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REVIEW

Immunotherapy for tuberculosis: future prospects

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Abstract: Tuberculosis (TB) is still a major global health problem. A third of the world's population is infected with *Mycobacterium tuberculosis*. Only ~10% of infected individuals develop TB but there are 9 million TB cases with 1.5 million deaths annually. The standard prophylactic treatment regimens for latent TB infection take 3–9 months, and new cases of TB require at least 6 months of treatment with multiple drugs. The management of latent TB infection and TB has become more challenging because of the spread of multidrug-resistant and extremely drug-resistant TB. Intensified efforts to find new TB drugs and immunotherapies are needed. Immunotherapies could modulate the immune system in patients with latent TB infection or active disease, enabling better control of *M. tuberculosis* replication. This review describes several types of potential immunotherapies with a focus on those which have been tested in humans.

Keywords: tuberculosis, HDT, immunotherapy, treatment

Introduction

Tuberculosis (TB) remains a major global public health problem. It is estimated that a third of the world's population is infected with *Mycobacterium tuberculosis*, the causative agent of TB. There are ~9 million new cases of TB with 1.5 million deaths annually.[1] Effective management of TB infection and TB disease requires treatment for at least 6 months. This long treatment duration, coupled with side effects of anti-TB drugs, leads to noncompliance resulting in the emergence of drug-resistant TB. Of note, drug-resistant TB is more difficult to treat and significantly increases TB control program costs in high TB endemic countries which have meager resources to begin with.[2]

The World Health Organization reports that several countries have increasing numbers of patients with multidrug-resistant (MDR)-TB, TB caused by *M. tuberculosis* resistant to at least isoniazid and rifampin.[1] To make the situation worse, only 20% of MDR-TB cases were started on appropriate drugs, with <50% successful treatment outcome.[1] Furthermore, the number of MDR-TB cases increased three-fold between 2009 and 2013, mainly due to lack of effective treatment.[1] In addition, several countries with high prevalence of MDR-TB also suffer from increasing numbers of cases of extensively drug-resistant (XDR)-TB with resistance to isoniazid, rifampin, fluoroquinolones, and aminoglycosides. The treatment of XDR-TB is even more difficult and the outcome unpredictable.[1,3] Thus, MDR- and XDR-TB are major global public health problems because of the lack of effective treatment, the need for a much longer duration of treatment with second line

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or experimental drugs, and the risk of further spread locally and more widely through immigration. Enhanced efforts to develop new TB therapeutics are urgently needed. The progress in TB drug development has been slow and none of the new drugs tested so far have allowed standard treatment regimen shortening.[4] Host-directed therapy using immunomodulators is a promising approach which must be explored for better control of TB. This paper reviews the strategies and prospects for TB host-directed therapy immunotherapeutics.

TB latency, host immunity, and *M. tuberculosis* adaptation

A better understanding of the nature of host–pathogen interactions is required for the development of immunotherapeutics and to predict the roles of new immunotherapeutics for the management of TB infection and/or disease. It is interesting to note that only ~10% of *M. tuberculosis*-infected individuals develop TB, but how the majority of infected people control or clear the infection is not fully known. Until recently, it was believed that latent TB infection (LTBI) is a state of mycobacterial dormancy during which the immune system contains virtually all persisting *M. tuberculosis* organisms in a static state within granulomas.[5–8] An emerging consensus resulting in a paradigm shift in the field maintains that both active TB and LTBI represent dynamic spectra with variable levels of actively replicating and inactive bacilli in different granulomas present in the same infected individual.[9,10]

The immune response can greatly alter the proportions and absolute numbers of actively replicating *M. tuberculosis* in infected persons with concomitant changes in TB disease risks. Because the infection is largely intracellular during paucibacillary LTBI and early reactivation disease, T-cell responses are critically important for protective immunity. CD4+, Th1, and CD8+ T-cell responses are involved in the control of *M. tuberculosis* replication in vivo, as are the cytokines they produce (eg, interferon [IFN-γ], tumor necrosis factor [TNF]-α, and interlukin [IL]-2).[11–13] However, these responses alone appear insufficient for bacterial clearance as these T-cell subsets peak during active TB disease and decrease after spontaneous immunologic control without eradication of TB infection. Other immune subsets which tend to accumulate in mucosal tissues, including γδ T-cells,[14,15] CD1 restricted T-cells,[16] and mucosa-associated invariant T-cells,[17,18] can impact on the levels of protective responses. Figure 1 summarizes protective and counterproductive immune responses in TB.

