Sodium/Proton Antiporter Activity is Essential for Virulence of *Yersinia pestis*

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Abstract

We found that a strain of *Yersinia pestis* (KIM8) which lacked the nhaA gene was fully attenuated in a plague model. This gene produces a protein of the sodium proton antiporter family which expel sodium ions from the bacterial cytoplasm in exchange for hydrogen ions, or protons, from the surrounding environment. A Y. pestis strain that contained the nhaA mutation showed a significant decrease in its ability to survive in both sheep’s blood and serum. Decreased growth rates were also observed when the nhaA deficient strain was tested in the artificial serum media Opti-MEM®when compared to the wild type strain. A similar growth phenotype was observed when wild type and nhaA mutant strains were tested in LB media set to mimic pH and salt conditions of blood. These observations indicate that sodium-proton antiporter activity of *Y. pestis* is essential for the survival of the bacterium in certain environments, such as the blood of an infected host. 2-aminopyrimidine was used to inhibit NhaA activity, and when tested in Opti-MEM®, bacterial growth rates decreased. These findings lead us to propose that sodium-proton antiporter inhibition is a novel way of treating bacterial blood-borne diseases.

Background

*Yersinia pestis* is a pathogenic bacterium that causes the fatal disease bubonic plague. Further development of the disease can lead to septicemia or pneumatic plague. During the middle ages this disease was known as “The Black Death” for the necrosis of tissue that occurred during infection. It was responsible for killing over one quarter of the people living in Europe during that time period. Through medical advances and the discovery of antibiotics, treatment of plague has continued. Much like the proton motive force (PMF) the SMF is controlled by the amount of sodium inside and outside of a given cell. Secondary pumps are called NhaA and NhaC. The roles of sodium pumps are to not only prevent the intracellular sodium levels to become toxic, but also to generate a gradients so that the sodium motive force (SMF) can continue. Much like the proton motive force (PMF) the SMF is controlled by the amount of sodium inside and outside of a given cell. It is this role of these secondary sodium pumps that are the focus of this investigation to whether or not sodium proton antiporters are essential for the virulence of *Y. pestis* in a host.

Conclusions

• The nhaA gene is essential for virulence of *Y. pestis*, likely due to the fact that without it, bacterial growth in blood or serum is hindered.

• Death occurs due to the levels of sodium that occur naturally in the blood, 140 mM. Without the NhaA protein the levels become toxic to the cell and it quickly dies.

• Inhibiting the NhaA protein with 2-aminopyrimidine shows a growth defect in the wild type strain in Opti-MEM® similar to that of the nhaA deletion.

• We hypothesize that the inability to grow due to the salinity of the blood of a host would allow for the host’s immune system to clear the infection before it becomes too overwhelming for the body to deal with.

References


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Substrate (Protein, Amino Acid, Sugar, Etc.)