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Ubiquitylation in the development of somatic diseases: a mechanism of cellular regulation and a new therapeutic target

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ABSTRACT

At the present stage of medical science, an increasing role in the pathogenesis of various groups of diseases is assigned to the mechanisms of epigenetic regulation and posttranslational modifications of proteins. One of these mechanisms is ubiquitylation, which is able to regulate the functional activity of proteins, their stability, and also influence the processes of cell death. Involvement in a large number of metabolic pathways and presently identified associations with oncological, cardiovascular, neurological, and inflammatory diseases makes ubiquitylation of the enzymes involved a promising target to develop new therapy options. In this review, we consider the effect of ubiquitination on the development of diseases of the cardiovascular, nervous systems, diabetes mellitus, as well as the development of possible treatment options.

Keywords: ubiquitylation; ubiquitin proteases; apoptosis.

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Убиквитилирование в развитии соматических заболеваний: механизм клеточной регуляции и новая терапевтическая мишень

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АННОТАЦИЯ

На современном этапе развития медицинской науки все большая роль в патогенезе различных групп заболеваний отводится механизмам эпигенетического регулирования и посттрансляционным модификациям белков. Одним из таких механизмов является убиквитилирование, которое способно регулировать функциональную активность белков, их стабильность, а также влиять на процессы клеточной гибели. Вовлеченность в большое количество метаболических путей и уже выявленные ассоциации с онкологическими, сердечно-сосудистыми, неврологическими, воспалительными заболеваниями делает убиквитилирование и участвующие в нем ферменты перспективной мишенью для разработки новых вариантов терапии. В данном обзоре мы рассматриваем влияние убиквитинирования на развитие заболеваний сердечно сосудистой, нервной систем, сахарного диабета, а также разработку возможных путей лечения.

Ключевые слова: убиквитилирование; убиквитиновые протеазы; апоптоз.

Как цитировать

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BACKGROUND

Ubiquitylation is a process of posttranslational modification of proteins that leads to covalent binding of a small, highly conserved ubiquitin protein (ubiquitin, Ub) consisting of 76 amino acids with lysine residues of substrate proteins through a cascade of enzymatic reactions [1]. Ubiquitin contains seven lysines (K6, K11, K27, K29, K33, K48 and K63), each of which can be an acceptor of the next ubiquitin molecule. As a result of such additions, there may appear macromolecules labeled with different types of ubiquitin chains, as well as branches of mixed composition [2]. These chain bonds lead to different levels of compaction of the polyubiquitylated chain and can modulate the functional properties of the formed compounds. For example, K11-linked chains, which have some degree of structural flexibility, are involved in mitotic degradation, whereas K63 chains, which have open, linear conformations, are associated with kinase activation. A well-studied type is the very compact K48-linked ubiquitin chain, which serves as a canonical signal for degradation by the proteasome [3, 4].

One of the important functions of ubiquitination is to regulate cell death processes. Cell death pathways have evolved to maintain tissue homeostasis and eliminate potentially harmful cells inside the body. Apoptosis, which is known to destroy cells predominantly in a non-inflammatory way, is controlled by two main branches: the internal and external pathways of apoptosis. While the internal pathway is regulated by members of the Bcl-2 family, the external pathway is controlled by death receptors, members of the tumor necrosis factor (TNF) receptor superfamily. Death receptors can also activate a pro-inflammatory type of cell death, necroptosis, when caspase-8 is inhibited. It is known that the pathways of apoptosis are tightly regulated by posttranslational modifications, especially ubiquitination [5]. It is obvious that ubiquitination plays an important role in the regulation of both apoptotic and necroptotic pathways, elucidation of the mechanisms underlying ubiquitin-mediated control of cell death can provide evidence to develop new treatments for diseases that have impaired cell death pathways, such as cancer, neurological, cardiovascular, autoimmune diseases [6, 7].

