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Ubiquitin-Proteasome System: Promising Therapeutic Targets in Autoimmune and Neurodegenerative Diseases

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Abstract Ubiquitin-proteasome system is emerging as an immensely important enzymatic pathway playing central roles in protein degradation and signaling in numerous human diseases. Building on the prolific success of targeting the ubiquitin-proteasome system in cancer, the broader scientific community is currently seeking to elucidate the potential roles of this enzymatic system in other diseases such as autoimmune and neurodegenerative. A number of promising protein targets for these disorders have been identified in the recent years, and this review briefly summarizes the most recent advances in the field.

Keywords Ubiquitin-proteasome system · Autoimmunity · Neurodegeneration · Systemic lupus erythematosus · Multiple sclerosis · Parkinson's disease · Alzheimer's disease

1 Introduction

Autoimmune and neurodegenerative diseases are associated with damages to the immune system and the central nervous system (CNS). Understanding molecular principles underlying the disease initiation and progression has long been a major priority in the field. Therefore, identification of disease-associated proteins and subsequent development of small-molecule modulators to target those proteins represents a potential route to create new treatments.

2 Autoimmune Diseases

Multiple sclerosis (MS) and systemic lupus erythematosus (SLE) represent two common chronic autoimmune diseases with largely unknown etiology. MS is characterized by demyelination of axons in brain and spinal cord tissues, whereas SLE is associated with aberrant B cell function and mainly affects connective tissue integrity.

Recently, UBE2L3 (a.k.a. UbcH7) E2 ubiquitin-conjugating enzyme was reported as a potential target in multiple autoimmune diseases [1, 2]. A genome-wide association study demonstrated that UBE2L3 could be a novel therapeutic target in SLE. UBE2L3 was identified as the key E2 enzyme for linear ubiquitin chain assembly complex (LUBAC) and essential for LUBAC-mediated activation of NF-kB. UBE2L3 over-expression was found to promote NF-kB activation that is involved in the regulation of inflammatory and autoimmune diseases.

TRIM21 (a.k.a. Ro52) is an E3 ubiquitin ligase that plays an important regulatory role in both physiological and pathological immune responses, and was proposed as another potential target in SLE [3]. TRIM21 over-expression can result in break of tolerance that triggers generation of TRIM21 autoantibodies in genetically susceptible SLE patients [4]. In addition, over-expressed TRIM21 could lead to decreased cell proliferation and increased apoptotic cell death observed in SLE, and thus could contribute to induction of autoimmune B and T cell responses. Patients with SLE and

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Sjogren's syndrome were demonstrated to have increased levels of TRIM21 in PBMC cells [5].

TNFAIP3 (a.k.a. ubiquitin-editing enzyme A20) was demonstrated to play an important role in MS, SLE, and several other immune disorders [6, 7]. TNFAIP3 is critical for the regulation of B cell homeostasis, prevention of autoimmune responses caused by autoreactive B cells, and restriction of CD40-induced NF-kB signals [8]. In addition, genetic studies demonstrated that *TNFAIP3* potentially serves as a susceptibility gene for SLE, and therefore, TNFAIP3 could represent a good target protein for therapeutic intervention [9, 10].

Proteasome is considered as a highly promising target in autoimmune diseases. Circulating proteasomes and respective anti-proteasome autoantibodies were detected in serum samples from patients with autoimmune diseases such as SLE, MS, and rheumatoid arthritis (RA) [11]. Proteasome inhibitors carfilzomib and bortezomib are approved anticancer drugs with mechanism of action based on selective inhibition of 26S proteasome. Both compounds have been tested in SLE animal models and demonstrated decreased levels of autoantibodies and retarded disease development [12]. The therapeutic effect was accompanied by diminished number of plasma cells and suppressed production of interferon alpha by plasmacytoid dendritic cells (PDCs). Although bortezomib is approved for the treatment of multiple myeloma, it is also currently being tested in clinical trials against several autoimmune diseases such as proliferative lupus nephritis, refractory cold agglutinin disease, and IgA nephropathy. Important to note that refractory SLE patients were shown to respond to the bortezomib-based therapy [13].

A novel approach to suppress inflammation was presented based on targeting the p53 activation pathway through inhibition of its major regulator E3 ubiquitin ligase MDM2. It was demonstrated that Nutlin-3a, a potent small-molecule MDM2 inhibitor (Fig. 1), was able to reduce systemic inflammation in SLE through abrogated formation of immune complex and suppressed abnormal expansion of all T cell subsets linked to systemic inflammation [14]. MDM2 suppression substantially lowered lymph proliferation through depletion of autoreactive T cells and plasma cells, and also inhibited production of autoantibodies. The results provide evidence to support MDM2 as a potential therapeutic target for the treatment of SLE and other autoimmune diseases.

