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Role of Cytokine's Functional Single Nucleotide Polymorphisms in Tuberculosis

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Dear editor,

Single-nucleotide polymorphism (SNP) is one of the most common types of DNA sequence variants in human genome (1). Each SNP shows a difference in only one nucleotide. More than 10 million SNPs are mapped in human genome, so in average, there is one SNP in every 300 nucleotides. Single-nucleotide polymorphisms can be located in coding or noncoding regions, within a gene or outside of it. As stated in the definition of polymorphism, SNPs are not involved in disease occurrence directly, but they could be disease-associated via their functions (2). In this regards, there is a definition for functional SNP when it is ascertained that the polymorphism has an influence on the gene function (3). Obviously, when the SNP occurs in a gene (like splicing site) or a gene's regulatory region (like promoter, the 3' and 5' untranslated region), it may have a direct role in gene function. Therefore, they could be considered as a group of disease- associated SNPs. The border between a disease associated SNP and a disease causing mutation is very narrow, and in most cases, there is controversy for a SNP to be disease associated (4).

Functional SNPs are of the reasons of differences in normal range functions of proteins, which could turn out to be one of the susceptibility factors of the disease, but not the major cause of the disease. For instance, the role of genetic polymorphism in the cytokine function can be considered. A part of immune system consists of cytokines, which regulate the immune responses. These molecules are secreted by immune cells to stimulate target cells in a special pathway. The function of cytokines and their receptors are crucial in inflammatory responses (5).

It is clear that the level of cytokine secretion influences the kind of immune response pathway. Many studies have revealed that cytokine gene polymorphisms influence the amount of cytokine production in the normal range. It means that according to the genotype of SNPs, there are three kinds of cytokine production: low, intermediate, and high. Most of these functional polymorphisms are located in a promoter region of cytokines, thus could affect the level of gene transcription and expression (6), which may influence susceptibility, severity, and outcome to different diseases. T-helper cells are crucial in determining the immune response pathway and have two major subsets, Th1 and Th2, based on the production of interferon γ (IFN-γ) and interleukin (IL)-4 cytokines, respectively. This subset differentiation is signaled by IL-12 and IL-4 for Th1 and Th2, respectively. Th1 cells are essential for immune responses against intracellular and Th2 for extracellular pathogens. Th17 cells are a new subset of T- helper cells, which play an important role in inflammatory diseases (7). Since the SNPs affect the cytokine production, SNPs affect the subset differentiation of T-helper cells. Therefore, the genetic basis of individuals is determining their Th1/Th2 balance normally that forms their immune response basis (7). Mycobacterium tuberculosis (Mtb) is an obligatory intracellular bacterium and the causative agent of tuberculosis (TB). As the Th1 cells are the main arm of cellular immunity, the production of IFN-γ and IL-2 is the basis of resistance to TB, whereas IL-4 and IL-13 are representatives of Th2 associated with disease status. The SNPs + 874A/T and + 2109A/G in intron 1 and -56C/C in the promoter region of the IFN-γ gene are associated with TB development in several populations (8). Many studies have revealed that these SNPs are putatively affective on the cytokine secretion and protein level (9). There is the same story for the IL-2 cytokine. Functional polymorphism -330T/G in a promoter region of the IL-2 gene is considered a susceptibility variation for TB. This polymorphism has an influence on IL-2 production. These patterns of SNPs prevent the production of Th1 cytokines and then create limitations in complete function of Th1 cells. Thus, the immune system is not able to eliminate Mtb completely.

Interleukin-4 is representative of Th2 cells. Some studies have been conducted on the role of variations of these

cytokines in TB. One of the most known functional SNPs in the IL-4 gene promoter is -589 C/T, associated with the activity rate of IL-4 cytokine (10). In active TB, the high level of Th2 cytokines like IL-4 is responsible for down-regulation of macrophages, which makes Mtb latent or aggressive.

In conclusion, it should be regarded that certain SNPs are considered as normal variations of a gene which are not disease causing, but they may have influences on function of the products of the gene. Cytokines have a critical role in progression or resistance of TB; so, it seems reasonable that functional SNPs be important in susceptibility to TB.

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