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TUMOUR EVOLUTION

Metastasis takes a different route

> in 65% of the patients … lymphatic and distant metastases had an independent subclonal origin in the primary tumour

Cancer cells from primary tumours can metastasize to regional lymph nodes and distant organs. The widely held view of metastatic progression is that it proceeds sequentially wherein lymph node metastases give rise to distant metastases. This concept of the metastatic cascade forms the basis behind both the tumour-node-metastasis (TNM) staging system and the controversial surgical removal of tumour-draining lymph nodes. Now, new data published in *Science* present a different view of the origins of lymphatic and distant metastases in human colorectal cancer.

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To trace the evolutionary relationship between lymph node and distant metastases, Naxerova *et al.* used phylogenetic reconstruction methods with retrospectively collected formalin-fixed and paraffin-embedded biopsy samples from primary tumours, lymph nodes and distant metastases of 19 patients with colorectal cancer. A total of 239 samples were collected from multiple tumour regions and normal tissue from an initial cohort of 19 patients and subjected to a PCR-based assay detecting insertion and deletion (indel) mutations in hypermutable, non-coding polyguanine repeats. The resulting genotypes of each sample were then used to calculate a pairwise distance measure, known as the Jensen–Shannon distance, which represented how much a sample had genetically diverged.

The phylogenetic analysis of polyguanine repeats revealed varying indel mutation patterns among the patients with colorectal cancer, with the frequencies, for example of deletions, ranging from 45% to 100%. The authors attributed this finding to additional genetic alterations, for example, in specific DNA repair proteins, and demonstrated that colorectal cancers with microsatellite instability due to loss of MLH1 expression had larger deletions than those of microsatellite-stable cancers. To validate that the accrual of indels in polyguanine repeats was not directly related to cancer, the authors also tested whether such mutations could be found in age-matched normal intestinal stem cells (ISCs). Clonal mutation frequencies increased with age in normal ISCs indicating that polyguanine mutations accumulate over time. However, the mean clonal mutation frequency was substantially lower in normal ISCs than in cancer cells of a similar age implying that, although a proportion of this mutation type is present in all intestinal cells before colorectal cancer formation, polyguanine indels are not a cancer- specific phenomenon.

Surprisingly, investigation of the genetic distances among all the samples of primary tumours, lymph node and distant metastases found that, for 73% of lymph node metastases (33 out of 45 samples), the distance to the primary tumour was shorter than the distance to distant metastases and that, for 69% of distant metastases (31 out of 45 samples), the distance to the primary tumour was shorter than the distance to any lymph node metastases. This indicated that, in most instances, the two types of metastatic lesion were seeded from different subclones in the primary tumour. Moreover, grouping the data by patient, the authors found that in 65% of the patients (final data set: 11 out of 17) lymphatic and distant metastases had an independent subclonal origin in the primary tumour and that in only 35% of the patients (6 out of the 17) was a shared common subclonal origin for metastases identified.

Overall this study suggests that two discrete patterns of metastatic spread exist in colorectal cancer and that seeding of distant sites from lymphatic metastases is not as common as might have been predicted. It will be interesting to see if this pattern of metastatic dissemination holds true for other cancer types with different organotropism than that of colorectal cancer.

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ORIGINAL ARTICLE Naxerova, K. *et al.* Origins of lymphatic and distant metastases in human colorectal cancer. *Science* **357**, 55–60 (2017)