j. What immune cells do during HCV infections where the patient develops a chronic HCV infection

In chronic hepatitis C, T cells that specifically recognize antigens of HCV are ineffective and functionally impaired. They are terminally differentiated and do not proliferate well. Moreover, they are impaired in their effector functions due to upregulation of inhibitory molecules, such as programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4).

These HCV-specific T cells are present at very low frequency in both blood and liver of chronically HCV-infected patients, typically comprising less than 0.05% of all the peripheral blood lymphocytes (55).

Once chronic HCV infection is established, NK cells are activated, but the activated NK cells are ineffective against the infection. Activation of NK cells is determined by the expression of CD69, a membrane-bound protein of NK cells.

k. In HCV infections, IL-12 stImulates NK cells to express IFN-gamma

In HCV infection, plasmacytoid dendritic cells are the main sources of IFN-alpha. This expression of IFN-alpha can influence the behavior of NK cells. The continual expression of IFN-alpha by plasmacytoid dendritic cells may contribute to the observed polarization of the NK cell phenotype towards cytotoxicity (56). The NK cell's cytotoxicity kills hepatocytes that are infected by HCV, accounting for the elevated levels of serum liver enzymes that occur during HCV infections. NK cells kill HCV-infected hepatocytes by the mechanism of antibody-dependent cell cytotoxicity (ADCC). ADCC was explained in this textbook, in the earlier chapters on mechanism of action.

The following concerns a mechanism of action that is more subtle than ADCC, namely IL-12's effect of stimulating NK cells to express IFN-gamma (Fig. 28.1). Nellore and Fishman provide a drawing showing one of the sequences of events taking place during HCV infection (57). In this sequence, HCV infects dendritic cells (DCs), the DCs express IL-12, the expressed IL-12 contacts NK cells and stimulates the NK cells to express IFN-gamma, and the IFN-gamma travels to nearby HCV-infected hepatocytes and inhibits the replication of the HCV virus inside these hepatocytes.

IL-12 in the bloodstream or other extracellular fluids binds to the IL-12 receptor. With binding, the receptor transmits a signal into the cell, resulting in the formation

[55] Ahlenstiel G, Titerence RH, Koh C, et al. Natural killer cells are polarized toward cytotoxicity in chronic hepatitis C in an interferon-alfa-dependent manner. *Gastroenterology*. 2010;138:325–335.

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[57] Nellore A, Fishman JA. NK cells, innate immunity and hepatitis C infection after liver transplantation. *Clin Infect Dis*. 2011;52:369–377.