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Personalized medicine approach in mycobacterial disease

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Abstract

Mycobacterial diseases are a group of illnesses that cause a considerable number of deaths throughout the world, regardless of years of public health control efforts. Personalized medicine is a new but rapidly advancing field of healthcare. Personalized medicine in the field of mycobacteriology may be applied in the different levels of management such as prevention, diagnosis, treatment and prognosis. A genetic predisposition and a protein dysfunction study are recommended to tailor an individual approach in mycobacterial diseases.

Keywords

Mycobacterial; TB; NTM; Personalized medicine

1. Introduction

1.1. Mycobacterial disease

Mycobacterial diseases are a group of illnesses that are caused by the mycobacterium species. They include *Mycobacterium tuberculosis* (MTB) complex, nontuberculous mycobacterium (NTM), and *Mycobacterium leprae*.

MTB is a member of the MTB complex causes tuberculosis (TB); other members include *Mycobacterium africanum* and *Mycobacterium bovis*. In 2010, there were 8.8 million (range, 8.5–9.2 million) incident cases of TB worldwide; 1.1 million (range, 0.9–1.2 million) deaths from TB among human immunodeficiency virus (HIV)-negative people and an additional 0.35 million (range, 0.32–0.39 million) deaths from HIV-associated TB [1].

NTM are ubiquitous organisms that are prevalent in the environment. NTM has been isolated from domestic water supplies, workplaces, and hospitals [2]. Currently, more than 125 different species of NTM exist in the environment, many of which cause human illness [3]. The prevalence of NTM diseases was reported as 1.6–1.8 per 100,000 individuals in most industrialized countries. Recent studies proposed that NTM pulmonary disease is becoming increasingly prevalent in North America, with annual incidence rates of 13 cases

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Conflict of Interest
There is no conflict of interest regarding this manuscript for the author.

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per 100,000 in people ≥50 years of age [4]. It was speculated that the burden of NTM disease might soon exceed that of tuberculosis in industrialized nations [5].

M. leprae (the bacteria responsible for leprosy) grow slowly and mainly affect the skin, nerves, and mucous membranes. Leprosy is still a health problem in some parts of the world [6].

2. Personalized medicine

Personalized medicine is a new but rapidly advancing field of healthcare. Personalized medicine is about making the treatment as individualized as the disease. It involves identifying genetic, genomic, proteomic and clinical information in order to make accurate predictions about a person's susceptibility to developing disease, the course of disease and its response to treatment.

In order for personalized medicine to be used effectively by healthcare providers and their patients, these findings should be transformed into precise diagnostic tests and targeted therapies. This has begun to happen in certain areas of infectious diseases, such as testing patients genetically to determine their likelihood of having a serious adverse reaction to HIV medications [7].

Personalized medicine should not be confused with "genetic medicine". Genetics, a field more than 50 years old, is the study of inheritance of a gene or a group of genes. It investigates individual genes and their effects on health. Genetic diseases, seemingly "simple" hereditary disorders, can be influenced by other genes, as well as by environmental factors such as diet and exposure to toxins [8].

Genomic and personalized medicine aspire to target more complex diseases, such as cancer, heart disease, and now infectious diseases, which are primarily influenced by environmental factors and their interaction with the human genome. Because these diseases have strong multigene components—and in some cases the diseases might be caused by errors in the DNA between genes instead of within genes—they can be better evaluated using a whole-genome approach. Increasing concern about confidentiality of genetic data was addressed by the Genetic Information Non-Discrimination Act of 2008 (GINA) [9] that prohibits the use of genetic/genomic information by health insurance companies in order to determine a person's eligibility for insurance, or to determine insurance premiums, as well as by employers in order to make decisions regarding hiring and firing, assigning jobs, and promoting and demoting. Because consumers should now be able to obtain their genome profiles and other genetic information without fear of retribution, GINA is reinvigorating the field of genomic testing.

Rapid and affordable single nucleotide polymorphism (SNP) genotyping over the whole genome is now possible, allowing for genome mapping uncovering novel associations not possible with a candidate gene approach.

The genome-wide association studies (GWAS) allocate the genotyping of the most frequent genetic polymorphism in the genome without hypothesizing about the genomic location of

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the causal variants. The completion of the human genome sequence, the deposition of SNPs into public databases, the rapid improvements in SNP genotyping methods and the International HapMap (haplotype map) project have allowed the genetic association field to progress to the stage that this approach is feasible. Previous investigations [10,11] and the International HapMap project have shown that most common variations in the genome can be represented by approximately 300,000 SNPs in White populations [12]. African and other populations with greater variation and less linkage disequilibrium need more SNPs to ensure coverage of the entire genome [13].

