Loss of UCHL1 Expression Increases Metastatic Potential in Pancreatic Neuroendocrine Tumors

Brendan Finnerty[1]; Maureen Moore[1]; Irene Min[1]; Marco Seandel[1]; Todd Evans[1]; Rasa Zarnegar[1]; Thomas Fahey[1]

[1]New York Presbyterian Hospital – Weill Cornell Medicine

Background: Well-differentiated pancreatic neuroendocrine tumors (WD-PNET) metastasize even in the setting of low Ki67 index. We have previously identified UCHL1, a post-translational modifier that targets proteins for lysosomal degradation, as differentially expressed in metastatic and localized PNETs. Here we aimed to elucidate how UCHL1 may contribute to the metastatic phenotype.

Methods: Two PNET cell lines, BON (lymph node of metastatic PNET with no UCHL1 expression) and QGP (primary tumor of metastatic PNET with very low UCHL1 expression) were stably transfected with an inducible UCHL1 gene and the cells then studied with and without UCHL1 expression for cell viability, apoptosis, growth, cell-cycle arrest, and cellular invasion. These in vitro assays were compared to the cell lines transfected with an empty vector (BON-EV and QGP-EV) as negative controls.

Results: UCHL1 expression in BON cells (BON-UCHL1) resulted in a higher percentage of BON-UCHL1 cells in the G0/G1 phase of the cell cycle as compared to BON-EV cells (47±4% vs. 37±3%, p=0.03). Similarly, there was a higher percentage of QGP-UCHL1 cells compared to QGP-EV in the G0/G1 phase (68 ±6% vs. 61±4%, p=0.02). BON-UCHL1 cells were also observed to have lower numbers of colonies per low-power field than the BON-EV cells (667±36 vs. 895±43, p<0.001) in an anchorage independent colony growth assay. In a cell adhesion assay, BON-UCHL1 cells displayed decreased adhesion with a lower fraction of non-adherent cells when compared to BON-EV (63±7% vs. 92±5%, p<0.001). A modified Boyden chamber assay for cell invasion was also noted to be decreased in BON-UCHL1 cells after 24-hours (12 cells vs. 74 cells per transwell plate, p=0.03).

Conclusion: Loss of UCHL1 gene expression is associated with metastasis in well-differentiated PNETs. Re-expression of UCHL1 in 2 PNET cell lines was associated with findings consistent with decreased metastatic potential. Further in vivo studies are warranted to confirm these findings.

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