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Review

Immune-related gene polymorphisms in pulmonary diseases

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ABSTRACT

Between the DNA sequences of two randomly-selected human genomes, which consist of over 3 billion base pairs and twenty five thousand genes, there exists only 0.1% variation and 99.9% sequence identity. During the last couple of decades, extensive genome-wide studies have investigated the association between single-nucleotide polymorphisms (SNPs), the most common DNA variations, and susceptibility to various diseases. Because the immune system's primary function is to defend against myriad infectious agents and diseases, the large number of people who escape serious infectious diseases underscores the tremendous success of this system at this task. In fact, out of the third of the global human population infected with *Mycobacterium tuberculosis* during their lifetime, only a few people develop active disease, and a heavy chain smoker may inexplicably escape all symptoms of chronic obstructive pulmonary disease (COPD), lung cancer, and other smoke-associated lung diseases. This may be attributable to the genetic makeup of the individual(s), including their SNPs, which provide some resistance to the disease. Pattern recognition receptors (PRRs), transcription factors, cytokines and chemokines all play critical roles in orchestrating immune responses and their expression/activation is directly linked to human disease tolerance. Moreover, genetic variations present in the immune-response genes of various ethnicities may explain the huge differences in individual outcomes to various diseases and following exposure to infectious agents. The current review focuses on recent advances in our understanding of pulmonary diseases and the relationship of genetic variations in immune response genes to these conditions.

1. Introduction

The complexity of the immune system, the intrinsic genetics, polymorphisms and interactions with the extrinsic environment, are all predetermined factors governing disease progression and pathogenic outcome. The generation of a balanced immune response by the host is critical to counter environmental factors, and genetic variations can result in varied outcomes.

Before the widespread use of rapid sequencing techniques, the primary focus of research was to determine the presence or absence of specific genes or to observe their level of expression (transcription and translation) in response to stimuli. Due to this approach, genetic diseases were considered rare compared to physiological causes of disease. However, with the innovations in sequencing protocols and technological advancements, detailed understanding of the genetic variability between individuals, and even between cells, and the connection of these variations to disease outcomes has been revealed. It is now becoming apparent that genetic polymorphisms are not only an important factor in disease development, but also can be employed as biomarkers. Clinically, biomarkers are used as prognostic indicators as well as precautionary markers for some diseases (McGeough and Bjourson, 2013).

Various studies discussed in this review have demonstrated significant association of SNPs present in immune genes with increased susceptibility to diseases and infections. Additionally specific SNPs can be associated with the survival rate of the patient after treatment. Therefore, understanding genetic variations in key players of the immune system can have far-reaching effects on pathophysiology. The most frequently found variations in the genome include single-nucleotide polymorphism (SNPs), which arise from mutations and provide another level of diversity (Brookes, 1999).

Several SNPs in the genome are known to be responsible for complex phenotypes in terms of medical relevance, and may significantly affect multiple molecular pathways important in the adaptation of related individuals (Fig. 1) (Viana et al., 2015). Polymorphisms present in the DNA sequences of intergenic spacers are not lethal to organisms and are considered both stable and heritable. However, polymorphisms that cause changes in the amino acid sequence are

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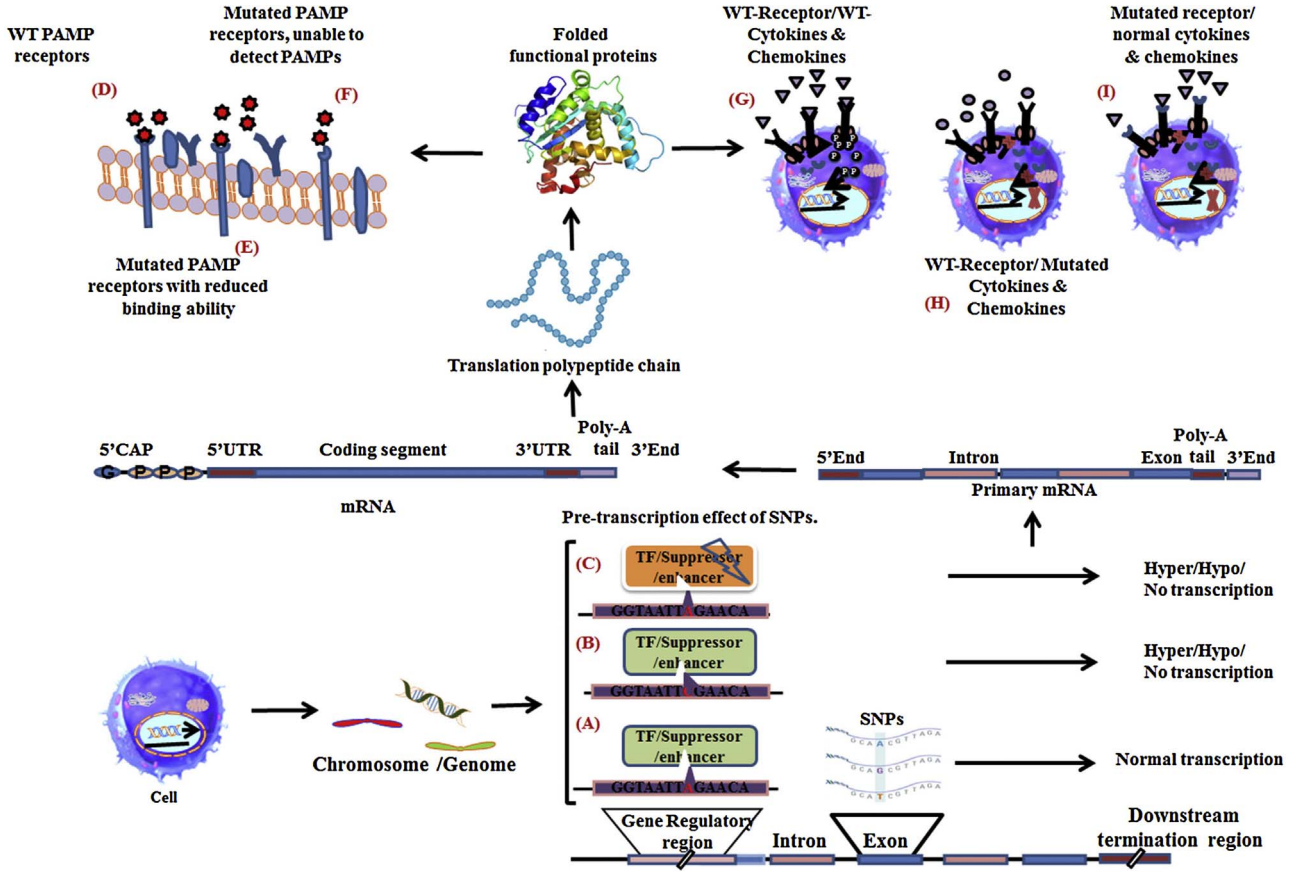

