Gene Therapy and Immunotherapy in Tuberculosis

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In 2016, there were 6.3 million new cases of tuberculosis (TB) around the world, which consisted of 490,000 cases of multi-drug-resistant tuberculosis (MDR-TB) [1]. Over the past years, the number of MDR-TB cases has risen worldwide, while no more anti-TB drug has been approved by the US Food and Drug Administration. During these years, new therapeutic options have been considered as adjunctive therapy for MDR-TB, including gene therapy and immunotherapy.

Previous studies showed a genetic basis of drug resistance, the severity of the disease, and the complications of treatment, such as drug-induced hepatitis (DIH) and tuberculosis related immune reconstitution inflammatory syndrome (TB-IRIS). A study on about 5,000 suspected MDR-TB in India showed that 75% of patients had S531L mutations and 94% had S531TI mutations that caused drug resistance [2]. In another study in India on 290 patients with MDR-TB, the S531L mutation was the most resistant etiologic to rifampin [3]. The mutations in the two genes of 2518 MCP-1GG and 1607 MMP-12G/2G are associated with increased tissue damage, severe disease and delayed response to treatment in TB [4]. The mutation in the gyr A gene results in high levels of resistance to gatifloxacin and moxifloxacin and a poor outcome in MDR-TB [5]. The ABCB1 gene polymorphism may result resistant to rifampin and ethambutol [6] and genetic polymorphisms of GSIM1, NAT2 and CYP2E1 genes cause changes in hepatic acetylation, and if slow acetylation occurs, the incidence of DIH increases [7]. In a study, LTA4H polymorphism was associated with the incidence of TB-IRIS in HIV/TB-co-infected patients, and occurrence of mutant genotypes of the gene (CT/TT) was more resulted to severe TB-IRIS compared to the wild type of the gene (CC) [8].

The role of cytokines in the incidence and severity of tuberculosis is also well known. On this basis, therapeutic interventions, especially in animal models has been performed. One study in infected-mice with MDR-TB showed an intra-tracheal Ad GM-CSF combined with anti-TB drug resulted in faster pulmonary cleaning [9], similar to another study, which achieved this result by immunotherapy with IL-2 and GM-CSF [10]. In another study in mice with MDR-TB, immunotherapy with a plasmid DNA boosted the immune system, shortened the treatment course, and improved the outcome [11]. However, in another study on 68 MDR-TB infected mice, immunotherapy reduced pulmonary inflammation, decreased number of microorganisms in the spleen and decreased interferon gamma, but did not affect the level of pulmonary bacilli [12]. It has also been suggested that MDR-TB is often associated with some immunocompromised status, and immunotherapy may boost the immune system and improve the disease’ outcome. Some cytokines that play a major role in immune function in TB, include IL-2, 12, 18 and interferon gamma, and the therapeutic use of these cytokines can improve the immune system and reduce cell death. In a clinical trial, administration of interferon-gamma has led to an improvement in MDR-TB [13].

However, during the preceding years, there has been a relative decline in the production of effective antibiotics for tuberculosis, especially MDR-TB, but several studies have been conducted on gene therapy and immunotherapy in these years, and the results from these studies, at least in animal models, has been promising. We hope human studies on gene therapy and immunotherapy will be completed and approved in the near future, not only as adjunctive treatment, but also as the main treatment for anti-TB and especially MDR-TB.

1Macrophage chemoattractant protein
2Matrix metalloproteinase
3Leukotriene A4 hydroxylase
4Adenovirus encoding granulocyte-macrophage colony-stimulating factor

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Bibliography


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