



Characterizing Ergothioneine Pathways and Potential Drug Targets via Intrinsically Disordered Protein Analysis

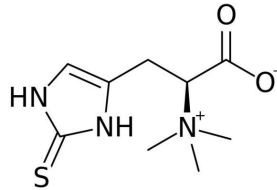
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Context | Ergothioneine's Therapeutic Potential



Ergothioneine

- Amino acid
- Observed cognitive benefits in mice
- Mechanism of action currently not well-characterized

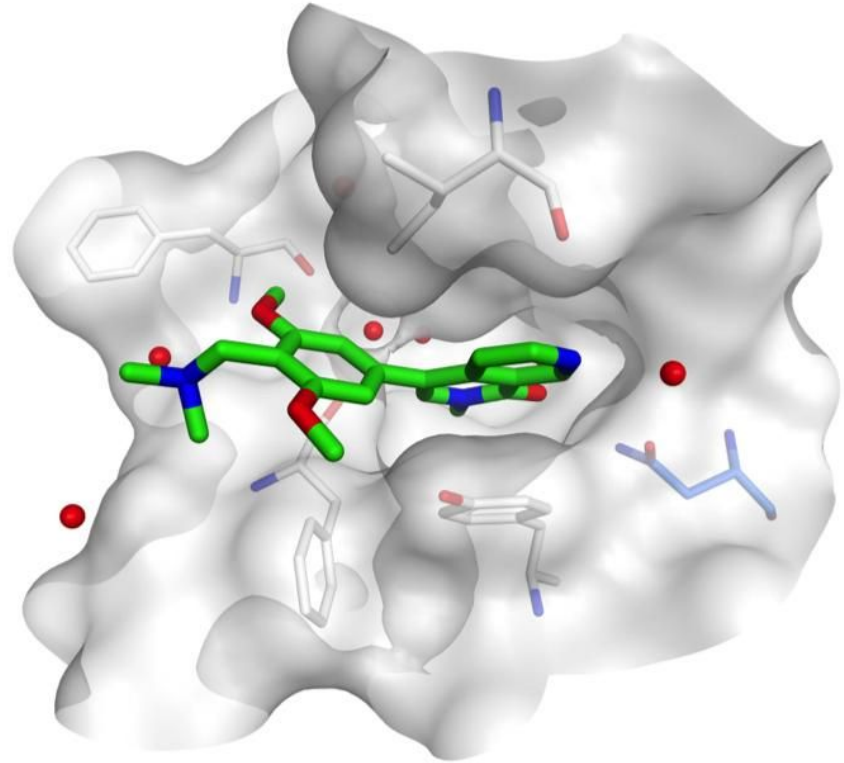


Low levels of ERGO in the blood are associated with:

- Parkinson's disease
- Cognitive impairment
- Cancer

Context | Drug Mechanics

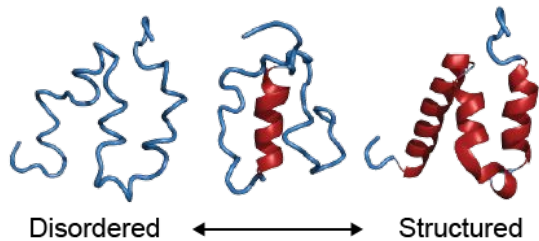
- ERGO is a potential drug that can bind to protein receptors
- Activates or inactivates the protein receptor



Context | High-Potential Protein Receptor Targets

Intrinsically Disordered Proteins (IDPs)

- Frequently implicated in diseases
- IDPs contain regions of order, plus regions of disorder (IDRs)

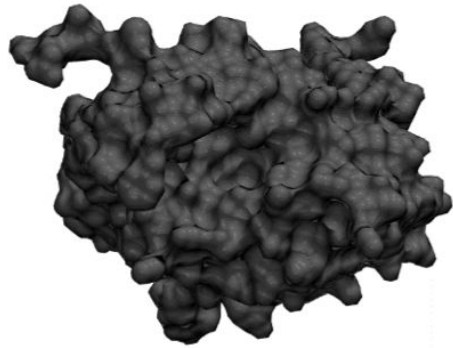


IDP Dual-Personality Fragments

- Exist at boundary between order and disorder
- These fragments have increased likelihood for binding with ligand (ERGO)
- Both stable and flexible

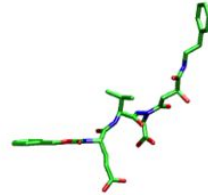


Context | Molecular Docking with Ergothioneine



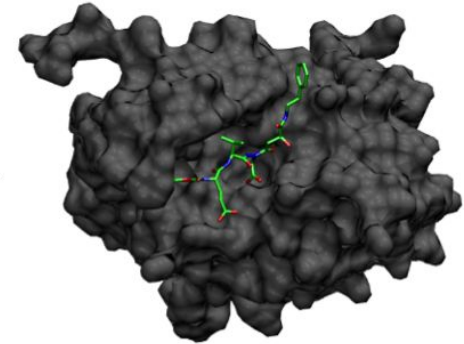
Protein

+



Ligand
(Ergothioneine)

docking



Protein-Ligand
Complex

Research Aims

- ① Characterize and identify new molecular pathways ERGO impacts, with focus on disease pathways
- ② Identify intrinsically disordered proteins that are high-potential ERGO drug targets

