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Resume: *Mycobacterium tuberculosis* requires iron for normal growth, but is subject to metal ion limitation due to its low solubility at biological pH and iron retention by mammalian hosts. The pathogen expresses a specific siderophore for Fe³⁺ to chelate the metal ion from insoluble iron and the proteins transferrin, lactoferrin, and ferritin. Siderophore-mediated iron uptake is essential for survival in tuberculosis disease, as knockout mutants defective in siderophore synthesis or uptake failed to survive in iron-deficient environments and in host macrophages. However, since excess iron is toxic due to its catalytic role in the generation of free radicals, iron uptake must be regulated to maintain optimal intracellular iron levels. The main objective of this review is to provide a comprehensive overview of iron homeostasis in *M. tuberculosis*, discussed in the context of mycobactin biosynthesis, iron transport across the mycobacterial cell envelope, and storage of excess iron.

Keywords: Tuberculosis, iron metabolism, iron free radicals,

Introduction: *M. tuberculosis* scavenges iron from host-cell transferrin by uptake of iron. Mycobactins are able to sequester iron from exogenous holotransferrin. Phagosomes containing live *M. tuberculosis* interact with early endosomes carrying holotransferrin. *M. tuberculosis* within the macrophage phagosome is able to accumulate more iron from transferrin than the nonpathogenic *M. smegmatis*. Mycobactins can also obtain iron from cytoplasmic pools supplied by holotransferrin and from hololactoferrin, which is more abundant than holotransferrin at the site of pulmonary infection. A recent study showed that gallium-loaded lipophilic mycobactin J from *M. paratuberculosis* (a surrogate for iron-mycobactin J and structurally close to mycobactin T) was exogenously added to macrophages and (1) infected and even equilibrated throughout the body. surrounds cells and is distributed between the aqueous and membrane domains of macrophages; (2) sequesters holotransferrin and scavenges cytoplasmic iron; and (3) is recruited as Fe-mycobactin to lipid droplets delivered via lipid trafficking to *Escherichia coli*-containing phagosomes. While these results are intriguing, exogenous addition of mycobactin does not mimic the in vivo situation, and the *E. coli*-infected phagosome does not mimic the *M. tuberculosis*-infected phagosome. In summary, *M. tuberculosis* evades host defenses by preventing phagosome

acidification and lysosome synthesis, by sequestering iron from host endosomal holotransferrin, and, if confirmed, by utilizing host lipids to deliver additional iron by mycobactin.

The number of patients with pulmonary tuberculosis with the involvement of other organs and systems has increased. One third of the world's population is infected with pulmonary tuberculosis. If a person is infected and does not undergo prophylaxis, he is at risk of developing a lifelong disease. Tuberculosis and medical care in Uzbekistan remain one of the serious problems of conservation [1,2, 3,4]. Every year, 3 million people die from tuberculosis worldwide, another 8 million become ill. It is especially alarming that the number of patients increases by 25-30% every year, and children and adolescents often become victims. Last year, the incidence of tuberculosis was 10.2 per 100,000 people. For comparison, in the region it ranges from 2.5 to 5.3.

Materials and methods: In reviewing the relationship between tuberculosis and iron, we aim to address biological and clinical issues, highlighting human conditions that may lead to iron overload in macrophages.

Results and analysis: Reviews of iron and tuberculosis have examined host iron levels and susceptibility to tuberculosis; data from experimental animal studies have shown that iron uptake is associated with disease progression, which overrides the iron-limiting response of the mammalian host to infection. Iron is essential for normal growth of *M. tuberculosis* within macrophages with low iron levels of 1 to 10 ng ml. This is maintained despite the high flux of metal ions within macrophages due to the destruction of erythrocytes and the internalization of iron through specific cell surface receptors for transferrin, lactoferrin, and hemoglobin-haptoglobin. However, a large proportion of the iron is transported to the bone marrow, and any free iron is bound to transferrin and lactoferrin. Lactoferrin, due to its ability to retain its metal ion even at acidic pH, plays an important role in the retention of iron by *M. tuberculosis* within alveolar macrophages in patients with pulmonary tuberculosis. Thus, it is necessary to develop siderophore mechanisms, as demonstrated by the sequestration of a metal ion by *M. tuberculosis* from holotransferrin and from hololactoferrin. When iron is available to the pathogen, as in macrophage cultures or in experimental animals infected with *M. tuberculosis*, the growth of the pathogen is enhanced. When iron is co-administered with the iron chelator deferoxamine or apo-transferrin, inhibition of pathogen growth occurs, clearly defining the role of iron in tuberculosis. These findings were subsequently confirmed using KO mutants with specific defects in iron uptake. As mentioned above, mycobactin biosynthesis and transport via the siderophore system are essential for in vivo pathogen survival, further confirming that iron uptake is associated with pathogen

virulence. The pathogen's exposure to iron deficiency within macrophages is evident from the upregulation of *mbt* genes. Thus, one or more components of the iron uptake mechanism may serve as marker(s) to reflect the iron status of the pathogen. Mycobacteria produce two types of siderophores, hydrophobic mycobactins and water-soluble carboxymycobactins, which scavenge iron from the immediate environment; saprophytic mycobacteria produce exochelins as the main extracellular siderophore. Mycobactin is confined to a cell envelope containing complex lipids, including highly hydrophobic mycobacterial mycolic acids. This lipid-rich organization makes the outer membrane of mycobacteria much more rigid than that of Gram-negative bacteria and requires the presence of two siderophores for iron uptake. In contrast to the TonB-dependent receptor-mediated internalization of the ferrisiderophore seen in Gram-negative organisms, it is more likely that iron is transferred from the ferric-carboxymycobactin outside the cytoplasmic membrane to the mycobactin. Iron transfer from ferric-carboxymycobactin to mycobactin has been shown and, as discussed later in this review, proposed to be mediated by a 28 kDa iron-regulated cell wall-associated protein, HupB, in *M. tuberculosis*.

Conclusions. The link between iron and tuberculosis has been strengthened by the elucidation of the *M. tuberculosis* genome, advances in immunology, and clinical trial results. Drugs that target mycobacterial iron uptake pathways for *M. tuberculosis* or host pathways that affect iron availability are worth developing and testing for anti-tuberculosis activity. The role of iron should be considered in future vaccine studies..

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