Molecular mechanisms governing heme regulation of Jumonji C domain-containing proteins in yeasts

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Heme, iron protoporphyrin IX, is a crucial metallonutrient and a major source of iron for living organisms ranging from bacteria to humans. In humans, 95% of functional iron is in the form of heme. Heme is a central molecule in oxygen metabolism and utilization. It serves as a prosthetic group or cofactor for many proteins and enzymes involved in oxygen utilization and metabolism. The utilization of heme as an iron source strongly influences the virulence of most pathogenic bacteria and some pathogenic fungi. For example, Candida albicans secretes a hemolytic factor and uses heme and hemoglobin as an iron source. Cryptococcus neoformans can subsist on solely heme- and hemoglobin-sourced iron. Further, Histoplasma capsulatum can only utilize iron in the form of heme. Consequently, disrupting heme uptake may be a viable approach to inhibit fungal infection. Additionally, understanding how heme acts to control various cellular processes should provide novel insights into how pathogenic fungi can be suppressed. Particularly, our lab has extensively investigated the molecular mechanisms underlying heme regulation of two yeast regulators, the heme activator protein Hap1 and the multi-functional regulator Gis1. Gis1 is a yeast orthologue of the KDM4/JMJD2 subfamily of proteins containing a Jumonji C (JmjC) domain, which functions as an α-ketoglutarate (AKG) and Fe(II)-dependent histone demethylase. Heme directly binds to Gis1 and promotes transcriptional and demethylase activities of Gis1. The molecular mechanism by which heme promotes Gis1 activities will be discussed.

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