M. tuberculosis has an incredible capacity to adapt in vivo to a variety of stressful conditions. Pathogenic *M. tuberculosis* can replicate intracellularly in professional

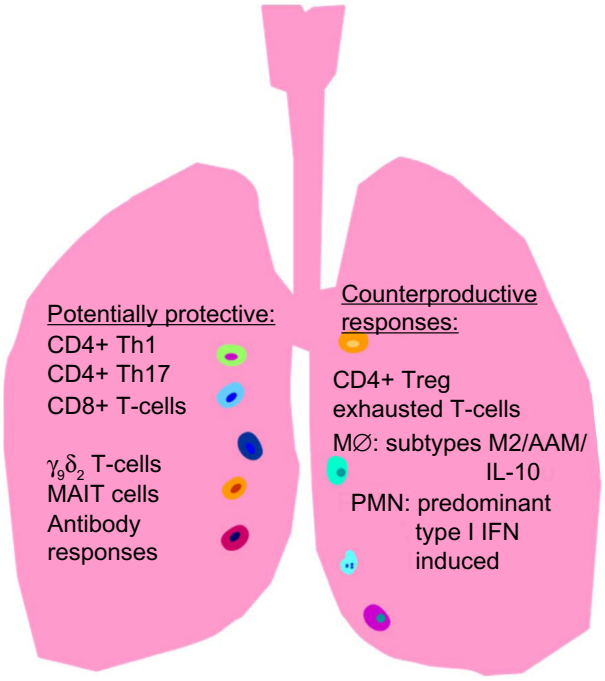

Figure 1 Tuberculosis (TB)-specific mucosal immune responses are important for protection against latent TB infection (LTBI) reactivation. Th1 CD4+ and Th17 CD4+ T-cells, CD8+ T-cells, $\gamma_9\delta_2$ T-cells, mucosa-associated invariant T (MAIT) cells, and sIgA/IgG antibody responses are potentially protective against LTBI reactivation which could reduce both TB disease and TB transmission.

Notes: All of these T-cell responses will be considered major targets for immunotherapy in this project because they can recognize intracellular *Mycobacterium tuberculosis*, the major pathogen reservoir during LTBI. Mucosal antibody responses also could protect against initial infection and transmission, and are being studied in other funded work by our consortium of investigators. CD4+ regulatory T-cell, T-cell exhaustion, alternatively activated macrophages unable to kill intracellular *M. tuberculosis* and type I IFN-induced polymorphonuclear (PMN) leukocytes can negatively regulate protective immunity in the lung.

mononuclear phagocytes despite numerous mechanisms available to kill intracellular bacilli. The pathogen switches from predominant glucose metabolism when replicating at high rates extracellularly to lipid-based metabolism after uptake in phagosomes of mononuclear phagocytes. The organism thrives in aerobic conditions reaching its highest levels of replication, but can also survive prolonged periods of microaerophilic and even anaerobic conditions. Certain gene sets or regulons are activated intracellularly (eg, *DosR*) and are thought to be involved in persistence of *M. tuberculosis* during LTBI.[19] In addition, other genes associated with reactivation of LTBI have been identified (eg, resuscitation-promoting factors).[20–22] Although previous data suggest that TB immunity is predominantly directed against antigens produced by replicating *M. tuberculosis*, there is a growing body of evidence that latency-specific antigens are targeted as well. *M. tuberculosis* mediates multiple immune evasion strategies, including blockade of major histocompatibility complex expression,[23–25] prevention of phagolysosomal fusion,[26–28] and inhibition of IFN-γ signaling.[29–34] However, the majority of

persons infected with TB never develop disease, indicating that the host–pathogen balance can be tipped in favor of the host leading to protective immunity.

Most primary and reactivation TB disease occurs in the lung, and this is the main source of TB transmission. These clinical facts combined with the accumulated knowledge in this area indicate that an optimally effective immunotherapy will need to target mucosal immunity in the lung.

