

VIEWPOINT

On the theory of tumor self-seeding: implications for metastasis progression in humans

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Abstract

Metastasis remains the leading cause of death among cancer patients because few effective treatment options are available. A recent paper proposes a new twist on metastasis. The paper shows that circulating tumor cells can return to the primary tumor, a process termed tumor self-seeding or cross-seeding, and that this helps breeding tumor cells that give rise to aggressive metastatic variants. A viewpoint presented here addresses the implications of these studies for human cancer metastasis.

Background

Cancer cells disseminate and lodge in target organs, producing a distinct and mostly predictable pattern of metastasis [1,2]. Metastatic cells may evolve in the primary tumor but also, following dissemination, at distant sites [1]. Numerous genes favoring or suppressing the multiple metastatic steps have been identified [1,2]. Moreover, primary tumor gene expression profiles revealed signatures that can predict poor treatment outcomes, most probably linked to metastasis development [3].

In spite of the progress, however, due to important confounding factors, the dynamics driving the emergence of metastatic variants in patients is poorly understood. First, patients presenting with non-invasive lesions (that is, ductal carcinoma *in situ*) already have disseminated tumor cells [1,4]. Second, the metastatic phenotype can be acquired in parallel in the primary lesion and in the organ-lodged disseminated tumor cells, and the latter may evolve after primary tumor surgery and without development of local recurrences [1]. Third, metastasis development can be remarkably delayed – suggesting that, before resuming growth and evolution, the lodged

disseminated tumor cells (minimal residual disease) can remain dormant [5]. In a recent study, Kim and colleagues propose that the ability of circulating tumor cells (CTCs) to return to and grow in the primary tumor might aid in selecting the seeds of metastasis [6].

Article

Kim and colleagues at the Memorial Sloan Kettering Cancer Center asked whether CTCs could reseed a primary tumor [6]. Furthermore, they tested whether this reseeded selects for variants endowed with specific genes driving metastasis.

The authors tagged breast and melanoma cell lines with fluorescent proteins and/or luciferase. The MDA-MB-231 human breast carcinoma cell line (MDA231) and its variant, selected via intravenous inoculations for enhanced lung colony formation (MDA231-LM2) [7], were primarily used in reseeded or cross-seeding experiments. Tagged and untagged tumor cells were injected separately into orthotopic contralateral sites. MDA231-LM2 cells were highly efficient in disseminating and self-seeding a contralateral MDA231-LM2 or MDA231 mass or in cross-seeding breast MCF7 or melanoma A375 tumors. Similarly, MDA231-LM2 lung colonies produced by intravenous injection also seeded orthotopically growing MDA231 tumors. Thus, regardless of their growth location, the MDA231-LM2 cells can seed an established tumor mass.

Curiously, MDA231-LM2 cells were not reported to spontaneously seed lungs from the primary tumor. This suggests that spontaneous seeding of a tumor mass is less restrictive than seeding of target organs. Alternatively, enhanced lung colonization selected through forced intravenous inoculation [7] might exacerbate cell traits that do not entirely recapitulate organ-specific metastasis.

In an important experiment, MDA231 cells that spontaneously seeded the same contralateral tumor were enriched (MDA231-S1a). Upon reinjection through different routes, MDA231-S1a cells spontaneously seeded a contralateral tumor, but apparently not lungs or other organs. Only after direct injection into the bloodstream did they seed bones, brain, or lungs. IL-6 and IL-8 produced by contralateral human tumors served as CTC

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attractants, and this might explain the preferred spontaneous tumor versus lung targeting. The role of human tumor versus mouse lung-derived cytokines directing this tropism, however, cannot be ruled out. MMP1, FASCIN1 and CXCL1 genes required here for tumor seeding are also part of a human breast cancer signature associated with metastasis development [7]. Further, stromal cells aided self-seeders and the latter cells also accelerated primary tumor growth.

The identified genes or the stromal cell involvement are not entirely new to metastatic progression [2,8-11]. All organ-specific metastasis genes being represented in the MDA231-S1a derivative, however, was a surprising observation. Possibly only few of these genes are required for tumor mass colonization, and the additional organ-specific genes are enriched because they facilitate but are not required for self-seeding. Alternatively, the contralateral tumor mimics a multiorgan microenvironment favoring selection of all variants simultaneously.

Overall, these studies show that important information on the mechanisms contributing to target organ colonization can be drawn from self-seeding or cross-seeding experimental models.

Viewpoint

Is there any parallel between these experiments and metastasis in patients, and what clinical scenarios could be envisioned for such a process? These experiments possibly model a rare phenomenon in patients where one malignant tumor (for example, prostate or breast carcinoma) metastasizes to a different second primary tumor, usually a benign lesion [12-14]. These are exceedingly rare cases even in the 2 to 3% of patients that develop two different cancers simultaneously. Kim and colleagues' study shows that, as in these rare cases, malignant cells will metastasize to a second tumor if available. In these patients, however, cross-seeding was simultaneous with multiple organ metastasis [14].

Self-seeding and the presence of a tumor mass may not be a *sine qua non* requisite because metastasis develops in patients after undergoing surgery (the majority) for small or larger invasive lesions, such as in breast cancer. If tumor masses are required [6], self-seeding would not select for metastatic variants during periods of minimal residual disease or favor local recurrences, unless local microscopic residual disease or a remaining reactive stroma is sufficient to fuel this process. Self-seeding, however, may occur in patients with inoperable primaries and metastases or in those that, after primary tumor surgery, still carry multiple metastases and may have a constant CTC population. Finally, the timing of metastasis must be considered. Why in some patients does it take 1 or 2 years but in other patients 10 years or more for the metastatic variants carrying the poor prognosis

genes [3,7] to grow into overt metastasis? Does this mean that the time to overt metastasis is regulated by other mechanisms and that self-seeding or cross-seeding is only relevant between established metastasis [15]? These and many other questions generated by this thought-provoking study will surely fertilize the field of metastasis to provide a clearer view on how to target this lethal step of cancer progression.

Abbreviations

CTC, circulating tumor cell; IL, interleukin.

Competing interests

The author declares that he has no competing interests.

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