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Review

Metformin: Candidate host-directed therapy for tuberculosis in diabetes and non-diabetes patients

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S U M M A R Y

Despite major advances in tuberculosis (TB) control, TB continues to be a leading cause of death worldwide. The discovery of new anti-TB treatment drugs and regimens that target drug-sensitive and drug-resistant TB are being complemented with a search for adjunct host-directed therapies that synergize for *Mycobacterium tuberculosis* (*Mtb*) elimination. The goal of host-directed therapies is to boost immune mechanisms that diminish excess inflammation to reduce lung tissue damage and limit *Mtb* growth. Metformin is the most commonly-used medication for type 2 diabetes, and a candidate for host-directed therapy for TB. Preliminary data suggests metformin may be beneficial for TB control by reducing the deleterious inflammation associated with immune pathology and enhancing the anti-mycobacterial activity of immune cells. In this review I summarize current findings, knowledge gaps and the potential benefits as well as points of caution for using metformin as adjunct therapy for TB in patients with and without type 2 diabetes.

Contents

1. Introduction

Tuberculosis (TB) affected 9.6 million and killed 1.5 million individuals in 2014 [1]. These statistics reflects the unmet need for

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improved treatments for all forms of *Mycobacterium tuberculosis* (*Mtb*) infection, including drug-sensitive and drug-resistant TB or latent TB infection (LTBI) [2]. Adjunctive therapy with immunomodulators that enhance TB immunity (host-directed therapy, HDT) could shorten treatment durations and improve TB and LTBI outcomes. A re-emerging concept for TB HDTs is to target the deleterious inflammation that leads to immune exhaustion and tissue pathology, to save the target organ and redirect the host response to more effective immunity against TB (Figure 1) [3]. That is, active TB is characterized by inflammation that can act as a double-edged sword. For example, a Th1 response contributes to *Mtb* containment, but strong Th1 responses have been identified in patients in whom the pathogen is not contained and who present with clinically severe forms of TB [4]. IL-17 appears beneficial for Mtb containment in early infection, but also contributes to chronic unproductive inflammation with increased neutrophil recruitment and pulmonary damage [5]. B-cells may have a protective role in TB, but appear to contribute to chronic inflammation in active TB [6]. Thus, adjuvants have been investigated for more than a decade to evaluate medications that limit tissue destruction during TB treatment (eg. corticosteroids, TNF blockers, thalidomide, non-steroidal anti-inflammatory medications), and optimization of these therapies may require knowledge of the host genotype [7,8]. In addition to reduction in deleterious inflammation to achieve the right balance of anti-mycobacterial responses, HDT should further enhance effective immunity against TB, such maturation of phagosomes and *Mtb* autophagy [3,9,10].

The current re-emergence of type 2 diabetes mellitus (T2DM) as a risk factor for TB may be timely to help identify candidate HDT targets for TB, given the many metabolic similarities between these two seemingly different diseases. That is, the underlying pathology of both diseases is characterized by hyperglycemia (transient; induced by fever in TB), higher levels of systemic pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), and oxidative stress [11–14]. So it may not be unexpected that the most frequently-prescribed medication for DM2, metformin (MetF), is a candidate HDT for TB/LTBI [2,7,15,16]. In this review I discuss the potential benefits and points of caution for using MetF as HDT for TB.