TB immunotherapeutics

Immunotherapies ideally should modulate the immune system in a way that helps the host control or eliminate *M. tuberculosis*. Whole mycobacteria,[35,36] mycobacterial products,[37–39] cytokines, and drugs have been considered as possible immunomodulators. Table 1 summarizes host-directed immunotherapeutics which have been tested for the treatment of TB in humans.

M. vaccae and other atypical mycobacteria

There are some controversies on the benefits of *Mycobacterium vaccae*-based immunotherapy. A single injection enhanced sputum culture conversion at 1 month and led to marked radiographic improvement at 6 months,[40] but these promising findings were not reproducibly found in other studies.[41] Nonetheless, meta-analysis of 54 studies using intradermal injection of *M. vaccae* reported that immunotherapy based on *M. vaccae* could enhance sputum conversion and improve radiographic changes.[36] Similarly, oral administration of *M. vaccae* enhanced sputum conversion in newly treated TB patients.[42] Other environmental mycobacteria, such as *M. indicus pranii*, also have shown promising results in animal models.[43]

RUTI®

RUTI is a therapeutic vaccine made of detoxified cellular fragments of *M. tuberculosis*, delivered in liposomes. It is prepared by mechanically disrupting colonies of *M. tuberculosis* in phosphate-buffered saline with 4% TritonX114, heating at 65°C for 40 minutes followed by lyophilization and encapsulation in liposomes made of phosphatidyl choline.[44] In mice and guinea pigs, this therapeutic vaccine was found to have potential for both prophylaxis and immunotherapy.[45] So far, it has been shown in Phase I and II clinical trials involving healthy volunteers and cases with LTBI that this vaccine is safe and immunogenic.[46,47]

Table 1 Immunomodulating host-directed therapies for treatment of TB in humans

Therapeutics	Composition	No. of patients	TB type (outcome)	Refs
Mycobacterium vaccae	Killed, intradermal	NA	Meta-analysis of 54 studies on newly diagnosed pulmonary TB (improved sputum conversion and X-ray changes)	36
	Capsule	41 (two arms)[Φ]	Faster smear conversion	42
RUTI®	Detoxified cellular fragments of *Mycobacterium tuberculosis*	NA	Phase I and II clinical trials on LTBI cases or healthy volunteers (immunogenic, reasonable tolerability)	46,47
Autologous MSC	MSC	30	MDR or XDR patients (21/30 with radiologic improvement)	54
V5 immunitor	Inactivated pooled blood	55 (two arms)	Re-treatment or proven MDR (higher rate of sputum conversion)	62
Cytokines and cytokine inhibitor	IL-2	50 (two arms)[¥]	MDR-TB patients (better sputum conversion rate)	73
		23 (three arms)	MDR-TB patients (decrease AFB smear counts with daily IL-2 compared to control or pulse IL-2)	71
		110 (two arms)[¥]	New TB patients (significant delays in culture conversion)	72
	IFN-γ	5	MDR-TB patients (all smear negative/improved)	67
		7	MDR-TB cases (no marked microbiologic effect)	68
		6	MDR-TB cases (no marked microbiologic effect)	69
	Etanercept	16[§]	HIV-positive TB cases (more rapid culture conversion compared to historical control)	76
Drugs/compounds	High dose steroid	187 (two arms)[§]	HIV-positive TB cases (increased culture conversion at 1 month)	79
	Levamisole	50[§]	Newly diagnosed pulmonary TB patients (improved radiology but no effect on smear conversion)	82
	Albendazole	135 (two arms)[§]	New pulmonary TB patients (no effect on clinical, radiologic, and microbiologic outcome)	83
	Thalidomide	15 (two arms)[¥]	9/15 HIV-positive (clinical improvement)	102
		30 (two arms)[§]	HIV-positive (no clinical difference)	103

Notes: Φ, different groups including drug-susceptible and drug-resistant cases; ¥, newly diagnosed pulmonary TB with drug-resistant or MDR-TB as exclusion criteria; §, newly diagnosed pulmonary TB and no drug susceptibility data reported. All TB cases were treated with multidrug-treatment regimen.
Abbreviations: AFB, acid-fast bacilli; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; LTBI, latent TB infection; MDR, multidrug-resistant; MSC, mesenchymal stem cells; NA, not applicable; XDR, extensively drug-resistant; TB, tuberculosis.

