Journal of Autoimmunity xxx (2017) 1–8

Contents lists available at ScienceDirect

Journal of Autoimmunity

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

SUMO proteins: Guardians of immune system

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ARTICLE INFO

Article history:
Received 1 August 2017
Received in revised form
4 September 2017
Accepted 4 September 2017
Available online xxx

Keywords:
Small ubiquitin-like modifier (SUMO) proteins
Innate immune system
NF-κB pathway
Interferon pathway
Autoimmunity

ABSTRACT

Small ubiquitin-like modifier (SUMO) proteins belong to the ubiquitin-like family and act to change the function of target proteins through post-translational modifications. Through their interactions with innate immune pathways, SUMOs promote an efficient immune response to pathogenic challenge avoiding, at the same time, an excess of immune response that could lead to the development of autoimmune diseases. This report discusses the general functions of SUMO proteins; highlights SUMO involvement in the innate immune response through their role in NF-κB and interferon pathways; the involvement of SUMO proteins in autoimmune diseases; and reviews bacterial, viral, and parasitic interactions with SUMO pathways. In conclusion, we speculate that targeting SUMOs could represent a new therapeutic strategy against infections and autoimmunity.

Contents

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http://dx.doi.org/10.1016/j.jaut.2017.09.001
0896-8411/

1. Introduction

Post-translational modifications by small ubiquitin-like modifiers (SUMOs) are crucial in activating protein functions, which lead to target effects at the molecular, cellular, and systemic levels. SUMOs belong to the ubiquitin-like (Ubl) family of proteins and are ubiquitously expressed in eukaryotic cells. Four SUMO isoforms have been identified, SUMO-1-4, with SUMO-2 and -3 almost identical in structure [1]. Conjugation of SUMO proteins with target substrates, sumoylation, resembles the ubiquitination process and involves three distinct steps. First, SUMO binds to the E1 activating enzyme, SAE1/SAE2, which results in the activation of SUMO. Activated SUMO is then transferred to the E2 conjugation enzyme, Ubc9. Ubc9 then acts to target SUMO to its specific substrate, which is bound to an E3 ligase (protein inhibitor of activated STAT [PIAS], Ran binding protein 2 [RanBP2], polycomb protein 2 [Pc2]), through covalent binding. Sumoylation differs from ubiquitination in the number of enzymes involved, with less SUMO-related enzymes known, and that E3 ligation is not always required for SUMO binding. In the consensus site on the target protein, characterized by the "ΨKXE" motif [2], SUMO binds to a lysine and then is released from the target protein through desumoylation, catalyzed by SUMO-specific peptidases (SENP1, 2, 3, 5, 6, 7) [3]. Thus, sumoylation is a dynamic and reversible post-translational modification process [4].

Although SUMO proteins have no function on their own, they are capable of modulating the functionality of hundreds of target proteins, with effects that are diverse and target protein-specific. Recently, SUMOs' role in the regulation of DNA activities, such as DNA synthesis and damage repair, has emerged as crucial. For example, SUMO regulates double-stranded break repair, a process critically important for maintenance of genome stability [4]. SUMO is also involved in DNA-protein crosslink repair in yeast [5], binding to proliferating cell nuclear antigen (PCNA) and signaling the recruitment of the anti-recombinogenic DNA helicase, Srs2 [6]. In addition, sumoylation of the phosphatase and tensin homolog protein (PTEN) is required for the PTEN-dependent DNA damage response [7].

Sumoylation can occur at multiple points in the same pathway. Notably, during meiotic homologous recombination, there is a concomitant sumoylation of many proteins, which are then subsequently desumoylated to shut down the pathway [8]. In particular, the interference phenomenon of meiotic crossover is regulated by sumoylation, where topoisomerase II and Red1 sumoylation is a critical control mechanism [9]. Additionally, Ubc9 sumoylation determines the SUMO-modification state of target proteins, where switching from mono-sumoylation to poly-sumoylation, results in a change of function, essential for meiotic cell division [10,11]. Sumoylation events also safeguard somatic cell identity through repressing transition from one cell type to a different cell type [12].

