

mTOR Pathway Proteins are Not Upregulated in SDHB-Related Paragangliomas: Relevance to Future Therapeutic Options Using mTOR Inhibitors

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Background: Pheochromocytomas (PCCs)/paragangliomas (PGLs) are neuroendocrine tumors that may cause hypertensive crisis, myocardial infarctions, and death if not properly treated. However, medical therapy in patients with metastatic tumors is lagging behind. As new PCC/PGL susceptibility genes are being discovered that are associated with the mTOR pathway directly or indirectly, treatment targets focusing on this pathway are being explored.

Methods: Twenty human hereditary and sporadic PCCs/PGLs were analyzed from 2 tertiary care centers. Immunohistochemistry (IHC) analysis was performed for mTOR pathway proteins such as p-mTOR, p-S6K, and p-4EBP1. Other signaling pathway components associated with PCC/PGL such as PI3K and HIF-1 α were evaluated. Proliferation index, using MIB-1, was determined. Since p53 plays a central role in numerous other malignancies, staining was performed. Six SDHB-related PGLs and fourteen benign/sporadic PCCs, including one with *TMEM127* mutation were included in the study. The product of the intensity of staining and the percentage of cells that stained was calculated and reported as an H score.

Results: p-mTOR and p-S6K had significantly higher H scores in benign PCCs compared with SDHB-related PGLs. Whereas SDHB-related PGLs had higher H scores in PI3K and HIF-1 α compared to benign PCCs. No difference in these two groups of tumors in H scores was seen with p-4EBP1 and MIB-1. For p53, there was low staining in SDHB-related PGLs and absent staining in benign PCCs, but these differences were not statistically significant.

Conclusion: p-mTOR and p-S6K have higher protein expression in benign/sporadic PCCs as compared with SDHB-related PGLs. Proteins involved in other tumorigenic pathways such as PI3K and HIF-1 α are more highly expressed in SDHB-related PGLs than in sporadic PCC/PGLs. These results suggest that the use of mTOR inhibitors alone for SDHB-related PGLs may not achieve the desired therapeutic results of tumor shrinkage and decreased proliferation.