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IN THE SPOTLIGHT

Hello Out There...Is Anybody Listening?

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Summary: Using a murine xenograft model system, Kuznetsov and colleagues show the existence of systemic interactions between a primary tumor and the growth of distal tumors in both homotypic and heterotypic tissues. Importantly, they show that the characteristics of the primary tumor govern the histologic features of the distal tumor through distinct pathways, thus providing novel opportunities for risk assessment, prognosis, prevention, and intervention. *Cancer Discov*; 2(12); 1084-6. ©2012 AACR.

Commentary on Kuznetsov et al., p. 1150 (1).

The most exciting and groundbreaking scientific articles not only describe the answer to a specific question but also provide novel insights into fundamental biology. Such is the case with Kuznetsov and colleagues (1) in the most recent of a series of articles from the McAllister laboratory examining the molecular underpinnings of recurrent tumors. These articles identify multiple novel pathways that control tumor recurrence; show that different subtypes of tumors can activate different mechanisms promoting recurrence; beautifully show the systemic nature of the complex biology behind relapse and recurrence; suggest a predictive approach for identifying those individuals at greatest risk for recurrence; and highlight therapeutic strategies to address the systemic basis of tumor biology.

Epidemiologic studies have provided striking information suggesting a systemic aspect of cancer biology. Analysis of data from large surveillance cohorts shows that patients diagnosed with one malignancy have an increased risk for developing multiple independent primary malignancies in distal tissues and that these individuals also have a reduction in overall survival (2). Furthermore, a meta-analysis of 10 recent retrospective studies suggests that surgical removal of a primary breast tumor significantly improves the survival of patients who presented with distant metastases at the time of their primary diagnosis (3). These observations suggest that primary tumors can affect the behavior of other tumors residing at distant anatomic sites, although the mechanism(s) underlying these systemic interactions is unknown and understudied.

To examine the molecular basis for the systemic interactions between multiple tumors, McAllister and colleagues (4) designed a model xenograft system using 2 different human cancer cell lines. In this system, human cancer cells capable of forming vigorously growing tumors are subcutaneously injected into one flank of an immunocompromised mouse (potential “instigating” tumors), whereas different human

cancer cells incapable of forming vigorously growing tumors are subcutaneously injected into the other flank of the same mouse (“responding” tumor; refs. 1, 4, 5). When these authors examined the activity of these potential instigating tumors, they found that some, but not all, of these vigorously growing tumors can instigate the growth of the otherwise indolent responding tumors (4). This suggests that the ability to instigate the growth of an otherwise indolent tumor is not shared by all vigorously growing tumors and also provides a model system to investigate the molecular basis of tumor “instigation.”

Using this instigating/responding xenograft model system, McAllister and colleagues and Elkabets and colleagues previously examined the mechanism of instigation of 2 different triple-negative breast cancer (TNBC) cell lines (BPLER and MDA-MB-231 cells) on a responding breast cancer cell line (HMLER-HR cells; refs. 4, 5). They found that both TNBC-instigating tumors increase the incidence, size, and desmoplastic response of the responding tumors through the secretion of high levels of osteopontin (OPN; refs. 4, 5). OPN in turn “activates” bone marrow cells (BMC), causing them to home to the responding tumor and secrete granulins (GRN), which then induces resident fibroblasts to undergo myofibroblast differentiation and create a desmoplastic stroma (4, 5). All instigation-mediated phenotypes in responding tumors can be recapitulated by injecting mice with BMCs purified from mice bearing TNBC-instigating tumors or treating mice with GRN (4, 5). A positive correlation between GRN expression and tumor size, grade, and triple-negative subtypes and its negative correlation with survival in a large cohort of patients with breast cancer bring further credence to the relevance of these findings (5).

In this issue of *Cancer Discovery*, Kuznetsov and colleagues report on their use of an instigating/responding xenograft model system to examine the mechanism of instigation of luminal breast cancers (LBC), which are responsible for approximately 80% of human breast cancers (1). They used an “instigating” human LBC cell line (MCF7ras cells) and compared its instigating activity on a “responding” breast cancer cell line (HMLER-HR cells) to one of the TNBC cell lines (BPLER cells) previously studied (1). They found that the LBC-instigating tumors could also increase the incidence and size of the responding tumor to a similar extent as the TNBC-instigating tumors. However, when they examined

