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THE HALLMARKS OF TUBERCULOSIS AND THEIR CLINICAL SIGNIFICANCE

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Introduction: Heritable susceptibility to tuberculosis (TB) is complex and polygenic in nature. Only five to 10 percent of humans that meet 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 pro-inflammatory cytokines IFN- 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.

Findings: The genome-wide study found that three single nucleotide polymorphisms (SNPs) within the HLA class II loci were significantly associated with TB (Nat Gen, 2016) 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* and *F* genes were not.

Conclusion & Significance: Studying genetic risk by association analyses or genome-wide screening 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 (we suggest there are five hallmarks). The model suggests that every human population has its own mosaic of genetic risks for TB.

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