

The Role of IFN- γ in CD4 Effector Cell Trafficking and Protection in Response to Influenza Infection Deborah M. Brown, Allison M. Dilzer, Kim Sorrell and Susan L. Swain. Trudeau Institute, 154 Algonquin Ave. Saranac Lake, NY 12983.

Interferon-gamma (IFN- γ) is an important component of the anti-viral response; however, the contribution of CD4 derived IFN- γ in the response to influenza remains poorly characterized. Transfer of CD4 T cell effectors isolated from draining lymph nodes (DLN) or lung of sublethally infected BALB/c mice can confer protection to a subsequent lethal influenza infection. In contrast, transfer of CD4 effectors from the same organs of sublethally infected IFN- $\gamma^{-/-}$ mice do not promote survival after transfer and subsequent lethal infection, suggesting that IFN- γ is required for CD4 mediated protection. To further investigate the role of IFN- γ in protection against lethal influenza infection, TCR transgenic mice, recognizing the peptide HA₁₂₆₋₁₃₈ from influenza hemagglutinin, were used. CD4 T cell effectors from TCR transgenic wildtype (WT) or TCR Tg IFN- $\gamma^{-/-}$ mice were generated in vitro in the presence of Th1 polarizing conditions. Both WT and IFN- $\gamma^{-/-}$ effectors localized to the lung upon intravenous adoptive transfer, even in the absence of inflammation. Upon infection with a lethal dose of influenza, the numbers of WT and $\gamma^{-/-}$ effectors in the lung peaked by day 2 post infection (p.i.) and declined rapidly thereafter. Concomitant with the decline of CD4 effectors in the lung was an influx of host CD8 cells to the lung and airways by day 6 p.i. Surprisingly, both in vitro generated WT and $\gamma^{-/-}$ effectors could confer protection against lethal infection. The ability of in vitro generated effectors to promote survival correlated with in vitro cytolytic activity. Thus, CD4 effectors may utilize both IFN- γ dependent and IFN- γ independent mechanisms to control lethal influenza infection. Supported by PHS grants T32-AI49823 (DMB) and PO1-HL63925.