The copper ionophore elesclomol elevates cellular iron content by delivering copper to iron import machinery

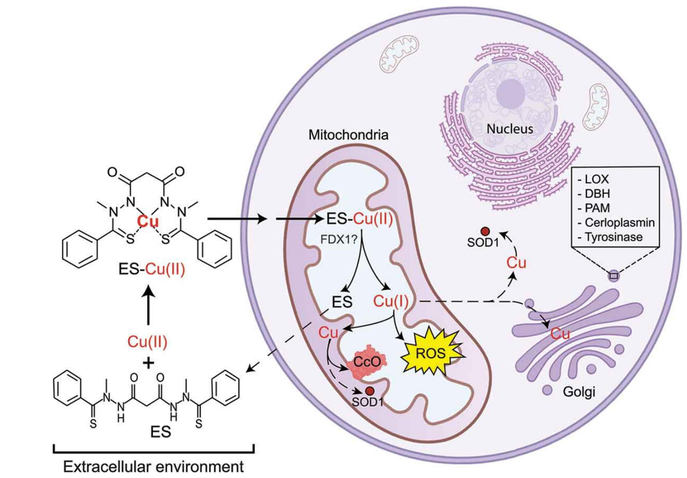
Natalie M. Garza and Vishal M. Gohil

Department of Biochemistry and Biophysics, Texas A&M University, College Station, Texas, USA

Abstract

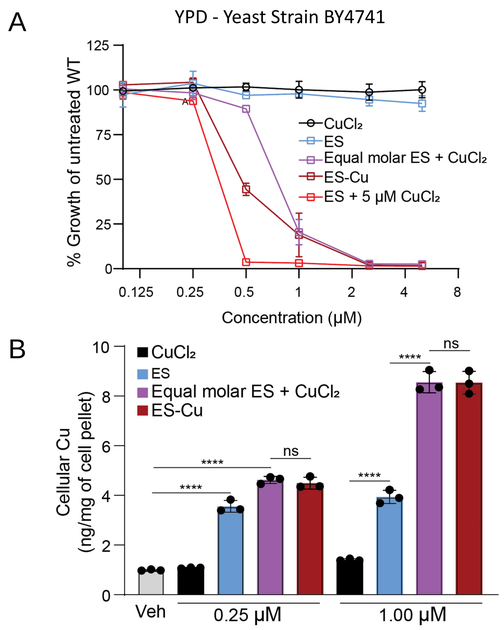
Copper and iron are redox active metals that act as cofactors for many critical cellular enzymes. Disruption in the intracellular homeostasis of either of these metals often results in debilitating and frequently fatal human disorders. Recently we reported that a copper ionophore, elesclomol (ES), can deliver copper to mitochondrial copper-containing enzymes and serve as a potential therapeutic agent for disorders of copper deficiency. Here, we sought to determine the specificity and efficacy of ES and ES pre-loaded with copper (ES-Cu) in cellular metal homeostasis. Using yeast, *Saccharomyces cerevisiae*, as a model organism we demonstrated that ES-Cu is more efficient at increasing cellular and mitochondrial copper content than ES alone. Surprisingly, treatment with either ES or ES-Cu also led to an increase in cellular iron content. In order to decipher the mechanism by which ES elevated cellular iron, we utilized yeast mutants of copper and iron transporters and discovered that ES-mediated increase in iron requires iron- but not copper- importers. Further investigations revealed that ES-mediated increase in cellular iron content is dependent on copper transport to Golgi, where Fet3, a critical component of iron import machinery receives copper. Our results demonstrates that copper brought into the cells by ES can be trafficked to the Golgi apparatus and inserted into cuproenzymes, including those required for cellular iron import. This study, thus, provides a basis for possible future applications of ES for the treatment of disorders of both copper and iron homeostasis.

Introduction

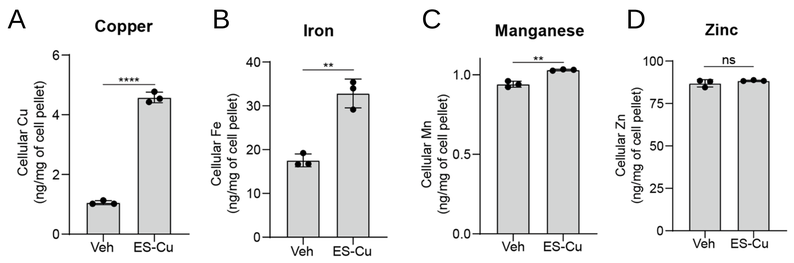


A proposed model of elesclomol-mediated copper delivery to the cell.
(Gohil V.M. *Expert Opin. Investig. Drugs* 2021, **30,** 1-4)

