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Cell-free methylation signatures non-invasively distinguish patients with MEN1 and provide insights into the biology underlying dpNETs

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BACKGROUND

Multiple Endocrine Neoplasia Type 1 (MEN1) is highly penetrant autosomal dominant disorder in which ~85% patients develop duodenopancreatic neuroendocrine tumors (dpNETs), the most common cause of MEN1-related death. While most MEN1-related dpNETs have an indolent course, 15-25% of these tumors develop distant metastases associated with poor survival. Given widespread access to genetic testing, patients are typically diagnosed prior to the development of dpNETs or while the tumor is still localized. Biomarkers identifying aggressive dpNETs with metastatic potential, therefore, would provide an opportunity for risk stratification and early intervention to prevent metastases in this population. In this pilot study, we hypothesized that the plasma cell free methylome (cfMe) can non-invasively distinguish localized from metastatic dpNETs in patients with MEN1.

METHODS

Plasma cfDNA from patients with wild type germline MEN1 with sporadic primary hyperparathyroidism (HPT) (n = 4) and MEN1 with localized (n = 6) or metastatic (n = 4) dpNETs underwent whole genome bisulfite sequencing (WGBS). Paired tumor-leukocyte DNA was sequenced when available (localized n = 1; metastatic n = 3). Reads were aligned to GRCh38 and methylation calls were extracted using Bismark. Data were smoothed across nearby CpG sites using bsseq and sites with < 5× coverage in all samples were removed. Global methylation was assessed with MethylKi, differentially methylated regions (DMR) were called with bsseq using a t statistic cutoff of 4.6 and filtered to include ≥ 3 CpGs and a mean difference >0.2.

RESULTS

No differences were observed in global methylation between patients with or without MEN1. 112 DMR were identified in MEN1 including hypermethylation of the promoters for *MEG3*, *PDX1*, and *CDKN1B* as well as hypomethylation of the *MGMT* promoter. Preliminary comparisons of MEN1 patients with localized versus metastatic dpNETs revealed 138 DMR, including hypomethylation of the SOCS3 promoter in metastatic dpNETs. Intriguingly, overexpression of SOCS3, a negative regulator the JAK2/STAT3 pathway, has been associated with cancer stemness and therapeutic resistance in other malignancies. Paired plasma and tissue had concordant methylomes.

CONCLUSIONS

In this feasibility study, we demonstrate that (1) cfMe non-invasively recapitulates epigenetic signatures previously associated with MEN1 dpNETs and (2) differentially methylated regulatory motifs in plasma cfME distinguish localized from metastatic dpNETs. Collectively, these findings hold promise for developing non-invasive biomarkers for the early detection and prognostication of MEN1 associated dpNETS. Furthermore, detection of specific DMR, e.g. SOCS3, may provide insights into the biology underlying metastatic dpNETs as well as inform therapy selection.

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