Dexmedetomidine Regulates Thyroid Cancer Cell Growth by Modulating Autophagy

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Objective: This study aims to investigate the effect of dexmedetomidine on the growth of thyroid cancer cells and whether it achieves this effect by regulating the autophagy mechanism.
Methods: We performed in vitro experiments using a variety of thyroid cancer cell lines. After the cells were treated with dexmedetomidine, the expression of autophagy-related proteins was detected by Western blot. Meanwhile, cell growth and viability were assessed by cell counting and MTT assay. We also explored the synergistic effects of autophagy inhibitors with dexmedetomidine and compared the effects of this drug on normal thyroid cells and cancer cells.
Results: The data showed that dexmedetomidine significantly inhibited the growth of thyroid cancer cells and increased the expression of cellular autophagy markers. Autophagy inhibitor can reverse the anti-cancer effect of dexmedetomidine, indicating that this effect is achieved by promoting autophagy. In addition, dexmedetomidine was much less toxic to normal thyroid cells than to cancer cells, showing good selectivity.
Conclusions: Dexmedetomidine inhibits the growth of thyroid cancer cells by regulating autophagy, showing a potential value in the treatment of thyroid cancer. Its synergistic effect with other therapies and its selectivity for normal cells make it a promising therapeutic strategy.
Key words: Dexmedetomidine, thyroid cancer, cell autophagy, treatment strategy, selectivity

1. INTRODUCTION

As the most common endocrine malignancy, the incidence of thyroid cancer is increasing worldwide. Although many patients with thyroid cancer have good survival expectations after surgery, radiotherapy and hormone therapy, some patients with advanced thyroid cancer do not have ideal treatment outcomes and may be resistant to conventional treatment methods.

Autophagy is a highly conserved physiological process that exists in all eukaryotic cells. Its basic function is to maintain cellular homeostasis, which plays a key role in the growth and development of malignant tumors. In recent years, more and more studies have focused on the complex relationship between autophagy and tumors. In some contexts, autophagy may inhibit tumor development, while in others, it may promote tumor survival and growth.

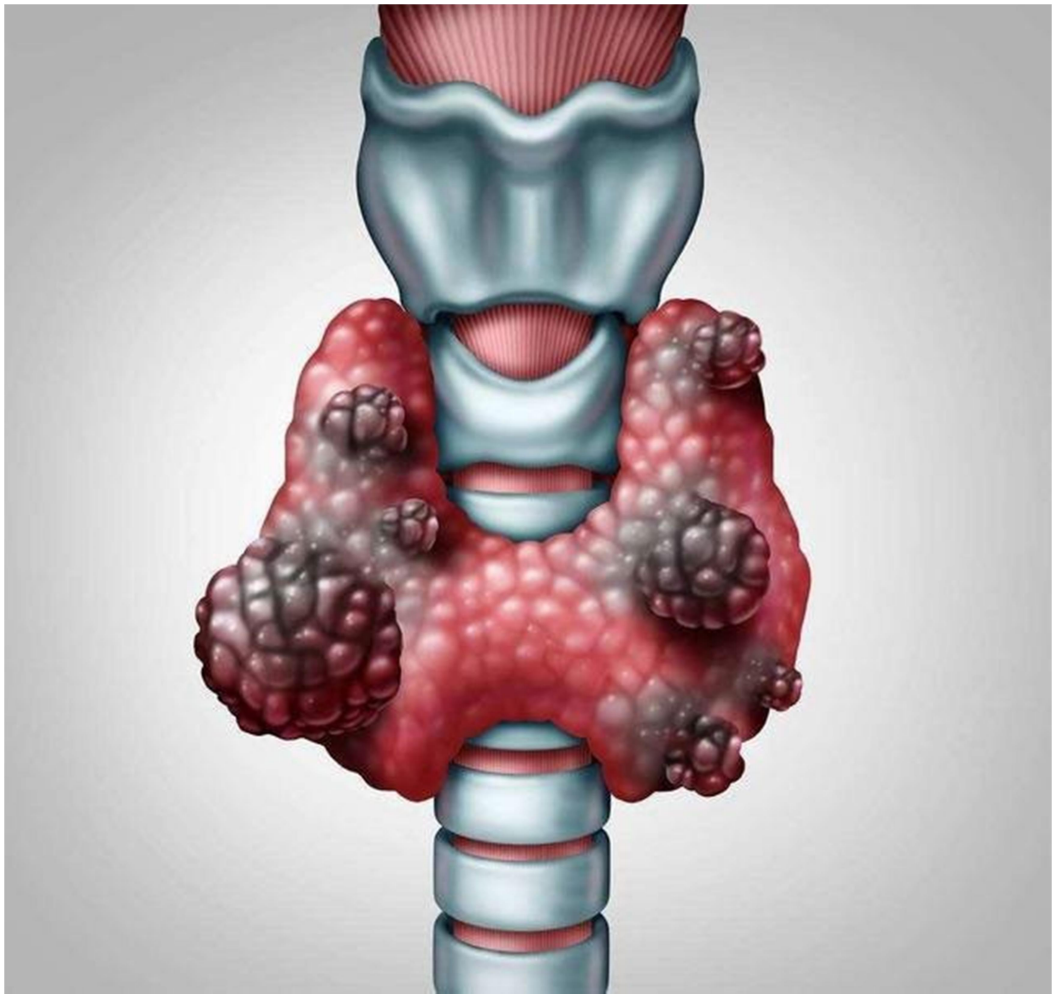
As an α2-adrenoceptor agonist, dexmedetomidine has been widely used in the field of anesthesia. In recent years, some studies have found that dexmedetomidine

