Journal of Antivirals & Antiretrovirals

Li et al., J Antivir Antiretrovir 2018, 10:2
DOI: 10.4172/1948-5964.1000e141

Editorial Open Access

ISG15 and ISGylation Regulate the Host Response to Viral Infections

Shuang Li[1], **Shilin Li**[1] **and Limin Chen**[1,2*]

[1]*Provincial Key Laboratory for Transfusion-Transmitted Infectious Diseases, Institute of Blood Transfusion, Chinese Academy of Medical Sciences and Peking Union Medical College, Chengdu, Sichuan, 610052, China*

[2]*Toronto General Research Institute, University of Toronto, ON M5G 1L6 Canada*

[*]**Corresponding author:** Limin Chen, Toronto General Research Institute, University of Toronto, ON M5G 1L6 Canada, E-mail: limin_chen_99@yahoo.com

Received date: June 28, 2018; **Accepted date:** June 29, 2018; **Published date:** June 30, 2018

Editorial

During viral infection, the host innate immune response provides early protection. To control virus spread, the host cells produce type I interferons (IFNs) as first line of defense, acting as antiviral and inflammatory cytokines. Type I IFNs binding with interferon α/β receptor (IFNAR) triggers the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway to induce the synthesis of a few hundred IFN-stimulated genes (ISGs) which inhibit virus replication at different steps of the virus replication cycle [1]. Ubiquitin-like protein ISG15 is one of the most strongly and promptly induced ISG following virus infection, and many studies have demonstrated that ISG15 can directly inhibit viral replication and modulate host immune response. ISG15 is one of the members of ubiquitin families, which include ubiquitin and ubiquitin-like modifiers (Ubls). ISG15 can covalently conjugate to target proteins *via* isopeptide bonds and this conjugation process of protein modification is known as ISGylation which is involved in the regulation of many cellular processes. To date, proteomic studies have identified a few hundred ISG15 target proteins [2,3]. Research of specific ISG15 targeted proteins have found that through competing with ubiquitin binding sites, ISG15 can inhibit protein ubiquitination, indirectly regulating protein degradation [4].

ISGylation can be reversed by the deconjugating enzyme Ubl carboxy-terminal hydrolase 18 (USP18), also known as UBP43 [5]. USP18 is a protease that can efficiently cleave ISG15 from its conjugated target ptoteins. In addition, independent of its deconjugating activity, USP18 also functions as a negative regulator of interferon signalling *via* competing with Janus kinase 1 (JAK1) to bind to the second chain of IFNAR2 complex [6]. Many studies have broadened our understanding on how ISG15 and ISGylation regulate viral replication and modulate host immune response.

Effects of ISG15 on viral replication and egress

Previous studies have shown that ISGylation of viral proteins could disrupt viral replication. Zhao et al. found that ISG15 inhibits influenza A virus (IAV) replication by conjugating to a specific viral protein NS1, the critical virulence factor of IAV, in virus-infected cells [7]. Later, Tang et al. reported that ISG15 conjugation onto IAV-NS1 protein prevents the formation of NS1 homodimers, and limits its ability to disrupt the antiviral response [8]. Another study found that ISGylation of avian infectious bronchitis virus (IBV) NP blocks oligomerization which reduces IBV replication. Similarly, human papillomavirus (HPV) capsid protein 1 can be ISGylated and the number and infectivity of viral particles were decreased [9]. In addition, the ISGylation of coxsackievirus B3 (CVB3) protease 2A (2APro) inhibits the cleavage of eIF4G during CVB3 infection which in turn reduce viral replication [10]. These data collectively demonstrated that ISGylation of viral proteins could disrupt viral protein function or inhibit the oligomerization of viral proteins to inhibit viral replication. Furthermore, ISGylated viral proteins fail to interact with host signaling pathways to alter the host antiviral response. Study from Kim et al. has shown that ISGylation inhibits human cytomegalovirus (HCMV) replication in multiply stages [11]. These data illustrate ISG15 binding with viral proteins could inhibit viral replication.

Several studies have found that ISG15 affects virus egress through modulating specific host proteins. Okumura et al. first reported that ISG15 inhibits ubiquitination of HIV Gag and Tsg101 and disrupts their interaction to inhibit HIV-1 release [12]. Later another group also found that ISGylation of Tsg101 inhibits the transportation of IAV hemagglutinin (HA) [13]. Moreover, ISG15 conjugation triggers multivesicular bodies (MVB) to co-localize with lysosomes which decreases MVB numbers and impairs exosome secretion [14]. A recent study found that the E3 ubiquitin ligase, ITCH, interacts with Ebola VP40 to regulate viral budding *via* an identical budding domain that is used by another E3 ubiquitin ligase NEDD4 [15]. These studies demonstrated that ISGylation of viral and host proteins that are involved in protein sorting and transport pathways is required for viral egress.

The role of ISG15 in immune modulation during viral infection

Previous studies have shown that recombinant ISG15 could stimulate IFNγ production, stimulate NK cell proliferation, dentritic cell maturation and recruit neutrophil [16]. Recently, LFA1 was identified as a cell surface receptor for ISG15, and in IL-12 treated cells the binding of LAF1 with ISG15 mediated the release of IFNγ and IL-10 [17]. Whether these immune modulation effects are mediated by intracellular or extracellular ISG15 remain to be determined. Nevertheless, these findings demonstrated that unconjugated ISG15 negatively regulates cytokine and chemokine production during certain viral infections.

Recent findings support ISG15 in the regulation of disease tolerance during IAV and Sendai virus infection (SeV) in a mouse model, and identified ISG15 targets pathways involved in apoptosis and autophagy [18,19]. Besides, proteomic studies have identified ISG15 targets hundreds of host proteins upon interferon stimulation [2,3]. Many of these are ISGs that are involved in the regulation of the innate immune response and host antiviral response, such as RIG-I, MxA, PKR, STAT1 and JAK1 [3].

Conclusion

Most recently, ISG15 has been widely known as an anti-viral protein against viral infections. ISG15 inhibits viral replication and increases the number of viral immune-evasion proteins through modulating viral and host proteins. In addition, ISG15 can also regulate cytokine responses, host damage and repair response and autophagy and metabolism. Still there are many important questions need to be answered, like what is the function of extracellular ISG15 during viral infection? How the ISGylated proteins affect the overall function in cells? Further studies on ISGylation pathway may identify new targets to control diseases progression, and to provide promising targets for antivirus treatment.

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