Self-Seeding in Cancer

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Abstract

Despite significant progress in our understanding and treatment of metastatic cancer, nearly all metastatic cancers are incurable. In this Review, we use breast cancer as a model to highlight the limitations and inconsistencies of our existing treatment paradigms for metastatic disease. In turn, we offer a new theory of metastasis, termed "self-seeding. " The self-seeding paradigm, well validated in mathematical, experimental and animal models, challenges the notion that cancers cells that leave a primary tumor cell, unidirectionally seed metastases in regional lymph nodes and/or distant sites. In contrast, there is mounting evidence that circulating tumor cells can move multi-directionally, seeding not only distant sites but also their tumors of origin. Here, we show that the self-seeding model may answer many of the quandaries intrinsic to understanding how cancer spreads and ultimately kills. Indeed, redirecting our research and treatment efforts within the self-seeding model may offer new possibilities for eradicating metastatic cancer.

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1 Introduction

In the last 20 years, notable advances in the fight against cancer include the evolving fields of cancer genomics, improved imaging and detection techniques, and targeted, less toxic therapies. Despite these advances, cancer metastasis continues to undermine cancer survivability. And as such, improving the trajectory of cancer mortality necessitates profound change in our treatment paradigms. Historically, accepted theories of metastasis focus on the notion of a progressive, unidirectional pathway from a primary tumor to metastasis. As a consequence of increasing cell accumulation and genomic aberrancies, primary tumor cells acquire the ability to travel to distant organs, first proliferating microscopically and then forming gross metastases. Reflecting the continued mortality of many cancers, these prevailing theories are riddled with unanswered questions. Using breast cancer as a model, here we review select quandaries and contradictions inherent in prevailing theories of metastasis. We in turn offer a new paradigm, termed "*self-seeding,*" which offers an alternative roadmap for understanding metastasis. Self-seeding refers to the proven ability of peripatetic cancer cells to migrate multidirectionally—seeding not only to regional and distant sites in the body, but also returning to their original source: the tumor itself. Merging both biological and clinical observations, the clinical implications of self-seeding are significant, from helping to explain many current enigmas, but most importantly, to shedding light on new diagnostic and therapeutic advances.

2 Self-Seeding Model of Malignant Growth: The Biological Basis for Self-Seeding

The self-seeding model of malignant growth contests the idea that cancer cells which leave a primary tumor—often called circulating tumor cells or CTCs—unidirectionally seed metastases in regional (lymph nodes) or distant sites. The concept of

tumors self-seeding by CTCs was first published in 2009 after validation of the theory in diverse experimental models including colon and breast adenocarcinomas as well as melanomas [1, 2]. They demonstrated that CTCs can travel to and from distant and primary tumor sites. By this model, a large tumor may not only be a cause of distant seeding—the conventional concept—but also a result of self-seeding. In this sense, a large tumor grows from the "outside in" as opposed to from the "inside out." Kim et al. further demonstrated that the ability to seed is necessary but not sufficient to generate colonies in seeded sites; indeed, cells can lie dormant for decades in such sites without growing [1–3].

CTCs face many barriers for infiltrating and growing in distant organs. These include tight vascular capillary endothelial walls and an unfamiliar microenvironment. Thus, only the most adaptable and rare CTCs are successful in distant seeding of organs. However, CTCs re-entering the primary tumor itself face a leaky neovasculature and a fertile concentration of all the tissue-specific factors which initially permitted their circulatory exit [4]. Tumor-derived inflammatory cytokines, such as IL-6 and IL-8, act as CTC attractants. The self-seeding CTCs also express MMP1/collagenase-1, the actin cytoskeleton component fascin-1, and CXCL1 which promote accelerated tumor growth, angiogenesis, and the recruitment of myeloid cells into the stroma.

Using human cancer cells, it has been shown that the genetic toolkit for generating successful metastases appears to be site-specific, with unique signatures for lung, bone, and brain involvement [4–7]. The gene sets required for self-seeding, for example, the lung, brain, or bone overlap to some extent but are not identical [5–8]. The site-specific nature of metastases has been confirmed not only by in vivo experiments in mice using cell lines from human sources, but also by the analysis of recurrence-free survival curves in patients whose tumors have been classified by molecular signatures. Lastly, in support of the self-seeding experiments, there are increasing pathology reports of tumor-to-tumor metastases [9].