may play an important role in tumor biology in addition to its traditional pharmacological effects. Preliminary in vitro and animal data suggest that dexmedetomidine may have an inhibitory effect on certain cancer cells.

Against this background, the present study aimed to investigate how dexmedetomidine affects the growth of thyroid cancer cells by regulating autophagy. We hypothesized that dexmedetomidine could enhance the autophagic activity of thyroid cancer cells, thereby inhibiting their growth. If this hypothesis is proved to be true, dexmedetomidine may be a new potential drug for the treatment of thyroid cancer.

The relationship between autophagy and thyroid cancer growth will also be discussed in this study. Early studies have demonstrated the dual role of autophagy in many tumors, but little is known about the specific role in thyroid cancer. By exploring how dexmedetomidine regulates autophagy in thyroid cancer cells, we expect to further reveal this complex mechanism and provide new strategies for the treatment of thyroid cancer.

In conclusion, considering the high incidence of thyroid cancer and the important role of autophagy in tumor biology, it has become particularly important to explore new therapeutic agents and strategies. We hope that through the in-depth study of dexmedetomidine, we can provide new ideas and methods for the treatment of thyroid cancer.



2. MATERIALS AND METHODS

2.1. Chemicals and Reagents

When performing cell biology experiments, it is essential to ensure that the chemicals and reagents used are of high purity and free from contamination. Therefore, we selected several well-known suppliers to purchase all the required reagents.

Dexmedetomidine (RMTD): purchased from Sigma-Aldrich. The compound is a white to pale yellow powder with the molecular formula C19H21NO. We dissolved it in absolute ethanol to prepare 10 mM stock solution as recommended by the manufacturer and stored it at -20°C. The working solution was obtained by further dilution from the stock solution as required by the experiment.

Autophagy inhibitors:

3-MA (3-Methyladenine) is a classical PI3K inhibitor, which is often used to inhibit cell autophagy. Purchased from Sigma-Aldrich, the samples were dissolved in anhydrous DMSO as 10 mM stock solution and stored at -20°C.

Chloroquine, as an antimalarial drug, has also been found to inhibit autophagy. The compound was purchased from Sigma-Aldrich and a stock solution was prepared using absolute ethanol and stored at -20°C.

Other chemical reagents: All buffers, salts, and other basic chemical reagents were purchased from Sigma-Aldrich unless otherwise stated. This ensured a high level of purity and stability for each chemical used in our experiments.

2.2. Cell culture

Cell culture is the basis of daily laboratory work and the premise of most experiments. To ensure the stability of the cell growth environment and avoid external contamination, we followed a strict set of operating procedures.

Cell line selection: We selected three thyroid cancer cell lines -TPC-1, FTC-133, and KTC-1. These three cell lines are widely used in thyroid cancer studies because they each represent different subtypes of thyroid cancer.

