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Navigating the path to distant metastasis

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Abstract

How ‘difficult’ is it for somatic evolution to produce a cell that is capable of leaving the primary tumor and growing in a distant organ? In this issue, Reiter et al. assess genetic diversity across metastatic lesions and identify a tight selective bottleneck preceding distant metastasis.

Cancers evolve¹. Classically, distant metastasis was presumed to be the ‘end result’ of cancer evolution, occurring only after a permissive combination of functional genetic ‘driver’ alterations was acquired². In other words, the evolution of a metastatic clone was proposed to be a long and tortuous stepwise path through the evolutionary landscape.

However, multiple recent lines of evidence have challenged this simplistic view. First, the hunt for genetic drivers of metastasis has not been particularly fruitful and has revealed only a handful of genes mutated at significantly greater frequency in metastases than primary tumors³, whereas a long list of genes have been implicated in primary tumor formation^{4,5}. Given the multiple complex processes involved in tumor cell dissemination, it is perhaps surprising that evolved genetic control of metastasis is not more prevalent or easy to find.

Second, recent evidence suggests that metastasis often occurs early, close to the time of establishment of the primary tumor. The proportion of mutations shared between metastatic and primary lesions quantifies the timing of metastasis⁶ (with some caveats), because cells that metastasize early carry only the truncal mutations of the primary tumor (those carried by every cancer cell) but not the subclonal mutations that arise later. In comparison, late-arising metastases carry additional mutations that evolved in the premetastatic primary subclone. In most colorectal cancers⁶ (the focus of the work by Reiter et al.⁷), as well as in lung and breast cancers⁸, analysis of mutation clonality suggests that metastatic dissemination is often an early event.

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Competing interests

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Third, tumor cell invasion may not be a clonal event. In our own recent study, we spatially mapped the locations of colorectal cancer subclones and observed that many different clones invaded the submucosa⁹. This ‘polyclonal invasion’ was previously observed in breast cancer through spatially resolved single-cell sequencing¹⁰. These observations challenge the classical description of invasion as a single rare evolutionary trajectory.

Overall, the emerging consensus, primarily for colorectal cancer, is that many clones are capable of invading locally, and distant metastasis occurs early and is not necessarily triggered by a specific genetic event.

Against this backdrop, Reiter et al. contrasted the evolutionary trajectories of local (lymph node) versus distant metastasis. In their previous work, the authors showed that local and distant metastases in colorectal cancer have distinct evolutionary origins¹¹. They genotyped polyguanine tracts—loci where the mutation rate is high and so the signal of clonal ancestry is abundant—and constructed phylogenetic trees showing the distinct ancestral relationships between primary and metastatic lesions.

In their new article, the authors revisited these data and realized that distant metastases typically make up a distinct phylogenetic clade, thus indicating that they formed from a single clone (that is, are monophyletic). In contrast, local lymph node metastases are genetically diverse and often derived from multiple distinct precursors clones (that is, are often polyphyletic; Fig. 1). Similar observations have recently been made by Hu et al.⁸. Of note, local metastases do not confer the poorer clinical outcomes associated with distant metastases (<https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/survival>), suggesting distinct biology of distant versus local disease.

Reiter et al. then quantitatively assessed the degree of genetic heterogeneity between the local and distant metastatic lesions. Genetic diversity is decreased by a population bottleneck—such as the founding of a metastatic lesion by one or a few cells—and it increases the post-bottleneck as each lineage independently accrues new mutations. Thus, by measuring genetic diversity, the magnitude of the selective bottleneck can be inferred (Fig. 1).

To quantify genetic diversity between metastatic lesions on a phylogenetic tree, the authors created a statistic termed the root diversity score, which calculates the probability of chance alone explaining the observed degree of clustering of metastatic lesions on the phylogenetic tree. In their 36 colorectal cancer cases, distant metastases were far less genetically diverse than local lymph node metastases, and the same was true in additional cases of colorectal and renal cancers, and in a breast cancer model system. Further simulations indicated that only a relatively small proportion of the primary tumor was likely to be capable of seeding distant metastasis, whereas a larger area was able to generate locally invasive clones. Within-metastasis genetic diversity was also lower in distant versus local metastases.

Together, the analysis by Reiter et al. indicates that the selective bottleneck for distant metastasis is much tighter than it is for local metastasis. How do these inferences fit with existing knowledge?

Reiter et al. say that local metastasis is comparatively easily formed. This claim is consistent with prior reports of early polyclonal invasion and with the paucity of detected metastasis-specific genetic drivers. However, the observation that the evolutionary road to distant metastasis is more tortuous is harder to reconcile.

Heritable epigenetic changes (DNA methylation and chromatin structure) determine cancer cell phenotypes¹² but remain broadly unexplored in distant metastases of solid tumors. Epigenetic drivers of distant metastases may exist but are yet to be found. Indeed, our own analysis of the evolutionary dynamics in primary lesions, primarily colorectal cancer, suggests a widespread role of (epigenetically driven) cellular plasticity in tumor evolution, because we observed adaption without evidence of clonal selection^{9,13,14}.

If distant metastasis is difficult to achieve, we might expect it to occur late, when evolution has had sufficient time to ‘find’ the metastatic (epi)genotype–phenotype combination. This hypothesis is at odds with observations of early distant metastasis in colorectal cancer⁶. One possibility is that measures of metastasis timing are biased toward earlier times. Reiter et al. suggest that in colorectal cancer, distant metastases arise from only a small region of the primary tumor. If this region is not sampled for sequencing, then only truncal mutations would appear to be shared between primary tumors and metastases, thus leading to an erroneous conclusion of early metastasis. Further sampling bias may arise from unavoidable preferential analysis of the largest and fastest-growing distant metastases, thus potentially neglecting smaller and slower-growing but nevertheless distinct clones. Inadequate sampling seems highly unlikely to explain all observations of early metastasis^{6–8}, but it may explain some. Another confounding factor is inter-metastasis seeding, which would dilute the signal of both rarer founder clones and slower-growing clones. Potentially distant metastases are formed from many clones (similarly to local metastases), but the current resolution of the data is too low to detect them. Exhaustive single-cell-sequencing studies to map clones across primary tumors and metastases are needed to address this possibility.

Conceivably, whether metastases arise early or late may one day guide personalized cancer therapy. This study illuminates another section of the evolutionary road to metastasis.

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Fig. 1 |. Selective bottlenecks in metastasis.

Multiple distinct tumor clones metastasize to lymph nodes (orange, yellow, light- and dark-blue clones), whereas distant metastases are dominated by a single clone (cyan). Analysis of the between-metastasis genetic diversity suggests a narrower selective bottleneck during distant metastasis formation.