IFN-γ-MEDIATED IMMUNITY IN DENGUE VIRUS INFECTION. MECHANISMS OF INDUCTION AND ACTION

Caio T. Fagundes, Leda Q. Vieira, Danielle G. Souza and Mauro M. Teixeira

Departamento de Bioquímica e Imunologia, ICB, UFMG

Dengue is a mosquito-borne infection which has become a major international public health concern. IFN-γ may play an important role in the control of viral infections. However, the factors involved in host control of IFN-γ production and its role during Dengue infection remain obscure. IFN-γ production started 5 days after DENV2 infection and peaked at day 7. IFN-γ expression was increased especially in $CD4^+$, NK and NKT cells and was preceded by systemic production of IL-12 and IL-18. In IFN-$\gamma^{-/-}$ mice, DENV2-associated lethality was earlier and greater than in WT mice. This was associated with a more rapid and severe clinical manifestation, as assessed by enhanced hemoconcentration and thrombocytopenia. There was also reduced control of dengue virus replication. After DENV2-infection, IL-12p40$^{-/-}$ and IL-18$^{-/-}$ mice showed decreased IFN-γ production, which was accompanied by increased hemoconcentration and thrombocytopenia, and enhanced lethality. However, the viral titers in spleen of both IL-12p40$^{-/-}$ and IL-18$^{-/-}$ mice were similar to those found in WT infected-mice. Blockade of IL-18 in IL-12p40$^{-/-}$ resulted in complete inhibition of IFN-γ production, greater DENV2-replication, and enhanced disease manifestation. DENV2-infected endritic cells produced increased levels of NO infected in presence of IFN-γ. NOS2$^{-/-}$ mice had elevated lethality, enhanced thrombocytopenia and hemoconcentration, and markedly increased viral loads after DENV-2 infection. Thus, IL-12/IL-18-induced IFN-γ production, and consequent NOS induction and NO synthesis are of major importance to host resistance to Dengue virus infection. Strategies that improve the production of these factors by the host could be useful during the control of primary infection by the Dengue virus.

Keywords: Dengue, IFN-gamma, Immunity