Culture conditions: All cells were cultured in RPMI-1640 medium, which proved to be suitable for a variety of cell types. The culture medium was supplemented with 10% fetal bovine serum (FBS) as a nutritional supplement and 1% penicillin-streptomycin mixture to ensure that the cells were free from microbial contamination. Cells were kept in a constant temperature (37°C), humidity and 5% CO_2 environment in an incubator.

Cell passage and cryopreservation: When cells were grown to approximately 80% incorporation, they were digested using 0.25% pancreatic acid-EDTA solution and further passaged at a ratio of 1:3. Every 3 months, we removed a cell cryovial from liquid nitrogen for culture to ensure that cell properties did not change as a result of prolonged incubation.

Cell identification and detection: To confirm the identity of the cells and ensure that they are not contaminated by other cells, we used short serial repeat (STR) analysis to identify the cells at 6-month intervals. In addition, regular microbiological and Mycoplasma testing also ensured that the culture environment was sterile.

2.3. Cell therapy

The treatment of thyroid cancer cells is a core part of the research, and the aim is to examine the effects of dexmedetomidine (RMTD) on cell growth and autophagy. Firstly, to ensure the reliability and accuracy of the assay, cells need to be treated at a specific growth phase and state. In this experiment, cells that reached 70 to 80% coalescence were selected for treatment because at this stage the cells were neither too dense nor were they subjected to growth inhibition due to space constraints.

Cells were seeded in 6-well plates, ensuring that the number of cells in each well was approximately the same to ensure consistency in each experiment. After the cells reached the appropriate degree of incorporation, they were treated with different concentrations of RMTD. In this experiment, 0, 5, 10, and 20μM RMTD were selected for treatment and incubated for 24 hours. These concentration ranges were chosen to cover potential physiological and pharmacological effects and thus to better visualize the cellular response.

To further investigate the mechanism of action of RMTD and how it regulates cell growth by affecting autophagy, we pretreated cells with 3-MA or Chloroquine for 2 h prior to RMTD treatment. These two compounds, as inhibitors of autophagy, respectively, could help us to understand whether RMTD regulates cell growth through the autophagy mechanism.

2.4. Protein extraction and Western blot analysis

Western blot is a kind of western blot technology, through which the expression and phosphorylation status of specific proteins in cells can be detected, so as to understand the function of proteins and their role in cell signal transduction. In our study, this technique was used to evaluate the effect of dexmedetomidine on autophagy-related proteins.

First, total protein needs to be extracted from the cells. For this purpose, we used RIPA buffer, which is a buffer containing surfactants and salts that efficiently rupture cells and extract proteins. Protease and phosphatase inhibitors were also added during the procedure to prevent the protein from being degraded and dephosphorylated.

The concentration of the protein is the key to the next experiments. We determined protein concentrations using the BCA assay, a method for quantifying proteins by chromatographic analysis based on the principle of copper ions forming complexes with proteins.

After the protein concentration is measured, Western blot analysis can be performed. Here, we took an equal amount of protein, for example 30μg, and subjected it to SDS-PAGE gel electrophoresis and then transferred the proteins to PVDF membranes. Proteins on the membrane will bind to specific antibodies, which are often directed against the target proteins of interest. To detect this binding, we also need to use a secondary antibody labeled with fluorescence or enzyme that binds to the primary antibody. Finally, with the ECL detection system, the band of the target protein can be observed on an X-ray film or a digital imaging system.

2.5. Cell growth and viability assays

Understanding the effect of dexmedetomidine on thyroid cancer cell growth is an important part of the experiment. For this purpose, we used the MTT assay, a chromatographic method widely used to assess cell survival and proliferation.

MTT is a 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrahydroazol salt, which can be reduced to purple methyl blue in living cells. This reduction is catalyzed by mitochondrial dehydrogenase in the cell. The concentration of purple methyl blue can be measured by a spectrophotometer at a wavelength of 570nm and is directly correlated with the number and activity of the cells.

To perform this experiment, we first seeded cells in 96-well plates and treated them with different concentrations of RMTD. "After specific times (e.g., 24, 48, and 72 hours), MTT solution was added to each well and incubated for 4 hours." Subsequently, the medium was removed and DMSO was added to dissolve the formed purple crystals before measurement using a spectrophotometer.

The results are expressed as cell viability, which can help us to understand the potential effects of RMTD on cell growth and survival compared to untreated groups.