DNA vaccines

A number of DNA vaccines expressing relevant *M. tuberculosis* genes, Hsp65, ESAT-6, and Ag85A, have demonstrated activity in *M. tuberculosis*-infected mice resulting in a one to three log improvement in *M. tuberculosis* clearance.[48–51] More interestingly, an intramuscular DNA vaccine containing *Hsp65* and IL-12 genes improved the survival of mice infected with MDR-/XDR-TB.[52] This particular vaccine uses plasmid cDNA3.1 as a vector expressing Hsp65 and IL-12 incorporated into virus-free envelopes derived from the hemagglutinating virus of Japan. Furthermore, this same DNA vaccine provided a 40% improvement in survival of *M. tuberculosis*-infected primates.[52] These encouraging results suggest that some DNA vaccines may advance into human clinical trials as adjuncts to chemotherapy.

Autologous MSC

Mesenchymal stem cells (MSC) are progenitor cells constituting a small proportion (0.01%) of the bone marrow.[53,54] MSC are present in various tissues and organs, including lungs,[55,56] and are involved in the repair of damaged tissues.[57,58] These cells have been tested for their potential to transform chronic tissue inflammation into an environment capable of inducing robust pathogen-specific immune responses. A recent review describes the interaction of MSC with different cells of the immune system.[59] Immunomodulatory functions of MSC are mediated by both cell-to-cell contact and release of soluble mediators, such as tumor growth factor (TGF)-β and prostaglandin E2.[59] A Phase I study with MSC given to 30 MDR- or XDR-TB patients demonstrated that administration of MSC within 4 weeks of initiation of anti-TB drugs was safe and improved radiological changes.[54]

V5 immunitor

V5 immunitor, derived from chemical- and heat-inactivated pooled blood from hepatitis B and C virus-positive blood donors, was originally developed for the management of chronic hepatitis B and C.[60] The exact contents and how this product modulates the immune system remain to be investigated. It has been assumed that some of the blood donors had LTBI and may have circulating *M. tuberculosis* antigens which may stimulate immune responses.[61] It is also possible that circulating cytokines and/or chemokines in the pooled blood, if they are not inactivated during chemical/heat treatment, enhance T-cell responses to *M. tuberculosis* antigens in TB patients. Alternatively, other unknown components present could have adjuvant properties. In a Phase I clinical trial, V5 immunitor oral therapy resulted in a markedly better sputum smear conversion at 1 month after initiation of treatment.[62,63]

Cytokines and inhibitors

M. tuberculosis is an intracellular organism residing mainly in monocytes/macrophages.[64] This makes cellular immune responses essential for inhibiting intracellular growth and limiting dissemination. *M. tuberculosis*-specific T-cells produce cytokines and effector molecules, such as perforin, granzymes, and granulysin.[65,66] Thus, cytokines which enhance the expansion of T-cells and activation/differentiation of antigen presenting cells may help control infection. To this effect, IL-2, IFN-γ, IL-12, and anti-TNF-α have been tried in small numbers of clinical cases. Although it is difficult to develop definitive conclusions from limited, and in most cases nonrandomized trials, the adjunct use of cytokines or anticytokines has shown some promise. Moreover, host inflammatory response mediated by Th1 cytokines can cause substantial morbidity; therefore, the doses and timing of administration of cytokines may affect the outcome. The adjunct use of IFN-γ and IL-12 in some cases of MDR-TB resulted in favorable outcomes.[67–69] Adjunct aerosolized IFN-γ administered at a dose of 500 μg three times a week for a total of 4 weeks to five MDR-TB patients was well tolerated and led to smear conversion in all cases.[67] A similar study on six MDR-TB patients using aerosolized IFN-γ at a dose of 2 million units three times a week for 6 months showed that all patients reverted back or remained culture positive at the end of treatment.[69] This may also indicate that the response to IFN-γ may vary from patient to patient. In murine TB models, IFN-γ administered with intranasal IgA resulted in decreases in *M. tuberculosis* load in the lungs.[70] Despite some controversial results regarding the effects of IL-2 tested in new TB cases,[71,72] intradermal injection of 500,000 IU of IL-2 every other day at the first, third, fifth, and seventh months of drug treatment of 25 MDR-TB patients led to a higher rate of sputum conversion compared to controls receiving only drug-treatment.[73] IL-2 also enhanced the activities of a pyrophosphate to enhance γδ T-cell responses and decrease residual *M. tuberculosis* in the lungs of infected monkeys.[74] Anti-TNF-α antibodies which are commonly used for treatment of severe rheumatological disorders increase the risk of reactivation of TB.[75] However, in active TB, anti-TNF-α may enhance culture conversion when combined with TB multidrug therapy,[76] probably by delaying the formation of the so-called "persister" forms of tubercle bacilli, leading to increased susceptibility to drug-mediated bactericidal activity. Etanercept, an anti-TNF-α, administered at a dose

