Tuberculosis treatment strategies using 'host directed' therapeutics: Can we win the war

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Abstract

Tuberculosis is aerosol generated infectious disease caused by *Mycobacterium tuberculosis* and its treatment remains challenging. Improved treatment strategies are needed to address the problem and to achieve the millennium target of disease elimination. Host-target therapies are a promising approach to tuberculosis treatment and have the potential to reduce the treatment duration and capability of modulation of host immune responses to reduce lung injury by enhancing autophagy, innate immune responses as well as by modifying specific host immune pathway reducing lung inflammation and matrix destruction. Persistent efforts have increased our understanding in the area of host-pathogen interaction and immune responses and it is now thought that the introduction of host targeted drugs can improve the current TB regimen and may lead to shorter treatment time, reduce in lung inflammation and lower risk of development of drug resistance or re-infection. Several options for host-directed therapies are being explored and are being discussed here for better clinical outcomes.

Keywords: Mycobacterium tuberculosis; host-pathogen interaction; inflammation; drug-susceptibility

Introduction

Human TB continues to be one of the major public health problems in the world. It is responsible for over 1.4 million deaths and about 9 million new cases worldwide annually [1]. The bonhomie between human immunodeficiency virus and *Mtb* infections combined with the emergence of MDR and XDR strains of *Mtb* have fuelled the fear of the spread of TB epidemic [2, 3]. Although drug-susceptible TB can be effectively treated with a cocktail of four 'front-line' drugs — rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (ETB) — given daily by the oral route, the current therapy regimen is very lengthy (6 to 9 months) and often leads to patient noncompliance. Incomplete adherence to drug therapy sets the stage for treatment failure, contributing both to the continued spread of *Mtb* throughout communities, as well as to the development of drug-resistant bacilli. Additionally, problems with systemic toxicity of current therapeutic regimens and increasing multidrug resistance urge the discovery and

development of new drugs and therapeutic strategies [4]. Thus, the development of a curative and sterilizing anti-TB therapy regimen of shorter duration could have an enormous positive impact on TB control around the globe.

In this direction, repurposing of in-market drugs, such as the recently reported anti-TB activity of anti-inflammatory agent ibuprofen [5], antiarrhythmic drug verapamil [6], and antidiabetic drug metformin [7] highlights the possibility of expanding the spectrum of currently available therapeutic agents against TB. Recently, cholesterol-lowering drug simvastatin has been shown to reduce *Mtb* survival when used along with first-line anti-TB drug [8], and ATP-competitive inhibitor of kinases AKT and PKA, H-89, has been shown to inhibit proliferation of *Mtb* in mouse bone marrow-derived macrophages [9]. The FDA approved anti-cancer drugs such as Imatinib, an inhibitor of Abelson family tyrosine kinases (ABL) [10, 11], and inhibitors of Epidermal Growth Factor Receptor (EGFR) [12] and Vascular Endothelial Growth Factor receptor (VEGFR) [13] have been recently demonstrated to reduce infection burden and limit bacterial dissemination in animal models.

Effective innate and adaptive host responses including autophagy, a cell degradation of the unnecessary and dysfunctional cellular component using lysosome, have been required for the effective control of intracellular pathogens [14] and are regulated by mammalian target of rapamycin (mTOR) complex 1 [15]. Perturbations in the autophagy network and adenosine monophosphate-activated protein kinase (AMPK) signaling have been previously shown to be associated with *Mtb* virulence [16] [17]. Several mTOR dependents and independent autophagy-inducing agents have been recently proposed as new anti-TB agents [18, 19]. Furthermore, the interaction of *Mtb*–macrophage lipids with host peroxisome proliferator-activated receptor γ (PPARγ) has been shown to enhance the survival of the pathogen by modulating macrophage function, which indicates that the antagonists inhibiting PPARγ are attractive candidates for the adjunct anti-TB therapy [20].

