

## Hypoxia-inducible factor-1 dependent nuclear entry of factor inhibiting HIF-1

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The role of FIH-1 in the regulation of HIF-1 transcriptional activity has been known for some time, but is limited to the understanding that in the nucleus FIH-1 hydrolyzes asparagine at the C-terminus of HIF-1 $\alpha$  to prevent the interaction between HIF-1 $\alpha$  and associated cofactors, resulting in suppressed activation of HIF-1. FIH-1 is a cytoplasmic protein. When does FIH-1 move into the nucleus? This was specifically addressed in Dr. Y. James Kang's laboratory in the Regenerative Medicine Research Center at Sichuan University in China and is reported in the November 2015 issue of *Experimental Biology and Medicine*.

The researchers used dimethyloxalylglycine (DMOG) to increase the level of intracellular HIF-1 $\alpha$ , which was soon found to be localized in the <u>nucleus</u>. At the same time the FIH-1 level was also increased in the nucleus. Gene-silencing of HIF-1 $\alpha$  dramatically decreased intracellular levels of HIF-1 $\alpha$  and eliminated its nuclear location. Under this condition the nuclear entry of FIH-1 was blocked although the total <u>protein level</u> of FIH-1 in the cells was not decreased. Further analysis found that using tetraethylenepentamine (TEPA) to reduce intracellular levels of copper led to a decrease in both intracellular levels of HIF-1 $\alpha$  and its nuclear location. Under this condition, the total FIH-1 protein level in the cells was not reduced, but the FIH-1 protein level in the nucleus was dramatically reduced. Therefore, the nuclear entry of FIH-1 is triggered by the process of HIF-1 $\alpha$  translocation from the cytoplasm to the nucleus.



Dr. Kang said "Since the increase in the cytoplasmic level of HIF-1 $\alpha$  and its nuclear location require the presence of copper, the reduction of intracellular copper levels thus also suppresses the nuclear entry of FIH-1, but does not reduce the total level of FIH-1 in the cells." Further studies are needed to demonstrate how FIH-1 enters into the nucleus and the HIF-1 $\alpha$  nuclear entry-dependent regulatory mechanism. Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine* said "Dr. Kang and colleagues have done an elegant job of demonstrating the role of copper in FIH-1 nuclear entry."

**More information:** K. Liang et al. Featured Article: Hypoxiainducible factor-1 dependent nuclear entry of factor inhibiting HIF-1, *Experimental Biology and Medicine* (2015). DOI: <u>10.1177/1535370215570821</u>

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