The cross talk between host and pathogen starts with recognition of bacterial signatures through pattern recognition receptors (PRRs), which mobilize downstream signaling cascades. We investigated the role of the cytosolic adaptor caspase recruitment domain family, member 9 (CARD9) in tuberculosis. This adaptor was critical for full activation of innate immunity by converging signals downstream of multiple PRRs. Card9(-/-) mice succumbed early after aerosol infection, with higher mycobacterial burden, pyogranulomatous pneumonia, accelerated granulocyte recruitment, and higher abundance of proinflammatory cytokines and granulocyte colony-stimulating factor (G-CSF) in serum and lung. Neutralization of G-CSF and neutrophil depletion significantly prolonged survival, indicating that an exacerbated systemic inflammatory disease triggered lethality of Card9(-/-) mice. CARD9 deficiency had no apparent effect on T cell responses, but a marked impact on the hematopoietic compartment. Card9(-/-) granulocytes failed to produce IL-10 after Mycobacterium tuberculosis infection, suggesting that an absent antiinflammatory feedback loop accounted for granulocyte-dominated pathology, uncontrolled bacterial replication, and, ultimately, death of infected Card9(-/-) mice. Our data provide evidence that deregulated innate responses trigger...
excessive lung inflammation and demonstrate a pivotal role of CARD9 signaling in autonomous innate host defense against tuberculosis.