Cytokine & Growth Factor Reviews 26 (2015) 379–387

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Survey

Sensing and responding to cytosolic viruses invasions: An orchestra of kaleidoscopic ubiquitinations

Xing Liu [1], Qiang Wang [1], Youdong Pan, Chen Wang *

State Key Laboratory of Cell Biology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China

ARTICLE INFO

Article history:
Available online 1 April 2015

Keywords:
Ubiquitin
RIG-I
STING
Post-translational modification
Innate immunity

ABSTRACT

Ubiquitin is a versatile molecular signature that modulates diverse cellular processes via proteasome-dependent and proteasome-independent mechanisms. The covalent and/or non-covalent binding of mono-ubiquitin and/or poly-ubiquitin chains to a target protein broadens the dynamic and functional spectra for signal integration. Different linkages of poly-ubiquitin chains determine specific physiological or pathological functions of target proteins. Accumulating evidences has revealed the essential roles of ubiquitination in orchestrating the host defenses against cytosolic RNA or DNA from viral infections. In this review, we summarize the current progress regarding the understanding of ubiquitin-mediated regulation of the RIG-I and STING antiviral signaling pathways and discuss certain critical issues that remain to be resolved in future studies.

Contents

1. Ubiquitin and the ubiquitination system

Most proteins are covalently modified by certain small chemical group(s) after translation. This process, termed post-translational modification (PTM), broadens the function of target proteins temporally and spatially, thereby fine-tuning the corresponding biological processes. The post-translational modification groups include not only small molecules (phosphates, methyl/acetyl groups or carbohydrates) but also peptides such as ubiquitin and ubiquitin-like proteins [1].

Ubiquitin is a highly conserved peptide (76 aa) that is ubiquitously expressed across the eukaryotic domain. Ubiquitin was initially characterized as a label for the proteasome-dependent degradation of target proteins. The carboxylic acid group of the C-terminal glycine residue of active ubiquitin covalently conjugates to the ε-amino group of an acceptor lysine residue on a target protein via a stable isopeptide bond. This process, referred to as ubiquitination, is an ATP-dependent enzymatic cascade reaction that involves three classes of enzymes termed ubiquitin-activating enzymes (E1s), ubiquitin-conjugating enzymes (E2s) and ubiquitin ligases (E3s) (Fig. 1A). Ubiquitination is dynamically reversed by a family of deubiquitinating enzymes (DUBs). A few E1s and E2s and many E3 and DUBs constitute the precise ubiquitination system.

Ubiquitin per se contains seven lysines (K6, K11, K27, K29, K33, K48 and K63), each of which can conjugate to another ubiquitin,

* Corresponding author. Tel.: +86 2154921185.
E-mail address: cwang01@sibcb.ac.cn (C. Wang).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.cytogfr.2015.03.001
1359-6101/