Fig. 1. Schematic diagram representing a general mechanism of SNP mediated regulation of gene function. The expression of a gene is tightly regulated from the promoter region. Sequence of promoter region recognized by transcription factor, enhancer or suppressor molecules for optimal activation. Any variation in the promoter region sequence may lead to defective binding of transcription factor/enhancer/suppressor which may lead to no-, hypo-, or hyper- transcription. A. Normal (wild type) regulatory region of the gene and their transcription factor/suppressor and enhancers. B. SNP in the promoter region. C. Mutated transcription factor/enhancer/suppressor. Mutation in the Exon region may also lead to mutated protein. D. Normal PAMP receptors. E. Mutated receptor with less binding affinity for PAMPs. F. Mutated receptor with no binding ability for PAMPs. Figure also demonstrates the regulation of immune responses which involve recognition of cytokines and chemokines by their receptors. Any change in this interaction may lead to reduced or hyper immune response as demonstrate in: G. Wild type (WT)-Receptor/WT-Cytokines & Chemokines. H. WT-Receptor/Mutated Cytokines & Chemokines and I. Mutated receptor/normal cytokines & Chemokines.

called non-synonymous changes and may lead to alterations in protein structures and function (Cargill et al., 1999; Sunyaev et al., 2000). Of these, the SNPs that are linked to phenotypic risks and are within genes of functional importance are considered for association studies (Yuan et al., 2006). SNPs may influence protein conformation, promoter activity or pre-mRNA and RNA splicing. (Cartegni and Krainer, 2002; Prokunina et al., 2002).

Those SNPs present at transcription factor binding sites in the promoter or intronic enhancer regions can also influence transcriptional regulation (Prokunina and Alarcón-Riquelme, 2004; Prokunina et al., 2002). Moreover, SNPs may also function by disrupting exonic splicing enhancers or silencers (Cartegni and Krainer, 2002). Therefore, each individual SNP in a gene might exert a different effect on pathophysiology. SNPs have been identified in several genes (~582 genes) known to play crucial roles in human survival by interfering with metabolism and immunological functions. Several of these are also known to regulate variable morphological characteristics in humans (Norrgard and Schultz, 2008). Furthermore, genetic variants can not only cause disease conditions, but also may provide resistance to infection and disease.

Interestingly, the genetic variability of pathogens allows them to switch host species leading to the spread of new strains, which is both a major veterinary and public health concern. The genetic alterations resulting in these adaptations are still being investigated (Viana et al., 2015), although in general it is believed that mutations help pathogens overcome various host challenges resulting in their rapid spread. During the recent Ebola outbreak in 2014 several SNPs, including amino acid changes, were identified and found to be unique to the new strains (Gire et al., 2014). Similarly, recent Zika virus epidemic may be attributed to SNPs, which may adapt their codon usage bias to mimic that in humans (de Melo Freire et al., 2015). The focus of this review is to provide information about the genetic associations of immune-related genes with known significance in pulmonary diseases. Due to the occurrence of both protective and predisposing alleles for the same molecule, a comprehensive understanding of the molecular mechanisms associated with alterations in immune-related genes will be helpful for designing better therapeutic strategies to combat pulmonary diseases. To this end, we will discuss the role of SNPs associated specifically with pattern recognition receptors, transcription factors, cytokines, and chemokines.

1.1. Pattern recognition receptors (PRRs) and their impact on lung disease susceptibility

The Immune system consists of innate and adaptive arms that must act cooperatively to successfully combat a wide-variety of potentially detrimental external and internal stimuli and for healing of damaged tissue. The innate immune system contains PRRs that identify both pathogen-associated molecular patterns (PAMPs) and endogenous molecules released by damaged cells, termed damage associated molecular patterns (DAMPs), to invoke inflammatory responses. The families of PRRs include transmembrane toll-like receptors (TLRs), C-