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Sharpening nature's tools for efficient tuberculosis control: A review of the potential role and development of host-directed therapies and strategies for targeted respiratory delivery☆

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ABSTRACT

Centuries since it was first described, tuberculosis (TB) remains a significant global public health issue. Despite ongoing holistic measures implemented by health authorities and a number of new oral treatments reaching the market, there is still a need for an advanced, efficient TB treatment. An adjunctive, host-directed therapy designed to enhance endogenous pathways and hence compliment current regimens could be the answer. The integration of drug repurposing, including synthetic and naturally occurring compounds, with a targeted drug delivery platform is an attractive development option. In order for a new anti-tubercular treatment to be produced in a timely manner, a multidisciplinary approach should be taken from the outset, including stakeholders from academia, the pharmaceutical industry, and regulatory bodies keeping the patient as the key focus. Pre-clinical considerations for the development of a targeted host-directed therapy are discussed here.

Contents

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1. Introduction

Tuberculosis (TB) infection, caused by the pathogen *Mycobacterium tuberculosis* (*Mtb*), represents a global public health crisis traversing centuries. Recent figures published by the World Health Organisation (WHO) cite TB as the leading cause of death by infection alongside Human Immunodeficiency Virus (HIV), responsible for 1.5 million deaths annually [1,2]. Compounding this crisis is the rising number of drug-resistant cases of Mtb infection. Multi-drug-resistant TB (MDR-TB), defined as resistance to at least the two first-line anti-bacterials (isoniazid and rifampicin), and extensively drug-resistant Mtb (XDR-TB), characterised by additional resistance to second-line therapeutics, have complicated the already arduous treatment regimens [3]. Despite reductions in the global burden of TB following the WHO's introduction of directly observed treatment, short-course (DOTS) in the 1990s, and recently the adoption of a more holistic approach by incorporating patient care, policy, and research, the stated aim of reducing TB deaths and incidence by 90% and 80%, respectively, between 2015 and 2030 remains a substantial challenge [1,4]. The TB Alliance, established in 2000, has placed significant emphasis on the development of new combinatory regimens, and crucially, new drug candidates, by bringing organisations together using its product development partnership approach (PDP) [5]. Two new drugs, delamanid and bedaquiline, have recently been licensed for the treatment of MDR-TB. However, as with conventional anti-mycobacterials, acquired resistance to these novel agents has already been reported, emphasising the limitation of pathogen-directed therapies in treating this heterogeneous and dynamic disease [6].

Our natural defences, however, should not be underestimated. Despite one third of the world's population living with latent tuberculosis infection (LTBI), just 9.6 million people developed active disease in 2014 [1]. The host immune response to TB infection, therefore, is capable of successfully limiting infection in the majority of individuals. Thus, a logical question is how can the immune response be enhanced in patients where active disease takes hold? The concept of 'host-directed therapies' (HDT), whereby therapeutics targeting the human host's immune response to infection for the purpose of augmenting beneficial and reducing harmful features, have garnered significant international interest, evidenced by the recent publication of several high-quality reviews on the topic [7–9]. The most obvious attraction of this approach is the lower likelihood of development of treatment-resistant strains of Mtb in comparison to conventional pathogen-directed therapies. Additionally, HDTs hold potential in a myriad of settings—as vaccine adjuncts, as prophylactic therapies for close contacts of cases, as strategies to limit infectivity and shorten treatment duration, as well as improving overall survival outcome and reducing the lung tissue damage resulting from excessive inflammation. Furthermore, "drug repurposing" of currently licensed medications has already been highlighted as an approach to tackling the TB pandemic, given the benefits of faster market access and reduced development costs [10,11]. Several drugs currently licensed for other indications (some of which are also off-patent) are showing promise as potential HDTs, offering affordable provision to the underdeveloped economies that most require novel TB therapies.

The host immune response to Mtb infection, however, is layered with complexity. Many immune functions that are vital early in host defence prove detrimental in advanced infection [12]. Consequently, in addition to agents that enhance the natural host immune response to TB, a large number of anti-inflammatory agents that work through attenuation of the destructive effects of excessive immune responses are also under investigation as potential HDTs. The temporal events of infection and disease progression must be understood and considered in order to maximise efficacy of new therapies and, crucially, to prevent undesired harmful outcomes. Additionally, several promising HDTs – including vitamins that are discussed in detail in this review – have been demonstrated to influence host metabolism; therefore, variable host nutritional status may be important in determining the efficacy of various approaches to manipulation of immune response. Genetic variations in host immunity are also likely to impact individual response to HDT to a far greater extent than conventional pathogen-targeted antimicrobials [13], potentially suggesting a role for the integration of pharmacogenomics and a "personalised medicine" approach into the development of HDTs, tailoring therapies to an individual's "immune signature" [14,15]. Although such measures at present are still considered novel and consequently costly for the treatment, accompanying diagnostics and multidisciplinary care, if governments and policy makers truly wish to overcome this pandemic, then the potential of this

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