

of IFN- γ . Dr. Jake Liang has acknowledged that IFN- α is a weak inducer of IFN- γ in PBMCs in vitro (81).

According to Dr. Robert Lanford, the effect of IFN- α , as it pertains to IFN- γ , may not be to stimulate expression of IFN- γ . Instead, the effect of IFN- α , as it pertains to IFN- γ , may be to potentiate the anti-viral effect of IFN- γ (82). This means that the combination of IFN- α and IFN- γ has stronger anti-HCV activity than either cytokine alone.

n. Diagrams of the immune network in immune response against HCV

Figure 28.1 shows a sequence of events that makes use of IL-12 and IFN- γ . HCV expresses various viral proteins when it infects a dendritic cell, and some of these proteins are processed to antigens, and then presented via MHC to T cells. The event of processing and presentation is not shown in the figure. But what is shown is that when the virus infects the DC, the DC responds by expressing IL-12 which, in turn, causes NK cells to express IFN- γ , where the IFN- γ then inhibits viral replication.

Figure 28.2 shows a sequence of events involving IFN- α and IFN- γ . A hepatocyte is shown infected with an HCV virus. Evidence suggests that the infected hepatocyte contacts (touches) a plasmacytoid DC, causing the DC to secrete IFN- α . Takahashi et al. (83) provide evidence that the infected hepatocyte causes the plasmacytoid DC to secrete IFN- α , by direct contact. Once IFN- α contacts an NK cell (or CD8⁺ T cell), the IFN- α may stimulate the NK cell (or CD8⁺ T cell) to secrete IFN- γ , where the IFN- γ has a direct effect on inhibiting HCV replication (84). In characterizing the influence of IFN- α on expression of IFN- γ , Huang et al. (85) found that the G allele at -764 confers a stronger induction of the IFN- γ gene and favors viral clearance and response to exogenous IFN- α -based therapy. The authors also concluded that their discovery took the form of a polymorphism variant in the IFN- γ promoter (-764C/G), where this variant regulates IFN- γ gene expression.

o. Methodology tip – populations of leukocytes in the bloodstream

In assays of gene expression from leukocytes, expression results will depend on method used for purifying the cells, and the homogeneity of the cell type. The most typical

⁸¹ Liang J. E-mail of April 6, 2011.

⁸² Lanford RE. E-mail of April 7, 2011.

⁸³ Takahashi K, Asabe S, Wieland S, et al. Plasmacytoid dendritic cells sense hepatitis C virus-infected cells, produce interferon, and inhibit infection. *Proc Natl Acad Sci USA*. 2010;107:7431–7436.

⁸⁴ Huang Y, Yang H, Borg BB, et al. A functional SNP of interferon- γ gene is important for interferon- α -induced and spontaneous recovery from hepatitis C virus infection. *Proc Natl Acad Sci USA*. 2007;104:985–990.

⁸⁵ Huang Y, Yang H, Borg BB, et al. A functional SNP of interferon- γ gene is important for interferon- α -induced and spontaneous recovery from hepatitis C virus infection. *Proc Natl Acad Sci USA*. 2007;104:985–990.