IFN-gamma has stronger anti-HCV activity than either cytokine alone.

l. Diagrams of the Immune Network in Immune Response Against HCV

Figure 29.1 shows a sequence of events that involves IL-12 and IFN-gamma. HCV expresses various viral proteins when it infects a DC, 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. What is shown, however, is that when the virus infects the DC, the DC responds by expressing IL-12 which, in turn, causes NK cells to express IFN-gamma, where the IFN-gamma then inhibits viral replication.

Figure 29.2 shows a sequence of events involving IFN-alpha and IFN-gamma. A hepatocyte is shown infected with a HCV virus. Evidence suggests that the infected hepatocyte contacts (touches) a plasmacytoid DC, causing the DC to secrete IFN-alpha. Takahashi et al. (166), provide evidence that the infected hepatocyte causes the plasmacytoid DC to secrete IFN-alpha, by direct contact. Once IFN-alpha contacts an NK cell (or a $CD8^+$ T cell), the IFN-alpha may stimulate an NK cell (or $CD8^+$ T cell) to secrete IFN-gamma, where the IFN-gamma has a direct effect on inhibiting HCV replication (167). In characterizing the influence of IFN-alpha on expression of IFN-gamma, Huang et al. (168), found that the G allele at −764 confers a stronger induction of the IFN-gamma gene and favors viral clearance and response to exogenous IFN-alpha-based therapy. The authors also concluded that their discovery took the form of a polymorphism variant in the IFN-gamma promoter (−764C/G), where this variant regulates IFN-gamma gene expression.

m. Methodology Tip—Populations of Leukocytes in the Bloodstream

In assays of gene expression from leukocytes, expression results will depend on the method used for purifying the cells, and the homogeneity of the cell type. The most typical preparation of partially purified white blood cells is peripheral blood mononuclear cells (PBMCs). PBMCs, which include T cells, B cells, NK cells, and monocytes, are typically prepared by isolating leukocytes using density gradient centrifugation (169). This method excludes denser cells, such as red blood cells and polymorphonuclear leukocytes (neutrophils). According to Huang et al. (170),

[166]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;107:7431−36.

[167]Huang Y, Yang H, Borg BB, et al. A functional SNP of interferon-gamma gene is important for interferon-alpha-induced and spontaneous recovery from hepatitis C virus infection. Proc. Natl. Acad. Sci. USA 2007;104:985−90.

[168]Huang Y, Yang H, Borg BB, et al. A functional SNP of interferon-gamma gene is important for interferon-alpha-induced and spontaneous recovery from hepatitis C virus infection. Proc. Natl. Acad. Sci. USA 2007;104:985−90.

[169]Delves P, Martin S, Burton D, Roitt I. Roitt's essential immunology. 11th ed. Hoboken (NJ): Wiley-Blackwell; 2006. p. 138.

[170]Huang YH, Rönnelid J, Frostegård J. Oxidized LDL induces enhanced antibody formation and MHC class II-dependent IFN-gamma production in lymphocytes from healthy individuals. Arterioscler. Thromb. Vasc. Biol. 1995;15:1577−83.