A TeNaCious Foundation for the Metastatic Niche

Irina Matei,[1,5] Cyrus M. Ghajar,[4,5] and David Lyden[1,2,3,*]
[1]Departments of Pediatrics and Cell and Developmental Biology, Weill Cornell Medical College, New York, NY 10021, USA
[2]Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA
[3]Champalimaud Metastasis Programme, Lisbon, Portugal
[4]Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA
[5]These authors contributed equally to this work
*Correspondence: dcl2001@med.cornell.edu
DOI 10.1016/j.ccr.2011.08.004

In the July issue of *Nature Medicine*, Massagué and colleagues define a biphasic role for the extracellular matrix protein tenascin C as a metastatic niche component in lung colonization by breast cancer cells. These results provide a rationale for designing therapies targeting metastatic progression by disrupting its very foundations.

While dissemination can occur early during tumor progression (Hüsemann et al., 2008; Podsypanina et al., 2008), the ability to colonize distant sites may not be so ''easily'' achieved. The dynamics of metastatic growth vary widely among patients, perhaps reflecting the extent to which the primary tumor is able to cultivate a supportive niche at the distant site prior to dissemination (i.e., a premetastatic niche) or how pre-adapted disseminated tumor cells (DTCs) are to ''foreign soil.''

The contribution of bone marrow-derived cells in establishing the premetastatic niche is well described, and effectors (e.g., fibronectin, lysyl oxidase, MMP-9, S100A8/A9, and TNF-α) that prime a microenvironment for DTC growth continue to be uncovered (Kaplan et al., 2005; Psaila and Lyden, 2009) (Figure 1). The tumor cells' ability to elicit distant expression of such factors influences organ tropism (Kaplan et al., 2005), and the presence of extracellular matrix (ECM) proteins and ECM-remodeling enzymes at the premetastatic site reflects the requirement for signaling through specific adhesion receptors to support engraftment and survival of incoming metastatic cells (Psaila and Lyden, 2009). But how this extracellular milieu changes during progression from a premetastatic to metastatic microenvironment remains ill defined. Moreover, little is known about the properties of the first DTCs that colonize and build the foundations of the metastatic niche, or the mechanisms by which they conquer ''foreign soil.''

A recent *Nature Medicine* paper provides a functional characterization of an organ-specific driver of metastasis, the ECM glycoprotein tenascin-C (TNC) (Oskarsson et al., 2011).

In this study, Massagué and colleagues build upon their earlier work (Minn et al., 2005) to elegantly define a novel role for TNC in initiating and sustaining lung colonization by breast tumor cells (Oskarsson et al., 2011). The authors show that while TNC knockdown does not hinder mammary tumor growth, it restricts the progression of lung micrometastases. The presence of TNC at the borders of metastatic lesions suggests it may provide a supportive scaffold that fosters progression of lung metastases. This conclusion is reinforced by the array of biochemical interactions supported by TNC's molecular structure.

TNC is a complex hexabranchion containing EGF- and fibronectin-like repeats and a C-terminal fibrinogen-like globular domain, which mediate its interaction with ECM proteins and cell-surface molecules. TNC may signal directly or within macromolecular scaffolds, suggesting that TNC binding triggers signaling in a context-dependent fashion determined by whether it is coupled to other ECM molecule(s), the identity of said molecules (e.g., fibronectin or fibrinogen), and the size of the signaling complex formed (which could theoretically affect integrin clustering and signal strength) (Hynes, 2009). These factors may underlie cancer cell type- and organ-specific responses to TNC, and thus dictate the efficacy of therapeutically targeting TNC in a given setting. These properties also form the basis for TNC's pleiotropic effects during development, inflammation, and tumorigenesis. Since TNC is dramatically downregulated in adult tissues, its reinduction in tumors and the surrounding microenvironment may reflect the acquisition of a migratory or stem cell-like phenotype by tumor cells (Ben-Porath et al., 2008).

To address the significance of TNC in breast tumor colonization of the lung, Oskarsson et al. (2011) knockdown TNC after tumor cells engraft the lung. In so doing, they demonstrate that the dynamic and reciprocal interplay between a cell and its microenvironment that generally drives tissue specificity (Bissell et al., 1982) also forms the foundation for signaling between ''seed'' and ''soil'' within a metastatic niche. While ablation of TNC expression in DTCs early during the metastatic process inhibits the outgrowth of lung metastases, late inhibition does not affect progression from micro- to macrometastases. By this later time point, metastatic cells have already induced lung stroma activation, which coincides with increased expression of TNC by lung cells. The simplest interpretation of these results is that stromal TNC obviates the need for tumor-derived TNC, a hypothesis that could be rigorously explored via tissue-specific knockdown. Moreover, determining whether preexisting TNC expression by nontumor cells in the lung can compensate for lack of DTC-derived TNC upon arrival and identifying the cellular source of TNC in the reactive lung would provide further insight into TNC's role in the metastatic niche, as would elucidating the mechanism that drives paracrine TNC signaling during metastatic progression. Addressing such issues is crucial to determining whether