Ubiquitination is counteracted by ubiquitin proteases (Ubiquitin-specific proteases, USPs) called deubiquitinating enzymes (DUBs), which remove ubiquitin chains and maintain a cellular pool of free ubiquitin monomer. DUBs are divided into seven subfamilies: ubiquitin-specific proteases/ubiquitin-specific processing proteases, ubiquitin C-terminal hydrolases, ovarian tumor proteases, Machado–Joseph disease protein domain proteases, Jab1/MPN domain, metalloisopeptidase-associated domain proteins, a motif interacting with the Ub-containing new DUB (MINDY) family and ZUFSP/C6orf113 [8]. Ubiquitylation of substrates followed by proteolytic degradation is a unidirectional process involving the physical unfolding and cleavage of protein. However, prior to proteasome treatment, ubiquitin removal can be catalyzed by DUB, preventing proteasome cleavage and leading to protein stability. DUBs are becoming important players in development, and the identification of a growing number of substrates is in the spotlight in a wide variety of systems. They are involved in chromatin regulation, transcription control, and modulation of mitogenic pathways. Their function is often impaired in malignant neoplasms, which leads to stabilization of oncogenic or antiapoptotic factors [9].

In this review, we consider the effect of ubiquitination on the development of somatic diseases, as well as the development of possible ways to correct them.

UBIQUITINATION AND PATHOLOGY OF THE CARDIOVASCULAR SYSTEM

The regulatory role of deubiquitinating enzymes as important regulators of cellular signaling in cardiovascular diseases has become increasingly prominent in recent years. For example, myocardial-specific expression of the deubiquitinating enzyme A20 improves left ventricular function and reduces myocardial hypertrophy caused by myocardial infarction [10], USP4 [11] and USP18 [12] can alleviate hypertension-induced pathological cardiac hypertrophy by direct binding to cytosolic serine/threonine protein kinase (TAK1), USP19 facilitates Dox-induced cardiomyopathy by deubiquitination of receptor-associated factor TNF (TRAF2) and preventing its degradation [13]. One of the important mechanisms in the regulation of which ubiquitination is involved is atherosclerosis, an inflammatory disease that is mainly localized in the walls of arteries, occurs due to the accumulation of low-density lipids (LDL) and lipid proteins. Various cell types are involved in this process, including smooth muscle cells, macrophages, neutrophil granulocytes, and endothelial cells [14]. Existing studies have demonstrated the key role of cryopyrin (NLRP3), interleukin-1β (IL-1β) and TNF in atherosclerosis [15]. Recent studies have highlighted the significant involvement of USP in the progression of atherosclerosis and have shown that USP9X, USP10, USP14, USP17, USP20 and USP36 play a regulatory role in the atherosclerotic process. Macrophages absorb excess lipids, which leads to the proliferation of macrophages and the secretion of inflammatory factors, which causes the formation of foam cells, thereby exacerbating atherosclerosis [16]. This process depends on the activity of receptors, including CD36, SR-A and SR-B1 [17]. Notably, USP9X has been identified as a suppressor of lipid uptake by macrophages, demonstrating lower expression levels in atherosclerosis compared to normal cells. Mechanically, USP9X removes polyubiquitin chains from SR-A63, thereby inhibiting lipid uptake by macrophages, preventing the formation of foam cells and reducing the subsequent inflammatory response [18]. In addition, USP9X, along with USP14 and USP36, promotes the regulation of endothelial cells. Accordingly, in patients with atherosclerosis,

there is a decrease in the level of USP14, and it inhibits the inflammatory response in endothelial cells. This suppression prevents the activity of NF-κB and the degradation of its associated regulatory factors, which are stimulated by oxidized LDL [16]. On the other hand, USP36 promotes the progression of atherosclerosis through the exosomal microRNA-197-3p signaling pathway [19]. In addition, both USP14 and USP36 play a role in the proliferation and mobilization of human aortic smooth muscle cells [20]. USP14 and USP10 can increase foam cell formation by removing ubiquitin from CD36, thereby stabilizing CD36 protein and promoting LDL uptake [21]. Thus, USP14 has demonstrated an effect on endothelium, smooth muscle and foam cells in the development of atherosclerosis. Moreover, USP20 facilitates inflammation in smooth muscle cells in TNF and IL-1β-induced atherosclerosis by deubiquitinating serine/threonine protein kinase (RIPK1), a vital factor in inflammation and cell death [22].

UBIQUITINATION AND DIABETES

Ubiquitination is involved in metabolic regulation, and one of the most significant metabolic pathologies is diabetes mellitus. Diabetes mellitus is a chronic epidemic disease characterized by the presence of high blood glucose levels, which can cause various complications, including diabetic retinopathy, diabetic nephropathy, diabetic neuropathic pain, diabetic foot, diabetic cardiomyopathy and other complications [23–25]. It is classified into type 1 diabetes (DM1) and type 2 diabetes (DM2). Recently, numerous studies have been conducted on USP in diabetes, shedding light on the complex role of USP in this disease. Further study of USP in diabetes may provide insight into new treatment strategies for this disease and related complications.

