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Host-targeted therapy for tuberculosis: Time to revisit the concept

Prabha Desikan & Aseem Rangnekar

Department of Microbiology, National Reference Laboratory for Tuberculosis, Bhopal Memorial Hospital & Research Centre, Bhopal, India

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Tuberculosis (TB) is an important cause of morbidity and mortality worldwide. Every year millions of people die due to TB. Drug resistance has been a major factor that has obstructed successful control and treatment of TB. As the rate of spread of drug-resistant TB outpaces the rate of discovery of new anti-tubercular drugs, targeted therapy may provide a new approach to TB cure. In a scenario where drug resistance is spreading rapidly, and existing drugs regimens seem to be dwindling away, this review summarizes the concept of host-targeted therapy which may be the ray of hope for the effective management and control of the rapidly spreading drug-resistant TB (multidrug resistant and extensively drug resistant).

Key words Host-targeted therapy - micro RNA - multidrug-resistant/extensively drug-resistant TB - VEGF

Introduction

Tuberculosis (TB) is still associated with major mortality worldwide. In 2015, 1.4 million people died due to TB[1]. Drug resistance has been a major factor that has obstructed successful TB treatment and control. Globally, the new cases of multidrug-resistant TB (MDR-TB) are estimated to be 480,000 and an additional 100,000 people with rifampicin-resistant TB (RR-TB) who were newly eligible for MDR-TB treatment[1]. Approximately a quarter million people have died of MDR-TB/RR-TB, and an estimated 9.5 per cent of people with MDR-TB have extensively drug-resistant TB (XDR-TB). At the end of 2015, XDR-TB had been reported from 117 countries[1].

The existing therapeutic options available for drug-sensitive *Mycobacterium tuberculosis* infection are fairly efficient in bacillary clearance, as long as the patient remains fully compliant throughout the course of the drug therapy. Unfortunately, non-compliance, inadequate dosing and incomplete treatment regimens are a reality in many settings. These issues, along with the capacity of *M. tuberculosis* to cause latent infections that may become non-responsive to the existing anti-TB drugs, have led to an upsurge in the number of MDR-TB[2]. The overall fitness of drug-resistant strains may be comparable with that of the drug-sensitive strains, and transmission of drug-resistant strains outnumbers the drug resistance acquired due to therapeutic fiasco. The transmission of such drug-resistant strains can be fairly rapid, which is an alarming trend[3].

In such a situation, one would expect to look for revised drug combinations and better regimens or

newer antibiotics to treat and to arrest the transmission of drug-resistant TB. To cater this need, a few new or repurposed anti-TB drugs have been developed. Drug trials on these newer compounds are in progress. Phase II trials are being undertaken for a novel anti-TB drug candidate (SQ 109)[4]. A number of new therapeutic regimens for drug-sensitive and/or drug-resistant TB are undergoing Phase II or Phase III trials. In addition, the WHO has issued interim guidance on the use of bedaquiline and delamanid[5,6].

This rate of development of newer drugs for TB is much slower than the rate of spread of MDR-TB. The process of discovery and development of new antibiotics or finding new and effective drug combinations is inherently time-consuming. Long treatment times for TB and the mandatory combination therapy add to this problem. Toxicities may not become apparent until late in clinical trials. The field, besides ethical issues, also faces challenges in terms of funding and logistics, requiring a long-term commitment. Many funding agencies and pharmaceutical companies balk at this since these timelines seem very sluggish compared to their usual business cycles[2].

It may, therefore, be time to revisit the concept of host-directed therapies (HDTs) as an alternative option to the standard treatment regimens with existing anti-tubercular drugs.

Surgery

Historically, before anti-tubercular drugs came into existence, HDT for TB consisted of surgery. Collapse therapy (inducing pneumothorax or pneumoperitoneum, phrenic crush, thoracoplasty) is a surgical modality that has been used[7,8]. Adjuvant therapies directed against tubercular granuloma can help in limiting the spread of TB. It can also improve the response to antimicrobial drug treatment. A common adjunctive treatment in patients who fail treatment with conventional anti-tubercular therapy is surgical lobectomy[8].

