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### Costimulatory Molecules and the Immune Response to Viruses: Role of 4-1BB/4-1BBL

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The interaction of CD28 on T cells with its ligands B7-1 and B7-2, together with signals through the TCR provides important signals in initial T cell activation. However, subsequent to these initial events, a number of additional costimulatory receptor-ligand pairs are upregulated on the T cell and antigen presenting cells, respectively. These costimulatory molecules may be involved in sustaining, diversifying or amplifying the immune response. In particular members of the TNFR/TNF ligand family, including 4-1BB/4-1BBL, CD27/CD70 and OX40/OX40L appear to be important in sustaining T cell responses subsequent to initial activation. One of the current challenges is to understand the specific roles of these costimulatory pathways during the immune response to infection. 4-1BB is a member of the TNFR family expressed on activated CD4 and CD8 T cells. Its ligand, 4-1BBL, is expressed on activated APC and is regulated by CD40 ligand. *In vitro*, 4-1BBL stimulation acts after CD28-mediated costimulation to augment both CD4 and CD8 T cell proliferation and survival. 4-1BBL also enhances the development of effector function by both CD4 and CD8 T cells. *In vivo*, 4-1BB/4-1BBL-mediated costimulation plays a role in the secondary CTL response to influenza virus, but has little effect on the neutralizing antibody response to vesicular stomatitis virus (VSV) or on the CTL response to lymphocytic choriomeningitis virus (LCMV). However, 4-1BBL can play a role in the response to LCMV under conditions of suboptimal antigenic stimulation. Analysis of T cell expansion in response to influenza virus shows that CD28 is important in early T cell expansion following influenza virus infection, whereas 4-1BBL appears to play a role only late in the immune response.