

Is Iron Overload a Risk Factor for Mycobacterium Tuberculosis and a Potential Target of Therapy?

Abstract

Mycobacterium TB infection remains a significant global health problem. The increase in resistant forms of TB to once effective antibiotics has called for improved understanding of the organism's metabolism and host response to help develop new therapeutic strategies. Clinical observations have identified patients with iron overload that are at higher risk for mycobacterium tuberculosis and may have a greater risk of mortality. Understanding mechanisms of iron homeostasis have led to important experiments addressing the pathogenicity of mycobacterial species. Conditions that favor high iron concentrations serve to promote mycobacterial growth and render a survival advantage for the pathogen. Iron trafficking in the host is a complex process but serves as an important feature in the host immune response. In-vitro studies demonstrate Siderocalin molecules interfere with the function of pathogenic siderophores and inhibit the growth of mycobacterium tuberculosis. Thus, exciting therapeutic opportunities exist in the potential targeting of siderophores. In addition determining patient-specific hepcidin activity may be useful in ascertaining risk for mycobacterial infection in endemic regions.

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Introduction

Infections due to mycobacterium tuberculosis remain a significant global health problem. The WHO (World Health Organization) estimated that TB remains one of the top ten causes of death worldwide, accounting for roughly 1.37 million deaths in 2015 alone. TB is treatable however drug resistant forms to rifampin as well as multi and extensively drug resistant strains are growing at a significant rate. The success rate of treating MDR and XDR is lower than susceptible forms with a rate of 48% and 29% respectively [1]. In addition the rise in incidence of non-tuberculous mycobacterium in patients who are immunocompromised and in vulnerable populations such as sickle cell disease by mycobacterium avium and mucogenicum infections are reported [9]. Both organisms require similar prolonged durations of therapy as with mycobacterium tuberculosis although the reported resistance is lower. It is therefore relevant to discuss potential alternative strategies to address the burden associated with these drug resistant forms of mycobacteria. Before we can do so, understanding the basis of virulence of mycobacterium infection and the immune response is necessary. In the subsequent descriptions of TB and non-tuberculous mycobacterium I will refer to both as mycobacterium and mycobacterial diseases for ease of description. We will predominantly focus on the clinical observations which have led to the discovery of important pathways in iron trafficking and further discuss the therapeutic implications in the treatment of mycobacterium tuberculosis.

Clinically derived association of high total body iron and risk of mycobacterium tuberculosis infection

Clinical observations have found that exposures linked to high iron states maybe important risk factors for mycobacterium

infection such as TB (Table 1). Patients diagnosed with iron overloaded (i.e. high macrophage iron content), quantified by measuring splenic iron post necropsy, were associated with a 17 fold greater odds of mycobacterial tuberculosis infection and possibly death [2]. The implications of mycobacterium infection due to an iron rich environment in those with chronic obstructive pulmonary disease who are smokers raise the possibility of an underappreciated risk factor for development of pulmonary TB [3]. Lastly a case control study from Zimbabwe demonstrated that increased dietary iron from local beer consumption was associated with a 3.5 fold increase in mycobacterial tuberculosis, higher indices for total body iron, and 1.3 fold increase in death after age and sex adjustment [4]. Lastly genetic polymorphisms in hepcidin demonstrated differing functionality in iron handling and patients diagnosed with pulmonary TB were found to have 3.1 fold greater odds of (2-4.8) of G allele hepcidin polymorphisms [5].

Mediators of Iron trafficking and their potential role in understanding the immune response against mycobacterial infection

The immune system currently combats mycobacterial infections via advanced cytokine responses which trigger innate, cell mediated and humoral immunity. The major antimicrobial mechanisms that target mycobacterial infections include macrophage mediated phagocytosis, T-cell mediated sensitization via CD4 T-helper cells thus promoting granuloma formation [6]. Indeed patients who are immunocompromised such as in untreated HIV are susceptible to mycobacterial infections for this reason. Disease transmission and pathogenesis varies depending on the specific characteristics of the host and the species of mycobacterium (Table 2).

Table 1: Risk of mycobacterium tuberculosis infection in cohorts with exposure of high total body iron concentration.

