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Long-lived plasma cells and memory B cells are the primary cellular components of long term humoral immunity, and as such are critically important for the protection afforded by most vaccines against infectious diseases. We recently discovered that mice lacking expression of SAP/SH2D1A generate strong acute IgG antibody responses after a viral infection (LCMV), but exhibit a near complete absence of virus-specific long-lived plasma cells and memory B cells, despite the presence of virus-specific CD4<sup>+</sup> T cells (Crotty et al, *Nature* 2003). This defect is due to a surprising inability to form germinal centers.

The human genetic disease XLP, caused by mutations in the gene *SH2D1A*, encoding SLAM-associated protein (SAP), is frequently characterized by an inability to control chronic infections—particularly Epstein-Barr Virus (EBV)—and by progressive hypogammaglobulinemia. We therefore examined the immune responses and pathology in SAP deficient animals during a chronic lymphocytic choriomeningitis virus (LCMV) infection as a model of the human clinical disease. Illness and weight loss were much more severe in SAP<sup>-</sup> mice compared to wild type mice. SAP<sup>-</sup> mice exhibited prolonged viremia and viral replication in tissues. This inability to control a chronic LCMV infection was associated with both T cell and B cell response defects. Immunopathology was correlated with hyperactive CD8 T cell responses. Germinal center formation was blocked, and hypogammaglobulinemia was observed in the chronically infected SAP<sup>-</sup> animals. These results were consistent with the heightened T cell expansion, germinal center defects, and absence of long-lived plasma cell production we observed in both primary and secondary SAP<sup>-</sup> immune responses to viral infection. These findings in a chronic viral infection mouse model recapitulate key features of human XLP, and clarify SAP's critical role in the regulation of both cellular and humoral immune responses.