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COMMENT

New therapeutic effects of cardiac glycoside: anti-cancer and anti-aging

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Aging is an unavoidable topic in everyone's life, and the aging problem has been puzzling scientists for many years. For thousands of years, we've used many tools to extend life span, and today, new technologies and medical treatments have extended the average human lifespan by about two years in a decade. The incidence of heart disease, tumors and degenerative diseases increases with age. Traditional Chinese Medicine believes that the use of herbs or guidance techniques can improve blood circulation, increase heart function, delay aging and prevent the development of tumors. Cardiac glycosides (CGS) are glycoside compounds that stimulate cardiac muscle significantly. They are commonly used in the treatment of heart failure and atrial fibrillation. CGS is a class of steroid derivatives extracted from plants. It is the specific ligand of cell membrane protein Na^+/K^+-ATPase. CGS was used as a drug to treat diseases as early as 1500 years ago. More than 200 years ago, CGS was used as a cardiac tonic to treat heart failure, and it is still used to treat heart failure and atrial fibrillation. CGS is used to treat tumors, dating back to the 8th century in Arab countries. Doctors in ancient China also used toad venom extracted from toad to treat tumors. The main component of toad venom was digitalis derivatives, which later proved to have the effect of inhibiting the proliferation of various tumor cells [1]. It has been reported that cardiac glycoside drugs, such as digoxin, digitoxin and ouabai, could prevent and treat malignant tumors. Subsequent studies have shown that cardiac glycosides can selectively inhibit the proliferation of human tumor cells and induce apoptosis, but have no significant effect on normal cells. Therefore, CGS is likely to become a new type of tumor therapy. In order to further confirm the clinical value of CGS anti-tumor therapy.

Recently, the cell proliferation research group published a paper on Nature Metabolism and found that cardiac glycoside drugs that increase cardiac output also have anti-aging and tumor growth effects [2, 3]. The drug not only treats heart disease but also selectively kills aging cells in the body and increases the tumor-suppressive effects of anticancer drugs. In this study, the researchers found that senescent cells had sensitization to uabain-induced apoptosis, which was mediated in part by inducing the pro-apoptotic BCL-2 family protein. The results highlight the potential of cardiac glycosides as a broad-spectrum anti-aging agent. More and more studies have found that CGs not only has the function of ion pump but also has the function of signal transduction and participates in cell proliferation, apoptosis and other processes [4, 5]. In addition to acting as an ion pump to maintain the Na^+/K^+ concentration difference on both sides of animal cell membranes, Na^+/K^+-ATPase is also a very important signal receptor on animal cell membranes. It through combined with cardiac glycoside and activation, the activation of Na^+/K^+-ATPase and sarcoma viral protein kinase (Src) combined with cause the activation of Src kinase, raise the epidermal growth factor receptor into the domain signal microstructure after membrane aperture, assembled into different complex signal transduction, further to transmit signals inside the cell, the cell reaction. What is interesting is that the binding of Na^+/K^+-ATPase to cardiac glycoside on the cell membranes of different tissues induces different cellular responses. For example, it acts on cardiomyocytes, causing them to contract. On vascular smooth muscle cells and renal tubular epithelial cells, cell proliferation was induced. However, when it acts on tumor cells, it causes apoptosis. Recent studies have found that cardiac glycosides have a strong killing effect on human tumor cells, and nmol/L concentration levels can strongly inhibit the proliferation of human tumor cells and induce their apoptosis. Current studies suggest that the selective killing of human tumor cells by cardiac glycosides may be due to differences in Na^+/K^+-ATPase on the cell membranes of different

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tissues of the same individual, between normal and tumor tissue cells.

Further exploration revealed that cardiac glycosides also have synergistic effects with anticancer drugs, killing tumor cells and removing accumulated senescent cells after radiation or in elderly mice [6]. Not only that, but uabain also eliminates pre-aging tumor cells. The researchers found that after several months of observation, the aging mice injected with cardiac glycoside drugs showed no significant difference in their indicators from the young mice and showed no other abnormalities.

But getting rid of senescent cells isn't as easy as it might seem. First of all, cell aging is harmful to the role of the body is not all, cell senescence in inhibition of tumor formation, wound healing, embryonic development, tissue regeneration plays an important role in the process and can promote insulin secretion from pancreatic beta cells in the process of aging, so must pay attention to choose to get rid of the senescent cells time, location, mode. Second, although many small molecule drugs targeting senescent cells have been reported, the off-target effects of these compounds are widespread. Third, senescent cells in different tissues have different sensitivity to different therapies, so when designing drugs, it is not only necessary to select the type of targeted cells, but also to enrich drugs in specific tissues.

Researchers have found that digitalis has an inhibitory effect on breast cancer, and the mortality rate of patients using digitalis is significantly lower than that of patients not using digitalis [3]. In addition, drug efficacy analysis was conducted on patients who were treated with digitalis due to heart disease, and it was confirmed that the higher concentration of digitalis in the blood was significantly correlated with the lower incidence of blood and urinary system tumors [7]. Now the study of cardiac glycosides against tumors has been paid attention to by many researchers. At present, researchers have conducted a series of studies on the anti-tumor activity of cardiac glycosides in vitro, animal experiments, clinical studies, anti-tumor mechanism, sensitization, and structural modification of anti-tumor cardiac glycosides, etc., confirming that cardiac glycosides have a strong anti-tumor effect in vivo and in vitro [8].

In conclusion, cardiac glycosides can selectively clear senescent cells in the body and are safe. It may also act on tumor cells through a variety of mechanisms and is an effective anticancer drug [9]. Considering the prevalence of cardiac glycosides acting on senescent cells, the use of these cells to treat age-related diseases is worth further exploration. Although these drugs show broad prospects of anti-aging and anti-cancer, due to the different effects of cardiac drugs on different intensity, speed and duration of maintenance are greatly different, they still, need to pay attention to the rational use of drugs. The therapeutic window of cardiac glycosides is very narrow, and the excessive plasma concentration of cardiac glycosides is likely to cause arrhythmia or even death of individuals, and the tolerance of cardiac glycosides to the human body is quite different. Current studies have shown that cardiac glycosides require higher concentrations of drugs to inhibit tumor growth than they do to treat heart disease. Therefore, the commonly used cardiac glycosides such as digoxin and digitalis cannot be directly used in the treatment of tumors.

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