To Understand the Role of Heme Molecules in the Survival and Pathogenesis of *Mycobacterium tuberculosis*

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**Abstract**

*Mycobacterium tuberculosis* is an aerobic gram positive pathogen which causes deadly disease called tuberculosis (TB) which is still a major threat to life. *Mycobacterium tuberculosis* Pathogen enters in host by inhalation of air because these pathogens are present in air droplets released by other TB infected persons. It ultimately reaches to lung alveoli and gives rise to primary TB. In macrophages Mycobacterium replicates itself and increases its number in host cell. Artemisinin is a drug obtained from the plant Artemisia which target the heme molecule in mycobacterium and stop its replication.

**Keywords:** *Mycobacterium tuberculosis*; H37Rv; Rv0203; Heme molecule; Artemisia afra

**Abbreviation**


**Introduction**

*Mycobacterium* is gram positive and aerobic bacteria. *Mycobacterium* strains are present in air and enter in host through nasal inhalation as these pathogens are present in air droplets which are released by sneezing or coughing of *Mycobacterium tuberculosis* infected person and ultimately reach to the lungs which infect lungs in primary infection and lymphoid organs in secondary infection in lymphoid organs. In body circulation pathogen enters by respiratory tract through air droplets and attack on macrophages for its replication.

*Mycobacterium tuberculosis* H37Rv is a highly successful pathogen and it successfully attacks on host [1]. Besides respiration, this pathogen also enters in host circulation by Micro fold cells. Microfold cell can directly mediate primary infection by *Mycobacterium* and facilitate distribution beyond the mucosa [2] as shown in Figure 1.

According to WHO report of 2016, In 2015, 6.1 million new T.B. cases were notified to national authorities and reported to WHO and an increment was observed in T.B. from 2013-2015 [3].

Iron is the molecule which is required for the survival of this pathogen because it is a co-factor for at least 40 enzymes in mycobacterium and it also maintains the iron homeostasis [4]. The virulence of Mycobacterium depends on its ability to assimilate iron; it synthesizes and utilizes siderophores (low-molecular-weight iron chelators) to sequester iron [5]. The uptake of oxygen is possible only when the heme is in ferrous (Fe^{2+}) in host circulation. Reduction is defined as a loss of O_2 (O_2 + e^-→O_2^•−). On phagocytosis of Mycobacterium, lung macrophages and neutrophils produce large quantities of reactive oxygen species (ROS) and reactive nitrogen species (RNS). NADPH oxidase catalyses one-electron reduction of O_2 using NADPH as electron donor, generating O_2•− 2O_2 + NADPH → O_2^− + NADP^+ + H^+[6].

![Figure 1: Mycobacterium infection in host.](image)

Mycobacterium has developed so many mechanisms to uptake iron, one of them is it uses siderophore molecules to scavenge iron from host body and another way of iron uptake is through heme molecule as shown in Figure 2.

As we have discussed in above lines that heme is the molecule which accepts only nascent oxygen to generate aerobic environment for survival of pathogen. Heme is a protein molecule which might be translated by a gene Rv0203 in pathogen. Rv0203 has a unique fold and it is highly atypical in heme transfer proteins. It has alpha-helical structure contains dimer of dimmers where each monomer consists 5
alpha-helices. The dimer is formed by antiparallel interactions between the alpha-1 helix and four helices of the dimer form an antiparallel helical sheet. Two dimers join and form off-tilt cage like structure in which alpha 5-helices form a weak hydrophobic core [7]. The ability to acquire heme has been discovered in two species: Staphylococcus aureus and Escherichia coli.

The role of Rv0203 was investigated by double knockout experiments. The mutation experiment was performed by tagging Mycobacterium protein. Histidine was tagged (Rv0203-His) and native protein was non tagged (Rv0203-notag). Rv0203-His binds to heme by his-his co-ordination bond. It was discovered in mutagenesis experiment that Rv0203 bind efficiently to heme with the help of some residues His63, His89 and Tyr59. The rate of heme binding to Rv0203-His and Rv0203-notag is same which is measured by stopped flow techniques [8]. In a recent study a plant has identified known as Artemisia afr a which belongs to family Asteraceae. Artemisia a fr a is a plant from which a medicine Artemisinin has been isolated. By this drug the replication is completely stopped because it attacks on heme molecule which senses the reduced oxygen for the survival of pathogen. Artemisinin inhibit the replication by dichloromethane extract. The activity of Artemisinin was observed that it clear the Mycobacterium tuberculosis infection up to undetectable level [9]. It is commonly found in Africa and widely distributed in South Africa and grows in loamy sands, to sandy or calcareous clay loams of volcanic or granitic origin [10].

Artemisia afr a also exhibits powerful pharmacological activities including antimicrobial, antioxidant, CNS-effects (sedative, antidepressant), cardiovascular, and spasmylic activity which has been well documented and reviewed recently by Liu et al. [11].

Conclusion

I would like to summaries my words that Mycobacterium tuberculosis is a lethal disease which is caused by different strains of Mycobacterium in different regions. Pathogens are present in air and entered in host by inhalation and microfold cells. This is an aerobic bacteria and heme protein which translated by gene Rv0203, provide a site for oxygen binding. The binding of oxygen activate the heme and heme scavenges iron from host machinery. Artemisinin is a recent drug which stop Mt replication in host and almost clear TB.

An approach toward TB treatment

We have some experimental approach that if in Mycobacterium tuberculosis a mutation experiment was performed on His63, His89 protein but not on Tyr59. Tyr 59 is also important for heme binding and we can mutate Tyr59 and can check its activity for T.B. infection. This mutation can be done by gene insertion or deletion by enzymatic reaction or by radiation as shown in Figure 3.

![Figure 2: Iron uptake by using heme molecule.](image)

![Figure 3: An approach for Tyr59 mutation.](image)

![Figure 4: An approach for generating a synthetic molecule to change Heme structure.](image)
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References