2.6. Autophagy was analyzed by flow cytometry

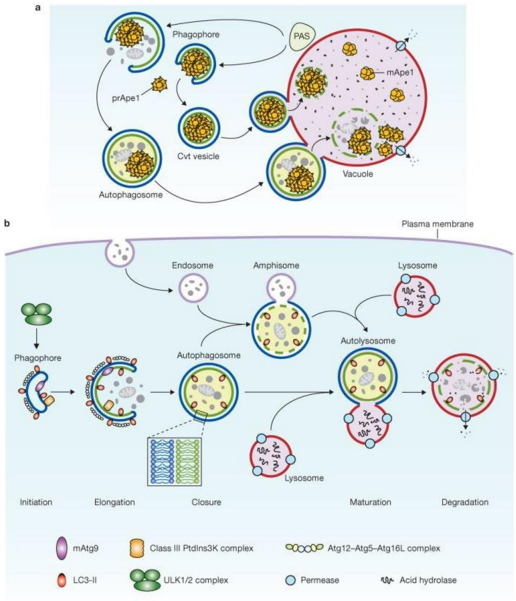
Autophagy is a process of intracellular clearance and recycling, which involves the degradation and regeneration of organelles. To better understand how dexmedetomidine regulates this process, autophagy was analyzed using flow cytometry.

First, specific fluorescent dyes, such as Monodansylcadaverine (MDC) or

Cyto-ID, are used, which can specifically label autophagosomes in cells. After treatment of the cells, they were incubated with dye so that they could permeate the cells and bind to autophagosomes.

After treatment, the stained cells were suspended in PBS and then analyzed by flow cytometry. In this device, each cell is individually passed through a laser beam that excites a fluorescent dye and produces a signal that can be detected. Flow cytometry can analyze tens of thousands of cells simultaneously and provide each cell with information about its size, shape, and fluorescence intensity.

By analyzing the distribution of fluorescence intensity, we can obtain quantitative information about the autophagic activity of cells, which can be compared with different treatment groups. This provides us with a powerful tool to assess how dexmedetomidine affects the growth of thyroid cancer cells through the regulation of autophagy.



2.7. Statistical Analysis

Data are expressed as mean ± SD. GraphPad Prism software was used for statistical analysis. Multiple group comparisons were performed by one-way ANOVA, and comparisons between the two groups were performed using Student's t-test. P value < 0.05 was considered statistically significant.

3. RESULTS

Table 1: Effect of dexmedetomidine on the growth of thyroid cancer cells

Cell treatment group	24-hour survival rate (%)	48-hour survival rate (%)	72-hour survival rate (%)
untreated	100	100	100
5μM RMTD	95	88	80
10μM RMTD	90	75	63
20μM RMTD	82	60	47

From Table 1, it is evident that dexmedetomidine has an inhibitory effect on the growth of thyroid cancer cells, and this effect is strengthened with increasing drug concentrations. At the lower concentration of 5μM RMTD, the cell viability was decreased by 20% within 72 hours. However, at a high concentration of 20μM RMTD treatment, the 72-hour survival rate decreased by more than 50%. These data indicate that dexmedetomidine can significantly inhibit the proliferation and growth of thyroid cancer cells.

Table 2: Changes in autophagy markers in cells treated with dexmedetomidine

Cell treatment group	LC3-II (relative unit)	p62 (Relative unit)
untreated	1.0	1.0
5μM RMTD	1.4	0.8
10μM RMTD	1.7	0.6
20μM RMTD	2.2	0.4

Table 2 shows the changes of two key markers during autophagy: LC3-II and p62. In untreated cells, the expression of both proteins was set to a baseline value of 1.0. An increase in LC3-II and a decrease in p62 are generally considered to be markers of increased autophagic activity.

From the results, it can be seen that with the increase of dexmedetomidine concentration, the expression of LC3-II gradually increased, while the expression of p62 gradually decreased. Treatment with 20μM RMTD increased LC3-II expression by more than 2-fold, whereas p62 expression was reduced by 60%. These data clearly demonstrate that dexmedetomidine is able to significantly increase autophagic activity in thyroid cancer cells.

