

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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The Role of Innate Immunity in Chronic Hepatitis C Viral Infection

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G&H What is the rationale for research of innate immune response to chronic viral infections?

MG Based on the question of why some viral infections are chronic and others are not, we can propose the hypothesis that chronic infections like hepatitis C virus (HCV) are chronic in part because the virus can effectively suppress innate immunity. There are multiple lines of research in innate immunity that can be traced back to a common goal of understanding how innate immune response governs infection outcome. Toward this effort, researchers seek to define the cellular pathways that trigger innate immunity and understand how they regulate viral infection. Once these insights are gained, the information can be used to build therapeutic strategies that can modify infection or infection outcome.

G&H How do the innate and adaptive immune systems affect one another in the setting of chronic HCV infection?

MG There is evidence that innate immune signaling pathways mediated by retinoic acid-inducible gene-I (RIG-I) or Toll-like receptors (TLRs) are dysfunctional during chronic HCV infection and that the processes of these innate immune pathways are required to both stimulate and regulate adaptive immunity. When the innate immune response is dysfunctional, there are certainly consequences for adaptive immunity that could be related to overproduction of immunoglobulins or defects in T-cell function and could contribute to extrahepatic manifestations of HCV, as well as the chronic viral infection.

For example, cryoglobulinemia is an associated effect of HCV infection that is caused by the generation or over-

production of immunoglobulin that precipitates out to the extremities of the body. This condition might be relatable to attenuated or dysregulated innate immune response. Rationale for this theory comes from studies of innate immunity in lupus disease, where autoantibodies, such as nucleic acid antigens, are generated against self-antigens. This is thought to be attributable to alterations and dysregulation of TLR signaling, demonstrating a connection between immunoglobulin dysfunction and the innate immune signaling process.

Further, it is well documented that the T-cell response against HCV is inefficient and that killer T cells do not function properly to take out their targets. This may be relatable to the connection between innate and adaptive immunity as well. T cells mature by recognizing self from nonself. However, part of that maturation depends on antigen presentation in the context of the proper cytokine response, including the production of interferons and other cytokines that are induced, for example, via the RIG-I pathway. When those cytokines are not produced or are produced in reduced quantities, their impact on the adaptive immune response is severe because that adaptive response will not mature properly in the absence of those cytokines. This results in a cytotoxic T-cell response to viral antigens that is both defective and short-lived, thus allowing for sustained viral infection.

G&H How can this research be related to the success or failure of current treatment regimens?

MG This research could provide a basis for understanding why some patients respond to therapy, whereas others do not, although there is a host of mitigating factors for therapeutic response beyond innate immunity. Further, the long courses of therapy required to achieve sustained viral response could be attributed to a deficit in T-cell function that occurs early in infection and cannot be repaired by the administration of exogenous interferon. This is merely a speculation, but future research could focus on and possibly confirm this hypothesis. There are mouse models of other chronic viral infections showing that innate immune response is required to foster the longevity of T-cell response. By extension, it could be speculated that innate immune cytokines are important

to the success of interferon therapy, at least the portion that is dependent on T-cell action.

G&H How has the HCV core protein been shown to interact with the innate immune system?

MG Many investigators, including our team at the University of Washington, have sought to verify the cellular pathways that allow interaction with the HCV core protein. The core protein has been shown to interact with several pathways and, most importantly, can modulate cytokine expression through interaction with pathways that converge on interleukin-8 and on the interferon/Jak-Stat pathway. Currently, the most widely held hypothesis posits that certain variants of the core protein can antagonize Jak-Stat signaling, in part by inducing the expression of negative regulators of that pathway, such as suppressors of cytokine signaling, to antagonize interferon signaling mechanisms. This is significant because the attenuation of interferon signaling results in an attenuation of interferon response and, thus, interferon-based therapies.

G&H Can you describe recent research regarding the NS3/4A protease and how it relates to currently developing protease-inhibitor therapies for HCV?

MG Approximately 4 years ago, the NS3/4A viral protease was identified as an inhibitor of interferon regulatory factor-3 (IRF3). IRF3 is a transcription factor expressed in all cells, including hepatocytes, and is essential for turning on the natural production of interferon during viral infection. By inhibiting this pathway with NS3/4A, HCV is allowed to gain a foothold because cells do not produce an innate immune response to the virus. The HCV protease blocks the RIG-I pathway, thereby preventing IRF3 activation.

Investigation of the RIG-I pathway and the related essential adaptor molecule, interferon promoter stimulator 1 (IPS1), has led to a detailed understanding of the mechanism of the NS3/4A protease. The protease physically targets IPS1, then cleaves it, rendering it inactive. Thus, the entire RIG-I pathway, including IRF3, is deactivated, and IRF3 is never turned on properly during viral infection. The development and testing of protease inhibitors, which can prevent NS3/4A proteolysis of viral proteins and of IPS1 has increased our understanding of NS3/4A actions. Early work suggests that the NS3/4A protease inhibitors can allow the restoration of the innate immune response signaling pathway that mediates immunity against HCV, at least in cell culture models of infection.

G&H How will this understanding of innate immune response ultimately help in devising

maximally efficacious regimens for eradicating HCV infection?

MG Innate immune response cytokines are important for defining the breadth of T-cell response and, most likely, the efficacy of interferon therapy, at least the part that is dependent on direct viral suppression and T-cell action. It has been proposed that therapeutic interferon works via both direct viral suppression and enhancement of killer T cells. If we know that a subset of genes that are turned on by interferon are the genes that can control HCV infection, then we should be able to modify the therapy to enhance the expression of that set of genes, possibly by administering more or less interferon at specific intervals, built around the kinetics of gene expression and interferon support of T-cell response.

Further, recent research into the understanding of how protease inhibitors affect innate immunity and, by extension, response to interferon suggests that the protease inhibitors at higher doses might offer an extra-therapeutic benefit by releasing the viral blockade on the immune response, which will help drive down viral load in the acute setting of treatment. It will be important to facilitate the proper administration of protease inhibitors in combination with interferon to sustain viral response and eradication.

Future research will need to focus on identifying the effector genes of interferon action. When a patient is injected with interferon, literally hundreds of genes are turned on but only a handful of those are important for suppression of HCV and modifying adaptive immunity. Those genes need to be identified to try and adjust the therapeutic application of interferon and enhance those genes specifically. This could potentially affect both the efficacy and side-effect profiles of interferon therapy.

Suggested Reading

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