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Molecular Profiling of Small Intestinal Neuroendocrine Tumours

Anna Karpathakis[1]; Andrew Feber[1]; Tiffany Morris[1]; Harpreet Dibra[1]; Christodoulos Pipinikas[2]; Dahmane Oukrif[2]; Joshua Francis[3]; Dalvinder Mandair[4]; Christos Toumpanakis[4]; Tim Meyer[1,4]; Marco Novelli[1]; Tu-Vinh Luong[4]; Martyn Caplin[4]; Matthew Kulke[5]; Matthew Meyerson[3]; Stephan Beck[1]; Christina Thirlwell[1,4]

[1]University College London Cancer Institute, London, UK
[2]University College London, London, UK
[3]The Broad Institute, Boston, MA 02142, USA
[4]The Royal Free Hospital Neuroendocrine Tumour Unit, London, UK
[5]Dana-Farber Cancer Institute, Boston, MA 02215-5450, USA

Background: Aberrant DNA methylation plays an important role in the pathogenesis of human cancer, however little is known about its role in small intestinal neuroendocrine tumour (SINET) development. We report the first unbiased genome-wide DNA methylation analysis of a large cohort of SINET, aiming to identify epigenetic changes specific to SINET which may contribute to tumorigenesis.

Methods: Infinium HumanMethylation450 Array analysis was performed on DNA extracted from SINET primary tumours (n=49) and normal small intestine (SI) (n=21). Publicly available methylation data on >600 samples from The Cancer Genome Atlas was assessed for comparison (colorectal, pancreatic and gastric adenocarcinoma and healthy tissue). Gene expression was determined using Illumina DASL arrays on RNA from primary SINET (n=32) and normal SI (n=6). Analysis was performed using *ChAMP* and *limma* R packages. A Bonferroni adjusted significance threshold of $p<0.05$ was used throughout.

Results: Comparison of SI NET with normal SI identified 130,083 significant Methylation Variable Positions, including 1841 sites hypermethylated by over 30% in tumour compared to normal tissue. 626 genes were found to have significant >3 fold differential expression between SINET and normal SI. Integrated analysis identified a group of 11 candidate genes where altered methylation and expression was significant and concordant (downregulated: *CDX1, FBP1, C20orf54, GATA5*; upregulated: *PTPRN, PCSK1, PRLHR, CELSR3, GIPR, LMX1B, SCGN*). Hypermethylation of *GIPR* (gastric inhibitory polypeptide receptor) was seen in 92% of SINET (median methylation 0.67 vs normal 0.29, $p<2.2e^{-16}$). Hypermethylation at *GIPR* was sensitive for the detection of SINET compared to other GI malignancies with an AUC of 0.991 (95% CI 0.991-0.999).

Conclusions: This study is the first comprehensive analysis of the epigenetic profile of SINET and identifies hypermethylation of *GIPR* as a potential novel biomarker. Novel radioligands targeting *GIPR* have been developed for use as imaging tools and it is a promising target for novel therapeutics.