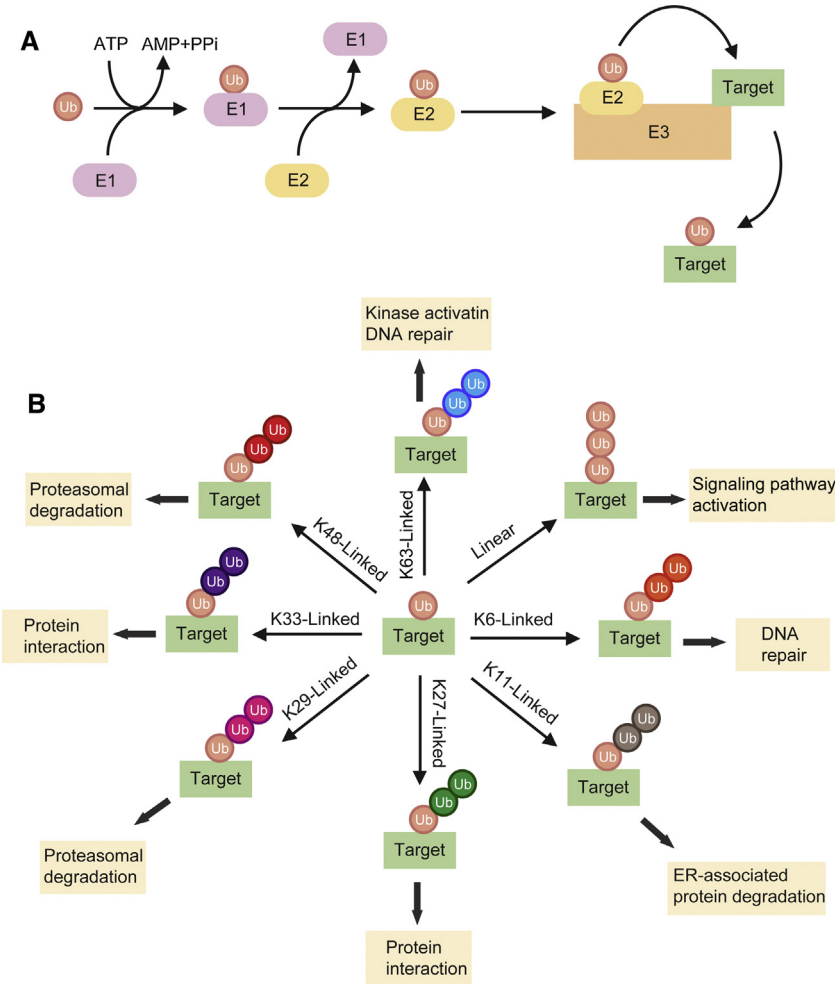

Fig. 1. The enzymatic ubiquitination cascade and the biological functions of ubiquitination. (A) Ubiquitin is conjugated to substrates via a three-step enzymatic reaction. Ubiquitin is initially activated by a ubiquitin-activating enzyme (E1) in an ATP-dependent manner; this reaction couples ATP hydrolysis to the formation of a thioester bond between the active-site cysteine of the E1 and the C-terminal glycine residue of ubiquitin. Activated ubiquitin is then transferred to a ubiquitin-conjugating enzyme (E2) and finally to its substrate via a substrate-specific ubiquitin ligase (E3). (B) Ubiquitin polymers can form in which internal lysine residues (K6, K11, K27, K29, K33, K48 and K63) or N-terminal methionine of one ubiquitin are attached to the C-terminal residue of another ubiquitin. Poly-ubiquitin chains containing different branching linkages perform distinct biological functions.

thus forming an array of poly-ubiquitin chains displaying different linkages. Recent studies have also revealed the "head-to-tail" linear poly-ubiquitin chain, in which the C-terminal glycine residue of ubiquitin directly binds to the N-terminal methionine of another ubiquitin [2,3]. Notably, the different linkages of poly-ubiquitin chains determine the distinct functional consequences of the modified proteins (Fig. 1B) [4]. K48-linked poly-ubiquitination generally targets the substrates for proteasomal degradation, whereas K63-linked poly-ubiquitination modulates non-proteolytic processes including membrane trafficking and signal transduction [5–8].

Over the past few years, mounting evidences has demonstrated the essential roles of ubiquitination in orchestrating the host defense against cytosolic RNA or DNA from viral infections. Precise ubiquitination events serve to either boost or dampen relevant antiviral innate immune signaling, ensuring that viral infection is rapidly contained and/or eliminated and that the detrimental effects of excessive host responses are minimized. Aberrant ubiquitination leads to the propagation of viruses or autoimmune diseases. Here, we summarize the current understanding of the ubiquitin-mediated regulation of the innate RIG-I and stimulator of interferon genes (STING) antiviral signaling pathways and emphasize important questions for future exploration.

2. The host innate immune signaling pathways against viral infection

Innate immunity is the first line of host defense against viral invasion and is critical for eliciting subsequent adaptive immunity to ultimately eradicate an infection [9,10]. The initiation of the innate immune response is based on the recognition of invading viruses by host cells via the detection of pathogen-associated molecular patterns (PAMPs) by an array of host germline-encoded pattern recognition receptors (PRRs) [11,12]. The first family of virus-specific PRRs that were identified is the membrane-bound Toll-like receptors (TLRs), of which TLR3, TLR7/8, and TLR9 are capable of detecting viral nucleic acids [13–15]. In contrast to TLRs, which survey the presence of non-self signatures in the endosomal milieu of immune cells, RIG-I-like receptors (RLRs) have been characterized as ubiquitous sensors of cytosolic RNA viruses during primary host responses [16–19]. Recent studies have identified and characterized several potential DNA-binding proteins including cyclic GMP–AMP synthase (cGAS, also referred to as MB21D1), interferon-inducible protein 16 (IFI16) and DEAD box polypeptide 41 (DDX41), which monitor the presence of viral DNAs or DNA intermediates of retroviruses in the cytoplasm [20–22]. Upon recognition of the corresponding