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Influenza Virus Neuraminidase alters CD4⁺ and CD8⁺ T Cell Responses

The activity of viral neuraminidase (NA) is essential for the release of virus particles from the host cell surface. Antibodies and drugs that neutralize its activity therefore provide an effective means to curtail infection with influenza. NA cleaves the terminal sialic acid from glyco-conjugates on the cell surface. Since sialic acid plays an important role in regulating the interactions between cells we predicted that the immune response to influenza virus, or to other antigens presented by influenza virus-infected cells, would be altered by NA.

We established an *in vitro* system to examine the consequences of influenza virus on dendritic cell (DC) function. NA did indeed influence the response: both CD4⁺ and CD8⁺ T cell proliferation to allogeneic DC was greater after infection with relatively low doses of influenza virus A/PR/8/34. The enhanced response was NA-dependent: it was blocked in the presence of reagents that neutralized NA activity, and treatment of DC with purified NA resulted in an enhanced response. The enhanced proliferative CD4⁺ T cell response was, however, dependent on the dose of A/PR/8/34 used to infect DC. Enhanced responses were observed at low, but not high multiplicities of infection. At high virus doses, the enhanced proliferative response was restored by neutralization of TGF- β 1. Since virus particles are evident in the supernate of DC infected with high but not low doses of influenza virus and NA activates TGF- β 1, it is likely that NA present on virions released from DC infected with high doses of PR8, activates TGF- β 1 in the culture medium.

Since CD8⁺ T cells lack a receptor for TGF- β 1 proliferation of this cell type was not dependent on the dose of influenza virus. Increased CTL activity was induced both *in vitro* and *in vivo* by NA-treatment of peptide-presenting DC. Since the generation of CTL in response to influenza virus infection does not require prior 'activation' of DC by CD4⁺ T cells, we asked whether NA activity contributed to this unconditional CD8⁺ T cell response. This was not the case.

Like proliferation, the quality of the T cell response was dependent on the dose of A/PR/8/34 used to infect DC. Optimal amounts of Th1 type cytokines, IL-2 and γ -IFN, were produced from T cells stimulated by DC infected with low doses of PR8, while Th2 type cytokines, IL-4 and IL-10, were only produced in response to DC infected with high doses of PR8. Our results show that the type of cytokine reflects the location of NA activity. These results suggest that the activity of NA may contribute to the mixed T helper response observed during influenza virus infection.