Sumoylation regulates many other processes that are important for cellular function. SUMO influences gene transcription, through both activation [13] and repression [14]. Intermediate filament proteins are also modified by SUMO, which are important for cytoskeleton structural functions and intracellular communications [15]. SUMO-2 plays a role in repressing the expression of provirus and endogenous retroviruses by pluripotent stem cells [16].

SUMO modifications have also been implicated in general health maintenance and systemic disease. Recent discoveries suggest that sumoylation plays a role in breast cancer [17], melanoma [18], renal carcinoma [19], and the response to heart failure therapy [20–22]. Given these wide-ranging effects and the importance of SUMO-dependent processes on health, the remainder of this review will examine the role of SUMO in the innate immune defense against pathogens and dissect how SUMO modulation impacts the immune response to infection and autoimmunity.

2. Role of SUMO in innate immunity

The innate immune response forms the first line of defense against invading pathogens. One important aspect of innate immunity is the recognition of pathogens and microorganisms that express pathogen-associated molecular patterns (PAMPs) by host cell pattern recognition receptors (PRRs). Activation of these receptors triggers signaling pathways that result in the production of anti-microbial mediators and the initiation of an immune response. PRR signaling cascades, stemming from both membrane-bound and intracellular receptors, culminate in the activation of the transcriptional regulators, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) or interferon regulatory factors (IRF) [23].

These pathways are tightly regulated by sumoylation [24,25], which promotes the production of anti-microbial molecules. SUMO modifications are also important in the negative regulation of these pathways, avoiding an excessive immune response that could be detrimental to the host and lead to the development of autoimmune disease or tissue damage. This balance between activation and resolution of inflammatory cascades is exemplified in the cellular response to viral infection. Viral DNA is recognized by cyclic GMP-AMP synthase (cGAS), which results in the activation of the adaptor protein, stimulator of interferon genes (STING). Tripartite motif containing 38 (TRIM38), a ubiquitin ligase, sumoylates and stabilizes cGAS and STING during the early phase of viral infection, amplifying the antiviral cell response. In the late phase of infection, cGAS and STING are desumoylated by sentrin-specific protease 2 (Senp2) and subsequently degraded, thus shutting off this pathway and limiting the immune response to avoid excess activation [26,27].

2.1. The NF-κB pathway

Among PRRs, Toll-like receptors (TLRs) form the frontline of immune defense. Upon ligand binding to membrane-bound TLRs, a signaling cascade is initiated that results in NF-κB activation, the canonical inflammatory transcription factor (Fig. 1). For example, when TLR4 recognizes lipopolysaccharide (LPS) on bacterial outer membranes, this triggers the recruitment of the adaptor protein myeloid differentiation primary response gene 88 (MyD88) and signaling molecules interleukin-1 receptor-associated kinases 1 and 4 (IRAK1, 4). IRAK1 and IRAK4 then associate with TNF receptor-associated factor 6 (TRAF6). TRAF6 activates the downstream TAK kinase, which leads to inhibitor of nuclear factor kappa-B kinase (IKK) complex activation. IKK complex then regulates the activation state of NF-κB, leading to nuclear translocation and the transcription of inflammatory cytokines and initiation of the innate immune response [1].

In this pathway, discussed further below, SUMOs act at different levels to influence signaling. At the beginning of the cascade, the Pellino protein associates with IRAK1, resulting in reciprocal phosphorylation. Pellino-1 is modified by SUMO-1, although the biological significance of this modification is still unclear [28]. Downstream of IRAK-1/TRAF6, SUMO-1 binds to TRAF family member-associated NF-kappa-B activator (TANK) and relieves its repression on TLR signaling. Acting on the IKK complex, SUMO-3 binds to IKK-γ (NEMO) which forms a complex with IKKα and IKKβ kinases, that then phosphorylate IκBα, an inhibitor of NF-κB, leading to its degradation and subsequent NF-κB activation.

SUMO-1 also negatively regulates this pathway through binding and protecting dephosphorylated IκBα from degradation, thus

Please cite this article in press as: S. Adorisio, et al., SUMO proteins: Guardians of immune system, Journal of Autoimmunity (2017), http://dx.doi.org/10.1016/j.jaut.2017.09.001