Genetically determined susceptibility to tuberculosis in mice causally involves accelerated and enhanced recruitment of granulocytes.

Abstract: Classical twin studies and recent linkage analyses of African populations have revealed a potential involvement of host genetic factors in susceptibility or resistance to Mycobacterium tuberculosis infection. In order to identify the candidate genes involved and test their causal implication, we capitalized on the mouse model of tuberculosis, since inbred mouse strains also differ substantially in their susceptibility to infection. Two susceptible and two resistant mouse strains were aerogenically infected with 1,000 CFU of M. tuberculosis, and the regulation of gene expression was examined by Affymetrix GeneChip U74A array with total lung RNA 2 and 4 weeks postinfection. Four weeks after infection, 96 genes, many of which are involved in inflammatory cell recruitment and activation, were regulated in common. One hundred seven genes were differentially regulated in susceptible mouse strains, whereas 43 genes were differentially expressed only in resistant mice. Data mining revealed a bias towards the expression of genes involved in granulocyte pathophysiology in susceptible mice, such as an upregulation of those for the neutrophil chemoattractant LIX (CXCL5), interleukin 17 receptor, phosphoinositide kinase 3 delta, or gamma interferon-inducible protein 10. Following M. tuberculosis challenge in both airways or peritoneum, granulocytes were recruited
significantly faster and at higher numbers in susceptible than in resistant mice. When granulocytes were efficiently depleted by either of two regimens at the onset of infection, only susceptible mice survived aerosol challenge with M. tuberculosis significantly longer than control mice. We conclude that initially enhanced recruitment of granulocytes contributes to susceptibility to tuberculosis.