In patients with drug-resistant TB, surgical intervention may be effective. Lung resection has been tried in patients with failed medical treatment, who persist to be sputum positive, despite taking proper medication for adequate duration, and for sputum-negative patients with localized cavitary disease or bronchiectasis, despite being treated by anti-tubercular drugs. Resection of the lung can save lives of patients with massive haemoptysis and cavitary or bronchiectatic disease[8]. Embolization of the bronchial artery has been found very effective albeit a few cases of recurrence have been reported[8]. Surgical intervention can also be one of the therapeutic modalities for the treatment of pulmonary complications of TB in selected patients with HIV-TB co-infection. Another economic and successful approach for draining a chronic TB-associated empyema thoracis is ambulatory drainage[8].

A systematic review and meta-analysis to evaluate the effectiveness of surgery as an adjunct to chemotherapy for MDR-TB suggested that surgery (as an adjunct to chemotherapy) was associated with improved treatment outcomes in MDR-TB patients[9].

Activating macrophage autophagy to increase innate immune response against *M. tuberculosis*

Mycobacterium thrives and multiplies inside host macrophages, by arresting phagosome maturation. The host cells then induce autophagy which leads to elimination of the bacteria. Autophagy inducers, therefore, may be investigated as potential candidates for novel anti-TB medication. Rapamycin (sirolimus) and everolimus, currently approved for clinical use to avert transplant rejection, are highly effective autophagy inducers[10,11]. Unfortunately, these are also immunosuppressive and therefore, cannot be administered systemically in cases with active TB. To obviate this drawback, instillation of these drugs directly to the lungs (direct drug delivery method) has been proposed[11-13].

Vitamin D and interferon-gamma (IFN-γ)-induced autophagy has been shown to boost lysosomal fusion with phagosomes containing *M. tuberculosis* and to consequently reduce mycobacterial burden in the host[14-19]. Clinical trials to test effectiveness of vitamin D as a dietary adjuvant in TB therapy, however, have been inconclusive[20]. However, the prospects of vitamin D and IFN, as part of the future anti-TB therapy or as an adjuvant, cannot be ruled out completely.

Nitazoxanide, a niclosamide derivative, used in the clinical practice as an anti-protozoal agent, has been found to be a potent inducer of autophagy[21,22]. Other known inducers of autophagy include anti-epileptics and mood modulators such as lithium, carbamazepine, sodium valproate, nortriptyline and fluoxetine; anti-cancer drugs such as tamoxifen (and its derivative, ridaifen-B), gefitinib and imatinib; statins and anti-diabetic drugs such as metformin[23-34]. As all these Food and Drug Administration (FDA)-approved drugs are now found to act as

autophagy inducers, these can be the new prospects for TB care, which can be used in combination with the existing anti-TB therapies or as complementary drugs[23-31]. Furthermore, experimental DNA vaccines with plasmids containing *M. tuberculosis* DNA (from *Ag85*, *Hsp65* and the 23 members of *Esx* gene family) have been found to stimulate INF-γ production and cascading the induction of autophagy[35-38].

In effect, strategies to evoke one or more of the following macrophage responses would be effective candidates for HDTs for TB[39] which include the following: (*i*) Production of intracellular factors such as free radicals and antimicrobial peptides; (*ii*) Production of cytokines and chemokines; (*iii*) Induction of assemblies such as phagolysosomes; and (*iv*) Induction of autophagy or apoptosis. Such responses may be induced using drugs currently approved for other uses.

Stimulation of healing: An equilibrium between extracellular matrix destruction and production

Cavity formation is a serious complication of TB. The role of matrix metalloproteinase (MMP) activity in TB pathogenesis and cavity formation has been the focus of attention. One of the most important mediators involved in the pathogenesis seems to be the neutrophil. Furthermore, neutrophil influx has been found to be associated with collagen destruction, which in turn leads to adverse disease outcomes. The destruction of collagen induced by infection was obliterated by doxycycline. Doxycycline at sub-antimicrobial doses is known to inhibit MMPs. Recent studies have documented the rise of neutrophil extracellular traps holding the MMP-8 from TB samples[40]. In addition, it has been shown that doxycycline is effective at limiting collagen destruction by inhibiting the *M. tuberculosis*-mediated neutrophil-derived nuclear factor-kappa B (NF-kB)-dependent MMP-8[40]. This may lead to inhibition of the process of cavity formation, thus affording some relief in patients having active TB.

