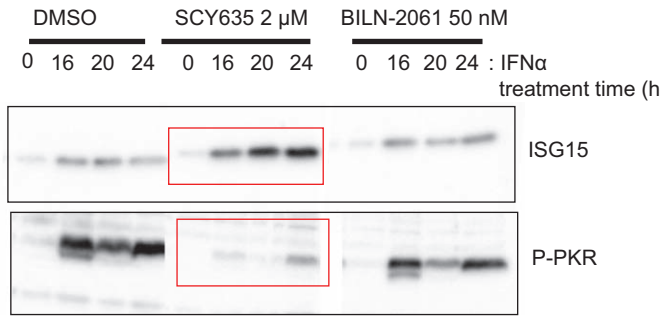

Figure 11.12 Prevention of PKR phosphorylation in response to IFN treatment, and consequent induction of anti-viral ISG protein production, by SCY-635 in HCV (JFH-1)-infected hepatocytes. Inhibition of viral replication using BILN-2061 (HCV NS3/4A protease inhibitor) does not show similar activity.

HepG2 cells.[175] These results clearly point to a role for CypA in the HCV NS5A-mediated interaction with innate immune responses by controlling transcription.[175] A further line of investigation by Watashi *et al.* focused on HCV-mediated blocks on translation and has revealed yet another mechanism by which HCV exploits CypA (Figure 11.12).[208] Interferon-induced activation of PKR resulting in phosphorylation of the translation initiator eiF2α to prevent translation of antiviral proteins, including interferons, is recognized as a mechanism by which HCV subverts innate immune responses.[209] The demonstration that SCY-635, but not an HCV protease inhibitor, significantly reverses the interferon-induced activation leading to expression of antiviral proteins, such as ISG-15, implicates CypA in the HCV-induced block on immune responses.

Clearly, these recent findings of a role for CypA in HCV-mediated avoidance of immune surveillance present opportunities for the use of Cyp inhibitors as immune restoration agents in HCV therapy. The full evaluation of this activity may require human clinical studies since fully immune-competent models of HCV infection are currently lacking.

11.5 Conclusion

The opportunity to separate cyclophilin inhibition from calcineurin activity using modified CsA derivatives has allowed the biology of these abundant proteins to be evaluated more fully over the course of the last 10 years. While the HCV field has seen the use of non-immunosuppressive cyclophilin inhibitors mature into an accepted host-targeted antiviral approach, the recognition that cyclophilins are key players in the replication cycle of many viruses bodes well for future cyclophilin-directed strategies. The ubiquitous use of CsA as the starting point for most of the recent drug discovery efforts is a consequence of the well-established cyclophilin inhibitory activity of this