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MAGNESIUM-ASSISTED CISPLATIN INHIBITS BLADDER CANCER CELL SURVIVAL BY MODULATING WNT/B-CATENIN SIGNALING PATHWAY

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Summary. *Magnesium plays a role in the activation of various transporters and enzymes. The present study aimed to investigate the possibility of applying magnesium to enhance the eficacy of cisplatin which is still ranked as one of the major chemotherapeutic drugs for bladder cancer patients. Our indings reveal that magnesium could contribute to cisplatin-based chemotherapy bymoderately regulating the Wnt/β-catenin signaling pathway*.

Bladder cancer is the most frequently diagnose durinary system malignancy with a nestimated 573,278 new cases and 212,536 deaths worldwide in 2020. Although great advances have been made in the management of bladder cancer, there are still undefined molecular mechanisms that inluence the therapeutic outcomes of this disease.

Over the past few decades, cisplatin has been one of the most widely used first-line chemotherapeutic drugs for the treatment of various solid tumors, including lung, ovarian and bladder cancer. Despite positive clinical outcomes, substantial side effects or drug resistance development have been reported in many studies of cisplatin monotherapy. Alternatively, platinum-based combination chemotherapy is considered the preferred initial therapy for bladder cancer. The action of magnesium as an essential mineral micronutrient may lead to it playing a unique role in both cancer development and therapy.

The Wnt/β-catenin signaling pathway is a canonical pathway of signal transduction in physiological and pathological processes. This signaling pathway is intimately associated with various biological processes, including embryonic development, proliferation, apoptosis, and cell cycle distribution. The aberrant regulation of the Wnt/β-catenin cascade leads to the development and progression of cancer. Wnt signaling is controlled by various secreted Wnt glycoproteins that function via autocrine and paracrine pathways in mammalian cells. Aberrations in Wnt/β-catenin signaling are shown to be closely associated with bladder carcinogenesis. Thus, regulating Wnt/β-catenin signaling could contribute to cisplatin-based cancer therapy in the context of adjusting magnesium abundance.

Combination therapy of cisplatin with other drugs is emerging as a promising means to overcome drug resistance and attenuate cytotoxicity. The present study confirmed that cisplatin could inhibit cell proliferation in both UC3 and UC5 bladder cancer cells. In addition, both MgCl2 and MgSO4 was found to strengthen the inhibitory effect of cisplatin on the survival rate of bladder cancer cells, suggesting that magnesium could play an important role in cancer treatment.

Programmed cell death, including apoptosis and autophagy, is closely involved in oncogenesis and metastasis. Therefore, deciphering the signaling pathways underlying programmed cell death could aid the development of novel targeted antitumor therapeutic strategies. In this study, the results of the annexin V-FITC and PI staining indicated that the proportion of apoptotic and necrotic cells in cisplatin-treated cells was increased by MgCl2 treatment. In addition, the ratio of Bax/Bcl-2 was also the highest in cells that received combinatorial treatment with MgCl2 and cisplatin among the examined groups, further confirming the enhanced pro-apoptotic role of combinatorial treatment. Bax is a pro-apoptotic protein and Bcl-2 is an anti-apoptotic protein. It has been recognized that

high ratios of Bcl-2/Bax often lead to poor outcomes with decreased rates of complete remission and low overall survival in cancer patients. Additionally, the modulation of Bcl-2 and Bax family proteins using compounds has broad implications in cancer therapy. In this respect, magnesium may be conducive to strengthening the clinical usage of cisplatin. Certainly, the different forms of programmed cell death would jointly determine the fate of cancer cells. Autophagy is an evolutionary physiological mechanism that maintains cellular homeostasis in cells and may mediate autophagic cell death during development and pathogenesis. Growing evidence suggests that crosstalk between apoptosis and autophagy acts as a pivotal factor in cell fate determination. The results of this study showed that combinatorial treatment with cisplatin and MgCl2 promoted LC3-II expression, suggesting that autophagy had been induced.

Wnt/β-catenin signaling is suggested as one of the main driving factors ofvarious types of cancer. The results ofthe present study revealed that the decreased nuclear β-catenin could be further downregulated by combinatorial treatment with cisplatin and MgCl2. In addition, the expression of Wnt5a and c-Myc phosphorylation were also decreased in the combinatorial treatment group, further confirming that the Wnt/β-catenin signaling pathway was largely inhibited. Given its role signaling pathway in the initiation and progression of cancer, the Wnt/β-catenin signaling pathway is still being explored as a target for cancer therapy. In recent decades, several inhibitors, agonists, and antagonists have been developed to target this signaling cascade. BIO, a potent inhibitor of GSK3β that activates the Wnt/ β-catenin signaling pathway, is found to reduce cisplatin nephrotoxicity without compromising its anti-proliferation function. In this study, BIO treatment was showed to reduce the survival rate of UC3 cells and strengthen the inhibitory effect of MgCl2 on cell proliferation. In this study, activation of Wnt/β-catenin signaling by BIO could also promote the induction of autophagy.

MgCl2 can enhance the inhibitory effect of cisplatin on bladder cancer in many ways, including reducing cell activity, inhibiting cell proliferation, inducing apoptosis, interfering with cell cycle, and intensifying endoplasmic reticulum stress.

Magnesium can be properly adjusted by Wnt/β-Catenin signaling pathway is involved in cisplatin based chemotherapy. Moderate activation of Wnt/β-Catenin signal pathway can enhance the therapeutic effect, and how to precisely regulate it is worth further exploring.

In this study, activation of Wnt/β-catenin signaling by BIO could also promote the induction of autophagy. However, it should be noted that the expression of β-catenin was lower in cells that underwent combinatorial treatment with BIO and MgCl2 than in cells treated with BIO alone. Combined with the results showing that the expression of β-catenin was lower in cells treated with cisplatin alone, MgCl2 alone, and the combination thereof than in the control group, this possibly indicates that Wnt/β-catenin signaling contributes maximally to cancer therapy only when moderately activated. Therefore, the precise regulation of the Wnt/β-catenin signaling pathway to enhance magnesium based-cancer therapy should be exploited in future research.

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食品微生物检测样品保存装置

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Summary. *The utility model discloses a food microorganism detection sample storage device, which comprises a box body, wherein a fixing mechanism is installed inside the box body, and a turntable groove for fixing the sample is innovatively designed, which can cool evenly, avoid damaging the container during transportation, and solve the problem of the existing device, thus ensuring the quality of the sample.*