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REVIEW

Host genome polymorphisms and tuberculosis infection: What we have to say?

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Abstract Several epidemiology studies suggest that host genetic factors play important roles in susceptibility, protection and progression of tuberculosis infection. Here we have reviewed the implications of some genetic polymorphisms in pathways related to tuberculosis susceptibility, severity and development. Large case-control studies examining single-nucleotide polymorphisms (SNPs) in genes have been performed in tuberculosis patients in some countries. Polymorphisms in natural resistance-associated macrophage protein 1 (NRAMP1), toll-like receptor 2 (TLR2), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), interleukin-1 receptor antagonist (IL-1RA), IL-10, vitamin D receptor (VDR), dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN), monocyte chemoattractant protein-1 (MCP-1), nucleotide oligomerization binding domain 2 (NOD2), interferon-gamma (IFN-γ), inducible nitric oxide synthase (iNOS), mannose-binding lectin (MBL) and surfactant proteins A (SP-A) have been reviewed. These genes have been

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variably associated with tuberculosis infection and there is strong evidence indicating that host genetic factors play critical roles in tuberculosis susceptibility, severity and development.

Contents

Introduction

Tuberculosis remains a major global health problem by causing ill-health among millions of people each year and ranking as the second leading cause of death from an infectious disease worldwide [1]. The latest estimates were almost 9 million new tuberculosis cases and 1.4 million tuberculosis-related deaths in 2011 [1]. It has been well established that both innate and adaptive immune responses are required for host control of tuberculosis infection [2,3]. In tuberculosis pathogenesis, the host cellular immune response determines whether an infection is arrested as latent or persistent infection or progresses to the next stages, active tuberculosis infection. Efficient cell-mediated immunity hinders tuberculosis infection by permanently arresting the infection at latent or persistent stage, but if the initial infection in the lung is not controlled or if the immune system becomes weakened, *Mycobacterium tuberculosis* can cause active pulmonary or extra pulmonary tuberculosis [4]. Therefore, it is expected that the genetic variants of molecules involved in innate host-defense mechanisms are associated with host susceptibility to tuberculosis [5].

Approximately 90% of tuberculosis-infected individuals will remain asymptomatic with latent infection and only 10% will develop active disease, again, suggesting that host genetic factors play an important role to regulate the progression of tuberculosis infection [5]. Differential rates of tuberculosis infection and clinical outcomes among races, ethnicities, and families suggest a plausible genetic contribution toward tuberculosis susceptibility [6]. Complex interactions of *M. tuberculosis* with environmental and host genetic factors play a critical role in tuberculosis infection [6]. Several genomic studies demonstrate that host genetics strongly influence tuberculosis susceptibility [7–10]. Unraveling the mechanisms underlying the genetic variations that influence the susceptibility or resistance to tuberculosis may lead to better understanding tuberculosis pathogenesis and the development of novel strategies for prevention and treatment of tuberculosis [5].

Assessing the contributions and functional consequences of human genetic polymorphisms to tuberculosis susceptibility or disease progression remains a major challenge. In previous publications, our group has discussed the role of human genetic polymorphisms in sepsis and dengue virus infection [11–13]. Here, we will review the implications of specific human genetic polymorphisms related to susceptibility and severity of tuberculosis infection.

Discussion

Natural resistance-associated macrophage protein 1 (NRAMP1)

NRAMP1 is located on the endocytic compartment of resting macrophages and is recruited to the membrane of the phagosome depending on the pH gradient [14]. NRAMP1 acts as a divalent cation transporter or antiporter across phagosomal membranes that is expressed only in reticuloendothelial cells [6,15]. These facts suggest that NRAMP1 may inhibit the replication of intracellular pathogens by altering the phagolysosomal environment. NRAMP1 is a critical mediator in the innate immune response to tuberculosis infection which leads