Topic Review

Precision Medicine and Tuberculosis*

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The era of molecular medicine begun after the completion of the Human Genome Project in 2003 (NHGRI). The availability of the data base of approximately 3 billion base pairs and 30,000 genes in human DNA has led to a better understanding of physiological and pathological changes in the human body.

Precision Medicine Initiative

"Tonight, I am launching a new Precision Medicine
Initiative to bring us closer to curing diseases like
cancer and diabetes --- and to give all of us access to
the personalized information we need to keep
ourselves and our families healthier."
President Barack Obama, State of the Union Address,
January 20, 2015

Precision Medicine

After U.S. President Barack Obama proposed in 2015 the "Precision Medicine Initiative" and provided US$215 million for the program in obtaining the breach of human genome in associated with diseases, the Genome-Wide Association Studies (GWAS) started.

GWAS is considered the most powerful available tool to study the association between phenotypes and genotypes and also to identify common low-penetrance **susceptibility** loci in a particular disease. Each person gave a sample of DNA, from which millions of genetic variants are read using SPN arrays. If one type of variant (one allele) is more frequent in people with the disease, the variant is said to be associated with that disease.

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Tuberculosis

Tuberculosis is an infectious disease generally caused by inhaling *Mycobacterium tuberculosis* that occur to anyone at any age and all over the world, but only about 10% individuals are at a higher risk of acquiring the disease than others. Approximately 90% of those infected with *Mtb* have asymptomatic, latent TB infection, with only a 10% lifetime chance of progression to clinically active TB. Those 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, as well as diagnosed and treated by circumstantial and 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. In the present era of advanced genomic technology, medical practice is adapting to 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)*. On believing that through a genetic approach to finding genes and genetic variations such as the diversity of genetic susceptibility to diseases in human populations would verify the molecular mechanisms of tuberculosis pathogenesis.

Unfortunately, our extensive literature review of available reports indicated that most hypothesis-free efforts to revamp the idea of TB genetic susceptibility have not identified candidate genes playing an important role in active tuberculosis. Nevertheless, the hope remains from a few findings cited at the followings, although controversies remained, should be mentioned.

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).

5. Increased TB susceptibility was associated with the DR2allele 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).

6. Genome-wide SNP-based linkage in tuberculosis patients in Thais (Mahasirimongkol S, et al. Genes Immun 2008; 10: 77-83).

7. 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)

8. The DNA variations of the IFN-y gene *(IFNG)* were associated with TB susceptibility (Dorman SE, et al. The Lancet 2004; 364: 2113-21).

9. 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)

10. Identification of a novel association tagged by a single-nucleotide polymorphism (SNP) *rs4331426* at *18q11.2.* (Thye T, et al. Nat Genet 2010; 42(9):739-41)

11. Findings suggesting that host genetic risks for TB are affected by age at onset of TB (Mahasirimongkol S, et al. J Hum Genet 2012; 57:363-7).

Addendum

Diagnosis of tuberculosis nowadays, can be made by a molecular test which detects the DNA in TB bacteria. It uses a sputum sample and give result in less than two hours; Or by a urine test for detecting glycan antigen lipoarabinomannan (LAM), a marker of active TB. Both provide broad implications for pulmonary TB scanning and early treatment.

TB Vaccine: BCG vaccine has been in practice for preventing primary TB infection for almost a century (97 years). A new generation of vaccines intended to suppress the transition from infection to disease on person already infected (tuberculin-positive persons). Presumably they already have implants containing dormant bacilli.

Conclusions

At this point, the role of precision medicine has not been accomplished in the arena of tuberculosis practice. Although certain genetic risk loci at the positions 11p13 and 18q11 have been reported and it is possible that in the near future new generation vaccines, such as those of Lowrie DB, et al. would become available for use in suppressing the transition from infection to disease in tuberculin-positive persons.

Documents Used in Editing

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