The development of the above techniques to accurately assess diagnostic and prognostic profiles and select patients with mycobacterial diseases who will respond to a given therapeutic agent is highly desirable and is the foundation for the future delivery of personalized medicine.

2.1. Personalized medicine in mycobacterial diseases

The idea that mycobacterial disease is not only influenced by bacterium but also by both genetic and environmental factors was formally stated 59 years ago [14]. At the time it was stated in reference to TB, but new studies have suggested that it applies to NTM as well.

While the exposure to NTM is universal and billions of people have latent tuberculosis infection (LTBI), only a few persons develop clinical disease [15]. It may be reasonable to state normal host defense mechanisms must be effective enough to prevent the infection. The interactions between mycobacterium and its environment have been suggested. In a minority of cases there is an obvious identifiable risk factor such as in the HIV population and immunocompromised patients, such as those undergoing transplants and chemotherapy [3,16]. A substantial proportion of these patients have no preexisting lung disease and no demonstrable immunodeficiency. A small number of NTM are predominantly nonsmoking elderly women [17]. In the remainder, a complex interaction of genetic and environmental factors causes the development of clinical mycobacterial disease. However, potential mycobacterium-host interaction at the gene level is still very limited according to recent studies.

Personalized medicine in the field of mycobacteriology may be applied in the different levels of management, such as prevention, diagnosis, treatment and prognosis. The predisposition and protein dysfunction studies are recommended to tailor an individual approach to each patient (Fig. 1).

Personalized medicine may answer some pertinent questions, such as:

Who is at risk of contracting LTBI after exposure to MTB?

Who will convert to an active case?

How can the diagnosis, treatment, and prognosis of mycobacterial infection be improved?

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2.1.1. Who is at risk of contracting LTBI after exposure to MTB?—Indeed, the exposure to MTB happens in the environment, but the susceptibility to infection is a personal phenomenon.

Many investigations have confirmed that genetic factors are involved in whether or not one is susceptible to mycobacterial disease, and these investigations include results from adoption studies, twin studies, genome-wide linkage and population-based, case–control association studies [18].

Recently, an association was reported between NTM lung disease and the polymorphisms of the natural resistance-associated macrophage protein 1 gene [19].

This finding could raise the possibility of genetic susceptibility for patients with NTM lung disease. Afterward, toll-like receptors-2 (TLRs) [20], Interleukin-12 receptor beta-1 [21], interferon-gamma and interferon-gamma receptor-1 genes [22] were studied.

The identification of host genetic factors, such as human leukocyte antigens (HLA) of major histocompatibility complex and/or cytokines and related receptors associated with susceptibility or resistance to TB, may provide genetic markers to predict the development of mycobacterial disease after exposure to bacteria.

The immune mechanisms in TB have been investigated and it is known from the IL-12/IL-23/IFN-g pathway, together with other cytokines and factors, that they are vital for the immunologic response [23].

In previous studies, a candidate gene approach was carried out using SNPs associated with mycobacterial disease [15,24–26]. As a consequence, those studies had limited potential to uncover novel genomic regions that play a role in the etiology of mycobacterial disease.

Convincing evidence indicating the importance of IFN-g in particular in the control of mycobacterial infections has been found in both experimental and clinical studies [27,28]. IFN-g receptor genes may play a role here. However, the present study failed to show an association between IFN-gamma receptor 1 (IFNGR1) polymorphism and increasing susceptibility to TB [15], but the mutation in IFNGR2 increased the susceptibility in sporadic TB patients [29].

Polymorphism in IL-1 [30,31], IL-6 [32], IL-12 and its receptors [33,34], HLA [35,36], vitamin D receptor haplogroups [24,25], and mitochondrial DNA haplogroups [26] were extensively studied with some promising results.

2.1.2. Who will convert to an active case?—Susceptibility to developing TB disease after exposure is influenced by complex interactions between the host and the pathogen, and genetic and environmental factors [18].

Several genetic loci are involved in susceptibility to mycobacterial disease. Recently, it was shown that the mutation of a human gene encoding the chemokine (C-C motif) ligand 2 CCL2, which is essential for the recruitment of monocytes and T-cells, may increase the risk of developing active TB after exposure [37]. Recently a study showed new genetic targets

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which influence the risk of developing active TB among latently infected individuals by GWAS [38]. Finding the strong association between potential immune gene polymorphisms and LTBI will be progress with regard to patient selection for LTBI treatment in the future.

2.1.3. Personalized medicine may improve diagnosis of mycobacterial infection—Personalized medicine has improved the diagnostic approach to latent TB. Interferon-gamma release assays (IGRAs) can locate the patient's immunologic response to mycobacterial tuberculosis-specific antigens. It is a starting point for a personalized diagnosis of mycobacterial diseases.

