Journal of
Antivirals & Antiretrovirals
ISSN: 1948-5964

Li et al., J Antivir Antiretrovir 2013, 5:3
DOI: 10.4172/jaa.1000e107

Editorial Open Access

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

Yujia Li[1], shilin Li[1], Xiaoqiong Duan[1], Bing Liu[1], Peibin Zeng[1], Chunhui Yang[1] and Limin Chen[1,2]*

[1]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, Toronto, ON M5G 1L6 Canada

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 I (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 inimmuno 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 protein 1(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 NS5A 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

1. Kaisho T, Akira S (2006) Toll-like receptor function and signaling. J Allergy Clin Immunol 117: 979-987.
2. Kato H, Takeuchi O, Sato S, Yoneyama M, Yamamoto M, et al. (2006) Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. Nature 441: 101-105.
3. de Veer MJ, Holko M, Frevel M, Walker E, Der S, et al. (2001) Functional classification of interferon-stimulated genes identified using microarrays. J Leukoc Biol 69: 912-920.
4. Lanier LL (2008) Up on the tightrope: natural killer cell activation and inhibition. Nat Immunol 9: 495-502.
5. Biron C, Dalod M, Salazar-Mather T (2002) Innate immunity and viral infections. Immunology of infectious diseases. American Society for Microbiology, Washington, DC 139-160.

***Corresponding author:** Dr. Limin Chen, Toronto General Research Institute, University of Toronto, Toronto, ON M5G 1L6 Canada, Tel: 011-86-28-61648530; E-mail: limin_chen_99@yahoo.com

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

Citation: Li Y, Li S, Duan X, Liu B, Zeng P, et al. (2013) Modulating Innate Immune Response to Combat Viral Infections-Use HCV as an Example. J Antivir Antiretrovir 5: xvii-xviii. doi:10.4172/jaa.1000e107

6. Gale M Jr, Foy EM (2005) Evasion of intracellular host defence by hepatitis C virus. Nature 436: 939-945.

7. Doehle BP, Gale Jr M (2012) Innate Immune Evasion Strategies of HCV and HIV: Common Themes for Chronic Viral Infection.

8. Foy E, Li K, Sumpter R Jr, Loo YM, Johnson CL, et al. (2005) Control of antiviral defenses through hepatitis C virus disruption of retinoic acid-inducible gene-I signaling. Proc Natl Acad Sci U S A 102: 2986-2991.

9. Li K, Foy E, Ferreon JC, Nakamura M, Ferreon AC, et al. (2005) Immune evasion by hepatitis C virus NS3/4A protease-mediated cleavage of the Toll-like receptor 3 adaptor protein TRIF. Proc Natl Acad Sci U S A 102: 2992-2997.

10. Duong FH, Filipowicz M, Tripodi M, La Monica N, Heim MH (2004) Hepatitis C virus inhibits interferon signaling through up-regulation of protein phosphatase 2A. Gastroenterology 126: 263-277.

11. Bode JG, Ludwig S, Ehrhardt C, Albrecht U, Erhardt A, et al. (2003) IFN-alpha antagonistic activity of HCV core protein involves induction of suppressor of cytokine signaling-3. FASEB J 17: 488-490.

12. Geiss GK, Carter VS, He Y, Kwieciszewski BK, Holzman T, et al. (2003) Gene expression profiling of the cellular transcriptional network regulated by alpha/beta interferon and its partial attenuation by the hepatitis C virus nonstructural 5A protein. J Virol 77: 6367-6375.

13. Chen L, Sun J, Meng L, Heathcote J, Edwards AM, et al. (2010) ISG15, a ubiquitin-like interferon-stimulated gene, promotes hepatitis C virus production in vitro: implications for chronic infection and response to treatment. J Gen Virol 91: 382-388.

14. Chen L, Borozan I, Feld J, Sun J, Tannis LL, et al. (2005) Hepatic gene expression discriminates responders and nonresponders in treatment of chronic hepatitis C viral infection. Gastroenterology 128: 1437-1444.

15. Randall G, Chen L, Panis M, Fischer AK, Lindenbach BD, et al. (2006) Silencing of USP18 potentiates the antiviral activity of interferon against hepatitis C virus infection. Gastroenterology 131: 1584-1591.