In silico study of protein-protein interactions and metabolic pathways in Paragangliomas for therapeutic and diagnostic advances

Ana Luiza Ribeiro Bet[1], Cláudia Malheiros Coutinho Camillo[1]

[1.] ACCamargo/FAP, A.C.Camargo Cancer Center – Fundação Antônio Prudente, R. Taguá, 440 - Liberdade, São Paulo - SP, 01508-010;

Paragangliomas (PGLs) are a rare type of neuroendocrine neoplasm that originate in extra-adrenal paraganglia. The most common type of PGL is the carotid body, which accounts for up to 75% of cases. They are mostly benign neoplasms and about 10% are reported as malignant. However, there are no biomarkers that can predict malignant behavior in primary tumors. Therefore, the aim of this study was to explore and characterize protein-protein interactions (PPI) and metabolic pathways involved in the development of paragangliomas to identify new biomarkers and therapeutic targets to improve the diagnosis and treatment of these rare lesions.

Proteins were selected using the STRING database with a filter to select only high-confidence proteins with a score greater than 0.7, which included: SDHA, SDHB, SDHC, SDHD, SDHAF2, KIF1B, VHL, RET, TMEM127 and FH .The collected data was exported to Cytoscape, a platform that allows the visualization and analysis of complex networks, such as protein-protein interactions. Cytoscape's Network Analyzer application was used to calculate centrality metrics, including closeness centrality, which allowed to identify central proteins in the network. After that, the core proteins were submitted using ClueGo, a Cytoscape plugin that integrates genes into biological function clusters and visualizes gene ontology (GO) terms, for mapping metabolic and functional pathways, using GO and KEGG databases. Enrichment analyzes were performed to identify metabolic pathways significantly associated with the proteins in the network. The results were visualized as network graphs where related pathways were grouped, facilitating the interpretation of biological interactions and functions.

SDHA, SDHB, SDHC and RET were identified as core proteins highlighting the importance of the succinate dehydrogenase (SDH) complex and RET signaling pathways in PGLs. The SDH complex is fundamental to the tricarboxylic acid (TCA) cycle, a metabolic pathway crucial for cellular energy production. Changes in SDH complex subunits have been associated with mitochondrial dysfunction and the accumulation of succinate, an oncometabolite that can promote cell proliferation and tumor progression. In addition to TCA, functional enrichment analysis using ClueGO revealed glycolysis as another metabolically significant pathway associated with core proteins. This suggests that PGL cells may rely on both oxidative and glycolytic metabolism to sustain their proliferation, a common feature in many cancers known as the Warburg effect.

These findings highlight the proteins SDHA, SDHB, SDHC and RET as potential biomarkers for the diagnosis of PGLs. Furthermore, these proteins represent promising targets for the development of new therapies. Inhibitors targeting SDH complex subunits or modulators of RET-associated signaling pathways can be explored as therapeutic strategies, potentially disrupting metabolic pathways critical for tumor survival.

Detailed analysis of PPI interactions and metabolic pathways in PGLs offers a new perspective on the pathogenesis of these lesions. The identification of core proteins and associated metabolic pathways not only improves the biological understanding of PGLs but also opens new opportunities for the development of more effective diagnostic and therapeutic strategies. These results are a significant step toward a more personalized and precise approach to the clinical management of PGLs.

Agradecimentos: I would like to express my gratitude to all the people who contributed to the completion of this work. Firstly, I would like to thank my supervisor, Prof. Dr. Cláudia Malheiros Coutinho Camillo, for her guidance, continuous support and dedication. His experience and knowledge were fundamental to the conduct and completion of this study. I would also like to thank my laboratory colleagues and friends, who always helped and motivated me. Finally, I would like to thank my family for their unconditional love and support, always believing in my potential and encouraging me to move forward, even in the most challenging moments.