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Tuberculosis Risk is Spread within the Hallmarks of the Disease

Abstract

Statement of the Problem: Heritable susceptibility to tuberculosis (TB) is complex and polygenic in nature (1,2). Only five to ten percent of humans that come in contact with the bacterium *Mycobacterium tuberculosis (Mt)* will manifest the disease, provided no acquired- or congenital immunodeficiency were present. We still lack a viable explanation for the observed epidemiologic fact.

Background: Activation of macrophages via proinflammatory cytokines IFN-γ and Interleukin (IL)-17 can kill intracellular bacteria such as *Mt*. Instead, macrophages stimulated by the Toll-like receptor (TLR)-10 agonists show an anti-inflammatory effect. The TLR-10 acts by inhibiting the TLR-2 signaling from the cell membrane. The TLR-2 is the *Mt*-binding protein by which activated macrophages can internalize (and kill) *Mt*. Inactivation of the TLR-2 protein might convey a risk for developing the disease. This was supported by our finding that TLR2 gene polymorphisms, which either inactivate the TLR2 gene product or have a dominant-negative role in TLR-2-signaling are associated with elevated risk for tuberculosis in the Croatian Caucasian population (5).

Findings: The genome-wide study found that three single nucleotide polymorphisms (SNPs) within the HLA class II loci were significantly associated with TB (2) suggesting that adaptive immunity is of paramount importance for defense against TB. In our studied population, an SNP in the TLR10 gene was associated with risk for TB, analyzed by the dominant model of inheritance, however, this was contrasted by the fact that SNPs in the IL17A&F genes were not (4).

Conclusion & Significance: Studying genetic risk by association analyses (3,4) or genome-wide screening (2) led us propose that clinical manifestation of TB is a state above certain “risk-threshold”. Threshold is reached by accumulation of seemingly minor susceptibilities divided between the hallmarks of the disease (Fig 1). The model suggests that every human population has its own mosaic of genetic risks for TB.