Immune tolerance is established centrally in the thymus and bone marrow for both T and B cells, respectively. However, autoreactive cells escape into the periphery where they are subjected to several mechanisms of peripheral tolerance. Failures in inducing central or peripheral tolerance are hallmarks of autoimmune diseases (Theofilopoulos et al, Nat Immunol 2017). These are a diverse and complex array of disorders that target self structures. They are characterized by autoreactive T or B lymphocytes attacking self either within an organ (organ-specific autoimmunity) or systemically (systemic autoimmunity). MHC restriction together with other genetic factors as well as environmental triggers contribute to the pathogenesis of autoimmune diseases (Rioux et al, Nature 2005). Recent advances in host-microbiota research underscore also the microbiome as a fundamental component in the development of autoimmunity (Ruff et al, Trends Mol Med 2015). Autoinflammatory disorders are differentiated from autoimmune disorders by innate inflammation in the absence of aberrant adaptive immunity. Rapid progress in genomics have led to definition of multiple new autoinflammatory diseases (Park et al, Nat Rev Immunol 2012). Their phenotypes explain key roles of innate immune components in health and disease. Similarly to autoimmunity, the microbiome has also been recognized as a modulator of these disorders (Lukens et al, Nature 2014). Taken together, autoinflammatory and autoimmune diseases arise due to a combination of innate or adaptive immune dysregulation, and environmental and microbiota influences in a genetically prone host.