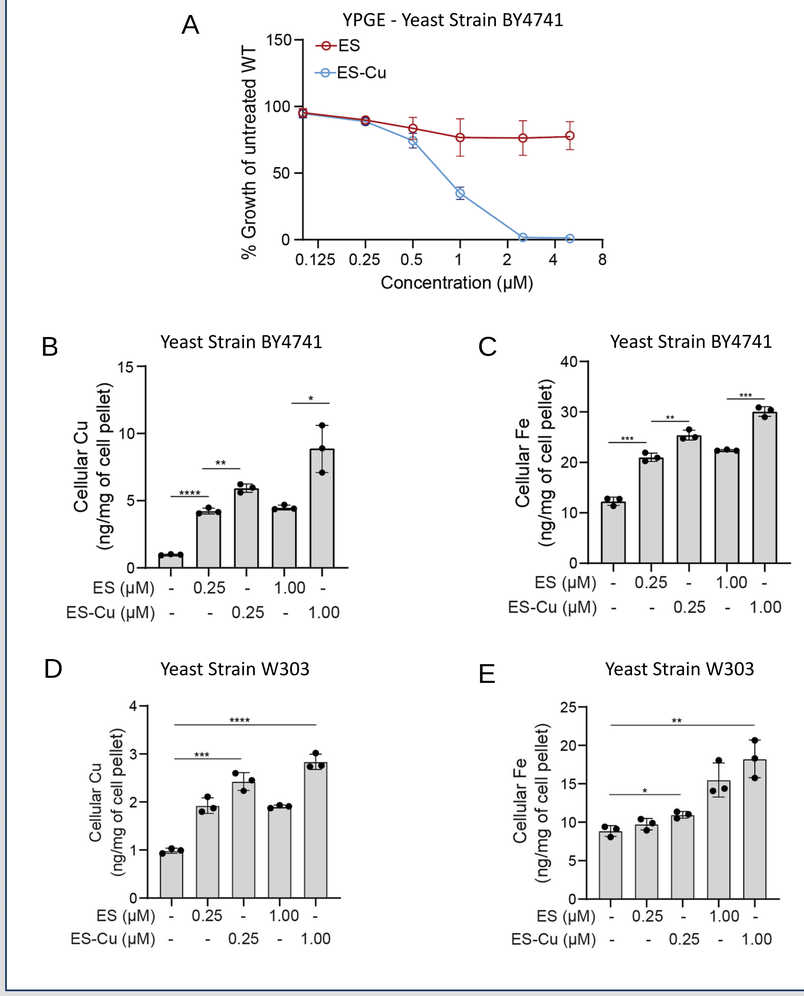
The toxicity of ES is dependent on copper availability



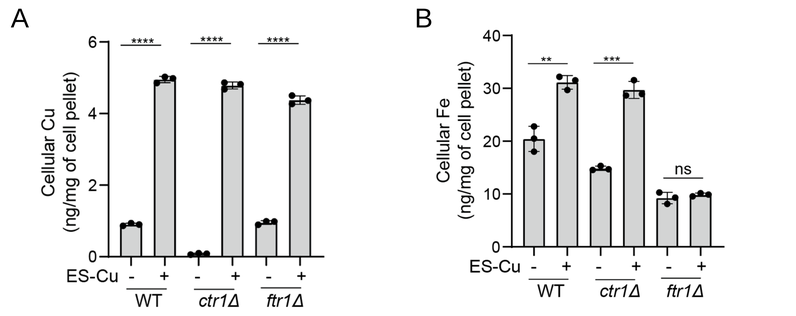
ES-Cu causes a large increase in intracellular iron content



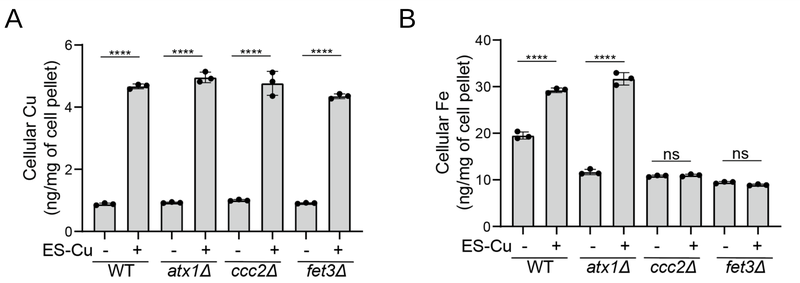
ES-mediated increase in Cu and Fe is independent of yeast strains and growth media composition



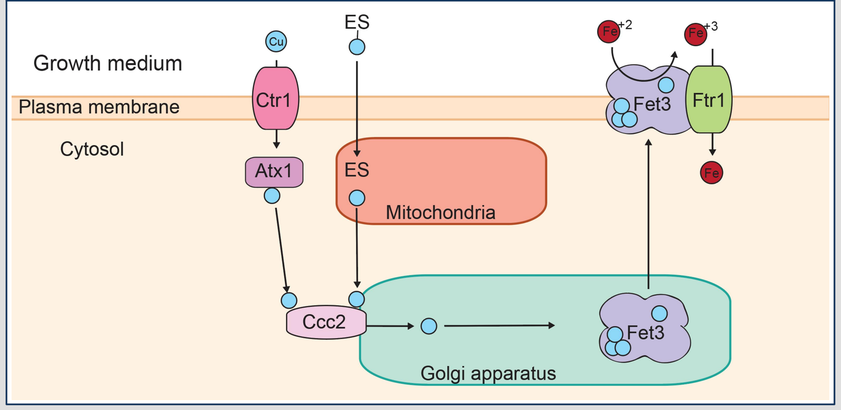
ES-mediated increase in iron levels is dependent on iron import machinery



ES-mediated increase in iron import is dependent on Fet3 and Ccc2 but not copper transporting proteins



Proposed model



Conclusions

1. The efficiency of ES to import extracellular copper is dependent on availability copper.
2. ES supplementation impacts cellular copper and iron homeostasis.
3. ES-mediated increase in cellular Cu is independent of yeast strains, growth media or the presence of Cu or iron transporters.
4. Ccc2, Fet3, and Ftr1 are required for ES-mediated elevation of intracellular iron content.

Acknowledgements

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