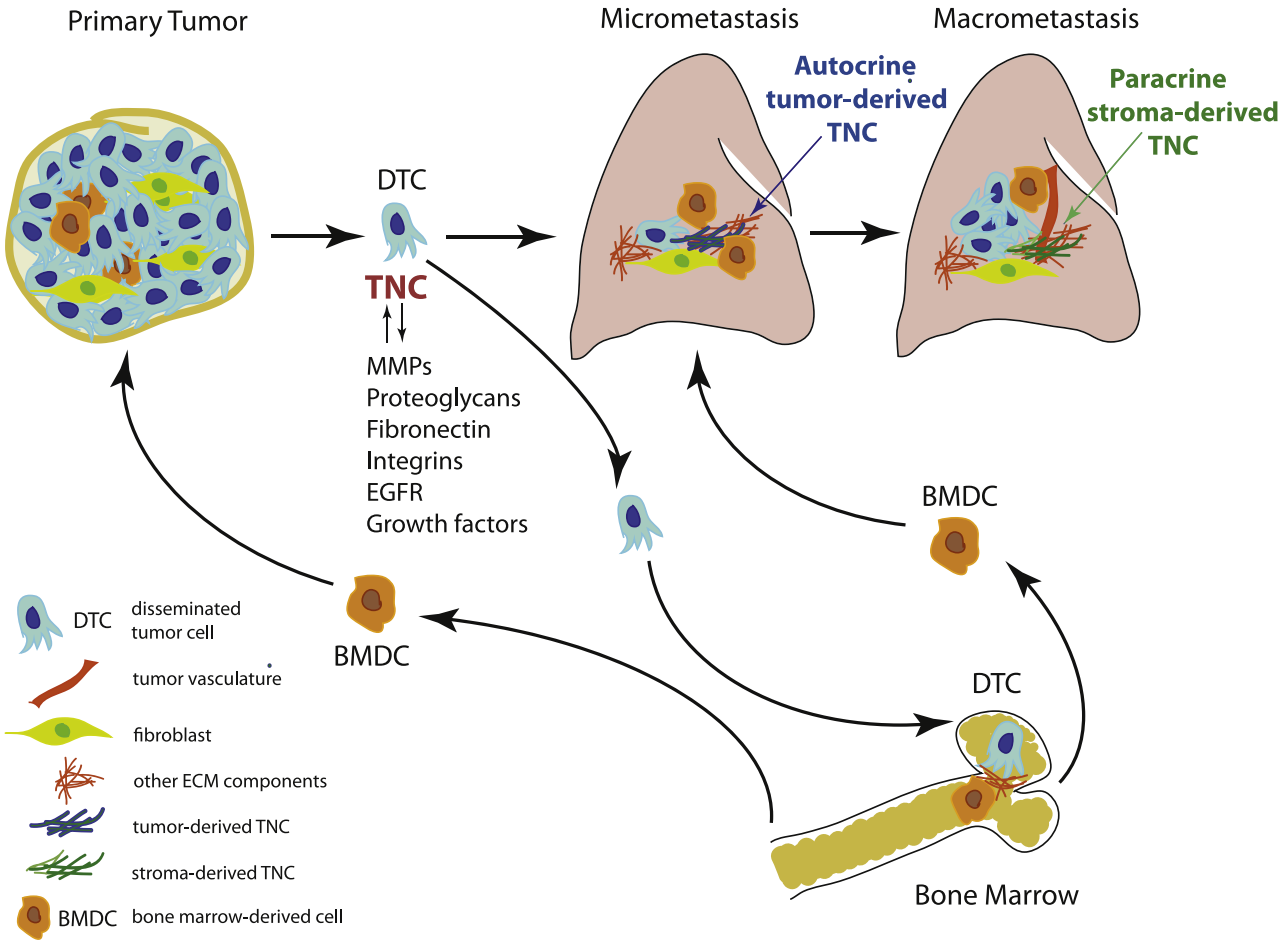

Figure 1. Biphasic Roles of Tenascin C in Breast Cancer Metastasis

TNC may promote tumor cell dissemination and survival during the early steps of metastasis by concentrating growth factors (e.g., EGF, FGF) or through reciprocal interactions with ECM components such as fibronectin, heparan-sulfate proteoglycans (e.g syndecan 4, versican, perlecan, aggrecan) and fibrinogen, enzymes such as matrix metalloproteinases, and cell surface receptors such as EGFR and integrins. During progression from micro- to macrometastasis, activation of surrounding lung tissue elicits expression of TNC in the host organ (green matrix), in addition to that derived from the tumor cells (blue matrix). While the cellular source of host TNC and the specific effects of tumor- and host cell-derived TNC on various cell types within the metastatic milieu remain to be determined, it is likely that at least some of the niche-derived TNC is of endothelial origin. TNC may be a key component of the metastatic niche within organs other than the lung, including bone marrow. The organ specificity of TNC-mediated interactions between breast cancer cells (as well as other cancer types) and other host organs remains to be elucidated.

