Multiple tumors without kinship occur simultaneously in the small intestine in neuroendocrine cancer

November 5 2021

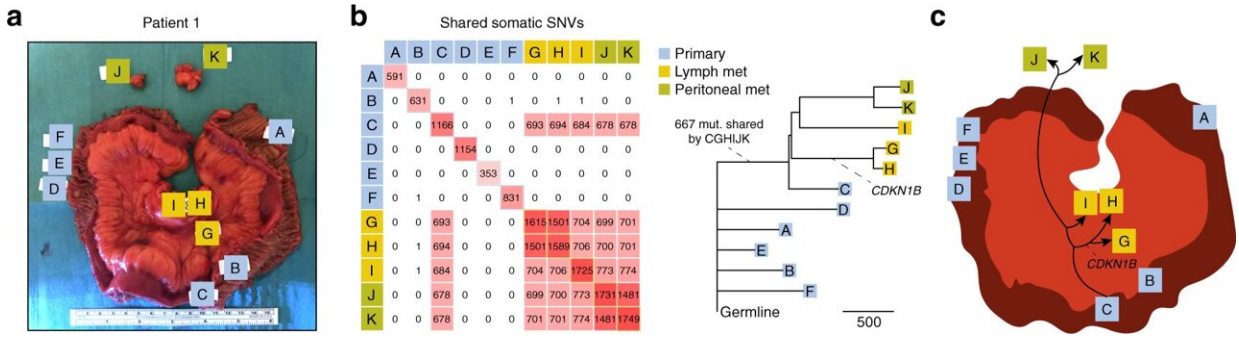

Fig. 1: Whole genome sequencing of 11 primary tumors and metastases from a single SI-NET patient supports independent clonal evolution. a Section of the small intestine from a patient (Patient 1) harboring six primary tumors (A–F), three lymph node metastases (G–I), and two peritoneal metastases (J–K). b Pairwise analysis of shared somatic SNVs based on whole genome sequencing. Primary tumor C and the five metastases shared a common set of 667 mutations. A maximum parsimony phylogenetic tree is shown, with the number of SNVs in each branch given by the scale marker. An indel in CDKN1B, a known driver event, is indicated. Bootstrap support was > = 98% for all major branches. c Proposed model, where all metastases originate from a single primary tumor, and where all primaries are unrelated in terms of somatic evolution. Met, metastasis; SNV, single nucleotide variant. Source data are provided as a Source data file.
Credit: DOI: 10.1038/s41467-021-26581-5

Neuroendocrine cancer can manifest itself as many small tumors in a cluster in the small intestine. New research shows that, surprisingly, these tumors originate from different cells that have mutated independently. The finding that the tumors are not related, which has been published in *Nature Communications*, came about through a close collaboration among clinical and basic science researchers at the University of Gothenburg and Sahlgrenska University Hospital.

Neuroendocrine cancer of the small intestine is a relatively rare cancer, affecting a few hundred people in Sweden every year. At the same time, it is the most common form of cancer of the small intestine. The disease is also called SI-NET (Small Intestine Neuroendocrine Tumor). Because the cancer grows slowly, patients can live with the disease for a long time.

"When we remove neuroendocrine tumors in the small intestine, we often find many tumors in the same place, which is unusual. No other cancer really looks like this," says Erik Elias, an endocrine surgeon at Sahlgrenska University Hospital and a post-doctoral researcher at the University of Gothenburg. "The cancer is also unusual because known driver mutations are largely absent."

Elias asked Erik Larsson Lekholm, a professor of bioinformatics at the University of Gothenburg, to join him in searching for answers to the question of how the tumor clusters form. They emphasize that their collaboration is largely translational in nature, where bioinformatic analyses in state-of-the-art research have been applied to a concrete question from everyday life in the clinic.

The researchers began by mapping complete genome sequences from 11 tumors and metastases found in a single patient. By comparing non-driver mutations (known as passenger mutations) in the different tumors, they could map their family trees.

Surprising answer

The result was both unambiguous and surprising. The intestinal tumors had developed independently. Yet the metastases were clearly related and could be traced back to a specific bowel tumor.

"Usually we think that cancer emanates from a single cell, where the balance in cell division has been disrupted due to genetic changes," says Erik Larsson Lekholm, who believes the finding opens the door to a new field of research. "Tumor development then occurs in stages. In the worst case, it can eventually lead to metastatic cancer, which can spread both locally and to other places in the body. In this case, the process has been started not just once, but several times in the same tissue.

"What can actually account for this? How can several different cells in roughly the same place in the body simultaneously develop similar cancer properties, and without obvious driving mutations? Our hypothesis is that there may have been a change in the environment in which the cells are located, and we have begun to investigate this further."

After the first surprising result, the whole genome sequencing of tumors, metastases, and blood from another ten patients was repeated, partly using material from a local biobank that has been built up over many years through a collaboration between endocrine surgery and pathology at Sahlgrenska University Hospital. Arman Ardalan, a post-doctoral researcher in bioinformatics in Larsson Lekholm's team, has done an important job with the data analysis.

All tumors need to be removed

In addition to the finding that the tumors evolved independently, the

study provides another surprising insight: often not just one, but several of these tumors give rise to metastases. For surgeon Erik Elias, the discovery has great clinical relevance:

"This study underscores the importance of removing all tumors in the intestine. In surgical care, we need to discuss whether we should use greater margins when operating, removing more bowel so that we can be more confident we have removed all bowel tumors. It is quite possible that the late relapses in the disease that we unfortunately sometimes see can be prevented by such a measure. Obviously, this would be of great importance for the individual patient."

More information: Erik Elias et al, Independent somatic evolution underlies clustered neuroendocrine tumors in the human small intestine, *Nature Communications* (2021). DOI: 10.1038/s41467-021-26581-5

Provided by University of Gothenburg