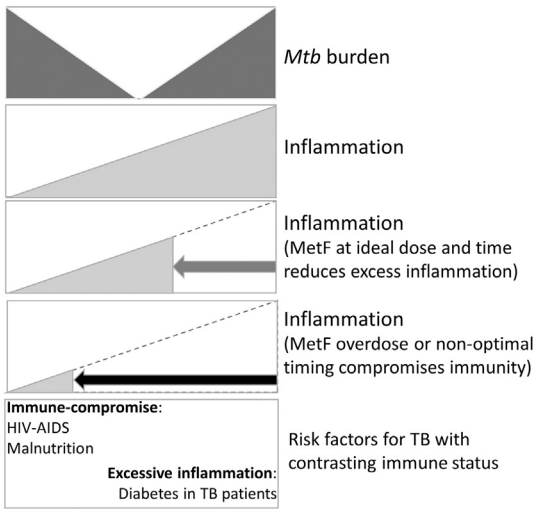

Figure 1. Relationship between *Mtb* burden and inflammation, and influence of MetF. Highest *Mtb* burden in TB patients correlates with either diminished immune responses to *Mtb* (e.g. in immunocompromised hosts with HIV-AIDS or malnutrition) or dysfunctional immunity with excessive inflammation (e.g. in TB and DM co-morbidity). MetF has the potential to reduce the excessive (deleterious) inflammation and improve *Mtb* containment when given at the right dose and time (gray arrow). However, the anti-inflammatory effects of MetF have the potential to hamper effective immunity against *Mtb* when dosing and/or timing of administration is not appropriate (black arrow). Dark gray, Mtb burden; light gray, inflammation levels.

2. Immune modulation by MetF

The anti-inflammatory effect of MetF is mediated, at least in part, by activating a major energy-sensing kinase, AMP kinase (AMPK). AMPK detects low intracellular ATP and promotes a switch from glycolysis to oxidative phosphorylation [17]. This reduces the proliferation of inflammatory cells which burn glucose for energy (glycolysis) and promotes non-inflammatory cells which burn fatty acids instead (fatty acid oxidation). Accordingly, MetF reduces inflammation by promoting the formation of anti-inflammatory M2 macrophages (vs pro-inflammatory M1) and T-regulatory and CD8 memory T cells (vs proliferating, Th1, Th2, Th17, T-effector, lymphocytes) [18–20].

3. Why is MetF an attractive candidate for HDT for TB?

First, in studies unrelated to TB, MetF has been shown to promote phagocytosis, phago-lysosome fusion and autophagy in macrophages, and differentiation of memory CD8 T cells, which are important for intracellular *Mtb* killing [15,21] and long-term containment of *Mtb*, respectively [18,22]. A recent publication reported beneficial immunomodulatory effects of MetF on TB [15]. Singhal et al. found that macrophages exposed to MetF in-vitro (vs no MetF) had higher mycobactericidal capacity attributed to increased mitochondrial reactive oxidative species (ROS) [15]. These effects were associated with activation of AMPK by MetF. Autophagy was induced by MetF but this process did not appear to contribute to *Mtb* killing. In mice, MetF treatment reduced mycobacterial growth and tissue inflammation and pathology. In a retrospective analysis of 220 DM patients, Singhal et al. also showed that MetF treatment for DM was associated with a lower prevalence of LTBI (26%) vs alternative DM treatments (42%). However, among the LTBI + DM patients, those taking MetF (vs other DM meds) were more likely to have T cells reactive to CFP10 and ESAT6. From these studies in DM patients the authors concluded that MetF enhances *Mtb*-specific T-cell responses that may protect against LTBI [15]. Finally, Singhal et al. reported that DM patients on MetF had less cavitation and better survival rates than DM patients without MetF treatment [15].

Second, MetF is ideally suited for re-purposing as HDT for TB because it has been widely used for the management of DM2, is inexpensive and is well-tolerated (category B, no evidence of risk in humans) [23,24]. MetF therapy has a low risk of lactic acidosis in patients with altered liver or kidney function [25]. In contrast to insulin, MetF does not usually cause hypoglycemia (in DM or non-DM), given that its glucose-lowering effect is achieved by enhancing the activity of existing insulin (improve insulin sensitivity) and reducing hepatic glucose production [26,27].

Third, MetF improves glucose control in DM2 patients (with our without TB) that should help correct the dysfunctional immunity associated with hyperglycemia, such as delays in initiation of innate immunity to *Mtb*, or excessive expression of type 1 cytokines once TB has developed [28,29]. Epidemiological and immunological studies on TB and DM show the importance of glucose control, rather than DM in itself, to the higher risk of DM patients to TB [30–33] and to worse outcomes during TB treatment [34,35].

4. What we do not know about MetF and TB

4.1. Mechanisms by which MetF kills or contains Mtb growth

The experimental studies by Singhal et al. suggests that MetF

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