

The Janus face of costimulation during viral infection

Allan Randrup Thomsen, Faculty of Health Sciences, University of Copenhagen, Denmark

Costimulatory molecules play an important role in determining the consequences of antigen-specific stimulation of T cells. In this study we evaluated the role of CD80 and CD86 in the T-cell response to lymphocytic choriomeningitis virus. As we had previously found that CD28 is not essential for long-term control of this infection, we expected that CD80 and CD86 would also be superfluous. However, most CD80/86^{-/-} mice infected with a low dose of a viscerotropic variant of LCMV never completely cleared the virus, and detailed analysis of the virus-specific CD8 T cells in knock-out mice revealed important phenotypic and functional differences compared to the matched CD8 T cells of wild type mice. Moreover, memory responses of LCMV-primed CD8 T cells from CD80/86^{-/-} mice were severely impaired. Through analysis of CD80/86^{-/-} mice infected with a strain of LCMV not inducing persistent infection, we could show that while part of the difference between knock-out mice and their wild type controls were intrinsic to the absence of CD80 and CD86, persistent viral infection augmented the deficiencies in CD80/86^{-/-} mice. Based on the finding that costimulation was important for a stable antiviral immune response, we tried to improve the T-cell responsiveness of wild type mice using agonistic antibodies against different costimulatory molecules. Contrary to expectations we found that these antibodies caused deletion of virus-specific CD8 cells in association with LCMV infection, but not other viral infections tested. At least in one case we could show that elimination of Fas improved the CD8 T cell response of antibody treated mice suggesting that the involved T cells underwent activation induced cell death (AICD). The data presented show that costimulation is required during viral infection, but provided that virus-induced costimulation is already optimal, artificial augmentation may result in AICD.