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Infection Congress 2018: Tuberculosis risk is spread within the hallmarks of the disease - Zlatko Dembic - University of Oslo

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Statement of the Problem: Heritable susceptibility to tuberculosis (TB) is complicated and polygenic in the nature. 5-10% of humans that come in exposure with the bacterium Mycobacterium tuberculosis (Mt) will get 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 finish) Mt. Inactivation of the TLR-2 protein might create a risk for acquiring 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 related 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 Tuberculosis, 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 studies or genome-wide screening led us to propose that clinical manifestation of TB is a state above certain risk-threshold. Threshold is achieved by deposition of seemingly minor susceptibilities divided between the hallmarks of the disease. The model suggests that every human population has its own criteria's of genetic risks for TB.

Regarding genetic predisposition to tuberculosis, we advise that the maximal risk for clinical manifestation requires complementation of sub-risks divided among the hallmarks of the disease. Clinical tuberculosis would only be known if at least one from each group of the genes encoding putative 5 (perhaps 7) hallmarks of the disease are mutated or changed epigenetically. These mutations/changes could be either sporadic (usually by the influence of the environment like other infection (HIV), nutrition, smoking, radiation etc.) or inherited. Ignorance of the immune attack is one of the hallmarks for TB that is shared with cancer. Perhaps, a similar immunotherapy as the recent one used in treating immunogenic types of cancer (anti-PD1, or/and anti-CTLA4) could be also successful in therapy of (multi-drug) resistant TB.

Consequently, we believe that it is important to study genetic risk factors for TB in every human subpopulation similarly as it is done for cancer, especially now that novel immunotherapies, have opened new ways to treatment of advanced cases. Active tuberculosis is a multi-organ disease caused by primary infection or as a reactivation of hidden tuberculosis.

Accordingly, active tuberculosis could be primary tuberculosis or reactivation tuberculosis. Primary tuberculosis occurs when the immune system is unable to protect against the Mycobacterium tuberculosis bacterium (MTB) infection. Reactivation tuberculosis, as the name suggests, is the reactivation of contained mycobacterial infection. Reactivation Tb is the most common form of active tuberculosis, revealing 90% of the cases. The lung is the most commonly known organ; other organ systems commonly affected include the gastrointestinal system, the musculoskeletal system, the lymph reticular system, skin, liver, and the reproductive system.

The World Health Organization (WHO) estimates that, annually, around 8 million people get active tuberculosis globally, and nearly 2 million people die from this disease. Of every 10 people infected with M. tuberculosis, one may develop an active infection at any point of time in their lifetime. The WHO reported in 2017 that the estimated global incidence rate for tuberculosis has decreased by 1.5% each year since 2000. However, despite these substantial gains and drastic global efforts to eradicate tuberculosis, the disease still accounts for significant morbidity and mortality worldwide. Developing countries like India, Pakistan, the Philippines, China, South Africa, Indonesia, and Nigeria experience the highest morbidity and mortality rates. When combined, these countries accounted for 64% of all tuberculosis-related deaths in 2016, according to the WHO.

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