Finding the genetic susceptibility to facilitate the occurrence of drug-resistant mycobacterium might be another fascinating approach that has not yet been studied.

There is a significant demand for personalized biomarkers for the diagnosis of NTM infection in humans that needs to be addressed.

2.1.4 Personalized medicine may change treatment of mycobacterial infection —Finding personalized biomarkers to best define chemotherapy protocols, individualized treatment duration, and predict risk of adverse events with antibiotics would be other interesting markers for clinicians.

A study showed a polymorphism of the tumor necrosis factor gene (lymphotoxin A+252G/A genotype) in a pulmonary tuberculosis patient associated with impaired response to treatment [39].

Anti-TB drug-related hepatotoxicity is a serious worldwide medical problem among TB patients. It has been proposed that the production and elimination of the toxic metabolites depends on the activities of several enzymes, such as N-acetyl transferase 2, cytochrome P450 oxidase and glutathione S-transferase. It was shown that DNA sequence variations or polymorphisms at those enzymes loci could alter the activities of enzymes and increase the risk of hepatotoxicity. Since the prevalence of polymorphisms is different in worldwide populations, the risk of anti-TB hepatotoxicity varies in the populations. Thus, the knowledge of polymorphisms at those loci, prior to medication, may be a useful tool to evaluate the risk of anti-TB hepatotoxicity [40]. Another study showed that polymorphism of the N-acetyl transferase 2 gene is a risk factor for INH-induced hepatotoxicity [41].

2.1.5. Personalized medicine may improve prognosis of mycobacterial infection—The results of a recent study demonstrated that genetic polymorphisms of the IL-12+ IFN-g pathway may individually or jointly contribute to the prognosis of pulmonary TB [42].

Importantly, personalized medicine will help to bridge current treatment goals (bacteriologic cure) with patient cure. Currently, TB is treated and classified based on bacteriology response. However, the organ damage such as pulmonary fibrosis and its consequence effects are not explored enough. The current TB treatment must focus on a patient cure strategy other than cleaning mycobacterial agents from the body.

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The biomarkers should be located to predict pulmonary fibrotic changes after TB treatment to reach this goal.

Conclusion

The future needs to include the stratification of mycobacterial-infected patients with personalized biomarkers in order to reach management goals. The inconsistent treatment results in different studies come from heterogeneity of patients with different genetic pools. Personalized medicine may organize the diagnosis and treatment strategies making it possible to deliver a better quality of healthcare to patients.

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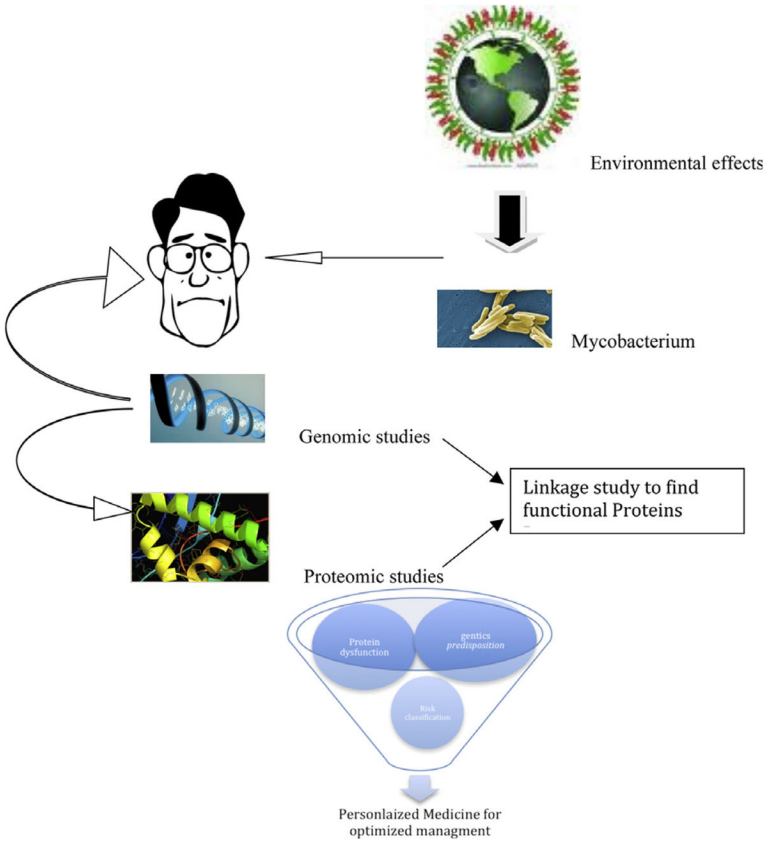

Fig. 1.
A strategy for personalized medicine in mycobacterial diseases.