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A Novel Mechanism of Ubiquitin-Like Protein ISG15 in Regulation of Type I Interferon Signaling: Implication for HCV Persistent Infection

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Brief Introduction to ISG15

Interferon-stimulated gene 15(ISG15), a 15 kDa ubiquitin-like protein (UBL), was first identified by Farrell et al in 1979 [1]. Because some antibodies directed against ubiquitin also react with ISG15, it was initially named as an ubiquitin cross-reactive protein (UCRP) [2]. This cross-reactivity is explained by the fact that ISG15 consists of two domains, each of which bears high sequence homology to ubiquitin. The function of ISG15 since its discovery in the 1980's remained mysterious or has been misunderstood to some extent until very recently. Over the past few years significant advances have been made to shed light on a clearer understanding of the function of ISG15 and its mechanisms. As one of the interferon stimulated genes (ISGs), ISG15 is abundantly induced by type 1 interferon and virus/bacterial infections. In addition, the mature form of ISG15 can be secreted by human monocytes and lymphocytes [3].

The Conventional Role of ISG15 in Regulation of Type 1 Interferon Signaling

ISG15 has long been identified as an interferon (IFN)-α/β-inducible, ubiquitin-like intracellular protein, playing a central role in the host's antiviral response against many viruses [4]. The most studied mechanism by which ISG15 exerts its function is its conjugation to various proteins (ISGylation). To date, ISG15 has been identified as a protein with multiple functions: works as a cytokine to modulate immune responses; regulates signal transduction pathways and antiviral response; regulates ubiquitination; participates in viral immune-evading mechanisms and plays its role in tumorigenesis, although the contradictory findings of the role of ISG15 as a tumor suppressor versus an oncogenic protein. Of all the functions studied, the hottest topic remains its role in regulating IFN signaling pathway. Many studies have reported that ISG15 and protein ISGylation play an important role in innate immunity, which indicates that they are critical for regulating IFN-α/β induced Janus tyrosine kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway. Indeed, mass spectrometry analysis has led to the identification of several hundreds of candidate proteins that can be conjugated by ISG15. Some of them are type I IFN-induced proteins, such as PKR and RIG-I, and some are the key regulators that are involved in IFN signaling, such as JAK1 and STAT1, implicating the role of ISG15 and its conjugates in type I IFN-mediated innate immune responses [5].

Studies from ISG15-Deficient Mice Indicated that ISG15 is Not Essential in Type I Interferon Signaling

A study has elegantly and unarguably showed that lack of ISG15 did not affect the development and composition of the main cellular compartments of the immune system in mice. In ISG15 knockout mice, interferon- or endotoxin-induced STAT1 tyrosine-phosphorylation remained unaffected. Thus ISG15 is dispensable for STAT1 and interferon signaling [6]. It is noteworthy that mice lacking ISG15 are not as susceptible to viral infection as IFN receptor knockout mice, indicating that ISG15/ISGylation contributes to, but is not solely responsible for, the antiviral effects of IFN in mice [7]. To further investigate the functional roles of protein ISGylation, Keun Il Kim et al. generated Ube1L (E1 enzyme for ISGylation) knockout mice lacking ISG15 conjugation but free ISG15 was not affected. Ube1L-deficient mice were healthy and fertile, without showing any abnormal responses to IFN treatment, and Ube1L+/+ and Ube1L -/- cells exhibited similar susceptibility to vesicular stomatitis virus (VSV) and lymphocytic choriomeningitis virus (LCMV) infection, indicating that Ube1L and protein ISGylation are not essential for IFN signaling. Further study indicated that it is the lack of ubiquitin specific peptidase 18 (USP18, a special proteolysis enzyme of ISG15), not the increase of protein ISGylation, that is responsible for the increased IFN-α/β signaling in USP18-deficient mice [8].

Current Understanding of the Novel Mechanism of ISG15 in IFN Signaling Pathway Revealed by ISG15-Deficient Humans

Studies from humans who are deficient in ISG15 demonstrated that ISG15 is a negative regulator of type I IFN signaling independent of its conjugation (ISGylation). Recent studies on six ISG15-deficient children indicated that all of them display abnormally strong IFN-α/β responses and this phenotype is due to the effect that ISG15 stabilizes USP18 through counteracting USP18 ubiquitination and degradation via SKP2-mediated proteolysis pathway. Therefore, ISG15 is a negative regulator of type I IFN signaling to prevent over-amplification of the signaling [9].

Conclusion

As one of the most rapidly-and abundantly-induced interferon stimulated genes, ISG15 plays its role in various biological and disease processes, especially in the regulation of host interferon signaling pathway to control the spread of viral infection and to prevent the over-amplification of the signaling. Previous study from our own lab indicated that ISG15 inhibited the anti-HCV effect of type I IFN (IFN α) to cause HCV resistance to IFN treatment and HCV persistence [10]. Most recently, the understanding of the role of ISG15 in IFN signaling has been re-visited. ISG15 exerts its role in IFN signaling response to

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viral infections not through its conjugation to proteins (ISGylation), but through stabilizing USP18. This novel mechanism of ISG15 in negative regulation of type I IFN signaling helps to explain why increased baseline ISG15 (and USP18) expression levels in the pre-treatment liver tissues of HCV patients contribute to treatment failure with IFN-based regimen[11]. HCV develops a various mechanisms to counteract the host immune attack to facilitate its persistent infection. Up-regulation of ISG15 following HCV infection may be one of the most important strategies the virus employs to evade the host immune surveillance.

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