Zlatko Dembic, J Infect Dis Ther 2018, Volume 6
DOI: 10.4172/2332-0877-C1-037

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Tuberculosis risk is spread within the hallmarks of the disease

Statement of the Problem: Heritable susceptibility to tuberculosis (TB) is complex and polygenic in nature. 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.

Method: Activation of macrophages via proinflammatory cytokines IFN-v 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, 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; suggesting that adaptive immunity is of paramount importance for defense against TB. In our studied population, 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.

Conclusion & Significance: Studying genetic risk by association analyses or genome-wide screening led us to 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.

Recent publications

1. Bretscher P A et al. (2017) Immune class regulation and its medical significance part II of a report of a workshop on foundational concepts of immune regulation. Scand J Immunol 85:242-250.
2. Sveinbjornsson G. et al. (2016) HLA class II sequence variants influence tuberculosis risk in populations of European ancestry. Nature genetics 48:318-322.
3. Vrbanec J et al. (2016) Genetic risk of tuberculosis is spread within the hallmarks of the disease. Immunother Open Acc 2:117.
4. Bulat-Kardum L. et al. (2015) Genetic polymorphisms in the toll-like receptor 10, interleukin (IL)17A and IL17F genes differently affect the risk for tuberculosis in Croatian population. Scand J Immunol 82:63-9.
5. Etokebe G E et al. (2010) Toll-like receptor 2 (P631H) mutant impairs membrane internalization and is a dominant negative allele. Scand J Immunol. 71:369-381 (2010).

Biography

Zlatko Dembic is a Professor of Immunology, Cell-Biology and Microbiology at University of Oslo. He has been working in science at various institutions in Academia (Medical Faculty, Zagreb, Croatia; Max-Planck Institute for Immunogenetics, Tubingen, Germany; Basel Institute for Immunology, Switzerland; Institute of Immunology, Oslo, Norway) and industry (Roche, Switzerland). He has his expertise in molecular biology shown by over 100 publications to date and a monograph about cytokines in immunology. He is co-inventor of the US patent (Roche) covering the production and use of etanercept (Enbrel), which is a successful (anti-TNF) biological used to treat several autoimmune diseases including rheumatoid arthritis. He was the president of the Norwegian Society for Immunology and Editor-in-chief of the *Scand J Immunol* (at present, Associate Editor). He is a Visiting Professor of Medicine at medical school in his hometown Rijeka (Croatia).

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