is involved in the growth, division, aging and death of cells. It is also closely related to the occurrence of tumors and plays an important role in the physiological and pathological processes of cells. Studies have confirmed that P21 can form a complex with cyclin D/cdk to arrest the cell cycle in the G1 phase; it can also interact with PCNA , blocking the activity of PCNA to activate DNA polymerase, thereby inhibiting DNA synthesis and arresting the cell cycle. 2.2 Mechanism of deuterated water regulating apoptosis of tumor cells.

Apoptosis is a form of cell death that occurs by initiating the cell's own internal death mechanism. The disorder of apoptosis plays an extremely important role in the occurrence and development of tumors and is an important marker of tumor cells [23]. At present, inducing cell death by repairing the apoptosis mechanism is the main means of tumor chemotherapy. The P53 gene is considered to be a tumor suppressor gene because the P53 protein can act as a checkpoint control factor to control excessive cell proliferation by regulating the cell from the G1 phase to the S phase and can promote cell apoptosis. P53 is an important upstream gene of the cycle regulatory gene P21 . Many experiments have shown that P53 is involved in the regulation of tumor cell apoptosis. Studies have found that the sensitivity of cervical cancer patients to chemotherapy is mediated by the P53-Bax regulatory pathway, which induces apoptosis [10]. Gy ÿngyi et al. [12] found that deuterated water can reduce the expression of oncogenes C-myc and Ha-ras and upregulate the tumor suppressor gene P53 in nude mice with transplanted tumors , thereby inducing apoptosis of tumor cells. Current studies have shown that the induction of cell death by the apoptosis mechanism may also be a potential mechanism for the adjuvant treatment of tumors with deuterated water. Gong et al. [15] found through in vitro and in vivo experiments that the apoptosis mechanism is involved in the inhibitory effect of deuterium-depleted water on lung cancer cell proliferation, suggesting that deuterium-depleted water may inhibit the growth of cancer cells by inducing cell S phase arrest and tumor cell apoptosis. In addition , the Bcl family and the Caspase family are currently considered to be closely related to tumor cell apoptosis. It is believed that with the in-depth study of deuterium-depleted water, the mechanism by which deuterium-depleted water induces tumor cell apoptosis will become clearer and clearer. 2.3 Deuterium-depleted water regulates the expression of miRNAs in tumor cells.

In recent years, microRNAs (miRNAs) have been widely used in regulating gene expression. MicroRNA has developed into an important force in the phenotype of tumor cells. It is closely related to cell proliferation[24-26], cell cycle progression[27-29], invasion[30-32] and differentiation [33-34], and is one of the important molecules in the occurrence and development of tumors. RNA. miRNA does not encode any protein, but regulates gene expression after transcription. Volinia et al. [35] analyzed the expression of miRNAs in more than 500 patients with lung cancer, gastric cancer, breast cancer, colon cancer, prostate cancer or pancreatic cancer , and found that 21 miRNAs with low expression in normal humans were overexpressed in tumor patients, such as miR-21, miR-17-92 and miR-191. Their research also fully demonstrated that miRNAs are widely involved in the pathological process of cancer and may promote or inhibit the occurrence of cancer. Zhang et al. [36]

studied 283 miRNA genes and found that 41 miRNAs had the same gene expression changes in breast cancer, ovarian cancer and melanoma , of which 26 genes increased and 15 decreased. Changes in miRNA expression can promote or inhibit tumor formation by regulating the expression of gene functions related to tumor cell proliferation and survival. Tumor cells can show many changes that can directly or indirectly affect miRNA expression. Many miRNAs are believed to have carcinogenic or tumor suppressor functions. In in vitro and in vivo experiments, miRNAs have been found to have tumor suppressive or tumor promoting effects, and some relevant miRNA targets have been reported [37-38]. In hepatocellular carcinoma (HCC), miRNAs can target and regulate the expression of proteins related to cell cycle, apoptosis, and metastasis [39]. In previous studies, our research group has demonstrated that deuterated water can inhibit the proliferation and invasion of HepG2 liver cancer cells [40]. Moreover, through gene chip analysis of the miRNA expression profile of HepG2 liver cancer cells , it can be found that among the differentially expressed miRNAs , there are both upregulated and downregulated ones. Therefore, there is reason to believe that the effect of deuterated water on the expression of miRNAs is one of its mechanisms of anti-tumors, tumor which is effect.