Type 1 diabetes (DM1) is an autoimmune disease characterized by the attack of T cells on the beta cells of the pancreas, which are responsible for the production of insulin and the regulation of blood glucose levels [26]. Several ubiquitin-specific proteases are involved in the development of DM1. DNA damage is severe in diabetes and exacerbates its development and progression. Suppression of USP1 has been demonstrated to improve diabetes outcomes by inhibiting DNA damage, preventing pancreatic β-cell apoptosis, preserving insulin secretion, and enhancing the maturation of β-cells in human islets [27]. In addition, the CLEC16a-NRDP1-USP8 complex mediates ubiquitin-dependent signaling, which promotes mitophagy and maintains the quality of mitochondria in β cells. This process helps maintain the precise function of beta cells and helps regulate blood glucose levels [28]. McL-1 is one of the Bcl-2 family of antiapoptotic proteins, the number of which decreases in islets in patients with DM1, and USP9X modulates the turnover of McL-1 protein mediated by cytokines to prevent the death of islet cells in β cells [29]. Moreover, a violation of the regulation of USP9X deubiquitinase activity may lead to a decrease in insulin utilization [30]. Dendritic cells controlled by USP18 play a significant role in impaired immune tolerance in autoimmune diabetes. Genetic deletion of USP18 can mitigate the growth of autoreactive $CD8^+$ T cells and provide protection against autoimmune diabetes [31]. In pancreatic β cells, USP18 acts as a crucial modulator of the IFN signaling pathway and three BH3 proteins, which have a significant effect on inflammation and death of β cells. Suppression of USP18 promotes inflammation through STAT signaling and exacerbates IFN-induced beta cell apoptosis due to cell death in mitochondria [32]. Moreover, USP18 reduces the expression of the gene associated with melanoma differentiation (*MDA5*), the candidate gene for DM1, which leads to suppression of the production of double-stranded chemokines induced by RNA and attenuation of the proinflammatory reaction of β cells [33].

Type 2 diabetes (DM2) is characterized by chronic inflammation, activation of immune factors and impaired insulin secretion and sensitivity, which leads to an increase in blood glucose levels [34]. Numerous studies have identified several USPS that play a role in DM2. The study shows that USP2A and USP2 can alter insulin sensitivity, and USP2A blocks insulin resistance caused by obesity through adipocyte-dependent mechanisms [35]. In addition, USP4 reduces the ubiquitination and degradation of insulin receptors, which leads to a decrease in insulin resistance. Gastrodin, a compound derived from Gastrodia elata, is reported to enhance the expression of USP4 and may represent a potentially new targeted treatment for DM2 [36]. However, some USPS can exacerbate DM2. It has been reported that USP7 can delay the negative feedback loop of insulin, which leads to stable insulin signaling by binding to pituitary-specific positive transcription factor (PiT1) and deubiquitination of the insulin receptor substrate [37]. In addition, endoplasmic reticulum (ER) stress plays a significant role in the development of DM2, and sustained ER stress activates USP14 [38]. Knockdown of USP14 reduces ER damage associated with glucose metabolism and improves hyperglycemia and glucose intolerance in obese mice [38]. Moreover, inhibition of USP19 has shown promise in regulating adipogenesis and improving glucose intolerance and obesity caused by a high-fat diet [39]. Subsequently, an increase in postprandial glucose and insulin levels promotes phosphorylation of USP20 [40]. Suppression of USP20 significantly reduces weight gain, serum and liver lipids, and improves insulin sensitivity and energy expenditure [40]. This is achieved by stabilizing HMG-CoA reductase (HMGCR), which serves as an enzyme that limits the rate of cholesterol biosynthesis [40]. In addition, ablation of USP21 in skeletal muscles increases energy consumption by stimulating the phenotype of oxidative fibers, which suppresses obesity and DM2 [41]. In mouse models with DM2, ferroptosis is observed in beta cells of the pancreas [42]. USP22 stabilizes sirtuin-1 (Sirt1) to inhibit HG-induced ferroptosis [42]. In addition, USP33 participates in the deubiquitination of the β2-adrenergic receptor (ADRB2), stimulating insulin sensitivity in skeletal muscles [43].