3 Mathematical Foundation of Self-Seeding

While the self-seeding model was born out of biological and clinical observations, it is buttressed by key mathematical concepts. We review the mathematical underpinnings of self-seeding in detail elsewhere, but we will briefly discuss certain evocative yet simple mathematical ideas [10]. It has been demonstrated experimentally and observed clinically that simple exponential or linear kinetics cannot explain the growth of a primary breast tumor [11]. For example, an average breast cancer takes roughly 2 years to grow from one cell to 10 billion cells. For that same tumor to grow by linear kinetics, it would take the tumor another 2 years to double in size. Were the tumor to grow by exponential kinetics, it would double in about 3 weeks. We know that neither scenario is uniformly true. Indeed, at varying time points, a tumor must grow by both linear and exponential kinetics [10].

Malignant growth is generally thought to be a result of mitosis, wherein one cell produces two. As such, at the nascence of a cancer's growth, the growth must be approximately exponential. However, as a cancer grows, it deviates from exponential kinetics, which in turn cannot be explained by mitosis. We now know that cancerous tumors must follow S-shaped curves intermediate between these two extremes, curves of the type described by Gompertz in 1825 [12, 13].

The self-seeding model accounts for an S-shaped Gompertzian growth curve. In the self-seeding model, CTCs are coming from the outside of any given mass which in turn suggests that a primary tumor is not one mass, but a conglomerate of contiguous masses. These contiguous masses grow as a function of surface area as opposed to volume. Since the stem-like cells are primarily on the surface (being defined here as the surface of each conglomerate) the ratio between the new cell production rate and the mass of the bulk of the tumor also drops as the tumor increases in size. Said differently, as the tumor increases in size, the ratio of its surface area to its volume decreases. This leads to a relative slowing of tumor growth, as is reflected in Gompertzian growth curves.

With an understanding of the biological and mathematical rationale behind the self-seeding theory, let us now evaluate the theory as it reconciles prevailing quandaries in clinical practice.

4 Prevailing Mysteries: Unpredictable Metastatic Pathways

4.1 Why do Some Patients Without Axillary Nodal Involvement Still Develop Systemic Metastases? And Why do Some Patients With Axillary Nodal Metastases not Develop Metastases Elsewhere, Even If Those Nodal Metastases are not Removed by Surgery or Irradiated?

At the end of the nineteenth century, William Halsted developed the basic concepts that underlie breast cancer surgery to this day. He asserted that the pathway of metastatic disease was predictably linear; cancer cells spread from the breast to the lymphatic system and then to the systemic circulation whereby they can seed distant organs. Consequently, surgically removing the whole breast surrounding the tumor as well as its attached ipsilateral axillary contents (radical mastectomy) would prevent metastatic disease [14]. And, as proof of his concept, radical mastectomies did and continue to cure many individuals of their breast cancer [15].

As further support of his surgical techniques, we now know that lymph node involvement portends a poorer prognosis than cancer-free lymph nodes [16]. Alternatively, if the first nodes draining lymphatic flow are without cancer cells, the rest of the axilla is nearly always free of cancer cells [17, 18]. This latter point underlies the basis for the practice of sentinel lymph node mapping.

Lastly, long-term experience continues to show that improved local control, such as with the addition of radiation therapy after breast conserving surgery, decreases the risk of local and distant recurrence [19]. The outcomes from the above-mentioned clinical practices—mastectomy, sentinel lymph node mapping, and improved local control—all seem to support a Halstedian view of malignant progression. Herein lies the conflict with his theory: some women with no axillary involvement may still develop distant metastases and some women with extensive axillary metastases may never develop distant disease.

In the face of the aforementioned paradox, Daniel Martin Shapiro, Bernard Fisher, Edwin Fisher and colleagues challenged Halsted's view of metastatic spread [20, 21]. They hypothesized that hematogenous as well as lymphatic pathways were necessary for metastatic spread. They posited and ultimately demonstrated that systemically targeted treatments such as select estrogen receptor modulators (SERMS) or chemotherapy were required to improve breast cancer survival [15]. Their early work provided the backbone supporting the use of adjuvant therapy, whereby chemotherapy and/or antihormonal treatments are given after the surgical removal of a primary tumor. In addition, several recent studies seemingly support their work. First, finding isolated tumor cells in axillary lymph nodes does not affect overall survival [22]. Second, patients undergoing breast conserving surgery and radiotherapy for small, hormone-responsive breast cancer and two or fewer involved axillary lymph nodes do not have increased rates of axillary recurrence if they do not have a complete axillary dissection. This is in spite of the fact that more than a quarter of those patients actually have residual axillary node metastases [23]. Third, two recent studies highlight the imperfect relationship between tumor size and lymph node status to clinical outcome. Specifically, Wo et al., demonstrate that in cases of extensive lymph node involvement, very small tumors may confer a more aggressive subtype than larger tumors with the same degree of lymph node involvement [24]. Work by Hernandez-Aya et al. indicates that in triple negative breasts cancers, the worse prognosis associated with lymph node involvement may not be greatly affected by the absolute number of positive lymph nodes [25].

