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Genomic analyses of multifocal ileal neuroendocrine tumors

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BACKGROUND

Small intestinal neuroendocrine tumor (SI-NET) is one of the major cancer subtypes of the small bowel. Most SI-NETs locate in the terminal ileum with a high incidence of multiple synchronous primary tumors. The only essentially curative treatment of SI-NETs is complete surgical resection; however, most SI-NET patients cannot undergo surgery as they typically present with an extensive metastatic disease. Several high-throughput sequencing studies have reported low somatic mutation rates in SI-NETs. Loss of heterozygosity at chr18 is the most frequent genomic event identified, occurring in ~60% of tumors, and the only established, recurrently mutated gene is CDKN1B, altered in ~8% of tumors. A deeper understanding of the molecular mechanisms underlying SI-NETs is urgently needed for the optimal treatment of the patients.

METHODS

Our sample cohort consisted of 144 well-annotated fresh-frozen tissue specimens from 23 de-identified SI-NET patients, including 85 primary tumors, 21 metastases, and 38 patient-matched normal ileum and/or whole blood specimens. Thirteen SI-NET patients had been diagnosed with multiple synchronous primary tumors. Whole-genome sequencing was used to characterize the genomic landscape of SI-NETs, and to study the potential roles of field cancerization and germline variation in their tumorigenesis.

RESULTS

We observed lack of shared somatic variation among the synchronous primary tumors of each multifocal SI-NET patient. There was rarely any overlap between the somatic mutational profiles of unifocal SI-NETs or between uni- and multifocal SI-NETs. Our data also indicated that multiple metastases from the same patient can originate from either one or several different primary tumors. We identified altogether >250 acquired genomic alterations among the normal ileum samples of SI-NET patients when compared to their matched whole-blood specimens, all of which were also present in the patient-matched primary tumor(s). None of these alterations were recurrent among the patients. Additionally, we have identified ~100,000 recurrent germline variants with a minor allele frequency of ≥5% among the SI-NET patients. We will next assess if these variants are enriched in our patient cohort.

CONCLUSIONS

Our results indicate major genomic diversity among uni- and multifocal SI-NETs, suggesting that SI-NETs originate independently. Different metastatic dissemination patterns highlight the need to identify and carefully remove all primary tumors. SI-NETs are unlikely to arise from normal small intestine due to field cancerization based on our current data. We are also pursuing other hypotheses that could elucidate the SI-NET tumorigenesis. Finding the cause(s) of SI-NETs is essential for decisions regarding prevention, treatment, surgery, and patient outcome.

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