TNC expressed by DTCs or lung cells presents a valid target for therapies meant to prevent micrometastases from thriving in the lung. Further clues may be gleaned by examining the kinetics of lung metastases in cancer patients with chronic obstructive pulmonary disorder, a disease characterized by TNC overexpression in the lung epithelium.

Oskarsson et al. (2011) further explore the mechanisms through which TNC confers lung-colonizing capacity upon breast tumor cells. Although silencing TNC in breast tumor oncospheres does not affect the expression of putative stem cell markers, Wnt and Notch signaling are downregulated, and restoration of Notch signaling is sufficient to circumvent the need for TNC in lung colonization. Thus, TNC evidently enhances the fitness of breast cancer cells in the lung, but not their self-renewal capacities, in a Notch and Wnt-signaling dependent manner.

One obvious question arises from these data: how does TNC regulate Notch and Wnt signaling in tumor cells? TNC may activate Wnt signaling indirectly by binding the transmembrane proteoglycan Syndecan 4, known to activate noncanonical Wnt signaling (Muñoz et al., 2006). In contrast, the presence of EGF-like repeats in TNC opens up the intriguing possibility that TNC may activate Notch signaling directly by acting as a non-canonical Notch ligand; biochemical and functional binding assays are necessary to test this hypothesis. Given that Notch signaling is required not only for normal mammary gland and breast cancer development but also for angiogenesis and vascular remodeling, it will be crucial to determine whether the altered balance of TNC in the metastatic niche engages Notch and Wnt signaling in the tumor-associated endothelium, activating a feed-forward loop that promotes angiogenesis and secretion of cytokines/chemokines, further supporting tumor growth.

An intriguing yet underexplored function of TNC is its potential involvement in the establishment and/or maintenance of

stem cell niches, as demonstrated during forebrain development. It is conceivable that TNC contributes to the generation of a stem-cell like niche supporting cancer-initiating cell survival and proliferation at newly colonized metastatic sites. Nevertheless, it remains to be determined whether TNC plays a role in normal mammary stem cell niches, and whether TNC is required for breast cancer initiating cell survival, proliferation, and homing in vivo.

Identifying factors involved in facilitating the early and late stages of metastasis may provide targeted therapies that effectively hinder disease progression. TNC may represent one such target that can be attacked to unravel the metastatic niche of the lung (and perhaps other tissues) at its foundation. Whether targeting stromal-derived TNC in addition to DTC-derived TNC will prove sufficient to cause regression of established metastases remains an open question. But as a major determinant of metastatic initiation and sustenance of both tumor and microenvironmental provenance, TNC may indeed represent one of the first opportunities to develop two-pronged therapies that simultaneously target a "seed-" and "soil-intrinsic" prometastatic factor.

REFERENCES

Ben-Porath, I., Thomson, M.W., Carey, V.J., Ge, R., Bell, G.W., Regev, A., and Weinberg, R.A. (2008). Nat. Genet. *40*, 499–507.

Bissell, M.J., Hall, H.G., and Parry, G. (1982). J. Theor. Biol. *99*, 31–68.

Hüsemann, Y., Geigl, J.B., Schubert, F., Musiani, P., Meyer, M., Burghart, E., Forni, G., Eils, R., Fehm, T., Riethmüller, G., and Klein, C.A. (2008). Cancer Cell *13*, 58–68.

Hynes, R.O. (2009). Science *326*, 1216–1219.

Kaplan, R.N., Riba, R.D., Zacharoulis, S., Bramley, A.H., Vincent, L., Costa, C., MacDonald, D.D., Jin, D.K., Shido, K., Kerns, S.A., et al. (2005). Nature *438*, 820–827.

Minn, A.J., Gupta, G.P., Siegel, P.M., Bos, P.D., Shu, W., Giri, D.D., Viale, A., Olshen, A.B., Gerald, W.L., and Massagué, J. (2005). Nature *436*, 518–524.

Muñoz, R., Moreno, M., Oliva, C., Orbenes, C., and Larraín, J. (2006). Nat. Cell Biol. *8*, 492–500.

Oskarsson, T., Acharyya, S., Zhang, X.H., Vanharanta, S., Tavazoie, S.F., Morris, P.G., Downey, R.J., Manova-Todorova, K., Brogi, E., and Massagué, J. (2011). Nat. Med. *17*, 867–874.

Podsypanina, K., Du, Y.C., Jechlinger, M., Beverly, L.J., Hambardzumyan, D., and Varmus, H. (2008). Science *321*, 1841–1844.

Psaila, B., and Lyden, D. (2009). Nat. Rev. Cancer *9*, 285–293.