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Metastasis seeding cells: Lone invaders or mass migrators?

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Summary

Lymph node metastases are among the best predictors of recurrence and of cancer related death in early stage colorectal cancers. Yet, despite their clinical and biological relevance, it remains elusive how lymph node metastases develop and whether metastatic seeding is a major bottleneck that restrains genetic heterogeneity of metastatic disease.

In this issue of Clinical Cancer Research, Ulintz and colleagues provide new insights into this process by studying several primary tumor regions and matched lymph node metastases from colorectal cancers by SNP-array, exome- and deep sequencing analysis(1). Consistent with prior results in colorectal and indeed most solid cancers(2), they identify intratumor heterogeneity of mutations and DNA copy number aberrations in each of the seven investigated cases. Moreover, applying a phylogenetic lineage tracing approach, they show that the metastatic deposits were seeded by several different subclones from the matching primary tumors in three of these cases. This demonstrates that metastatic seeding does not necessarily impose a tight genetic bottleneck that is only passed by a single subclone. Instead, metastases can inherit at least part of their genetic heterogeneity from the primary tumor.

Most strikingly, distinct subclones from the primary tumors were not only identified in different metastases but also within individual metastases. Such polyclonal metastases cannot be explained by the invasion of a lone explorer clone that then colonizes the new territory exclusively with its own progeny. Instead, these data suggest that lymph node metastases are often the result of mass migrations of multiple subclones from the primary tumor and potentially also between metastases.

The authors did not assess whether the distinct subclones they traced differed functionally and if their patterns of spread and the observed phylogenies were the result of Darwinian selection or simply the consequence of random genetic change and neutral evolution(3). It would for example be interesting to investigate if tumors with a high mutational burden, which are likely to be immunogenic and may hence be under increased selection pressure by immune cells in the lymph nodes, show different patterns of clonal spread compared to those with low mutational burdens. In addition, the dichotomy of lymph node metastases of

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monoclonal origin in some of the cases vs. metastases of polyclonal origin in others may indicate that the ability to metastasize was acquired at different time points. Metastases of monoclonal origin may point to the late acquisition of the metastatic competency in a single subclone of a heterogeneous primary tumor. And early acquisition of the metastatic capability, which was subsequently passed on to a genetically increasingly diverse progeny, may explain polyclonal metastatic seeding.

This study raises important clinical questions that now need answering. Understanding whether the risks of recurrence or death differ between patients with lymph node metastases of monoclonal vs. those of polyclonal origin may provide more accurate prognostic information. And assessing if one of these two groups benefits more from adjuvant treatment could help to tailor chemotherapy more accurately to patient needs. Together, such information may reduce overtreatment which is common in the adjuvant setting.

Importantly, the results from Ulintz and colleagues also show that subclones that evolved in distinct regions of the primary tumors - whose spatial structures are thought to restrict clonal intermixing - can get re-shuffled into new combinations in the lymph node metastases. This may enable new interactions: Clones that were spatially separated can perhaps start to cooperate with each other when they come into close spatial proximity in the metastases. Functional specialization may also allow a subclone with a superior ability to settle in a new environment to prepare the metastatic niche for colonization before other clones with different survival skills follow. These considerations raise the question whether clonal cooperation could be a major mechanism to enhance the fitness of a cancer population(4) that only comes into full swing at metastatic cancer stages. This may increase cancer resilience and evolvability and could potentially explain why metastatic cancers are hard to treat and why treatment successes are usually short lived. Answering these fundamental biological questions will require further analyses in larger patient cohorts and in model systems.

Another recent study that investigated the clonal relationship of metastases and primary tumors in colorectal cancer came to matching conclusions(5). Although intra-metastatic polyclonality was not assessed, this study found that lymph node and distant metastases were seeded by different subclones from the primary tumor in the majority of cases. Together, these two studies clearly show that the traditional sequential progression model (Figure 1A), where a single cell or single clone seeds lymph node metastases which eventually seed distant metastases, is too simplistic.

Ulintz and co-workers propose a new model of metastatic seeding and suggest that waves of subclones leave the tumor at different timepoints and gradually build these polyclonal cell populations in lymph nodes. This is a plausible explanation but even more dynamic scenarios where a constant supply of new migrant cells from the primary tumor feed clonal diversity of the metastases seems possible (Figure 1B). And with mass migration being a likely scenario between primary tumors and metastases in many cases, the possibility that re-seeding also occurs from metastatic sites into the primary tumor should also be examined. Such re-seeding dynamics have been described in tumor models(6) but to date, these concepts received little attention in studies analyzing patient samples.

Overall, these novel insights into metastatic seeding in colorectal cancers reiterate what the cancer research community has learned many times in the past: that cancer is often more chaotic and complex than imagined even by experienced researchers or acknowledged in textbooks. Individual cancers are monoclonal in origin but genetic, epigenetic and transcriptomic heterogeneity occur during progression in the primary tumor. Metastasis development has been described as a bottleneck that restrains the spread of this diversity but this concept is clearly challenged by the current study. Thus, for many cancers, metastasis development is no route back to monoclonality.

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Figure 1.

Models of colorectal cancer lymph node metastasis seeding **A:** Traditional model of monoclonal and sequential seeding. A single clone acquires the ability to leave the primary tumor and colonize the draining lymph nodes. This has the effect of a bottleneck that effectively prevents heterogeneity from the primary tumor from spreading to metastatic sites. Spread is sequential from lymph node station to lymph node station and eventually to distant metastatic sites. **B:** Revised model of polyclonal seeding. Multiple clones spread sequentially or simultaneously from the primary tumor to lymph node metastases, propagating

heterogeneity from the primary tumor and bringing previously spatially separated subclones into close contact which may enable novel interactions and cooperation.