УДК 2

MODULATION OF INCRNA H19 ENHANCES RESVERATROL- INHIBITED CANCER CELL PROLIFERATION AND MIGRATION BY REGULATING ENDOPLASMIC RETICULUM STRESS

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Summary. *The phytoalexin resveratrol exhibits anti-tumour activity in many types of cancer. In this study, we showed that resveratrol suppressed the survival of gastric tumour cells both in vivo and in vitro. Resveratrol promoted apoptosis, autophagy and endoplasmic reticulum (ER) stress in a dose-dependent manner. In conclusion, resveratrol inhibited cancer cell survival, while knockdown of lncRNA H19 resulted in increased sensitivity to resveratrol therapy.*

In recent decades, cancer- associated deaths have become the leading cause of human mortality. Among them, gastric cancer is the fourth leading cause of cancer deaths worldwide, with an estimated 0.77 million deaths in 2020. Chemotherapy is a common strategy for cancer treatment, and there have been numerous endeavours to design, develop, modify and evaluate anti- cancer drugs. Resveratrol, the best- known polyphenolic stilbenoid and exhibits many health beneficial properties, including anti- oxidation and anti- inflammatory activity. To date, a number of reports have documented the application of resveratrol in cancer treatment. Resveratrol has been shown to inhibit cellular proliferation, progression and invasiveness in various types of cancers. Several clinical trials evaluating the effects of resveratrol in cancer patients have been performed. However, reports have identified a number of limiting factors for resveratrol in human studies, including low bioavailability and potential side effects, such as mild gastrointestinal discomfort. Therefore, exploration of the underlying mechanisms in order to discover more potent cancer therapy strategies based on resveratrol treatment is still in progress.

Treatment with natural compounds frequently activates various signalling pathways, including endoplasmic reticulum (ER) stress. ER stress could either help to recover cellular homeostasis and maintain cell survival or it can induce cell death. In fact, both autophagy and ER stress have been found to contribute to the establishment of drug resistance in cancers. Correct modulating of autophagy and ER stress could facilitate the anti- tumour effects of natural compounds and help to overcome any potential subsequent chemoresistance.

The lncRNA NEAT1 has also been shown to play a role in resveratrol- mediated inhibition of proliferation, migration and invasiveness in multiple myeloma cells through modulation of the Wnt/beta- catenin signalling pathway. However, reports documenting the investigation of lncRNA in resveratrol treatment are still limited. Therefore, the present study aimed to provide evidence in support of the application of resveratrol in gastric cancer treatment by examining the modulation lncRNA- mediated cell death mechanisms.

The AKT/mTOR pathway is known to be essential for the regulation of autophagy. Analysis of AKT/mTOR phosphorylation by Western blotting indicated that exposure of SGC7901 cells to resveratrol for 24 h resulted in reduced levels of both phosphorylated AKT (Ser 473) protein and phosphorylated (activated) mTOR (Ser2448). ERK and Wnt/β- catenin are important pathways for cell survival. As shown in, phosphorylation of p38 MAPK and ERK was found to be upregulated after treatment with 50, 100 and 200 μM resveratrol. The expression of both β- catenin and Wnt3a mRNA was downregulated in resveratrol- treated cells, while β- catenin was also decreased in nuclear protein extracts from cells treated with 200 μM resveratrol. Meanwhile, immunofluorescence also confirmed that resveratrol treatment prevented the nuclear translocation of β- catenin. To summarize, these results indicate that Beclin- 1- independent autophagy was triggered in SGC7901 cells exposed to resveratrol via enhanced LC3- II formation and p62 accumulation, and AKT/mTOR, p38 MAPK/ERK and Wnt/β- catenin pathways were involved in this process.

We demonstrated that ER stress may play a role in resveratrol induced inhibition of gastric cancer cell survival. And resveratrol may inhibit cell migration by affecting the expression of EMT related genes. Resveratrol- treated A549 cells showed decreased viability and increased H19 expression, while BGC823 cells also exhibited a high level of H19 expression and similar reduced viability. Therefore, we chose lncRNA H19 for further investigation of function in resveratrol-treated gastric cancer cells. In addition, phosphorylation of AKT was decreased in cells exposed to the combined treatment. However, there was virtually no increase in β- catenin nuclear translocate induced by 50 μM resveratrol alone or in combination with H19 knockdown, when compared to the control. Overall, the role played by the Wnt/β- catenin pathway in SGC7901 gastric cancer cells should be further determined.

There are still large numbers of natural compounds that are far from being applied in a clinical setting. Demonstration of an ability to regulate genetic and epigenetic factors would strengthen the case for using such compounds in cancer therapy. Results from the present study showed that H19 was over- expressed at low concentration of resveratrol and downregulated at high concentrations. Silencing of H19 has been reported to prevent cell proliferation and migration in lung cancer by reducing methylation of E- cadherin promoter. We therefore wanted to examine the impact of downregulated H19 expression on the anti- tumour effects of resveratrol. In fact, we have previously shown that knockdown of H19 contributes to the increased sensitivity of cancer cells to pterostilbene (a dimethyl ether analog of resveratrol), reducing cell proliferation and invasiveness.

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调控 53BP1-P53 复合物提升紫檀芪抑制肺癌侵袭转移研究

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Summary. *Pterostilbene is a natural resveratrol dimethylated analogue that has anticancer effects against a variety of cancers. It has better and oral absorption than resveratrol. In this paper, the molecular mechanism of p53-53BP1 complex regulating pterostilbene on the proliferation of lung cancer cells was elaborated from the aspects of the regulatory mechanism of pterostilbene on lung cancer cells.*

Human beings have made certain progress in the fight against cancer, but the cancer prevention and treatment mechanism is still in the stage of gradually being cracked and improved. Pterostilbene is a natural resveratrol dimethylated analogue that has pleiopotent anticancer effects on a variety of cancer types, and has better lipophilicity and oral absorption than resveratrol, with higher cellular absorption, and longer half-life. The initiation of programmed cell death (PCD) is a key regulatory link for a variety of anticancer drugs, which involve two main types, apoptosis and autophagy. p53 accumulation is caused by phosphorylation (p-)AKT-mediated reduction in phosphorylation of specific MDM2. Once MDM2 is phosphorylated by p-Akt, p-MDM2 translocates to the nucleus and promotes ubiquitination of the target protein. MDM2 regulates the physiological level and function of p53 in normal cells through a continuous process of monoubiquitination.

The 53BP1 gene, located on chromosomes 15q15-q21, produces tumor suppressor p53-binding protein 1 (53BP1 protein), which interacts with the DNA-binding core domain of tumor suppressor p53 and enhances p53-mediated transcriptional activation. 53BP1 promotes non-homologous end-joining (NHEJ)-mediated DSB repair and prevents HR by counteracting BRCA1's function in homologous recombination (HR). This project intends to mine relevant databases through bioinformatics technology to analyze the target information of pterostilbene affecting the biological functions of lung cancer cell A549 cell line. A549 cells were treated with different concentrations of pterostilbene at different times, and cell proliferation was measured by CCK8 method. After that, soft agar experiment was used to further determine the proliferation of pterostilbene treated cells to explore the regulatory effect of 53BP1-p53 complex on pterostilbene and its role in