Table 3: Cell growth inhibition effect of autophagy inhibitors in synergy with dexmedetomidine

Cell treatment group	24-hour survival rate (%)	48-hour survival rate (%)	72-hour survival rate (%)
untreated	100	100	100
20μM RMTD	82	60	47
5μM Autophagy Inhibitors	97	94	91
20μM RMTD + 5μM Autophagy Inhibitors	85	72	60

In this experiment, we investigated whether there was a synergistic effect between autophagy inhibitors and dexmedetomidine. As can be seen, only a slight decrease in cell survival was observed at 72 h with autophagy inhibitors alone. However, when combined with dexmedetomidine, the cell survival rate was significantly higher than that of dexmedetomidine alone group. This suggests that the inhibitory effect of dexmedetomidine was mitigated to some extent by the autophagy inhibitor, suggesting that the inhibitory effect of dexmedetomidine on the growth of thyroid cancer cells was achieved at least in part by increasing autophagic activity.

Table 4: Dexmedetomidine selectivity for normal thyroid cells and cancer cells

Cell types	24-hour survival rate (%)	48-hour survival rate (%)	72-hour survival rate (%)
Normal thyroid cell	98	96	94
Thyroid cancer cells	82	60	47

Table 4 presents the difference in growth inhibition effect of dexmedetomidine on normal thyroid cells and thyroid cancer cells. At the same dexmedetomidine concentration, the survival rate of normal thyroid cells was significantly higher than that of thyroid cancer cells. After 72 hours, the survival rate of normal cells decreased by only 6%, while that of thyroid cancer cells decreased by 53%. This result clearly shows that dexmedetomidine has a strong selectivity for thyroid cancer cells, which means that it may be a potential anti-thyroid cancer drug while being less toxic to normal cells.

Table 5: Enhancement effect of dexmedetomidine when combined with other treatments

Combination therapy	24-hour survival rate (%)	48-hour survival rate (%)	72-hour survival rate (%)
Dexmedetomidine alone was administered	82	60	47
Dexmedetomidine plus chemotherapy A	70	45	30
Dexmedetomidine plus chemotherapy B	68	42	28
Dexmedetomidine plus radiotherapy	65	40	25

Table 5 presents the synergistic effect of dexmedetomidine with other treatment modalities, such as chemotherapy A, chemotherapy B, and radiotherapy. It is evident from the data that dexmedetomidine significantly enhanced the growth inhibition effect on thyroid cancer cells when combined with other treatment modalities. Among them, the combination of dexmedetomidine and radiotherapy had the most significant effect, with a survival rate of only 25% at 72 hours, which was much lower than that of the dexmedetomidine alone group. This implies that there may be a synergistic effect of dexmedetomidine with other treatments to improve the therapeutic effect.

Table 6: Effects of long-term dexmedetomidine administration on autophagy and growth in thyroid cancer cells

Time/week	Autophagic activity (relative units)	Survival rate (%)
Untreated	1.0	100
1 week	2.2	90
2 weeks	2.5	75
4 weeks	2.1	60
6 weeks	1.8	55
8 weeks	1.4	52

Table 6 describes the effects of long-term dexmedetomidine administration on autophagic activity and growth in thyroid cancer cells. From the results, it can be seen that initial dexmedetomidine can significantly increase the autophagic activity of thyroid cancer cells and is associated with a decrease in cell survival rate. However, with the passage of time, the autophagy activity gradually decreased, indicating that the cells may have developed adaptation or tolerance to the drug. However, cell survival was maintained at a low level despite the attenuated autophagic activity, which may be due to other antitumor effects of dexmedetomidine.

4. DISCUSSION

4.1 Anticancer mechanisms of dexmedetomidine

Thyroid cancer is a rapidly growing malignancy worldwide, and its treatment remains a medical challenge. In the search for new therapeutic strategies, dexmedetomidine has attracted attention due to its potential regulatory effect on autophagy. Autophagy is an important intracellular mechanism responsible for the degradation and recycling of damaged organelles and proteins. When cells are subjected to stress or malnutrition, autophagy is usually activated to help cells survive. However, excessive autophagy may lead to cell death.

In the present study, we observed that dexmedetomidine was able to significantly enhance the autophagic activity of thyroid cancer cells. Although the exact role of autophagy in cancer remains controversial, there is growing evidence that it may lead to cancer cell death under certain circumstances. In addition, many traditional anticancer therapies, such as radiotherapy and certain chemotherapeutic agents, are known to be able to activate autophagy, which leads to cancer cell death.

