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Review

Toxic medicine used in Traditional Chinese Medicine for cancer treatment: are ion channels involved?

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Abstract

Cancer has been one of the most serious public health issues in the world. Traditional medicines are widely used in adjunctive therapies in clinical cancer treatment in many countries. One of the unique traditional medicine usages in tumor treatment is the high-dose application of traditional toxin medicine, including venom or body from toxin animals. Evidence has shown that they are very likely to have direct effects on cancer cells. One of the potential pharmacological effects of traditional toxin medicines is their regulation of ion channels in cancers. Many ion channels are found critical in cancers. This study suggested that ion channels were involved in the effect of traditional toxin medicine on cancers. However, so far, the study of the effect of traditional toxin medicine on ion channels in cancers is relatively lacking. This perspective article urged the study in this field because, given the fact that these traditional toxin traditional medicines have been widely used in cancer treatment, the identification of the effective components and pharmacological targets can improve their clinical application.

Keywords: neoplasms; ion channels; venoms; toxin; medicine, traditional

1. INTRODUCTION

Cancer has been one of the most serious public health issues in the world.[1] Multiple strategies are adopted to reduce the incidence of cancers or treat cancer patients. Clinical major therapies for cancers including radiotherapy, chemotherapy, surgery, targeted therapy, and immunotherapy provide relatively effective treatment effects, these therapies usually also come with various concerns, such as drug resistance and side effects. Traditional medicine has been widely used in adjunctive therapies to reduce those issues in cancer treatments and has achieved desirable outcomes in some cases.[2,3] The clinical application of traditional medicine improves the life quality of cancer patients by (a) enhancing the effect of the therapy, (b) eliminating side effects, and (c) serving as a psychological placebo. In clinical cancer treatment, traditional toxic medicines are frequently used to treat cancer. Given that traditional toxic medicines have more safety concerns, studies of these medicines are essential to improve the safety and effectiveness of their clinical application. The purpose of this perspective article is to suggest a potential mechanism underlying the effect of traditional toxic medicine in cancer treatment.

2. CURRENT CLINICAL APPLICATION OF ANTI-TUMOR DRUGS IN TRADITIONAL MEDICINE

Most of the current anti-tumor drugs of traditional medicines are applied with other modern therapy such as radiotherapy, chemotherapy, surgery, targeted therapy, and immunotherapy. The clinical application of traditional medicine improves the life quality of cancer patients in several aspects. Firstly, some traditional medicines can enhance the effect of other cancer therapies. For example, Traditional Chinese Medicine was widely used in combination with platinum-based chemotherapy for lung cancers.[4] Secondly, traditional medicine can largely reduce the side effects of other cancer therapies. For instance, a study reported that the combination of traditional medicines with cisplatin or carboplatin reduced negative symptoms brought by the chemotherapy, such as vomiting, fatigue, pain, dry mouth, and diarrhea.[5] Last but not least, traditional medicine can serve as a psychological placebo that can decrease stress during the treatments. Placebo effects have been found to be one of the critical factors during clinical treatment.[6] In areas where traditional medicine is widely used, people have faith in traditional medicine, therefore, during cancer treatment, the placebo effect of traditional medicine cannot be ignored. Many patients believe in traditional medicine, which enhances their will to survive and obtain a positive attitude toward the treatment.[7] In fact, traditional medicine has been potentially practiced for thousands of years in the clinical treatment of cancer in the antient time, when people have

no idea what is cancer. At the present time, is traditional medicine widely accepted as a clinical alternative treatment for cancer. The clinical feasibility and practicality of traditional medicine to treat cancer are beyond doubt, as proved by evidence-based medicine. However, the clinical application of traditional medicine is subjected to the lack of understanding of the pharmacology of traditional medicine. This lack of understanding can lead to the clinical failure in cancer treatment by traditional medicine. Thus, more studies are required in the future to reveal the mechanisms underlying the pharmacological effects of traditional medicine on cancer patients.

3. A UNIQUE TRADITIONAL MEDICINE USAGE IN TUMOR TREATMENT

Herbal medicine is the most commonly used traditional medicine. In clinical cancer treatments, herbs have been used to regulate the immune system, reduce side effects, or directly affect cancers.[2] Yet, one of the unique applications of traditional medicine in tumor treatment is the high-dose application of traditional toxic medicine. This type of traditional medicine includes venom or body from toxic animals, such as snakes, scorpions, centipedes, toads, and cantharidin. The venom has been used for hundreds of years in some countries, for instance, venom from snakes has been used to treat arthritis, and venom from toad skin has been used as a painkiller in China and India.[8] The application of traditional toxin medicines in cancer treatment was well described in cancer prescriptions in traditional medicine with relatively high doses and the treatments achieve favorable outcomes in many cases.[9] However, much as some studies have revealed the pharmacological components and mechanisms of a few traditional toxic medicines, most of these medicines were applied to cancer patients without modern scientific understanding. In some cases, the inappropriate application of traditional toxic medicines might lead to adverse outcomes caused by drug-drug interaction or unexpected organ failure caused by excessive liver and kidney metabolism.

