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Novel Fusion Gene UBTF-MAML3 Drives Tumorigenesis in Neuroendocrine Tumor Cells

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BACKGROUND: Pheochromocytomas and paragangliomas (PCC/PGL) are rare neuroendocrine tumors (NET) derived from chromaffin cells. Of those individuals with PCC/PGL, 15-25% have metastatic disease, which can occur even many years after initial diagnosis. The drivers for metastatic disease are not well understood. The Cancer Genome Atlas (TCGA) first identified that 5% of PCC/PGL had a novel fusion gene involving MAML3, and this was associated with metastatic disease. We recently confirmed in a separate cohort that 7% of PCC/PGL had the UBTF-MAML3fusion gene. The aim of this study was to investigate the tumorigenic properties of the UBTF-MAML3fusion.

METHODS: Because there are no human PCC/PGL cell lines, three NET cell lines were used for in vitro studies, SK-N-SH, QGP1, and BON1. Functional assays were conducted after cells were transiently transfected with either UBTF-MAML3 fusion (Fus) or full length MAML3 (FL). Transcriptome analysis also was performed. All assays were done in triplicate and statistical significance was determined by ANOVA.

RESULTS: Both UBTF-MAML3 Fus and MAML3 FL overexpression showed increased invasion compared with empty vector control. In SK-N-SH, invasion across Matrigel increased by 40% ($p=0.0005$) and 31% ($p=0.0029$) for Fus and FL, respectively; and in QGP1, Fus had a 73% ($p=0.0036$) increase and FL had a 27% ($p=0.307$) increase, the latter did not reach statistical significance. Overexpression of UBTF-MAML3 Fus and MAML3 FL in QGP1 showed an increase in colony formation, 37% ($p=0.0036$) and 60% ($p<0.0001$), respectively. Investigation is ongoing into the mechanism of UBTF-MAML3 function. Transcriptome analysis of all three cells lines overexpressing MAML3 FL showed upregulation of the Wnt

pathway targets, in addition to canonical Notch targets, consistent with human PCC/PGL data in TCGA.

CONCLUSION: Overexpressed UBTF-MAML3 fusion gene increased invasion and colony formation, suggesting it is a driver of tumorigenesis and metastatic disease. The mechanism of action is still unknown.

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