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The role of Interferon Stimulated Gene 56 (ISG56) in Virus-Triggered Signaling and Cellular Antiviral Response

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Brief Introduction to ISG56

Human Interferon-stimulated gene 56 (ISG56, official gene symbol IFIT1) was discovered and cloned almost 3 decades ago. Although the baseline expression of ISG56 is very low in most cell types, a multitude of RNA- or DNA virus infection efficiently induces IFN-stimulated genes, including ISG56 expression [1-6]. These viruses include but not limited to parainfluenza virus, respiratory syncytial virus, sendai virus, reovirus, herpes simplex virus, West Nile virus, vesicular stomatitis virus (VSV), lymphocytic choriomeningitis virus (LCMV), cytomegalovirus, and adenovirus.

ISG56 is located in a cluster on chromosome 10 with five other closely related genes. It encodes a protein with tetratricopeptide repeats (TPR) [7]. The protein encoded by ISG56 was reported to inhibit viral replication and translational initiation. ISG56 regulates both viral and cellular functions such as translation initiation, virus replication, double-stranded RNA signaling, cell migration and proliferation [8].

Current Understanding of the Novel Mechanism of ISG56 in Virus-triggered Signaling and Cellular Antiviral Response

Innate immune systems are indispensable and crucial in host defense against microbial pathogen infections. Molecular patterns of microbial pathogens are recognized by pattern recognition receptors (PRRs), and then downstream signaling pathways are activated. Toll-like receptors (TLRs) are a large family of PRRs, and especially TLR3 recognizes viral double-stranded RNA (dsRNA). The cells produce type 1 interferons (IFNs) after the recognition of viral RNA by TLR3. IFNs are key cytokines in antiviral responses and induce IFN-stimulated genes (ISGs) to exert their functions. ISGs encode a variety of proteins to regulate diverse cellular functions.

IFN-stimulated gene 56 (ISG56), one of the first identified interferon stimulated genes (ISGs), is induced in cultured cells by type I interferons (IFNs), viruses, or double-stranded RNA (dsRNA) [9]. For example, In hepatocytes, as the primary target cells of HCV infection, retinoic acid-inducible gene I (RIG-I) and Toll-like receptor 3 (TLR-3) signaling are the two major pathways of host defense triggered by double-stranded RNA (dsRNA) leading to the production of type I IFNs.

One recent study demonstrated that knockdown of ISG56 inhibited the expression of mRNA and protein for MDA5, RIG-I, CXCL10 and CCL5, indicating that ISG56 did not act as a translation inhibitor. Further studies should be performed to explore the role of protein-protein interaction in the positive-feedback loop between ISG56 and MAD5,RIG-I. ISG56 also binds to the E1 helicase of human papillomavirus to inhibit the replication of this virus [10]. It has been reported that ISG56 was associated with the mediator of IRF3 activation (MITA) which was an adapter protein involved in virus-triggered induction of type I IFNs. Overexpression of ISG56 inhibited Sendai virus-triggered activation of IRF3, NF- κB, and IFN-promoter, while knockdown of ISG56 had opposite effects. ISG56 has also been implicated in antiviral activities of IFNs against West Nile virus and LCMV [11]. Taken all the data together, ISG56 may contribute to the antiviral response both through inhibiting the viral replication and through boosting the host immune responses.

Mechanism of ISG56 Anti-HCV Activity

ISG56 inhibits HCV replication because knockdown of ISG56 enhances HCV RNA replication. Previous study indicated that ISG56 contained multiple tetratricopeptide (TPR) [7], which mediated protein-protein interactions through scaffolds formed among tandem TPR repeats. ISG56 is induced in response to type I IFNs, double-stranded RNAs, and various virus infections [12], and it interacts with the translation initiation factor eIF-3 to inhibit viral and host protein translation.

Conclusions

ISG56 interacts with specific subunits of eIF3 and inhibits the translation of various cellular molecules and of hepatitis C virus, thus it has been considered to be an inhibitor of translation. However, the recent study has shown that knockdown of ISG56 inhibited the expression of both mRNA and protein for MDA5, RIG-I, CXCL10 and CCL5, which indicates that ISG56 does not work as a translation inhibitor. Therefore, it is immature to draw a conclusion based on the known functions of ISG56, and further studies are needed to understand the precise role of this effector molecule in early stages of HCV infection.

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