Ultimately, it appears that both Halsted and Fisher's ideas are feasible. Halsted's idea of an anatomic pathway for metastatic spread is correct, but so is Fishers' idea that malignant spread does not require a linear anatomic pathway. How then does the self-seeding theory resolve these seemingly opposing views?

The self-seeding hypothesis helps to reconcile the friction between existing paradigms and our clinical observations. Halsted proposed that breast cancer cells need mechanical access to the axilla to seed it, which in turn supports the importance of sentinel lymph-node mapping [14, 15]. Alternatively, Fisher's theory implies that some breast cancer cells can colonize an axillary lymph node should it reach it, but others may in turn skip the lymph nodes altogether and instead spread hematogenously to distant sites.

In the self-seeding model, seeding is site-specific, with some gene sets targeting the lungs for example, whereas others may target the bone or brain. While these gene sets correlate, they are not identical [2]. For example, breast cancer cells can remain dormant in the bone in a non-mitotic state, manifesting as clinical relevant metastases even decades later [26]. As a result of the site-specific nature of self-seeding, finding isolated cancer cells in a distant organ does not always align with clinically meaningful metastatic behavior. And, the presence of unresected axillary nodal disease does not necessarily portend distant metastasis, but neither does its absence ensure the absence of distant spread [23]. Furthermore, in the context of radiation to a conserved breast for women with 1-2 + lymph nodes, it remains to be determined why surgical removal of additional lymph nodes does not improve local regional recurrence, yet radiation to the axilla may improve overall survival [22, 27]. Perhaps in the case of radiation to the axilla, CTCs can seed but not colonize an area of irradiation. The irradiated axilla may act as a poisoned sponge, attracting CTCs. But, in the face of inhabitable stroma, colonization is not feasible. In further support of this hypothesis, there is clinical trial evidence that radiation therapy to the breast after systemic therapy reduces systemic recurrences more than such radiation given before adjuvant chemotherapy [28].

Lastly, the recent research which indicates that a subset of small tumors may be highly aggressive despite their size may simply reflect relative seeding capacities [24, 25]. For example, a tumor may be a particularly poor self-seeder but an efficient distant seeder, as in the case of small, highly aggressive tumors. In some instances, a tumor may be such a poor self-seeder that it is occult while distant metastases abound. This latter scenario may explain adenocarcinomas of unknown origin or the often classic presentation of pancreatic adenocarcinoma.

4.2 Why is it That so Few Patients Present With Gross Metastatic Disease, Even When They May Have Large Untreated Tumors for a Long Time?

In the developed world, >5% of patients present with stage IV disease. Patients presenting with denovo stage IV disease have frequently had a primary tumor for years. The best observation of this phenomenon comes from records from the early to middle nineteenth century, before mastectomies were common. Patients often lived for years before they developed fatal metastatic disease [29]. We hypothesize that patients rarely present with stage IV disease because their CTCs are drawn back to the primary tumor, as attracted by the concentrations of chemoattractants that initially engendered growth in the breast [4]. In this instance, the primary breast tumor acts as a sponge, soaking up the returning CTCs and contributing to an enlarging locally advanced breast cancer. We await further definitive studies into how the resection of a primary breast tumor in the setting of metastatic disease accelerates or diminishes overall survival [30–32].

5 Molecular and Genetic Implications of Self-Seeding

5.1 Why is DCIS so Molecularly and Genetically Similar to Invasive Cancer?

Ductal carcinoma in situ (DCIS) lesions of the breast are categorized as pre-invasive lesions as they rarely grow to large sizes and neither invade the basement membrane of the breast duct nor metastasize. On the contrary, untreated invasive ductal cancers (in an otherwise healthy woman) are invariably fatal as a result of unchecked metastatic growth into vital organs. Given their phenotypic diversity, one would expect significant genomic diversity between DCIS and invasive breast cancer. Indeed, genetic analysis of invasive cancers demonstrate innumerable genetic aberrations; however, unexpectedly, DCIS also has similar molecular changes [33, 34]. We believe that DCIS and invasive cancer may share molecular similarities but have small differences in self-seeding capacity. DCIS lesions may lack self-seeding capacities and as such neither develop into large tumors nor metastasize. Because these differences may be qualitative and in yet unrecognized self-seeding genes, the molecular differences are subtle [34, 35]. Seemingly minor differences in self-seeding efficiency could dramatically alter the clinical trajectory of a breast cancer.