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the histology of these responding tumors, they found dramatic differences depending of the instigating tumor subtype. For example, responding tumors formed in mice bearing TNBC-instigating tumors showed modest proliferation, limited vascularization, and no sign of necrosis, but robust desmoplastic response and infiltration with “activated” BMCs. In contrast, responding tumors formed in mice bearing LBC-instigating tumors showed high proliferation, extensive vascularization, and necrosis, but no desmoplastic response and infiltration with platelets. Importantly, the authors establish that instigating LBC cells do not express the high levels of OPN observed in the instigating TNBCs. Instead, they show that LBC-instigating tumors secrete proangiogenic factors such as CXCL1/GRO and platelet-derived growth factor-BB, which are taken up by platelets and released at the responding tumor site, inducing angiogenesis. Finally, they show that treatment of mice with aspirin inhibits the ability of LBC-instigating tumors to increase the incidence and size of responding tumors.

There are several novel and significant findings in this body of work by McAllister and colleagues (1, 4, 5). First, both triple-negative and luminal breast tumors can instigate the growth of an otherwise indolent responding tumor (Fig. 1). This provides a possible explanation for the clinical observations that patients with one tumor have an increased risk of developing multiple, independent tumors and that surgical removal of a primary breast tumor improves the survival of patients who presented with distant metastases at the time of their primary diagnosis (2, 3). Second, triple-negative and luminal breast cancers use very different mechanisms to instigate the growth of the responding tumor, and as a result, induce dramatically different phenotypes in the responding tumors. These distinct mechanisms of instigation could provide an explanation for the numerous reports documenting differences in the metastatic behavior of breast cancer subtypes. In one such publication, Kennecke and colleagues (6)

report that patients with luminal breast cancer have a lower immediate and cumulative risk for distant metastases than patients with TNBC. In addition, they report differences in the timing of metastases, with virtually all metastases presenting within the first 5 years in patients with triple-negative disease, whereas patients with luminal cancer continued to present with metastases between 5 and 15 years after treatment (6). Finally, they also report differences in the tissue spectrum of metastases, with TNBC patients having a higher percentage of brain, lung, and distant nodal metastases and a lower percentage of bone metastases than patients with luminal breast cancer (6). Strikingly, these studies also show that one type of primary tumor, for example, breast cancer, can influence the progression of other tumor types, for example, kidney cancer (Fig. 1).

Additional significant findings of these studies include the development of model systems that provide productive approaches to studying the systemic aspects of cancer biology with clinical ramifications for diagnosis, prognosis, prevention, and therapy. For example, the finding that platelets can be loaded with proangiogenic and proinflammatory factors produced by the primary luminal tumor and then home to the site of distant metastases for delivery of the prometastatic payload reveals a level of tumor communication that was previously unknown. Not only does this information tell us more about the biology but also provides us with potential tools to monitor the contents of platelets to assess the risk of recurrence, modify the delivery of platelets, or create competing payloads that may neutralize this systemic facilitation of tumor recurrence. These promising results seen with aspirin treatment in mice (1), as well as numerous published studies documenting the antitumorigenic and antimetastatic activity of aspirin (7, 8), underlie the potential of interfering with tumor recurrence. Similar approaches can be used to monitor and modulate the exposure to GRN or OPN produced by triple-negative breast tumors. Knowledge of these novel communication systems allows us to address the cells that are “speaking,” change the message, or change the ability of distal cells to “hear” the message. If we can find ways to control the message, we may be able to control the subsequent conversation.

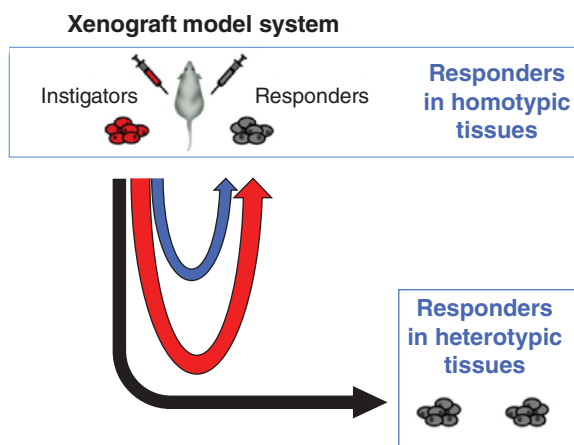


Figure 1. Results from xenograft model system. Both luminal (red arrow) and triple-negative (blue arrow) breast tumors can instigate the growth of an otherwise indolent responding breast tumor. The luminal and triple-negative instigating breast tumors use very different mechanisms of instigation, resulting in histologically distinct responding tumors. In addition, instigating breast tumors can facilitate the growth of otherwise indolent tumors from distal tissues (black arrow).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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