of 25 mg subcutaneously twice a week was tested on new pulmonary TB cases who were human immunodeficiency virus (HIV)-positive with a CD4 count >200/μL. The trial included age- and sex-matched controls and showed that sputum culture conversion was slightly more rapid in etanercept treated patients.[76] The role of etanercept administered in the continuation phase of treatment to shorten the duration of treatment may need to be studied. Similarly, inhibitors of IL-4 and TGF-β were shown to enhance Th1 type immunity and help reduce *M. tuberculosis* bacterial load in the lungs of infected mice.[77,78]

Antibodies

M. tuberculosis infection induces both celI-mediated and antibody responses. It has been shown that B-cell-deficiency leads to higher bacterial burden and worse outcome following *M. tuberculosis* infection.[79,80] Monoclonal antibodies against specific *M. tuberculosis* antigens have shown some conflicting results.[81–83] This could be partly because of differences in types of antibodies and routes of administration. Using sera from bacillus Calmette-Guerin (BCG)-vaccinated individuals, we had shown that antibodies enhance internalization of mycobacteria by phagocytic cells.[84] Interestingly, these antibodies from vaccinated individuals significantly increased the ability of macrophages to kill intracellular mycobacteria and led to marked increase in *M. tuberculosis*-specific cell-mediated immunity.[84] Further works to identify the combinations of monoclonal antibodies, routes, and frequency of administration in animal models may be needed before *M. tuberculosis*-specific antibodies are tested in clinical trials.

Drugs

Certain host-directed therapies focus on drugs as immunomodulators to facilitate *M. tuberculosis* clearance. Steroids, levamisole, and vitamin D have been tried in humans. High dose steroids have been tried in HIV-positive TB patients.[85] Although steroid-enhanced culture conversions at 1 month have been observed, the side effects appeared to outweigh the benefits. The antihelminthic drugs, levamisole and albendazole, have been tested in combination with standard anti-TB drugs in new cases of pulmonary TB. Helminth infections induce Th2 predominant immune responses.[86] Moreover, helminth coinfection leads to Th2 and regulatory T-cell dominant immune responses impairing TB-protective Th1 responses.[86,87] Therefore, treatment of helminth infections may modulate the immune response, inducing subsets more able to limit the progression of disease. Unfortunately, the results with antihelminthic drugs have not been very encouraging so far. Levamisole given to new TB patients resulted in improvements in radiological findings but no change in smear conversion rate.[88] Recently, a randomized clinical trial with albendazole for 3 days in combination with standard anti-TB drugs in patients with pulmonary TB and helminth coinfection demonstrated no difference in clinical score, smear conversion, and imaging changes compared to placebo.[89] The roles of nutritional status, degree of immunosuppression from TB disease, and HIV coinfection on the outcomes of the adjunct use of antihelminthic drugs need to be studied further. The use of vitamin D for TB predates TB chemotherapy. Vitamin D activates macrophages via toll-like receptor signaling pathway leading to increased production of mycobactericidal peptides, cathelicidin, and its active form LL-37.[90] Unfortunately, clinical trials with vitamin D supplements have resulted in controversial results.[91]