UBIQUITINATION AND NEUROLOGICAL PATHOLOGY

Ubiquitin molecules are abundantly expressed in neurodegenerative diseases: in the form of neurofibrillary tangles in Alzheimer's disease, Lewy bodies in Parkinson's disease and intranuclear inclusion in hereditary polyglutamine diseases [44–46]. Moreover, ubiquitin controls a variety of neuronal processes, including cell survival, cell fate determination, neuron growth, morphogenesis, synapse development and synaptic functions [47–50]. Ubiquitination of synaptic proteins can be controlled by acute or chronic changes in synaptic activity [51, 52]. Neurological inflammation can be induced by nuclear factor enhancing the kappa-light chain of activated B cells (NF-κB), upon activation of microglia, an active inducer of secondary spinal cord injury. The level of microglia is rigidly maintained in the central nervous system, however, in traumatic conditions, microglia is overly activated, inducing inflammatory cytokines and thereby exacerbating secondary damage and inflammation of neurons. Factor 6, associated with the tumor necrosis factor receptor (TRAF6), is an important adapter protein for NF-κB signaling and plays an important role in inflammation and immune response. In rat microglial cells, USP4 expression decreases after spinal cord injury. USP4 deubiquitinates TRAF6 and inhibits the TRAF6-stimulated NF-κB reporter gene and regulates NF-κB activation [53]. USP4 may be involved in stimulating the activation of microglial inflammation of neurons by deubiquitinating TRAF6 through regulation of the NF-κB signaling pathway [54]. In addition, USP4 is often expressed in glioblastoma tissues and cell lines. When treated with the anti-glioblastoma drug temozolomide, USP4 knockdown cells undergo apoptosis in a p53-dependent manner [55]. Collectively, these reports highlight the dynamic role of USP4 and probably other DUB in the regulation of various neurological pathways and disease pathologies. USP14 is a key DUB involved in maintaining monoubiquitin levels during synapse development, and is indispensable for synapse development and proper functioning of neuromuscular junctions. The loss of USP14 causes defects in the development of motor neurons. In mice with ataxia, Purkinje cells in the cerebellum express GABA-A receptors to a high degree, which undergo proteasome degradation. GABA-A receptors are among the most studied neurotransmitter receptors and contribute to the regulation of various brain functions and related disorders [56]. USP14 interacts with GABA-A receptors and regulates their stability and distribution on the cell surface [57]. Moreover, depletion of USP14 in mice with ataxia leads not only to perinatal mortality, decreased muscle development, structural and functional defects of neuromuscular connections, but also leads to depletion of free ubiquitin in the brain and spinal cord [58, 59]. The dominant-negative catalytic mutant USP14 in the nervous system of mice simulates many defective phenotypes, such as defects in the structure of neuromuscular connections, decreased muscle development and decreased motor activity [60]. However, the restoration of free ubiquitin levels in catalytically inactive USP14 mice causes an improvement in the structure of neuromuscular junctions and a decrease in the accumulation of phosphorylated c-Jun-N-terminal kinase (pJNK) in motor neurons, as well as a negative effect on muscle development and motor functions [60], indicating a crucial role for USP14 in synaptic development and functions.

PROSPECTS FOR THERAPEUTIC INTERVENTION

Over the past decade, treatments focused on the regulation of ubiquitination have shown great promise due to their crucial role in regulating a number of signaling pathways. Among posttranslational regulators, DUB has a number of advantages as therapeutic targets due to its specificity to cell type or substrate. Although DUBs show strong similarities between the cysteine site of the active enzyme and the histidine blocks, some DUB demonstrate critical differences in the availability of the catalytic domain [61]. Thus, the development of DUB-specific inhibitors may become an attractive alternative to develop new therapeutic agents for the treatment of malignant neoplasms, neurodegenerative diseases, metabolic diseases and pathology of the cardiovascular system. To date, several specific DUB inhibitors have been developed, including USP7 and UCH-L1 [61, 62]. Moreover, the findings show that inhibition of USP14 1 by 1-(4-fluorophenyl)-2,5-dimethylpyrrol-3-yl-2-pyrrolidine-1-ylethanone (IU1) increases the degradation of several proteins associated with neurodegenerative diseases [63]. A low molecular weight inhibitor of USP9X, WP1130, has demonstrated antiproliferative properties by inhibiting the growth of glioblastoma cells [64]. Although DUBs are a promising target in neurobiology, pharmacological inhibition of DUBs presents a number of challenges for the scientific community.

