Inflammation in mice ectopically expressing human Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome-associated PSTPIP1 A230T mutant proteins.

Abstract:

Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne Syndrome (PAPA syndrome) is an autoinflammatory disease caused by aberrant production of the proinflammatory cytokine interleukin-1. Mutations in the gene encoding proline serine threonine phosphatase-interacting protein-1 (PSTPIP1) have been linked to PAPA syndrome. PSTPIP1 is an adaptor protein that interacts with PYRIN, the protein encoded by the Mediterranean Fever (MEFV) gene whose mutations cause Familial Mediterranean Fever (FMF). However, the pathophysiological function of PSTPIP1 remains to be elucidated. We have generated mouse strains that either are PSTPIP1 deficient or ectopically express mutant PSTPIP1. Results from analyzing these mice suggested that PSTPIP1 is not an essential regulator of the Nlrp3, Aim2, or Nlrc4 inflammasomes. Although common features of human PAPA syndrome such as pyogenic arthritis and skin inflammation were not recapitulated in the mouse model, ectopic expression of the mutant but not the wild type PSTPIP1 in mice lead to partial embryonic lethality, growth retardation, and elevated level of circulating proinflammatory cytokines.