Dynamic distribution of hig2a between the mitochondria and the nucleus in response to hypoxia and oxidative stress

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Abstract
Mitochondrial respiratory supercomplex formation requires HIG2A protein, which also has been associated with cell proliferation and cell survival under hypoxia. HIG2A protein localizes in mitochondria and nucleus. DNA methylation and mRNA expression of the HIGD2A gene show significant alterations in several cancers, suggesting a role for HIG2A in cancer biology. The present work aims to understand the dynamics of the HIG2A subcellular localization under cellular stress. We found that HIG2A protein levels increase under oxidative stress. H_2O_2 shifts HIG2A localization to the mitochondria, while rotenone shifts it to the nucleus. HIG2A protein colocalized at a higher level in the nucleus concerning the mitochondrial network under normoxia and hypoxia (2% O_2). Hypoxia (2% O_2) significantly increases HIG2A nuclear colocalization in C2C12 cells. In HEK293 cells, chemical hypoxia with $CoCl_2$ (>1% O_2) and FCCP mitochondrial uncoupling, the HIG2A protein decreased its nuclear localization and shifted to the mitochondria. This suggests that the HIG2A distribution pattern between the mitochondria and the nucleus depends on stress and cell type. HIG2A protein expression levels increase under cellular stresses such as hypoxia and oxidative stress. Its dynamic distribution between mitochondria and the nucleus in response to stress factors suggests a new communication system between the mitochondria and the nucleus.

Author keywords
Cancer; HIGD2A; Hypoxia; Metabolic reprograming; Mitochondria; Oxidative stress