Innate immune responses are vital for pathogen defense but can result in septic shock when excessive. A key mediator of septic shock is tumor necrosis factor-$\alpha$ (TNF-$\alpha$), which is shed from the plasma membrane after cleavage by the TNF-$\alpha$ convertase (TACE). We report that the rhomboid family member iRhom2 interacted with TACE and regulated TNF-$\alpha$ shedding. iRhom2 was critical for TACE maturation and trafficking to the cell surface in hematopoietic cells. Gene-targeted iRhom2-deficient mice showed reduced serum TNF-$\alpha$ in response to lipopolysaccharide (LPS) and could survive a lethal LPS dose. Furthermore, iRhom2-deficient mice failed to control the replication of Listeria monocytogenes. Our study has identified iRhom2 as a regulator of innate immunity that may be an important target for modulating sepsis and pathogen defense.