EDITORIAL

Seeds and Soil: Unraveling the Role of Local Tumor Stroma in Distant Metastasis

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Distant metastasis is the chief cause of cancer mortality. This is particularly true for breast cancer, for which the last decades have brought notable advances in locoregional (surgical, radiation) and systemic (hormonal, chemotherapies) treatment approaches. However, metastatic progression remains a poorly understood process. Therefore, it has been difficult to predict the presence of occult micrometastases in patients and the molecular and cellular mechanisms critical for their formation and progression. As a result, devising novel anti-metastatic therapies has been and remains a great challenge in oncology.

Certain gene signatures (eg, MammaPrint, Oncotype DX) have shown statistically significant association with distant disease recurrence and are in clinical use as prognostic markers. These signatures appear to be driven predominately by genes reflecting the level of proliferation and hormone receptors in those tumors. But in addition to intrinsic properties of the cancer cells, a key role has been proposed for the tumor microenvironment in cancer cell survival and progression to metastasis. The contribution of the microenvironment may enhance an otherwise very inefficient process [1,2] and includes angiogenesis and the multi-faceted participation of activated fibroblasts and immune cells. Our understanding of this process is largely based on evidence from mouse models. However, the murine models have several limitations and may not fully reproduce the metastatic cascade in patients. Most metastasis studies have utilized experimental models in which cancer cells are injected as a bolus into the circulation upstream of the metastatic site. The limitation of such an approach is that it overlooks critical events taking place in the primary tumor and systemically prior to metastatic cell colonization. Models featuring spontaneous metastasis from a primary tumor are markedly better; however, these models generally do not metastasize to the same site(s) as the human disease they aim to model. Furthermore, such models are rare, and their metastatic cascade phenomena may represent only a small subset of possible human cases. Both implanted cancer cell models and genetically engineered mouse models—the current gold standard for understanding cancer biology—have these limitations.

Finally, although most new agents are first tested in the metastatic setting, more recently there has been considerable interest in evaluating novel therapeutic agents in the neoadjuvant (preoperative) setting for some aggressive subtypes of breast cancer (eg, triple-negative and human epidermal growth factor receptor 2 [HER2]-positive). This approach offers the potential for accelerated Food and Drug Administration approval if the agent demonstrates a substantial increase in the rate of pathological complete response of the primary cancer [3]. However, therapeutic effects on the primary cancer may not accurately reflect effects on micrometastatic disease in the setting of a different microenvironment. Preclinical studies often provide little insight in this regard, because most of them are done in primary tumors with no metastasis. This discordance may help explain the observation that drugs that increase pathological complete response rates have failed to decrease rates of metastatic disease.

In a report in this issue of the Journal, Rohan et al. examined whether the frequency of microstructural units formed by cancer cells, perivascular macrophages and endothelial cells—termed Tumor MicroEnvironment for Metastasis or TMEM—are associated with the risk of metastatic recurrence [4]. The authors identified the cancer cells that comigrate and interact with macrophages at intravasation sites based on the expression of Mena, which is an Ena/VASP protein family member and a key prometastatic factor [5]. The TMEM was previously discovered by the group of John Condeelis in preclinical models [6]. Using high-resolution, multiphoton-based intravital microscopy, the Condeelis group demonstrated that invasive carcinoma cells in mouse and rat mammary tumors comigrate and intravasate when associated with perivascular macrophages. The correlative clinical study performed by Rohan et al. [4] found a positive association between TMEM score and risk of distant metastasis in women with estrogen receptor (ER)-positive/HER2-negative breast cancer. In this subgroup, the TMEM score outperformed the validated IHC4 score, used here as a surrogate for the prognostic information provided by the Oncotype DX score. For ER-positive/HER2-positive cancers, the IHC4 score depends on the presence of progesterone receptors and on Ki67 expression, and thus mainly reflects cell proliferation [7]. Although the predictive ability of TMEM score alone was similar to IHC4 score, the authors found that further improvement in prediction of metastasis could be obtained by considering also clinical and treatment data. The composite score showed promise, yielding the area under receiver operating characteristic curve of 0.74 when statistically adjusted for fitting the model and evaluating it in the same population. While they certainly require additional validation prior to clinical use, the correlative data reported further our understanding and support the key role of the tumor microenvironment in the early steps of cancer metastasis as predicted by preclinical models. These intriguing results also raise many important questions for this critical area of cancer research.

Since the seminal work of Paget more than a century ago, it is widely accepted that seed (cancer cells from the primary tumor) will grow only in a congenial soil (metastatic site) (8). Our group has shown that the seed also brings along its soil (stromal cells) from the primary site, which can serve as a provisional stroma at the secondary site until the metastatic cancer cells recruit new stroma (9). The potential of stromal cells or immune cells traveling in circulating heterotypic clumps containing cancer cells has been recognized for decades in preclinical models (10). This included activated fibroblasts and myeloid cells (monocytes/platelets) in models of experimental metastasis. Such clumps have been identified by others in the blood circulation of cancer patients using microfluidic harvesting devices (11). Moreover, we showed that biopsies of brain metastases from patients with breast, lung, renal, and ovarian cancer seem to harbor stromal cells of the primary tumors (9). This makes the "metastatic stromal cell" a potential target for treatment. Finally, other studies have shown that metastases can initially grow intravascularly (12). These observations conflict with the standard view of metastasis, because adhesion and transmigration at the secondary site is not necessary, as initial lung metastases may first grow within the vasculature. They also highlight the fact that the widely accepted notion that single cancer cells crawl into blood vessels, adhere downstream to the endothelium, and then transmigrate in a manner similar to leukocytes is a good starting point, but needs to consider these emerging data and the contribution of the tumor microenvironment in this process. The role of TMEM in these contexts is unknown, but it is conceivable that it could play a role in the shedding of tumor fragments in circulation and growth and invasion at the secondary site. Future studies should address these important mechanistic issues.

Moreover, the crosstalk between a primary tumor and its metastases remains poorly understood. Some high profile studies have shown that a primary tumor can suppress the growth of a secondary tumor, whereas other high profile studies have shown the opposite. We explored the complexities around the effect of a primary tumor on the growth of a secondary tumor. These studies revealed that the outcome depended on the site of the primary tumor implantation (ectopic vs orthotopic), the size of the primary tumor, and whether the primary tumor was removed or left intact in the host after sterilizing it with radiation (13,14). Even one region (margin) of a tumor can affect its center. Conversely, there are also recent studies showing that cancer cells from the secondary lesion can travel to the primary lesion (15). The role of TMEM in these contexts, particularly in influencing the risk of recurrence in early-stage disease, also remains unknown. All these issues need to be addressed carefully as they have powerful implications for treating primary and metastatic lesions in patients.

This overwhelming complexity of the metastatic process highlights the importance of mechanism-based, tumor-type specific studies in clinically relevant murine models. As done by Rohan et al. (4) in the accompanying study, the findings should be validated in correlative clinical studies. This approach may greatly facilitate the development of efficacious anti-metastatic strategies.

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