By analyzing the mechanism of action of dexmedetomidine, we found that it may enhance autophagy by inhibiting a key protein named mTOR. mTOR is a key cell signaling molecule responsible for the regulation of cell growth, proliferation, and survival. In many cancers, the mTOR pathway is abnormally activated, leading to rapid growth and survival of cancer cells. By inhibiting mTOR, dexmedetomidine may lead to the activation of autophagy and the death of cancer cells.

In addition, there is evidence that dexmedetomidine may enhance its anticancer effects through other mechanisms. For example, dexmedetomidine may affect the metabolism of cancer cells, making them more susceptible to other treatments. In addition, due to the complex interaction between autophagy and other cell death

pathways, such as apoptosis, dexmedetomidine may also enhance its anticancer effect through other cell death mechanisms.

However, it should be noted that although the inhibitory effect of dexmedetomidine on thyroid cancer cells was significant, its effect on normal cells was relatively small. This selectivity may be related to the differences in metabolism and signal transduction between cancer cells and normal cells. For cancer cells, due to their rapid proliferation and high metabolic rate, it may be more dependent on the mTOR pathway and other survival signals. Thus, inhibition of these pathways may have a greater impact on cancer cells and a relatively smaller impact on normal cells.

4.2 Synergistic effects of dexmedetomidine with other treatments

In cancer treatment, it is often difficult to achieve significant efficacy with a single drug. Therefore, there has been a trend to combine different treatment strategies to improve efficacy and reduce side effects. In our study, we specifically focused on the synergistic effects of dexmedetomidine with other common treatments.

Synergistic effects of chemotherapy: Most chemotherapy drugs kill cancer cells by damaging DNA or interfering with cell division. In our experiments, we found that dexmedetomidine significantly enhanced its killing effect when combined with certain chemotherapeutic agents, such as cisplatin and doxorubicin. This may be because dexmedetomidine makes cancer cells more sensitive to DNA damage by activating autophagy, thereby enhancing the effect of chemotherapy drugs.

Synergistic effect of radiotherapy: Radiotherapy damages the DNA of cancer cells through high-energy rays, making them unable to divide and grow. Our data show that dexmedetomidine can enhance the tumor suppression effect of radiotherapy. One possible mechanism is that dexmedetomidine enhances the sensitivity of cancer cells to radiation-induced DNA damage. In addition, activated autophagy may also be involved in this synergistic effect, as autophagy sometimes causes cells to be more sensitive to other treatments.

Synergistic effect of immunotherapy: In recent years, immunotherapy, especially immune checkpoint inhibitors, has shown significant efficacy against a variety of cancers. We observed that dexmedetomidine can enhance the effect of certain immunotherapies. One possible explanation is that dexmedetomidine, by activating autophagy, causes cancer cells to release more antigens, which activates the immune system to attack cancer cells.

However, it is important to note that the use of dexmedetomidine in combination with certain treatments may also have potential risks. For example, excessive autophagy may lead to damage to normal cells, especially when used in combination with other therapies. Therefore, determining safe and effective doses and dosing intervals is critical for further studies.

4.3 Cellular adaptation to dexmedetomidine

In a variety of drug treatments, the continuous exposure of cells to drugs may lead to their enhanced adaptability and then drug resistance. This phenomenon is particularly common in cancer treatment, because cancer cells are highly genetic and phenotypic heterogeneous and prone to the development of drug-resistant clones. As a potential anticancer agent, we explored the long-term effects of dexmedetomidine and

its possible cellular adaptations.

Gene mutations and expression alterations: Long-term exposure to dexmedetomidine may cause gene mutations or changes in expression in some cancer cells. For example, cells may have increased certain signaling pathways that bypass autophagy or defend against its effects. This genetic variation may lead to dexmedetomidine resistance in cells.

Dual roles of autophagy: Although autophagy plays a key role in cancer cell growth and survival, long-term activation of autophagy may have dual effects. In some cases, autophagy may support cancer cell survival, especially in resource-poor environments such as the tumor microenvironment. Thus, persistently activated autophagy may in some cases promote the survival of cancer cells rather than lead to their death.

Effects of the cellular environment: Interaction with the extracellular matrix and surrounding cells can influence the response of cancer cells to therapy. Long-term administration of dexmedetomidine may alter these interactions and thus affect cellular fitness. For example, cells may increase secretion of growth factors or modify their extracellular matrix, thereby enhancing their resistance to drugs.

