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Review

Promising new therapeutic targets for regulation of inflammation and immunity: RING-type E3 ubiquitin ligases

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ABSTRACT

Ubiquitin–proteasome system (UPS) is a primary signaling pathway for regulation of protein turnover and removal of misfolded proteins in eukaryotic cells. Enzymes of the UPS pathway - E1 activating, E2 conjugating, E3 ligating - act together to covalently tag substrate proteins with a chain of ubiquitins, small regulatory proteins. The poly-ubiquitin chain then serves as a recognition motif for 26S proteasome to recognize and degrade the substrate. In recent years UPS has emerged as attractive enzymatic cascade for development of novel therapeutics against various human diseases. Building on the previous success of targeting this pathway in cancer – the broader scientific community is currently looking for ways to elucidate functions of E3 ligases, substrate-specific members of the UPS. RING-type E3 ubiquitin ligases, the largest class of E3s, represent prospective targets for small molecule modulation and their importance is reinforced by ever growing evidence of playing role in non-cancer diseases, primarily associated with inflammatory and immune disorders. In this review, we aim to briefly cover the current knowledge of biological functions of RING-type E3 ligases in inflammation and immunity.

1. Introduction

Intracellular signaling is primarily controlled by key post-translational modifications - phosphorylation, acetylation, and ubiquitination [1]. Ubiquitination is carried out by the ubiquitin-proteasome system (UPS) and is now widely recognized as the primary signaling event in regulation of inflammation and immunity. In the last two decades, scientists around the globe have witnessed increasing attention towards UPS that regulates protein turnover in eukaryotic cells. Research in this area substantially accelerated after the 2004 Nobel Prize in Chemistry was awarded to Aaron Ciechanover, Avram Hershko and Irwin Rose for their discovery of ubiquitin-mediated proteasomal protein degradation [2]. The currently well-known molecular mechanism of the UPS activity is regulated by consecutive action of three enzyme types (E1 activating, E2 conjugating, E3 ligating). These enzymes operate in a concerted manner to poly-ubiquitinate a substrate protein and define its subsequent fate (Fig. 1A) [3,4]. The chain of ubiquitin molecules, small 76 amino acid proteins, regulates molecular signaling depending on lysine linkage type of the poly-ubiquitin moiety, its length and additional post-translational modifications. Poly-ubiquitin chain that can be formed via seven distinct lysine residues (K6, K11, K27, K29, K33, K48, K63). For example, K48-linked chain directs ubiquitinated substrate

Abbreviations: ALS, amyotrophiclateral sclerosis; AP-1, activator protein 1; APC, antigen-presenting cell; APC/C, anaphase promoting complex/cyclosome; CLR, C-type lectin receptor; CRL, Cullin RING ligase; ERK, extracellular signalregulated kinase; FANC, Fanconi anemia ligase; FTD, frontotemporal dementia; GRAIL, gene related to anergy in lymphocytes protein; HIF-1α, hypoxia-inducible factor 1 alpha; IFN, interferon; IKK, IκB kinase; IL, interleukin; IRF, interferon-regulatory factor; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MAVS, mitochondrial antiviral signaling protein; MDM2, murine double minute 2; MHC, major histocompatibility complex; MS, multiple sclerosis; NFATc2, nuclear factor of activated T cells c2; NF-κB, nuclear factor–kappa-light-enhancer of activated B cells; NLR, NOD-like receptor; PBMC, peripheral blood mononuclear cell; PDC, plasmacytoid dendritic cell; PROTAC, proteolysis-targeting chimera; PRR, pattern recognition receptor; RA, rheumatoid arthritis; RBR, RING-between RING-RING ligase; RIG-I, retinoic acid-inducible gene-I; RING, really interesting new gene; RLR, RIG-I-like receptor; SCF, Skp1-Cullin-F-box complex; Skp2, S-phase kinase-associated protein 2; SLE, systemic lupus erythematosus; TAK1, transforming growth factor-β activated kinase 1; TAB, TAK1-binding protein; TBK, TANK-binding kinase 1; TCR, T cell receptor; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumor necrosis factor; TNFRSF5, tumor necrosis factor receptor superfamily member 5; TNRF2, tumor necrosis factor receptor 2; TRAF, tumor necrosis factor receptor-associated factor; TRIM, tripartite motif; VHL, von Hippel-Lindau disease tumor suppressor; UPS, ubiquitin-proteasome system

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