Therapeutic potential of targeting granuloma-associated angiogenesis

The most important effector cells of innate host defences that tackle *M. tuberculosis* following aerosol exposure are the alveolar macrophages[7]. *Mycobacterium* can survive intracellular killing by the macrophages. This ability is said to be important in setting up the first stage of *M. tuberculosis* infection. The typical host response is infiltration granuloma formation in the lung. The granulomatous inflammation, which is believed to limit *Mycobacterium* at the infection site and kill the organism, can fail miserably, resulting in extensive host tissue damage, necrosis, and cavitation due to uncontrolled inflammatory process, leading to the persistence and dissemination of infection. The inability of anti-tubercular drugs to attain effective therapeutic concentration inside the granulomatous lesion leads to poor treatment response[7]. This also can promote development of drug tolerance among *M. tuberculosis* strains in the lesions and contribute to the emergence of drug-resistance among these strains. Therefore, a host-targeted therapy promoting vascular perfusion in the granuloma has a potential to improve therapeutic outcome[41].

Vascular endothelial growth factor (VEGF) brings about angiogenesis and augments vascular permeability of endothelial cells. Serum VEGF levels have been found to be raised in individuals with active pulmonary TB when compared with inactive or latent TB infection and healthy individuals[41,42]. Therefore, modulating serum VEGF levels may help prevent loss of vascularity and consequently inhibit the development of caseous necrosis. Pazopanib, a VEGF receptor tyrosine kinase inhibitor, currently in clinical trials, may be a potential candidate for TB therapy targeting granuloma angiogenesis[43].

Potential of microRNAs

MicroRNAs (miRs) play key roles in the control of infectious diseases, due to their ability to regulate gene expression in various biological processes. The expression of miRs correlated with the change in concentration of several inflammatory mediators such as prostaglandins and cytokines, the levels of which are shown to be responsible for pathophysiology of several lung diseases[44]. Some evidence has been found for regulation of the immune response in TB by miRs. This could be the basis for HDT in addition to standard treatment in TB. The miRs regulate diverse cellular processes in pulmonary pathologies, and increases prostaglandin E2 in chronic obstructive pulmonary disease fibroblasts[44].

The potential use of miR mimics for repairing or replenishing the necessary miR stores or administration of anti-miRs to inhibit rebellious miRs which may play a key role in pathophysiology of disease must be evaluated further. Novel vectors may be explored for delivery of miRs *in vivo* to antigen-activated T-cells. Some of these may be lentiviral vectors, lipid conjugates or small exosome-like vesicles[44]. Using affinity chromatography, nanotechnology-based

antigen-specific exosome-like nanovesicles can be isolated. Target cells can be transfected with miR mimics or anti-miR, which can trigger the expression of desired miRs in the host[44]. These miR delivery methods are being assessed in animal models which may be used to study processes involved in human disease. When these yield desired results in animal models, these can be replicated and studied in human cells[44]. Although the possibility of their clinical application in the near future remains uncertain, these modalities remain very promising.

Host-targeted activity of pyrazinamide

Data from microarray analysis showed that pyrazinamide (PZA) treatment of *M. tuberculosis*-infected mice significantly altered the expression level of genes involved in the regulation of the pro-inflammatory mediators, lung inflammatory response and to toll like receptor (TLR) signalling networks[45]. Therefore, it is possible to hypothesize that PZA treatment modulates the host immune response to *M. tuberculosis* infection by reducing pro-inflammatory cytokine production. In other words, treatment of TB with PZA would be useful even if the organism is resistant to the antimicrobial activity of PZA[45].

Limitations of host-directed therapies

Host-targeted therapies can pose risk of adverse events on patients. Bronchial artery embolization and surgical lung resection require considerable surgical expertise, and invasive procedures bear a certain amount of risk to the patients[8]. Agents such as autophagy inducers and tyrosine kinase inhibitors have immunosuppressive effects on the host. In addition, animal studies have shown that induction of autophagy in the lungs may not cause significant reduction in bacterial load[11-13].

The way forward

To reach the "End TB" targets identified by the WHO, it is necessary to explore new technologies and their applications[46]. In line with this, the role of HDTs can be examined further.

Conclusion

The dearth of novel antimicrobial drugs for TB treatment has been the impetus for exploration of effective adjunctive HDTs. Advancement in this area will require utilization of pre-antibiotic era modalities as well as elucidation of the cell signalling pathways that control intersecting immunologic and metabolic regulatory mechanisms. Leveraging these options for the development of innovative next-generation HDTs may lead to new paradigms for the treatment of TB. These may provide the much-needed replenishment to the current depleted armamentarium against drug-resistant TB.

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For correspondence: Dr Prabha Desikan, Department of Microbiology, Bhopal Memorial Hospital & Research Centre, Bhopal 462 038, Madhya Pradesh, India
e-mail: prabhadesikan@yahoo.com