The development of new effective anti-TB drugs and identification of alternative therapies that can improve clinical outcomes in TB patients and overcome antimicrobial resistance is the current research priority set by the WHO for the effective control of TB [21] [22]. The development of shorter, easier and safer treatments to reduce the morbidity and mortality from *Mtb,* ii) reducing the impact of MDR and XDR TB and iii) reducing the TB-associated with co-morbidities for the elimination of TB from the world has now become the focus of attention to combat the disease.

Rationale and hypothesis for using host-directed therapies

The fear of the spread of MDR and XDR strains and the diminishing arsenal of effective treatment options has reinforced the need to develop new, effective anti-TB drugs to overcome the problem of drug resistance and to shorten the treatment course. However, there are currently fewer than ten compounds in clinical development, perhaps few to guarantee even a single new anti-TB drug soon [23] (http:// www.newtbdrugs.org/ pipeline.php and http://www.tballiance.org/). Conventional pathogen-targeted strategies suffer from the serious disadvantage of fostering microbial resistance and to circumvent this

problem, a new concept in drug discovery that involves therapeutic modulation of host cell responses to improve pathogen eradication [9, 24, 25] has emerged.

In recent years, scientists across the globe have abreast of recent increased interest in the repurposing of an approved drug for anti-TB therapy [28, 29]. Such"host-targeted" adjunct therapeutic strategies have potential to (i) augment the efficacy of antibiotic-based treatment, (ii) shorten treatment regimens for drug-susceptible and/or drug-resistant *Mtb* infections, (iii) less likely to engender microbial resistance than direct targeting of the pathogen with conventional drugs (iv) reduce the immunopathology associated with TB, and (v) promote the development of immunological memory that protects against relapse. The validation of this approach would have the advantage of requiring shorter clinical trials than those usually needed for new drugs.

It has become increasingly clear that *Mtb* modulates host lipid metabolism, autophagy pathways, kinase signaling, and immune functions for its survival. The ability of *Mtb* to maintain persistent chronic infection is critically linked to its capacity to use host cholesterol [30, 31]. Also, the cellular lipids found in foamy macrophages in granulomas play a crucial role in reactivation of latent TB [32]. It is therefore hypothesized that lipid-lowering drugs or medicines that influence host lipid metabolism or that augment lipophagy could potentially influence protective immunity to *Mtb* infection and may alter disease outcome in the infected host.

It is well recognized that the development of protective granulomas in the lungs post *Mtb* infection not only helps the host to contain bacilli and prevent dissemination but also provides a haven for dormant *Mtb* bacilli. Simultaneous inhibition of certain growth factor receptors (such as VEGFR and EGFR) using approved anticancer agents may intercept angiogenesis and architecture of granuloma and in turn, increase the distribution of conventional antibiotic drugs in the lung tissue and prevent persistent *Mtb* infection. An effective host immune system is a crucial factor for both the control of *Mtb* growth and its containment as latent TB infection (LTBI). The success of *Mtb* in infecting the host cells and maintaining long-term persistent infection is associated with the ability of bacilli to evade host innate as well as adaptive immune responses [33, 34]. The host cell innate antimicrobial arsenal includes the production of reactive oxygen and nitrogen species, as well as the capacity to destroy intracellular pathogens using the phagolysosomal machinery or autophagy pathway. Since autophagy is required for the effective control of intracellular pathogens including *Mtb* [14], and therefore autophagy inducing agents might serve as an effective adjunct for anti-TB therapeutic drugs.

Conclusion

Host directed therapies offer new hope for TB treatment and may provide a way forward for shorter and efficacious treatment. The pathways that may be targeted using Host directed therapies depend on the goal of treatment and include the modulation of host cell function. However, their use might come with risk and inhibition of host pathways may lead to other consequences and may have increased side effects and its level must be reconsidered. Host directed therapies that lead to increase immune response may lead

to hyper inflammatory condition leading to tissue damage. Simultaneously, any other co-morbidity such as diabetes, HIV/AIDS, etc. must also be considered so that Host directed therapies should not exacerbate the pathophysiology of the disease. However, the wonder drugs for TB treatment are still in the research and therefore provide the scope for Host directed therapies to be used as an adjunct to TB regimen.

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