Other drugs targeting tyrosine kinases and phagosomal acidification, autophagy, hydrolysis of cyclic adenosine monophosphate and cyclic guanosine monophosphate, inflammation, angiogenesis, and epidermal growth factor receptor have shown encouraging results in murine TB models. Imatinib is an inhibitor of Abelson tyrosine kinase used mainly in the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia. Because Abelson tyrosine kinase is important for the regulation of lysosomal pH in macrophages, inhibition of its function decreases lysosomal pH and enhances the ability of macrophages to kill *M. tuberculosis*.[92] Furthermore, the use of imatinib alone or in combination with rifampin has been found to decrease the bacterial load in the lungs of *M. tuberculosis*-infected mice.[93] This drug appears to be generally safe although there are case reports of interstitial lung disease associated with imatinib and nilotinib, a second generation tyrosine kinase inhibitor.[94,95] Metformin, an antidiabetic agent, is an autophagy inducer via activation of adenosine monophosphate-activated protein kinase. Metformin inhibited the intracellular growth of *M. tuberculosis*, restricted disease immunopathology, and enhanced the efficacy of conventional anti-TB drugs in mice.[96] Moreover, in a retrospective study of TB patients with diabetes mellitus, it was found that patients who were on metformin had fewer pulmonary cavities and significantly better survival.[96] Similarly, other autophagy inducers, such as statins (simvastatin, rosuvastatin) and gefitinib (an inhibitor of epidermal growth factor receptor), were shown to decrease bacterial load in *M. tuberculosis*-infected mice.[97,98] The safety and efficacy of imatinib, metformin, and statin in murine TB studies make them potential candidates for human clinical trials.

Treatment with the anti-inflammatory drug, ibuprofen, resulted in decreases in the size and number of lung lesions, decreases in bacillary load, and improvement in survival of *M. tuberculosis*-infected C3HeB/FeJ mice.[99] Ibuprofen also enhances the anti-TB activities of the anti-TB drug, pyrazinamide, during the initial phase of treatment.[100] Similarly, other drugs which may reduce inflammation, prostaglandin E2 and zileuton (a leukotriene inhibitor), decrease lung colony forming units and improve survival in mice infected with *M. tuberculosis*.[101] Phosphodiesterase inhibitors, such as sildenafil and cilostazole, likely by interfering with the breakdown of cyclic adenosine monophosphate and cyclic guanosine monophosphate and interfering with downstream signaling events, shorten the duration of TB treatment in mice.[102] CC-3052, a new phosphodiesterase-4 inhibitor and thalidomide analogue, decreased lung pathology and bacterial load significantly when combined with isoniazid in a rabbit TB model.[103]

Knowledge gaps and novel strategies

Most of the studies on immunotherapy so far have focused on TB treatment. This may help shorten standard treatments or improve the management of MDR/XDR-TB. Because a third of the population is infected with *M. tuberculosis*, immunotherapeutics which enhance the eradication of latent infection could have a major impact on TB control. The effects of new immunotherapeutics/vaccines on the progression or reactivation of LTBI in humans remain to be studied.

Because most cases of TB are pulmonary, immunotherapeutics may give a better outcome if they modulate mucosal immune responses. Lessons from TB vaccine studies should be applied to new immunotherapeutics. Numerous animal and human studies demonstrate that in general, mucosal vaccinations induce more effective mucosal immunity than systemic vaccinations. With regard to TB mucosal immunity, murine studies with BCG and new TB vaccines clearly demonstrated that mucosal vaccination via the intranasal route induced superior protection against subsequent aerosol challenges with *M. tuberculosis*.[104–106] It was further shown that mucosal T-cells present in the lung airways of mice post-vaccination were the best predictors of protective immunity, and when transferred intratracheally these cells alone could protect against *M. tuberculosis* aerosolized challenges.[105,107] Therefore, approaches which facilitate the recruitment of relevant *M. tuberculosis*-specific T-cells to the lung and limit nonspecific inflammation should be studied. Host-directed therapy potentially could provide exciting new avenues for the management of LTBI and TB disease, providing hope of shortening standard LTBI and TB treatments as well as improving treatment of MDR/XDR-TB.

Disclosure

The authors report no conflicts of interest in this work.

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