Abstract

Metals are abundant in nature and therefore, also an integral part of the life. The studies on metal geochemistry and biology are going on from ancient times but there are gaps to explore and enormous knowledge is hidden in the biology of metals. To fill some of the gaps in metal biology we studied the role of important metals like Mn, Co, Ni and Fe in *Escherichia coli* physiology.

The Chapter I is a review of literature where I tried to incorporate all the relevant literature regarding metal homeostasis and their functioning. Since some of the studies have highlighted the role of spermidine in metal chelation, I have also studied the subject to check such correlation. Therefore, we additionally included the literature reviews on polyamine homeostasis and the function of spermidine in metal homeostasis and in biological systems.

The Chapter II is dedicated to the manganese homeostasis and its impact on cellular physiology, specifically in a manganese efflux pump deficient strain of *E.coli*. In this chapter, performing microarray, proteomics, and other biochemical assays, we have shown that how manganese stress evokes reactive oxygen species production and affects ATP synthesis. However, we have shown that energy crisis, but not oxidative stress, plays a pivotal role under manganese toxicity. This energy crisis is stemmed from the perturbed iron homeostasis under manganese stress. Other observations include that manganese stress influenced various cellular processes, such as DNA metabolism, transcription, protein synthesis, protein folding, membrane biogenesis etc.

In the Chapter III, we explored cobalt and nickel toxicities and their synergy with Mn individually. We found that manganese could aggravate cobalt and nickel toxicities in synergy, depleting iron and ATP levels. In contradiction to some of the reports, we have demonstrated that the toxicity caused by cobalt and nickel does not work via stimulating oxidative stress in the cell. We have further demonstrated that cobalt and nickel damages DNA but inhibits DNA repair inhibiting SOS response. This could be the reason of cobalt and nickel poisoning. Interestingly, we have shown that acidic pH evolved due to acid fermentation could suppress the formation of metal hydroxide precipitates, thereby maintaining solubility of the metal ions. This could be another reason why cobalt and nickel are highly toxic to the cells.

In the Chapter IV, our study focussed on spermidine toxicity and its impact on metal homeostasis. We used a spermidine sensitive *E. coli* strain and performed microarray to observe the impact on global transcriptional profile. To support the microarray data, we performed 2D proteomics to show the consistency in gene expression. Overall, from the microarray, proteomics and the biochemical assays, we have shown that spermidine stress affected iron homeostasis, produced reactive oxygen species and perturbed usual redox state of the cells. Furthermore, we show that how spermidine homeostasis is important for the envelope integrity and its biogenesis. We have isolated a synthetic lethal mutant related to spermidine homeostasis that affects membrane architecture.

The references for all of the above chapters are included at the end. Reprint of the first page of my peer-reviewed publications are also included at the end. Not the less, the "Appendix" part of the thesis, which includes mostly microarray table for expression profiles and some figures, is a supplemental part of the thesis to interpret some of findings in our Chapters. The joint work of mine and other lab members are reflected in the Appendix.