2.4 DNA damage mechanism

Current research shows that excessive ultraviolet radiation and high concentrations of deuterium can damage DNA repair enzymes that are particularly sensitive to the concentration of deuterium in the body, causing disordered arrangement of DNA codons, which ultimately affects the mitosis of the organism. In the early 20th century, most research experts proposed that the content of deuterium in the body is closely related to the aging of the body. Certain enzymes and proteins play an important role in the process of DNA replication and repair and the formation of hydrogen bonds [41]. At the same time, studies have shown that deuterium can replace hydrogen atoms in the helical structure of DNA , leading to aging and tumorigenesis. This influence is mainly through promoting the phase shift, breakage, and replacement of the DNA double helix structure. On the other hand, it causes disordered arrangement of RNA, and even resynthesis and mutations [42]. 3 Summary The water content in the human body accounts for 65% to 70%. It can be said that water is the source of life. Hydrogen bonds are the basic chemical bonds of DNA and are involved in almost all life reactions of the body. Deuterium affects DNA inheritance and replication. Since 1934 , American scientist Yuri After the discovery of deuterium, people began to study deuterium. As the research on deuterium-depleted water deepened, people gradually discovered its application prospects in clinical medicine, and the effect of deuterium-depleted water on tumors has attracted much attention. It was not until 1990 that the Hungarian National Institute reported that deuterium-depleted water could induce complete or partial regression of spontaneous malignant tumors in cats and dogs, and registered and applied for the use of deuterium-depleted water as an anticancer drug in animals [43]. Deuterium-depleted water officially entered the fast lane of anti-tumor research. The occurrence and development of tumors are extremely complex and are the result of the interaction of multiple factors. The fundamental reason is the imbalance of cell homeostasis in organisms. There are many reasons for the imbalance of cell homeostasis, among which protein dysfunction, DNA mutation, chemical factors, etc. are considered to be the culprits of tumor occurrence. Due to the complexity of tumor occurrence, the current treatment of tumors is still mainly based on lethal chemical drugs. However, while chemical drugs kill tumor cells, they also have the

same killing effect on normal cells, which has a great impact on normal cells. During the treatment process, patients often experience varying degrees of toxic side effects, and even induce new tumors. Given the natural properties of deuterium-depleted water, it has almost no toxic side effects on the human body. At present, in vitro and in vivo experiments on deuterium-depleted water have confirmed that it has anti-tumor activity and has no toxic side effects on normal human cells. It even has the function of promoting normal cell growth, suggesting that deuterium-depleted water may also have the effect of activating cells and delaying aging [16]. Due to the complexity of tumorigenesis, the anti-tumor mechanism of deuterium-depleted water is also diverse. Studies have shown that deuterium-depleted water can reverse the transport of Na+ -H+ ion pumps and K+ -H+ -ATP, regulate intracellular pH and D/H ratio, inhibit tumor proliferation, and deuterium-depleted water can repair damaged and mutated DNA in the body and inhibit the occurrence and development of tumors. microRNA has been a hot topic in recent years. miRNA plays an important role in the differentiation, proliferation, and apoptosis of tumor cells. It is believed that with the in-depth study of deuterium-depleted water, deuterium-depleted water may regulate the expression of miRNA in the human body , thereby inhibiting the occurrence and development of y to be a major direction of deuterium-depleted water research. At present, the research on deuterium-depleted water is still in its early stages, and people's understanding of the specific anti-tumor mechanism of deuterium-depleted water is still very vague, and its anti-tumor mechanism needs further research. With the rapid development of molecular biology technologies such as gene chips, the mystery of the anti-cancer effect of deuterium-depleted water will surely be revealed for us.

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