Methods | Two-Stage Research Pipeline

1

In-Vitro Analysis

- Identify IDPs that are ERGO target candidates

2

In-Silico Analysis

- Leverage molecular docking to computational rank proteins by binding affinity

Methods | *In-Vitro* Analysis

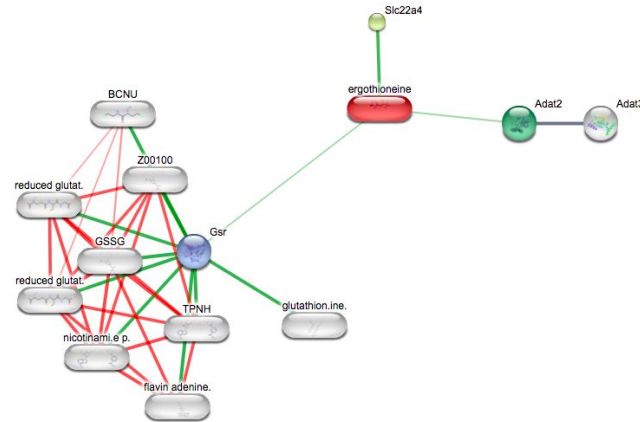
1

In-Vitro Analysis

- Identify 38 IDPs that are ERGO target candidates
 - 28 differentially expressed genes
 - 10 proteins of interest
 - 5 validation proteins
- KEGG and GO analysis to characterize molecular pathways

2

In-Silico Analysis



Protein-Protein Interaction Network

Methods | *In-Silico* Analysis

1

In-Vitro Analysis

Molecular Docking

- Data preprocessing
- Ensemble docking

Structure

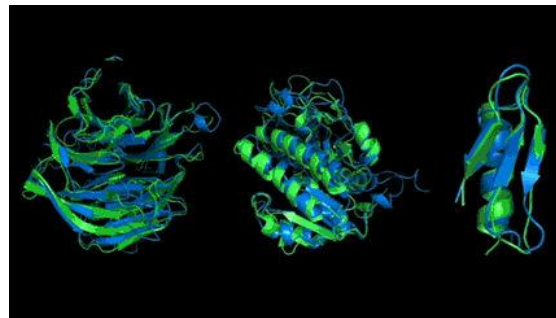
Disorder

Structure

Start and end residues of disordered region(s) on MobiDB

2

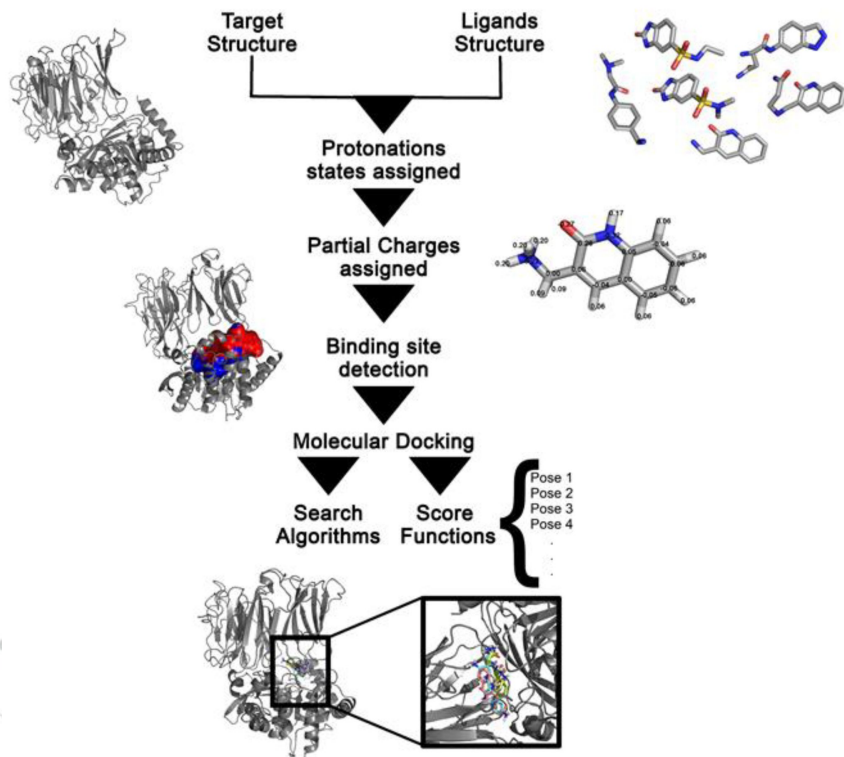
In-Silico Analysis



Google DeepMind's AlphaFold database

**Deep Dive on
Next Slide**

Methods | Molecular Docking Deep Dive



- Preprocessing (protonation, partial charges) enables software to correctly and efficiently calculate intermolecular forces
- Docking identifies poses with highest binding affinity

Results | Characterized Novel ERGO Targets and Pathways

Identified 15 novel protein targets

- Validated against proteins already known to interact with ergothioneine



Confirmed Known Pathways that:

- Lower risk of cancer
- Reduce inflammation

Identified Novel Pathways that:

- Decrease calcium concentration in muscle and blood (*potential kidney disease treatment*)
- Decrease blood clotting (*potential stroke treatment*)

Conclusion

- We validated cancer and inflammation pathways found in existing literature, and proposed new pathways that reduce calcium concentration and blood clotting
- We formulated a list of high-potential ERGO drug targets

Future Research

- Further validation of novel pathways and targets we identified in *in-vitro* and preclinical (animal) models
- Docking ERGO with the human analog proteins to test the molecule's clinical applicability



Acknowledgements

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