Modulating Innate Immune Response to Combat Viral Infections—Use HCV as an Example

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Innate immunity is host’s first line of defense against invading microbial pathogens, limiting pathogen spread. Two major players contribute to the innate immune response: type I interferon (IFN) and Natural killer (NK) cells. Type I IFN (α/β) functions as innate cytokine elicited in response to viral/bacterial infections. There are two distinct pathways that sense viral infection and initialize the induction of type I IFN. One is Toll-like receptors (TLR) mediated [1] and the other is retinoic acid-inducible gene 1 (RIG-I)/melanoma differentiation–associated gene 5 (MDA5) mediated [2]. These receptors recognize pathogen associated molecular patterns (PAMPs) which are conservatively present in the genome of viruses/bacteria, leading to the production of type I IFN. After binding to the receptors, IFN α/β activates Janus activated kinase (JAK)/signal transducer and activator of transcription (STAT) signaling to induce the expression of a few hundred interferon stimulated genes (ISGs) which are involved in immune regulation and host defense [3]. NK cell is another contributor to innate immune system activated by viral proteins via activating NK receptors (e.g. natural cytotoxicity receptor, NCR) [4]. Activated NK cells can not only mediate cytotoxicity through granule-exocytosis pathway or classical caspase-dependent apoptosis in target cells, but also produce some cytokines, for example, the IFN-γ [5], to activate a number of important signal pathways involved in direct antiviral function and/or immune modulation.

Unfortunately, some “smart” viruses, such as hepatitis C virus (HCV) [6,7], have developed several strategies to not only evade the host immune attack but also even exploit innate immune response to benefit their own replication. Immune evasion of HCV relies on blocking type I IFN production, interfering with IFN signaling and modulating effective molecules by different proteins of the virus. The HCV NS3/4A protease has been proved to antagonize interferon regulatory factor-3 (IRF-3), which is a key protein associated with IFN production in hepatocytes. It has been well established that NS3/4A can either prevent the virus-induced production of RIG-I [8] or hydrolyze adaptor protein TRIF which link TLR3 to IRF-3 [9] in a protease-dependent manner, resulting in the inhibition of IRF-3 activation and type I IFN production. Moreover, HCV could evade innate immunity by impairing JAK/STAT signal transduction. Phosphatase2A (PP2A) induced by HCV in liver cells stimulates the methylation of STAT1 to increase its binding affinity to protein inhibitor of activated STAT (PIAS1) [10]. PIAS1 is well known for its blocking function in the process that activated STAT binding to the promoters of target genes. Similarly, HCV core protein has been shown to induce suppressor of cytokine signaling (SOCS)-3 [11], which inhibits JAK, preventing activation of STAT. Finally, HCV evasion from host innate immunity could also be due to the modulation of ISG production and/or their antiviral effects. For example, Geiss et al. [12] have found that HCV N55A attenuated overall ISGs expression in several types of human cells. This attenuation is attributed to induction of IL-8which interferes with IFN production. Further studies [6,7] have revealed that HCV proteins could also interact with dsRNA-dependent protein kinase(PKR) and 5′-oligoadenylate synthetase (OAS)/RNase L pathway to inhibit these ISGs’ anti-viral activity.

ISG15 is the first ubiquitin-like protein identified that can be conjugated to a few hundred proteins (the process known as ISGylation). It has been shown that ISGylation plays an important role in innate immune response and ISG15 conjugation can be removed by USP18 (ubiquitin-specific protease 18) from its cellular targets. ISG15 has long been recognized as an important anti-viral ISG. However, this anti-viral effect of ISG15 may be virus-specific. Chen et al. [13] studied the effect of ISG15/ISGylation on HCV production by increasing and decreasing ISG15/ISGylation in HuH7.5 cell. They have shown that over-expression of ISG15 (leading to increased ISGylation) stimulates HCV RNA replication and viral particle production. In addition the increased ISG15/ISGylation blunts interferon anti-HCV activity. In line with this, a recent study [14] showed that chronic HCV patients with high pre-treatment hepatic expression of a subset of ISGs, including ISG15 and USP18, are resistant to standard pegylated IFN-α/Ribavirin (Peg IFN/RBV) therapy. As expected, silencing USP18 potentiates IFN anti-HCV activity in vitro [15].

Although much remains to be elucidated, some mechanisms contributing to the function of USP18 have been learned at the molecular level. In addition to negative regulation of ISGylation, USP18 has been shown to have protease-independent function that interferes with JAK-IFNAR2 interaction and inhibits downstream JAK/STAT signaling cascade. Most likely, USP18 may interact with other host and/or viral proteins to modulate the innate immune response. Thus, protease inhibitor or specific siRNA against USP18 may be a good target for the treatment of HCV.

References

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Received April 27, 2013; Accepted April 27, 2013; Published April 30, 2013


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