DUB activity in cells is specific to target substrates undergoing monoobiquitination or polyubiquitination, which include ubiquitin chains carrying bonds or mixed chains containing ubiquitin and ubiquitin-like proteins [65, 66]. Although proteasome inhibition is an important therapeutic strategy for various disorders related to neurobiology, non-selective inhibition of DUB activity may affect other cellular processes that depend on the 26S proteasome system. Some DUB are involved in the regulation of normal brain function as well as neurodegenerative disorders. For example, the USP14 inhibitor has a significant effect on the regulation of the level of proteins involved in neurodegeneration [63], but is also involved in the development of synapses and plasticity [60, 67]. Similarly, USP8 regulates synapses by deubiquitinating the long isoform of the leptin receptor (LepRb) and multiple domains of ankyrin repeats (SHANK3) [68], but also stabilizes the beta secretase enzyme (BACE1) involved in the development of Alzheimer's disease [69]. Thus, complete or almost complete pharmacological inhibition of DUB to control a neurological condition may have side effects.

USPS affect protein stability and can be regulated by low molecular weight inhibitors. Efforts have been made to develop drugs that meet the criteria for clinical use [70, 71]. For example, QingFeiPaiDu decoction and vogonoside have been reported to reduce USP14 levels, thereby alleviating pneumonia [72]. These compounds have been shown to reduce phosphorylation of transcription activation factor and the NF-κB signaling pathway stimulated by lipopolysocharides [72]. However, due to the complex composition of these compounds, the study of mechanisms is a serious problem [72]. In addition, gastrodin has been shown to increase the expression of USP4 and enhance the interaction between USP4 and insulin receptors in the treatment of diabetes [36]. Gastrodin has also been reported to increase the activity of pancreatic β-cells and stimulate insulin secretion, which ultimately improves the course of diabetes [36].

However, due to the high homology among members of the USP family, achieving specificity of USP inhibitors is a serious problem [73]. This leads to the fact that existing inhibitors lose their specificity and are often unable to act exclusively on one member of the USP, thereby somewhat limiting their usefulness. For example, drugs such as PR619 target a number of enzymes, including USP2, USP4, USP5, USP7, USP8, USP15, USP20, USP28, USP47, UCHL1, UCHL3, UCHL5, which highlights the need to create more selective agents [73]. A striking example is the subsequent USP1 inhibitor ML323, which demonstrates higher specificity compared to previous compounds such as pimozide and GW7647, thereby expanding its scope of application [73]. To achieve increased specificity of inhibitors, it is necessary to carefully consider the chemical structure of USP [73]. Currently, it is extremely important to seek and apply suitable biological testing methods for screening and identification of small molecule inhibitors of USP. Currently, existing methods include high-performance screening, bioinformatic approaches, virtual screening, and so on [74].

Moreover, the variety of pathways and physiological activity regulated by the USP has led to potential toxicity [73]. Deubiquitination practically controls many aspects of human cell biology and physiology, and any defects in these processes can lead to diseases [73]. For example, VLX1570 is an inhibitor of USP14. A clinical trial of VLX1570 in combination with dexamethasone in patients with multiple myeloma was stopped due to pulmonary toxicity [73]. In addition, USP30 controls the import of mitochondrial proteins, which indicates the potential toxic effects of the USP30 inhibitor [75]. Although numerous reagents have shown promising results in in vitro and animal experiments, there are few clinical trials confirming their specific effects and side effects. It is crucial to bridge the gap between experimental results and clinical significance through further research, including clinical trials, to establish the significance of USP in various inflammatory conditions. In addition, the solubility and stability of inhibitors in aqueous solutions significantly affect their pharmaceutical potential in clinical use [73]. This highlights the need for extensive research.

CONCLUSION

Thus, as we discover more and more phenotypes and mechanisms, USP are increasingly recognized as important modulators of inflammatory diseases. Further research will allow us to identify new directions and effective approaches to improving therapeutic treatment. It is important to continue researching the role of USP in somatic diseases in order to improve our understanding and develop targeted therapies to improve patient outcomes.

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