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Review on the Impact of Deubiquitinating Enzyme USP50 on the Degradation and Function of TMEM173

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Abstract: Deubiquitinating enzyme USP50 is involved in the regulation of various biological processes, including the cell cycle, innate immune response, DNA repair, and the regulation of the NF-κB signaling pathway. TMEM173 plays a critical role in antiviral and antitumor immune responses, making the regulation of TMEM173 by USP50 a focal point in the development of antiviral and antitumor drugs. An in-depth investigation into how USP50 affects the degradation and function of TMEM173 is expected to provide strong support for drug development targeting this important pathway and may open up new approaches for antiviral and antitumor therapies. Moreover, the regulatory effect of USP50 on TMEM173 may also be closely related to the pathogenesis of autoimmune diseases. Exploring the role of USP50 in these diseases may offer new insights into treatment strategies for autoimmune conditions.

Keywords: Deubiquitinating enzyme USP50; TMEM173; Degradation; Function

1. Research Background

Previous studies have demonstrated that USP50 plays a role in stabilizing the genome during replication and negatively regulates the G2/M checkpoint in the cell cycle by stabilizing the cell cycle inhibitor kinase Wee1, identifying it as a cell cycle regulator. The TMEM173 gene encodes the Stimulator of Interferon Genes (STING), an important signaling protein that plays a significant role in the innate immune response triggered by double-stranded DNA (dsDNA). The STING protein acts as a receptor for cyclic GMP-AMP synthase (cGAS), which is a key component of the cGAS-STING signaling pathway. This pathway plays a pivotal role in activating antitumor immune responses, and it is closely associated with the progression of liver cancer. The cGAS-STING signaling pathway's importance in the development of liver cancer cannot be understated. So far, there has been no research conducted on the relationship between USP50 and TMEM173. This study is based on the hypothesis that USP50 is a novel regulatory molecule for TMEM173. Using bioinformatics to predict the interaction between USP50 and TMEM173, we aim to validate this interaction through immunoprecipitation experiments. Additionally, we will investigate the impact of USP50 on STING protein at the transcriptional and post-translational modification levels and explore the degradation pathways of STING proteins affected by USP50, providing new insights for studying the role of deubiquitinating enzymes in regulating the cGAS-STING signaling pathway.

2. Research Significance

This project aims to explore the role of USP50 in the human innate immune mechanism, particularly its deubiquitinating effect on TMEM173 (also known as STING, Stimulator of Interferon Genes) and the specific mechanisms by which it regulates the degradation of TMEM173. This research direction goes beyond basic biological exploration and holds profound clinical and applied significance.

Firstly, the innate immune system is a crucial component of the body's initial defense against external pathogens such as viruses and bacteria. TMEM173 is a key regulatory factor in the innate immune response, responsible for sensing intracellular DNA and activating the expression of interferons and other immune factors through various signaling pathways. Therefore, studying how USP50 regulates TMEM173 can help clarify the overall regulatory mechanisms of the innate immune response. By establishing the cooperative role of USP50 in this process, we can gain deeper insights into how immune cells rapidly respond to infections.

Secondly, deubiquitination is an important protein regulatory process within the cell that involves the regulation of protein stability and functionality. As a deubiquitinating enzyme, USP50 may regulate the stability and function of TMEM173 by removing ubiquitin molecules attached to it. Specifically, USP50 might directly interact with TMEM173 to alter its ubiquitination status, thus affecting the degradation rate of TMEM173. Understanding this mechanism will help unveil the complexities of protein modifications in innate immune responses and provide a theoretical basis for research on the regulation of other key immune factors.

Furthermore, understanding the interaction between USP50 and TMEM173 may provide new avenues for the development of antiviral and antitumor drugs. As research on tumor immunotherapy deepens, modulating the function of TMEM173 may become a crucial strategy for enhancing antitumor immune responses. Additionally, the activity of TMEM173 is closely linked to the onset of various autoimmune diseases, thus positioning USP50 as a potential target for the development of novel therapeutic approaches.

In summary, this study is not merely an exploration of the fundamental science of USP50 and TMEM173 but also provides a new perspective for investigating human immune mechanisms. By gaining a comprehensive understanding of this complex regulatory network, we can better understand how the body responds to pathogen invasion and lay a solid foundation for future clinical applications, enhancing our abilities to prevent and treat related diseases. Therefore, this research holds significant importance and potential value at both basic biological and clinical medicine levels.

