Special Article

Precision Medicine and Tuberculosis

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Tuberculosis is an infectious disease generally caused by inhaling *Mycobacterium tuberculosis* that occur to anyone at any age and all over the world. But there are particular groups of individuals being at a higher risk of acquiring the disease than others, including individuals with insufficient or suppressed immune systems, i.e., infants, foreign-born individuals in TB prevalent countries, HIV/AIDS patients, diabetics, alcoholics, long-standing users of immune-suppressed drugs, e.g. corticosteroids, people live in poor sanitation and crowded countries such as formerly in South and South-East Asia Regions, and others.

Formerly, tuberculosis was prevented, diagnosed and treated by circumstantial and various clinical means. Such achievements depends largely on variable potentiality of attention and ambiguity of human responsible, which left of a good number of remaining infective sources. With the present era of advanced genomic technology, the medical practice has adapted to the comprehensive "Precision Medicine", but occur the question "Will precision medicine ever be possible to lead to the control of tuberculosis?"

In responding to such a question, one must intimately understand the molecular basis of tuberculosis and its causative organism that mostly is *Mycobacterium tuberculosis (MTB)*. In recent years human genetics has achieved tremendous progress with approach to understand the molecular basis of human diseases. The theme of human genetics is genes and genetic variations. The diversity of genetic susceptibility to common diseases in the human population enables researchers to understand the molecular mechanisms of diseases by the genetic approach.

Unfortunately, our extensive literature scanning of over 150 reports***, most hypothesis-free efforts on world-wide research to renovate the traditional idea of TB genetic susceptibility have not identified the candidate genes with important roles in containing *MTB* infection in association with active tuberculosis, and the TB-associated loci in the genome- wide association study (GWAS) harbors no gene with function in *MTB* infection. Nevertheless, the hope remains from a few findings cited at the followings, though controversies remained, should be mentioned.

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1. A few loci worthy of attention, i.e. *2q35* (Greenwood CM, et al. Am J Hum Genet 2000; 67: 405-16), *8q12313* (Baghdadi JE, et al. J Exp Med 2006; 203: 1679-84), and *20q13* reported in African populations (Stein CM, et al. PLoS One 2008; 3:e4094. PubMed: *19116662*), and *5p15* in linkage with delayed type hypersensitivity (Cobut A, et al. J Exp Med 2009;206:2583-91).
2. The linkage locus at *chr2q35* contains a candidate gene *SLC11A1*. The gene associated with TB is a solute carrier family 11 member 1 gene (*SLC11A1*) at *Chr2q35*, which is the natural resistance-associated macrophage protein 1 gene (*NRAMP1*); the genetic effect is absolutely unrelated to DTH response (Forget A, et al. Infect Immun 1981;32:42-47).
3. *NRAMP1* is a proton acting as a divalent-metal efflux pump at the phagosomal membrane of macrophage; it depletes divalent metal as Zn^{2+}, CU^{2+}, FE^{2+} and Mn^{2+} from bacteria-containing phagosomes. Deletion of these divalent metals may render the *MTB* more sensitive to the killing by oxygen radicals (Forbes JR, et al. Trends Microbiol 2001;9:397-403).
4. A number of studies have reported the genetic association of *HLA* class II polymorphisms with TB susceptibility. The DQbeta1Asp57 allele was associated with increased risk of progressive pulmonary tuberculosis. The DQbeta1Asp57 demonstrates reduced ability to bind to the immunogenic peptides of *MTB*, which may weaken the Th1 response. (Delgado JC, et al. J Immunol 2006;176:1090-7).
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7. Increased TB susceptibility was associated with the DR2 allele in Indonesian (Bothamley GH, et al. J Infect Dis 1989;159:549-55) and Asian Indian (Brahmajothi V, et al. Tubercle 1991;72:123-32), the DQB1*0503 allele in Cambodian (Goldfeld AE, et al. JAMA 1998;279:226-8).
8. Genome-wide SNP-based linkage in tuberculosis patients in Thais (Mahasirimongkol S, et al. Genes Immun 2008;10:77-83).
9. Toll-like receptors (TLRs) play an essential role in the activation of innate immunity against microbial infection (Takeda K, et al. Semin Immunol 2004;16:3-9). Davila S, et al. identified the TB association of the TLR7 and TLR8 locus in Indonesian cohort. This study highlights the potential function of the TLRs in anti TB immunity (PLOs Genet 2008; 4:e1000218; PubMed: 18927625)

10. The DNA variations of the IFN-y gene (*IFNG*) were associated with TB susceptibility (Dorman SE, et al. The Lancet 2004;364:2113-21).
11. MSMD mutations of the IL-12 signaling gene which have the phenotypes with low penetrance and better prognosis (Fieschi C, et al. J Exp Med 2003;197:527-35; Picard C, et al. Am J Hum Genetics 2002;70:336-48)
12. Identification of a novel association tagged by a single-nucleotide polymorphism (SNP) *rs4331426* at 18q11.2. (Thye T, et al. Nat Genet 2010;42:739-41.
13. Findings suggesting that host genetic risks for TB are affected by age at onse1 of TB (Mahasirimongkol S, et al. J Hum Genet 2012;57:363.

Additional Bibliographies

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3. Salie M, van der Merwe L, Moller M, Daya M, van der Spuy GD, van Helden PD, et al. Associations between human leukocyte antigen class I variants and the Mycobacterium tuberculosis subtypes causing disease. J Infect Dis. 2014;209(2):216-23.