3 Neurodegenerative Diseases

Parkinson's disease (PD) is a major neurodegenerative disorder driven by the loss of brain neurons and impaired mitochondrial quality control system. Parkin E3 ubiquitin ligase plays a central role in PD mediation—it is involved in mitochondrial homeostasis and protein regulation by stimulating degradation of damaged mitochondria and their subsequent clearance through mitophagy [15]. Parkin is translocated to damaged mitochondria and gets activated by PINK1 kinase that accumulates on the outer mitochondrial membrane upon mitochondrial depolarization [16]. Activated Parkin then associates with multiple mitochondrial substrates, outer membrane proteins, autophagy receptors, and the proteasome to eventually result in induced mitophagy [17].

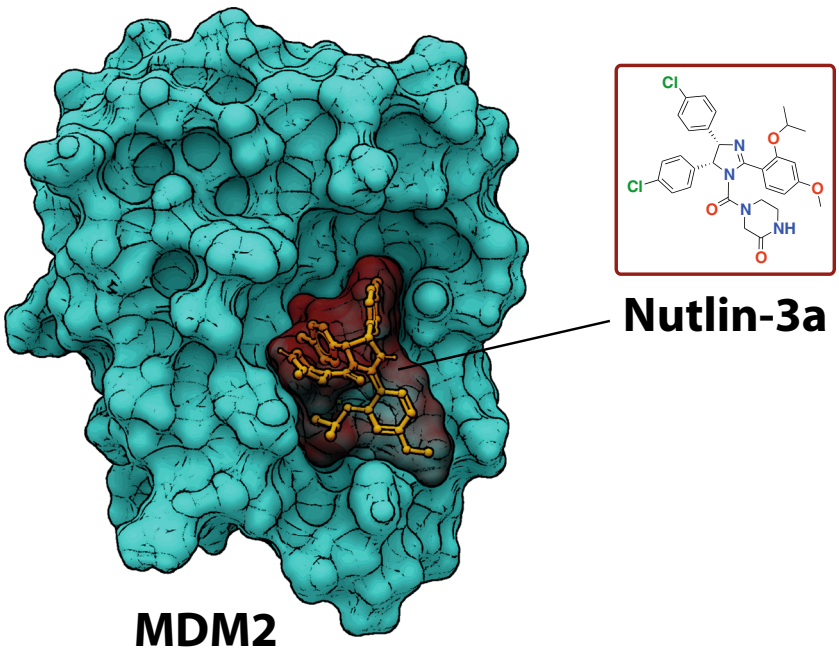

Fig. 1 Crystal structure of E3 ubiquitin ligase MDM2 in complex with its potent inhibitor Nutlin-3a (PDB 4HG7). An example of the small-molecule drug developed to therapeutically target the protein of interest

FBXO1, an F-box protein family member, is a substrate-recognition subunit of the SCF-type E3 ubiquitin ligase. A recent genomic study revealed that expression of *CCNF*, encoding FBXO1, can lead to aberrant ubiquitination and affect the mechanisms of neuronal degeneration in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) [18].

Alzheimer's disease is one of the most typical forms of dementia—its progression is associated with accumulation of beta-amyloid (Aβ) peptides and filament-forming protein Tau. Amyloid precursor protein (APP) uptake from plasma membrane to endocytic compartments leads to APP processing by secretases (β and γ) and subsequent generation of Aβ. APP metabolism was also shown to be regulated in a ubiquitination-dependent manner by FBL2, another F-box protein [19].

Endoplasmic reticulum-associated degradation (ERAD) is based on clearance of misfolded proteins in cytosol through ubiquitination and subsequent destruction by the ubiquitin-proteasome system. The endoplasmic reticulum (ER) stress can result in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases [20]. HRD1 E3 ubiquitin ligase was found to regulate ERAD by ubiquitination and degradation of substrate proteins such as APP [21]. The study demonstrated that HRD1 suppression or insolubilization promotes accumulation of APP and leads to increased generation of Aβ. Moreover, authors proposed that HRD1 could serve as a potential protein target for the development of novel therapies in neurodegenerative diseases.

In addition, CHIP E3 ubiquitin ligase targets misfolded chaperone substrates for proteasomal degradation and regulates Tau aggregation [22]. In addition, CHIP exerts its neuroprotective properties by stabilization of APP through induced refolding and by regulation of Aβ clearance.

4 Conclusions

The high potential of the ubiquitin-proteasome system in regulating many human diseases is beginning to receive a broad recognition. Proteins of the ubiquitin-proteasome system and E3 ubiquitin ligases, in particular, are emerging as promising molecular targets for drug discovery in various diseases, including autoimmune and neurodegenerative [23]. The progress in the field will require considerable efforts to perform screening and identify potent small-molecule modulators, elucidate crystal structures of target proteins [24], and provide detailed biophysical characterization [25].

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