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Inhibitors of the HIF pathway and novel therapeutic opportunities

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Abstract

Hypoxia plays critical roles in the pathobiology of heart disease, cancer, stroke, eye, and chronic lung disease, which are responsible for 60% of deaths in the United States. Hypoxia-mediated activation of the hypoxia-inducible-factor (HIF) pathway, leading to transcriptional changes in gene expressions, plays a fundamental role in the pathobiology of above diseases. Yet, molecular and biochemical mechanisms governing this fundamental pathway remain poorly understood. Since our initial identification of first iron(II), 2-oxoglutarate (2OG)-dependent dioxygenase involved in transcription regulation by the HIF pathway (*Science*, 2001, 292, 468-472; *Cell*, 2001, 107, 43-54), results from numerous studies have established a key role for these enzymes in epigenetic transcriptional regulation. Our long term goal is to use our experience in the HIF pathway and dioxygenases/demethylases to delineate their roles in normal development/ disease states, and identify small molecule modulators that can be used to develop more effective strategies for therapeutic intervention.We have recently shown that hypoxia induces the expression of a number of histone lysine demethylases/dioxygenases (KDMs) in cancer and retinal pigment epithelial cells. Moreover, we found that the expression of pro-angiogenic genes (ADM and GDF15) is dependent on KDMs under hypoxic conditions. Further, treating the cells with a general KDM inhibitor blocks the expression of these pro-angiogenic genes. Results from our studies suggest that specific inhibitors of KDMs such as JMJD1A can be a new therapeutic approach to treat diseases caused by the hypoxia.

Biography

Mridul Mukherji has completed his D.Phil. (Ph.D.) at the age of 29 years from the University of Oxford and postdoctoral studies from the Scripps Research Institute. At present, he holds a rank of Assistant Professor at the School of Pharmacy, University of Missouri-Kansas City. He has published more than 26 papers in reputed journals and serving as an editorial board member of Dataset Papers in Biology, Hindawi Publishing Corporation.