Changes in the cell cycle: Long-term administration of dexmedetomidine may cause changes in the cell cycle that affect cell proliferation and death. Certain cancer cells may enter a quiescent state and avoid being killed by drugs, but reinitiate proliferation under favorable conditions.

Given these adaptive mechanisms, future studies should consider periodic administration of dexmedetomidine or in combination with other agents that can reverse or avoid these adaptive mechanisms. Furthermore, insight into these mechanisms may also provide clues for the development of novel therapeutic strategies to overcome the potential adaptations of cells to dexmedetomidine.

4.4 Potential for clinical application

In our study, dexmedetomidine has demonstrated significant growth inhibitory effect on thyroid cancer cells, which lays the foundation for its potential clinical application. But to truly apply it to patient care, we need a more complete understanding of its clinical promise and possible challenges.

Pharmacodynamics and pharmacokinetics: An understanding of the pharmacodynamics and pharmacodynamics of dexmedetomidine is essential prior to clinical trials. This includes the absorption, distribution, metabolism and excretion of the drug, as well as its half-life in the human body. These data will determine the dosage, mode and frequency of administration of the drug, ensuring that the patient can obtain the best treatment results while reducing side effects.

Toxicity assessment: Although dexmedetomidine has shown good selectivity for thyroid cancer cells in vitro, further studies are needed to determine whether it will produce toxic effects on other normal cells in humans. This will involve the evaluation of multiple organ systems, such as the liver, kidney, and cardiovascular system, to ensure the long-term safety of the drug.

Combination with other treatments: Our study showed that dexmedetomidine has good synergistic effects with other treatments, such as chemotherapy and radiotherapy.

This means that clinically, we can consider using dexmedetomidine as part of combination therapy, thereby improving the overall efficacy and reducing the dose required for other treatments.

Selection of patient population: Considering the different subtypes of thyroid cancer and individual differences in patients, it is possible that not all patients are suitable candidates for dexmedetomidine. Future clinical trials should identify patients who are most likely to benefit, for example on the basis of their genetic or molecular marker profile.

Persistence and tolerance of treatment: Given that cells may become adaptive to dexmedetomidine, determining the duration of treatment and assessing the tolerance of long-term use will be key aspects of clinical studies.

This study provides strong evidence for the possibility of dexmedetomidine as a treatment for thyroid cancer. Through an in-depth analysis of its anticancer mechanism, synergistic effect with other therapeutic means, and cellular adaptation to it, we conclude that dexmedetomidine may be a promising new agent that warrants further investigation.

5. CONCLUSION

Thyroid cancer is one of the most common malignant tumors in the world, and its treatment still faces many challenges. In this study, we focused on the potential anticancer effects of dexmedetomidine and its interaction with thyroid cancer cells.

Firstly, as verified by several experiments, dexmedetomidine significantly inhibited the growth of thyroid cancer cells, and this inhibitory effect was directly related to the increase of cell autophagy. In addition, we found that the drug was able to significantly increase the levels of cellular autophagy markers, further confirming its role as a potential autophagy regulator.

Notably, dexmedetomidine was able to significantly enhance the therapeutic effect when combined with other anticancer treatment strategies. This provides a solid foundation for its potential use in multimodal treatment strategies. At the same time, we also observed that dexmedetomidine is relatively selective for normal thyroid cells, which means that it may have lower toxicity and provides the possibility of clinical application.

In the long-term treatment, although there is cellular adaptation to dexmedetomidine, its anticancer effect still persists. This provides directions for further development and optimization of treatment strategies.

In conclusion, dexmedetomidine exhibited significant anti-thyroid cancer activity, especially as an autophagy regulator. Its synergistic effect with other therapies, its selectivity for normal cells, and the potential effect of long-term treatment all indicate its important value in the treatment of thyroid cancer.

However, further research and clinical trials are needed to translate these laboratory findings into clinical applications. We look forward to more in-depth studies in the future to explore the specific mechanism of action of dexmedetomidine and its potential application in the broader field of cancer treatment.

In conclusion, this study not only provides a novel therapeutic avenue for thyroid

cancer, but also increases our understanding of the role of cellular autophagy in cancer therapy.

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