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Heme promotes transcriptional and demethylase activities of Gis1, a member of the histonemethylase JMJD2/KDM4 family

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The yeast Gis1 protein is a transcriptional regulator belonging to the JMJD2/KDM4 subfamily of demethylases that contain a JmjC domain, which are highly conserved from yeast to humans. They have important functions in histone methylation, cellular signaling, and tumorigenesis. Besides serving as a cofactor in many proteins, heme is known to directly regulate the activities of many proteins ranging from transcriptional regulators to potassium channels. This study reports a novel mechanism of heme regulation of Gis1 transcriptional and histone demethylase activities. We found that two Gis1 modules, the JmjN+JmjC domain and ZnF, can bind to heme specifically *in vitro*. *In vivo* functional analysis showed that the ZnF, not the JmjN+JmjC domain, promotes heme activation of transcriptional activity. Likewise, measurements of the demethylase activity of purified Gis1 proteins showed that full-length Gis1 and the JmjN+JmjC domain both possess demethylase activity. However, heme potentiates the demethylase activity of full-length Gis1, but not that of the JmjN+JmjC domain, which can confer heme activation of transcriptional activity in an unrelated protein. These results demonstrate that Gis1 represents a novel class of multi-functional heme sensing and signaling proteins, and that heme binding to ZnF stimulates Gis1 demethylase and transcriptional activities.

Biography

Tianyuan Wang is a PhD student in Department of Biological Sciences at the University of Texas at Dallas, under the guidance of Dr. Li Zhang. The Zhang lab is interested in investigating the molecular mechanisms underlying heme signaling in eukaryotic cells. She is currently focusing on the study of heme regulation on yeast transcriptional factor Gis1, which is highly homologous to the mammalian JmjC domain-containing KDM4B protein. Her research interests also include heme regulation of KDM4 subfamily demethylase activity and heme availability in lung cancer initiation and tumorigenicity. Prior to joining graduate school at the University of Texas at Dallas, she has obtained her Bachelor's degree in Biological Sciences at China Agricultural University, where she worked as a Research Assistant and was involved in the project proteomic analysis of Arabidopsis response to environmental stress.

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