3. Research status

3.1 Relationship between protein degradation and deubiquitinating enzyme activity

Deubiquitinating enzymes have been found to be able to prevent the recognition and degradation of target proteins by the proteasome by removing the ubiquitin tag from them. For example, UCH37 is part of the 26S proteasome complex, which affects the stability of substrate proteins by regulating their ubiquitination status. And UCH37 overexpression may lead to the abnormal accumulation of certain tumor suppressors or oncogenic proteins, thus promoting the occurrence and development of malignant tumors such as hepatocellular carcinoma.

Current studies have confirmed that ubiquitin C-terminal hydrolases (UCHs) are intracellular deubiquitinating enzymes. The UCH family has four members: UCH-L1, UCH-L3, UCH37 and BRCA1-associated protein-1 (BAP1). protein-1 (BAP1)[1].

3.2 Molecular Mechanisms Explored

A series of advanced techniques (e.g., immunoprecipitation, laser confocal, CRISPR-Cas9 gene editing, and small interfering RNA technology) have been employed by several laboratories to resolve how deubiquitinating enzymes interact with other proteins and affect their deubiquitination process. The most widely used third-generation gene editing technology is clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas), which has been used in the treatment of cancer, cardiovascular disease, sickle cell anemia, and neurodegenerative diseases. anemia and neurodegenerative diseases with impressive potential [3].

3.3 Disease correlation studies

3.3.1 Cancer-related research

Several deubiquitinating enzymes have been identified as potential drug targets because of their key role in tumor progression and drug resistance development. Ubiquitination is a process that covalently attaches ubiquitin proteins to other proteins, whereas deubiquitination is a process that removes ubiquitin molecules from proteins that have been ubiquitinated.[4]

3.3.2 Research in the field of neuroscience

Deubiquitinating enzymes are involved in protein quality control and toxic protein aggregation in a variety of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

Mitochondrial autophagy has been shown to selectively degrade mitochondria and is one of the major pathways of mitochondrial quality control (MQC) [5]. It is triggered by ubiquitin modification of mitochondrial surface proteins and thus mitochondrial autophagy is inhibited by deubiquitination. Deubiquitinating enzymes can affect mitochondrial autophagy in three different ways:

1) by regulating the stability of Parkin

2) by antagonizing Parkin activity

3) by regulating proteasome activity and levels of mitochondrial autophagy

3.3.3 Research in the field of immunology

The field of immunology is concerned with the effects of deubiquitinating enzymes on inflammatory responses, autoimmune diseases and immune cell activation signaling pathways. Deubiquitinating enzymes are one of the important enzymes that regulate intracellular protein degradation and play a key regulatory role in immune responses.

Therefore, the study of deubiquitinating enzymes in the field of immunology not only helps us to better understand the regulation of immune responses, but also provides new ideas and strategies for the treatment of related inflammatory and autoimmune diseases. [7]

3.3.4 Drug Development and Therapeutic Strategies

The design and screening of small molecule inhibitors targeting deubiquitinating enzymes has been a hot direction in drug discovery in recent years. By regulating the activity of specific deubiquitinating enzymes, the normal protein degradation balance can be restored, which is expected to be a novel therapy for the treatment of related diseases.

In recent years, a large number of studies have shown that uncontrolled protein homeostasis plays an important role in the progression of malignant tumors and other diseases. Among them, the abnormal ubiquitin-proteasome pathway is an important factor leading to the uncontrolled protein homeostasis. In this process, deubiquitinating enzymes, which are responsible for removing the ubiquitin chain from protein substrates, are crucial, and their aberrant activity or expression can cause functional changes in key oncogenic/oncogenic proteins, which can directly lead to tumor development and malignant evolution. Based on this, small molecule inhibitors targeting deubiquitinating enzymes have become a hot area for antitumor drug candidates.

4. Summary

USP50 is essential for various biological processes, including cell cycle regulation, innate immunity, DNA repair, and NF-κB signaling. Its role in regulating TMEM173 is critical for antiviral and antitumor immune responses, providing new avenues for drug development. Understanding how USP50 affects TMEM173 may lead to innovative therapies, particularly for autoimmune diseases. Ongoing research into USP50's functions and regulatory networks will inform the development of targeted and effective treatments, advancing both scientific knowledge and clinical applications.

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