5.2 Why Does Sampling a Random Tiny Portion of a Tumor Reflect the Behavior of the Larger Tumor?

The stem cell hypothesis states that only very few cancer "stem-cells" or tumor initiating cells have the capacity for unchecked proliferation and metastasis to distant organs [36, 37]. At the same time, we now examine patterns of gene expression (such as with Oncotype^{TM} or Mammaprint^{TM}) to prognosticate chemotherapy benefit and survival [38–40]. Yet these genetic analyses are based on only a small piece of a tumor. For molecular profiling to be viable, select stem cells would have to be disbursed throughout the cancer mass such that any random sampling would capture them. How is this possible?

In the self-seeding model, the tumor mass is not one large uniform mass but rather an amalgam of smaller masses. Because the tumor is a conglomerate, with some parts growing from a stem-like seed or "self-metastasis," it is disorganized architecturally. On a molecular and genetic level, any random sampling of the tumor will contain the cells that represent the relative metastatic propensity of the whole tumor.

5.3 Why is Mammographic Breast Density a Risk Factor for Breast Cancer?

Breast density reflects the structural components of the breast, such as collagen, and is independent of mitotic rates [41]. One of the highest risks for the development of breast cancer is mammographic breast density [42]. Alternatively,

postmenopausal lobular involution is associated with a decrease in breast cancer risk. However, the lowered risk associated with lobular involution correlates weakly with mammographic breast density [43, 44]. Hence, it is unclear how structural components of the breast effects breast cancer risk.

In the self-seeding model, a dense breast provides more scaffolding (collagen matrix) for self-seeds. Each self-seeding tumor, forming multiple masses, in turn promotes a more perilous framework for the surface/volume ratio of a transformed cellular state. This would explain the correlation between breast cancer risk and breast density as well as the association with lobular involution and decreased risk. Supporting this idea, recent research links increased stromal collagen to mammary tumor formation and metastasis [45].

6 Clinical Applications of Self-Seeding

At present, the development of cancer drugs is predicated on animal models which demonstrate primary tumor shrinkage. As such, the clinical endpoints both in animal and ultimately human clinical trials is an antimitotic effect on a primary tumor. Anti-metastatic effects are not directly evaluated but rather presumed based on the reduction of primary tumor burden. We propose that a more viable drug development approach would be to screen for anti-seeding (anti-metastatic) activity in addition to anti-mitotic effects [2]. Many of our successful standard therapies may already interrupt both the anti-seeding and anti-mitotic processes. In the era of targeted therapy, the development of drugs as either anti-mitotic (causing shrinkage) or anti-metastatic (disrupting seeding) may allow for a more rational design of combination drug therapies. As IL-6, IL-8, MMP-1, and fascin-1 have already been identified in the laboratory and animal models, these are notable possibilities for future drug development [2].

In addition to focusing on anti-seeding drug development, attention should also focus on the seeds themselves, CTCs [46]. We know that CTCs must survive in the circulation, likely by switching from an aerobic to anaerobic metabolism. Drugs that perturb this switch may be successful in reducing metastatic burden [47]. Immunological manipulation may also augment both CTC attraction and attracted-CTC killing. We envision a situation whereby tumor ablation by interventional radiology or the use of drugs such as anti-CTLA4, could lead to CTC attraction and subsequent cytotoxicity [48].

Lastly, recent studies suggest that an irradiated site may attract CTCs but lead to an inhospitable stroma for CTC growth. We await the ongoing results of experiments to evaluate the effect and the timing of therapeutic radiation.

7 Conclusion

Reconciling the nomadic properties of CTCs, the imperfect relationship between tumor size and lymph node infiltration, and the importance of tumor surface, self-seeding offers a new paradigm for understanding previously opposing clinical and

biological observations. As opposed to a linear, unidirectional pathway from primary tumor to distant metastasis, cancer cells may now be viewed as fluid seeds variably driven by mitotic (primary tumor), seeding (metastasis), and self-seeding processes. In particular, as oncology moves toward increasing personalized care, the self-seeding model will require an understanding of this tenuous balance in each patient. We believe that the self-seeding paradigm will reshape our drug and clinical trial development, offering new genomic and clinical endpoints. Understanding the multidirectional course of metastasis from a biological as opposed to anatomical perspective will engender new advances in cancer prognosis and cure. And as such, we hope that the self-seeding model will redirect the current trajectory of cancer mortality toward a more promising horizon.

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