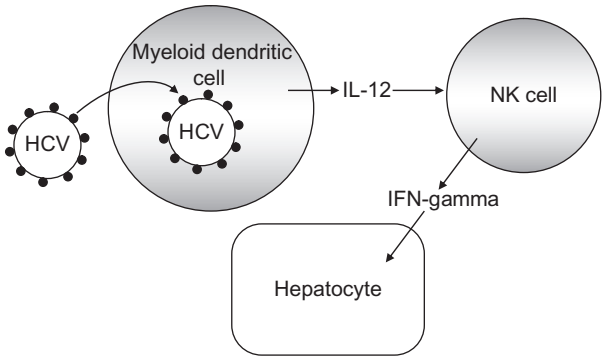

Figure 28.1 IFN-gamma-mediated inhibition of HCV replication via IL-12. Hepatitis C virus infects a dendritic cell where the DC responds by expressing IL-12. The IL-12 induces NK cells to express IFN-gamma

of the Stat4/Stat4 dimer and the Stat3/Stat4 dimer (58). These dimers then travel to the nucleus, where they bind to promoters of IL-12-responsive genes. Stat4 binds to promoters operably linked to a number of genes. The promoter that is used to regulate expression of the IFN-gamma gene has the DNA sequence (59):

TTAAGTGAATTTTTTGAGTTTCTTTTA

I. In HCV infections, IFN-alpha stimulates NK cells (or $CD8^+$ T cells) to express IFN-gamma

The following concerns yet another mechanism of action that involves NK cells, or $CD8^+$ T cells, but that is more subtle than ADCC. During HCV infection, plasmacytoid DCs infiltrate the liver, where they are in proximity of HCV-infected hepatocytes (60). Once inside the liver, contact of HCV-infected hepatocytes with plasmacytoid DCs stimulates these DCs to express IFN-alpha. In turn, the IFN-alpha stimulates NK cells, or $CD8^+$ T cells, or both, to express IFN-gamma, where IFN-gamma in turn inhibits replication of HCV (Fig. 28.2) (61).

Evidence for the scenario shown in Fig. 28.2 includes the following. In HCV infections, plasmacytoid DCs are the dominant IFN-alpha expressing cell (62).

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