Control of Lymphocytes by Protein Phosphatase-6 and SAPS1

Author(s)

David L. Brautigan

Authors affiliation(s)

Center for Cell Signaling, Department of Microbiology, Immunology & Cancer Biology. University of Virginia, Charlottesville, VA, USA

Abstract

Protein phosphatase-6 (PP6) is one member of the PPP protein Ser/Thr phosphatase family, conserved as an essential gene among eukaryotes starting with Sit4 in yeast. PP6 is distinct from its closest PPP relatives PP2A and PP4, because of specific association with conserved regulatory subunits called SAPS (*Sit4-Associated Proteins*). SAPS1 and PP6 participate in signaling that links TNFα to NF-κB and enhance the stability of Iκ-Bε. We discovered by proteomics that SAPS1 associates with one of three ANKRD (Ankyrin-repeat domain) subunits to form trimeric PP6 holoenzymes. SAPS1 also co-immunoprecipitates with DNA-PK (DNA-dependent protein kinase) and is required for DNA-PK activation in response to irradiation. We have produced SAPS1 deficient mice that display accelerated lethality in response to whole body irradiation.

We examined lymphocyte development in these *SAPS1*$^{-/-}$ mice. There were no differences in T or B cells in the primary lymphoid organs or in the mature B or T cells in the spleen or blood of SAPS1 deficient mice compared to control mice, however there was an increase in eosinophils. Eosinophilia is often associated with type 2 immune responses and we discovered a huge increase in serum IgE in SAPS1 deficient mice, as well as an increase in CD4 T cells producing IL-4. Our hypothesis is that SAPS1/PP6 constrains CD4 T-helper 2 (Th2) cells from inappropriate Th2 differentiation. More recent results examined SAPS1/PP6-dependent changes in intracellular signaling of CD4+ T cells from SAPS1 deficient mice, based on changes in gene expression and proteomics.