4. PHARMACOLOGICAL EFFECTS OF TRADITIONAL TOXIC MEDICINES

According to the traditional theory, toxic medicines were regarded as “cancer killers” that can “fight poison with poison”. In toxic Chinese medicine, pan beetle, whole scorpion, centipede, and toad are widely used for cancer treatment and can resist the tumor. For example, Fufang Banmao Jiaonang (复方斑蝥胶囊) was a traditional medical prescription for malignant neoplasm of the bronchus or lung, malignant neoplasm of the female genital organ, malignant neoplasm of the liver, and malignant neoplasm of the rectum proven by the Chinese FDA.[10] It can resist the tumor and the major effective component is the pan beetle.

Generally, there are two classes of toxic traditional drugs, including chemical poisonous drugs and protein toxins. An example of chemical poisonous drugs is poisonous metals, such as arsenic. The most commonly used traditional toxic drugs are toxin-like drugs. Modern evidence also showed that they are very likely to have direct effects on cancer cells. Many natural toxins from venomous animals have been suggested to be useful for cancer treatment.[11] *In vitro* studies have shown that some animal venoms inhibited multiple types of cancer cells.[12-14] *In vivo* studies also showed that some venoms suppressed metastasis of cancer cells.[15] However, the pharmacological understanding of traditional toxic medicines is insufficient, most of the affective components in traditional toxic medicines and their targets have not been identified.

5. ROLES OF ION CHANNELS IN ANTI-TUMOR TOXIC TRADITIONAL MEDICINE

Genome instability is one of the main alterations that result in cancers. Generally, these genetic alterations lead to common cancer cell genotypes with patho-physiological characteristics that promote tumorigenesis.[16] Among these alterations, membrane proteins have been found to potentially affect cancer cells. Tumor channel disease has been proposed as a special type of channel disease.[17] Ion channel membrane proteins are essential in intracellular and intercellular signal transduction, the coupling of extracellular events and intracellular reactions, and the maintenance of intracellular ion homeostasis. Therefore, the ion channel dysfunction results in various complex changes during tumor occurrence. This makes the ion channels potential pharmacological targets for regulating cancer cells.

One of the potential pharmacological effects of traditional toxic medicines on cancers is their regulation of ion channels. Roles of ion channels in anti-tumor toxic traditional medicine include inhibition of ion channels that promote cancer cells.[18,19] modulation of ion channels that regulated cancer.[20] and killing cancer cells by blocking the essential ion channels of cancer cells.[21] Current research aspects of toxic traditional medicines for cancers mostly focused on their general inhibition of cell viability, migration, or invasion, yet the detailed mechanisms underlying these inhibitions were blurred and very few studies reported the effect of traditional medicine on ion channels in cancer cells.

6. TOXINS IN TRADITIONAL MEDICINES AND ION CHANNELS IN CANCER

Many ion channels have been reported to play a role in cancers. The abnormal function of some ion channels was proposed to be one of the cancer hallmarks.[22] Studies have suggested multiple ion channels as potential targets for cancer treatment, including sodium channels,[23] calcium channels,[17] and other non-selective channels.[17,19] Notably, most traditional medicines for cancer, whose major components include toxins, are also included in the

prescriptions for the treatment of channelopathies, such as mania, convulsions, and epilepsy.[22,24,25] Being extracted and separated from the animal venoms, toxin proteins have been regarded as a desirable resource for ion channel drugs. For example, many natural venomous animals generate Nav channels targeting toxin peptides,[26] such as venom toad skin that has been used as a painkiller.[8] A great number of protein toxins extracted and isolated from the venoms of sea anemones, spiders, snails, scorpions, and centipedes are now being explored as possible ion channel drugs.[27]

This study suggested that ion channels are involved in the "fight poison with poison" effect of traditional toxin medicine on cancers. A few examples supported this perspective: antitumor peptide (ANTP), an effective anti-cancer toxin, has been identified from the venom of the Chinese scorpion Buthus martensii, an animal used as traditional toxin medicine.[28] ANTP is a long-chain toxin recognizing sodium channels.[29] It has been reported to inhibit the cell cycle of human colon cancer cell line SW480 and suppress the growth of gliomas cell line SHG-44.[30] Some other toxins have been found to inhibit pain-sensitive channel Nav1.7,[31] which were proposed to have functions in cancer cells.[23,32] In addition, mineral or sea products are frequently used in traditional prescriptions for cancer. These medicines might contain a high level of inorganic salts and heavy metal ions.[33] These ions might also interfere with the ion channels and co-regulated the ion channels with the toxin. However, so far, the study of the effect of toxic traditional medicine on ion channels in cancers is relatively lacking. Many studies on the role of ion channels in cancers are ongoing. As the field further understands the role of ion channels in cancers, the pharmacological effect of toxins in traditional medicines on cancer will be revealed.

7. SUMMARY

Given the fact that toxic traditional medicines have been widely used in cancer treatment, the identification of the effective components and pharmacological targets can improve their clinical application. The activity of toxins can be critical for the therapeutic effects of the traditional cancer prescription. As toxins are proteins that are sensitive to temperature, acidity, and other physical and chemical environments, the understanding of toxins in cancer can optimize the procession of traditional medicines to increase their therapeutic potency and reduce undesirable toxicity. For example, some critical toxin proteins should avoid being inactivated by heat or other denature procession, and some toxic medicine can be replaced by less toxic ion channel drugs. This perspective article urged more study on traditional medicines and ion channels in cancer in the future.

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