STUDY OF THE MOLECULAR REGULATION OF HIG2A PROTEIN: IMPLICATIONS IN THE REGULATION OF MITOCHONDRIAL PHYSIOLOGY

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Introduction and Objectives: Respiratory supercomplexes are dynamic supramolecular assemblies of complex I, III and IV within the inner mitochondrial membrane. Recently, the identification of proteins that mediate and/or regulate the stability and assembly of the respiratory supercomplexes has started. The protein HIG2A was described to mediate supercomplexes assembly. Knockdown of HIG2A causes impaired supercomplex formation. Our current objective is to study the molecular regulation of \textit{higd2a} gene encoding for HIG2A and analyze the implications in the regulation of mitochondrial physiology.

Materials and Methods: \textit{In silico} analysis of \textit{higd2a} gene and HIG2A protein. Study of the \textit{higd2a} gene expression by real time PCR and promoter reporter assay. Cell imaging analyses with confocal microscopy. Tests were performed in C2C12, HEK293 and SY5Y cell lines and in C57BL/6 mice.

Results: HIG2A has a hypoxia-inducible domain. Expression of \textit{higd2a} was increased significantly in C2C12 cells after 36 and 48 hours of hypoxia (5% oxygen). Promoter region of \textit{higd2a} gene possesses binding sites for PPAR-\(\alpha\) and E2F-1. We modulated chemically the transcription factors PPAR-\(\alpha\) and E2F-1 in C2C12 and HEK293 cells and this induces significant changes on the expression of \textit{higd2a}, suggesting that PPAR-\(\alpha\) and E2F-1 are involved in the regulation of \textit{higd2a} transcription. Expression of \textit{higd2a} shows differential tissue expression in C57BL/6 mice. Furthermore, we observed that in C57BL/6 mice injected with quercetin, a modulator of energetic metabolism, changes \textit{higd2a} expression from evaluated tissues. In spleen and bone marrow, \textit{higd2a} gene expression increase significantly with quercetin, while in liver, decrease significantly. Preliminary analyses suggest that knockdown of HIG2A in SY5Y neuroblastoma cells, causes a decrease in mitochondrial fusion.

Conclusions: Alterations in cellular metabolism lead to changes in \textit{higd2a} gene expression. HIG2A protein might function as a regulator of respiratory supercomplexes in response to changes in cellular metabolism.

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