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Expression of Human H Ferritin Prompts the Identification of A Hitherto Elusive Yeast Orthologue and Enables Parsing of Distinct Iron-Induced Cell Death Pathways in *Saccharomyces cerevisiae*

Michael T. Greenwood [1], Rawan Eid [1,2], Nada Gharib [1], Chamel Khoury [1,2,3], Nagla T.T. Arab [1,2], Eric Boucher [3], Craig A. Mandato [3], Paul G. Young [2]

[1] Department of Chemistry and Chemical Engineering, Royal Military College, Kingston, Ontario
[2] Department of Biology, Queen's University, Kingston, Ontario, Canada
[3] Department of Anatomy and Cell Biology, McGill University. Montreal, Quebec

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The identification of individual genes as well as their structural and functional characterization remains at the heart of a great deal of biomedical/biological research. The elucidation of the nucleotide sequence of whole genomes has facilitated this task. A variety of strategies has served to identify the function of the myriad of genes thus identified. One simple approach that has proven extremely useful is the identification of possible function due to strong sequence identity with a functionally characterized gene from another species. More recently, global approaches involving data obtained from experiments examining the subcellular localization of GFP tagged proteins, protein binding partners determined by methodologies such as two-hybrid interactive analysis as well as gene expression patterns under different growth conditions have also shed light on the possible function of uncharacterized genes. In spite of great advances there is, as of yet, no genome whose entire repertoire of genes has been functionally annotated. In humans, as many as 40% of the 30,000 or so genes encode Open Reading Frames (ORF) that remain unannotated. Many of these are bona fide and expressed genes based on the presence of orthologues in other species as well as experimental data such as their presence in ESTs. Even the relatively simple 6,000 or so genes in the genome of *S. cerevisiae* has a calculated 685 uncharacterized ORFs (http://www.yeastgenome.org/genomesnapshot). Although still substantial, the number of these ORFs that remain uncharacterized has decreased from an estimated

high of more than 1000 in 2007. The ability to generate yeast cells that are lacking or overexpressing individual genes and examine phenotypic changes has in the past and still continues to this day to be one of the most fruitful approaches to uncovering the function of uncharacterized genes. Clues to potential function based on shared sequence identity with functionally characterized genes are often overlooked because the shared regions are very small or because the percentage sequence identify is limited. Nevertheless, such approaches has proven useful as initial clues in the identification of numerous proteins including the key apoptotic regulators encoded by the yeast *MCA1* encoding metacaspase and the Bcl-2 containing *yBH3* gene.

Ferritins represent a protein fold/domain that bind iron and are involved in many aspects of cell biology. There are 12 different sub-families of ferritin like proteins and the sub-family that includes ferritins, bacterioferritins and DPS proteins is the most widely studied sub-group because of their critical roles in iron metabolism. All three ferritins protect cells from the toxic effects of excess iron. The ferritins and bacterioferritins, but not the DPSs, can form large buckey-ball like multisubunit structures that protect by sequestering the iron. These are also thought to serve as storage in times of deprivation. This is of importance given that bioavailable iron is actually quite low due to its limited solubility at least at neutral or near neutral pH. Although less well studied, the ferritins including the DPSs, can protect from iron toxicity by directly binding iron as dimers. Of interest, ferritins are also general pro-survival proteins that can prevent PCD in response to all manner of ROS generating stresses including H2O2 and UV light. We became interested in ferritin and iron when we identified human H-ferritin as a Bax suppressor and we further showed that it acts like a general pro-survival protein in yeast. The yeast *Saccharomyces cerevisiae* has proven to be extremely useful as a genetically amenable model system for basic cellular processes including cell cycle control, autophagy and more recently, apoptosis. In spite of having no identified ferritin, iron metabolism in yeast is so similar to the processes observed in mammalian cells that it is a commonly used model.

Here we report that we identified a weak similarity between an uncharacterized yeast gene, now called *yFerr*, and human H ferritin. Given that ferritin is an important negative regulator of Programmed Cell Death (PCD) as well as an effector of iron metabolism, we examined these as potential roles for *yFerr*. In effect, the analysis of cells overexpressing *yFerr* demonstrates that it is a pro-survival gene that confers resistance to iron toxicity. Further, cells lacking *yFerr* are hypersensitive to iron. Thus our results demonstrate that *yFerr* is a regulator of iron and PCD in yeast.