Patient Population	Exposure	Iron Content Marker	Outcome	Implications
Smokers and nonsmokers who underwent broncho-alveolar lavage.	Smoking	Higher iron content in broncho-alveolar macrophages	Lower transferrin concentrations in patients with chronic obstructive pulmonary disease. Symptomatic smokers had a 4.5-7 fold greater iron concentration than nonsmokers.	Smoking status maybe related to increased risk for mycobacterium tuberculosis although observational studies confirming this association are lacking.
Necropsy specimens of patients who died of Tuberculosis	Iron overload	High concentration of iron in spleens.	In patients that died of TB, there were 16.9 fold greater odds of elevated splenic iron [2].	Iron overload maybe a strong risk factor for risk of death to mycobacterial tuberculosis.
Patients with pulmonary tuberculosis	High levels of dietary iron determined by beer consumption	Reported beer consumption Serum Ferritin: Mean: 498 µg/L Range: 152-1517 µg/L Serum Transferrin saturation: 43 ± 21	Increased dietary iron was associated with 3.5 fold increase of mycobacterial tuberculosis and 1.3 fold increase of death. This risk increases substantially in HIV infection.	Among patients with pulmonary TB, iron overload appears to confer increased risk of infection among patients with elevated ferritin and transferrin.
Patients with tuberculosis	G allele Hpcidin polymorphism	Serum Iron: 53.5 ± 16.2 µg/dL Serum Ferritin: 39.6 ± 35.5 ng/mL	Compared to controls, patients with TB had 3.1 fold greater odds of (2 - 4.8) G allele hpcidin polymorphisms	Maybe a prognostic marker in patients with TB. Hpcidin-like molecules maybe a therapeutic option.

Table 2: Iron trafficking mediators and conditions associated with the inhibition and promotion of growth of mycobacterium tuberculosis.

	Inhibits Growth of Mycobacterium tuberculosis	Promotes Growth of Mycobacterium tuberculosis
TfR (transferrin)	Yes	No
Beta-2 microglobulin	Yes	No
HFE (Class 1 MHC)	Yes	No
Hepcidin	Yes	no
Iron Rich environment	No	Yes
Beta-2 microglobulin deficiency	No	Yes [7]
HFE deficiency	No	Yes [8]
Siderophores	No	Yes
Siderocalin	Yes	No

The process by which mycobacterium acquire iron from the host is complex and serves to promote organism growth and survival advantage. Not only is cell mediated immunity via phagocytosis of the organism necessary for successful elimination of mycobacterium but a mechanism of depriving mycobacterium from available iron molecules. Thus host mechanisms to limit iron acquisition by microorganisms involve the complex interaction of iron binding proteins such as TfR (transferrin receptor), beta-2 microglobulin and HFE as well as the up regulation of NRAP. In general surpluses of iron in vitro were found to further enhance

the growth of mycobacterium tuberculosis [4]. In response to infection, hepcidin which is intimately involved in the regulation of duodenal absorption of iron, is up-regulated and binds to ferroportin leading to internalization and degradation of the protein thus limiting dietary iron absorption. Other mechanisms for iron acquisition include phagocytosis of red blood cells and extraction from hemoglobin. Once mycobacterium infect macrophages however the release of interferon gamma down regulates TfR and HFE genes in order to limit iron acquisition by phagocytosed mycobacterium [9].

Mycobacterium is dependent on iron to activate promoters of vital genes and utilize iron for oxidative reactions including those involved in free radical formation or elimination [10]. In response to the host mechanisms of iron sequestration, mycobacterium regulate gene expression of iron binding proteins. Like the host, Mycobacterial organisms are also adapted to acquire iron molecules in iron poor environments. Iron molecules (Fe^{2+}) bind to repressor proteins during iron rich states thus inhibiting the synthesis of siderophores. Repressor proteins dissociate from Fe^{2+} when iron is scarce which leads to transcription of the siderophores. Siderophores secreted by mycobacterium function as small, high-affinity iron-chelating compounds and bind the iron in the Fe^{3+} ion state. The siderophore- Fe^{3+} complex is then taken up by the bacterium and upon entering the cytoplasm Fe^{3+} is converted to Fe^{2+} , the active form. Therefore siderophore molecules used by mycobacterium for iron acquisition maybe good targets for treatment because the bacteria's survival and virulence is related to host iron availability [11].

Exciting therapeutic opportunities exist in the potential targeting of siderophores. Small molecules called siderocalins that bind to siderophores as well as molecules that inhibit bacterial synthesis of siderophores are currently under investigation [12]. Treatment of infected macrophages *in vitro* with siderocalin limits the replication of mycobacterium tuberculosis within the macrophage [13]. The development of mycobactin siderophore analogues has similarly shown significant inhibition of mycobacterium tuberculosis growth. An alternative approach of treatment is gene manipulation through irreversible inhibition of iron dependent regulator protein (IdER). Activation of repressor protein of siderophore synthesis would be advantageous when the pathogen is iron deficient and depends on siderophore synthesis for survival [11]. The role of hepcidin molecules in therapeutics is less certain however determining patient-specific hepcidin activity may be useful in ascertaining risk for TB in endemic regions.

Conclusion

Mycobacterial infections particularly TB remain a significant public health problem. The development of resistant forms of TB as well as the often long treatment durations of mycobacterial infection poses tremendous challenges for clinicians and calls for newer ways to risk stratify and develop alternative therapies to address these pathogens. Understanding mechanism of iron acquisition in the host and by mycobacterial organisms offer insights into the disease mechanism, risk for infection and

potential targets of therapy.

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