Second Verse, Same as the First

Structures of Thioredoxin Proteins TrxA and TrxC from Mycobacterium tuberculosis

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Abstract

*Mycobacterium tuberculosis* (M. *tb*), the causative agent for tuberculosis (TB), infected 8.6 million people and took 1.3 million people in 2012 (WHO). TB is most prevalent in countries with a high incidence of infectious diseases, such as HIV, due to weakened immune systems. TB mainly affects the lungs, but can also affect other systems. When a host organism is infected with TB, the Mycobacterium in the lungs multiply, often resulting in pneumonia, chest pain, and prolonged coughing. In response, host macrophages, a part of the natural immune system, engulf the *Mycobacteria* and oxidize bacterial cell proteins in an attempt to destroy it. To protect itself against this attack, the bacterial thioredoxide system, consisting of the reduct protein thioredoxin reductase (*TrxR*) and the thioredoxin proteins TrxA, TrxB, and TrxC, gives electrons back to the oxidized proteins. As this system works to maintain cellular redox homeostasis, finding ways to stop it might provide a new method for treating people with TB. TrxA and TrxC have similar structures, thus it can be hypothesized that their functions are similar. Comparing binding sites between the proteins can provide insight if TrxA can react with TrxR similarly to TrxC. By modeling TrxA and TrxC with 3D printing technology, the Messmer SMART Team (Students Modeling A Research Topic) can compare the structures of the thioredoxins which may lead to new strategies for curing or preventing TB.

Introduction

About ¼ of the world’s population is infected with TB, an airborne disease. If a person with active TB goes untreated, they will infect approximately 10 to 15 people a year. TB usually infects the lungs, but can attack almost any part of the body. In many countries, tuberculosis is becoming increasingly problematic due to weakened immune systems from coinfection with HIV and drug-resistant due to incomplete treatment.

Figure 1. Route tuberculosis takes to enter the body through the respiratory system and into the alveoli. As a result, researchers are hoping to stop TB by learning more about TrxA and TrxC, 2 of 3 thioredoxin proteins that TB uses to protect itself from attacks by a host’s immune system. Thioredoxin proteins are responsible for helping maintain cellular redox homeostasis within the bacterial cell (see Figure 3a,b). TrxA's function is unknown; however, it is believed to be similar to the function of TrxC. If this is true, TB can possibly be stopped by inhibiting these proteins from functioning.

Conclusion

TB is increasingly becoming a world health issue due to its increasing drug resistance. HIV coinfection exacerbates the problem. New therapies are required to combat this global pandemic. In order to come up with new strategies, we need to know more about how TB behaves in its host. Part of this is understanding how the thioredoxin system protects the bacteria in the phagolysosome. If we knew how that worked, we could develop therapies targeting the thioredoxin system. By targeting the thioredoxin system, drugs would allow our bodies natural defenses to fight the *Mycobacteria*. TrxA is well-folded suggesting that it has a definite function, which is currently under investigation. Structural characterization of TrxA will allow for a better understanding of the thioredoxin system.

The Structure of TrxA

In order for a protein to have a defined structure and function it must be well folded. Previous work indicates that TrxA was not well folded and thus was thought to be non-functional. Each crosspeak (dot) in this Nuclear Magnetic Resonance (NMR), shown below, represents the chemical environment of an atom in TrxA. If the dots were on the same plane, but, the size of the planes are different between the proteins TrxA model highlighting amino acids predicted to be involved with binding interactions to TrxR. The amino acids highlighted on TrxA were chosen based on sequence similarities to TrxC. TrxA may not bind to TrxR but due to these structural differences, TrxA may not bind to TrxR in the same way.

References

1. World Health Organization, Global Tuberculosis Control 2010
2. Fig. 1: http://www2.bakersfieldcollege.edu/bio16/22_Resppictures.htm