
Cancer
Cell
Volume 22
Number 5
November 13, 2012
www.cellpress.com
TGFβ
TGFβ-Activated Stroma
Promotes Metastasis

Metastatic Ability: Adapting to a Tissue Site Unseen

Neil A. Bhowmick[1,2,3,*]
[1]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA
[2]Greater Los Angeles Veterans Administration, Los Angeles, CA 90073, USA
[3]Samuel Oschin Comprehensive Cancer Institute, 8750 Beverly Boulevard, Atrium 103, Los Angeles, CA 90048, USA
*Correspondence: bhowmickn@cshs.org
http://dx.doi.org/10.1016/j.ccr.2012.10.011

The microenvironment of the primary as well as the metastatic tumor sites can determine the ability for a disseminated tumor to progress. In this issue of *Cancer Cell*, Calon and colleagues find that systemic TGF-β can facilitate colon cancer metastatic engraftment and expansion.

Preventing the metastatic progression of tumors is a prevailing issue in cancer biology. In liquid tumors, like multiple myeloma, which colonizes the bone, we can imagine the cancer cells have pre-existing equipment required to survive and thrive in the bone microenvironment. For ovarian serous carcinoma dissemination and expansion within the peritoneal cavity, cell autonomous mechanisms of tumor proliferation, epithelial-to-mesenchymal transdifferentiation, and anti-apoptotic signaling may be predominant requirements for metastasis. However, the non-random metastatic tropism of solid tumors, such as that of the breast, colon, and prostate, often need to adapt to more than one distant site, including lymph nodes, bone, and soft tissue. In these examples, tumor size at the primary site and the number of circulating tumor cells are relatively less significant determinants of adaptation at the secondary site.

The extensive global sequencing efforts of the primary tumor epithelia have not helped to predict colon cancer metastatic potential (Jones et al., 2008). In contrast, profiling the microenvironment of the primary tumor seems to be predictive for liver and prostate cancer metastatic progression (Blum et al., 2008; Budhu et al., 2006). In this issue of *Cancer Cell*, Calon et al. (2012) report that measuring reciprocating signals by the tumor and host are likely going to be more predictive of colon cancer growth at the metastatic site. Specifically, the authors found that elevated levels of transforming growth factor-beta (TGF-β) expression was a superior predictor of metastatic growth of colon cancer rather than pathologic staging. They present a study addressing the apparent paradox characterized by high TGF-β levels in the tumor and mutational inactivation of TGF-β signaling observed in colon cancer epithelia. As such, the elevated TGF-β would be affecting the cells of the host, in particular, endothelia and fibroblasts, at the distant metastatic site. Calon et al. (2012) suggest that a stromal TGF-β response, involving IL-11, potentiates colon cancer engraftment and growth at liver and lung metastatic sites. The immune regulatory effects of TGF-β could not be specifically examined as the observations were made in immune-compromised xenograft mouse models. However, the work suggests a novel mechanism of colon cancer metastatic progression following the initial steps of tumor cell dissemination.

Multiple mechanisms of metastatic progression are possible. One such possibility is that tumor cells possessing stem-like features may have a growth advantage in a secondary site; their pluripotent potential could presumably facilitate adaptation to a new environment (Figure 1A). A tumor cell cannot evolve to adapt to an environment to which it has not been exposed. In this case, the success of the metastasis is reliant on the plasticity of the stem-like tumor cell. A recent report suggested that expression of the extracellular matrix component periostin in mammary tumors can support stem-like features to favor metastatic progression (Malanchi et al., 2012). In the process of prostate cancer and stromal coevolution in the primary tumor site, paracrine cytokines expressed by prostatic fibroblasts that lose TGF-β responsiveness alter the interactions of tumor epithelia, with its matrix enabling significant expansion in secondary bone tissue (Li et al., 2012). Another recent report supports the idea that specific changes in the matrix and its integrin interaction with primary lung tumor cells are critical determinants of metastatic progression (Reticker-Flynn et al., 2012). Figure 1B illustrates that an alternative means of successful metastatic progression can be a result of a disseminated tumor cell having the ability to survive in the secondary site until it can express factors that enable it to thrive (Stoecklein et al., 2008). The secondary tissue microenvironment can reciprocally respond to the disseminated tumor cell, such that a collaborative effort enables metastatic progression. Tumor dormancy, which is associated with micrometastases that are not visibly progressing, can involve the coevolutionary process at the metastatic site, which includes cell autonomous changes as well as those of the host vasculature and immune system. It has been clear for some time that TGF-β mediates processes associated with tumor cell extravasation in terms of increased motility and cell survival. However, these cell-autonomous TGF-β activities cannot be attributed to elevated metastatic potential, because TGF-β signaling is increasingly found to be impaired or completely absent in multiple cancer types, including colon cancer epithelia. Figure 1C illustrates changes that can occur in the primary and metastatic tumor microenvironment as a result of elevated systemic TGF-β. These changes may normalize the microenvironment of the two sites such that the metastatic niche is primed for tumor growth, as suggested in the study by Calon et al.

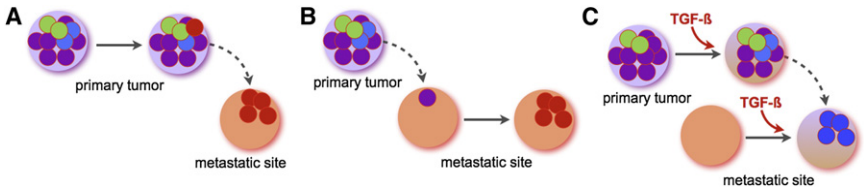

Figure 1. Scenarios for Metastatic Expansion

There are multiple possible mechanisms for metastatic progression. It is assumed that the rate limiting steps of metastasis do not necessarily involve the processes of tumor cell dissemination, but rather compatibility of tumor cells with their metastatic site.

(A) A primary tumor cell can acquire traits within the primary tumor that enable its progression in the metastatic site.

(B) Alternatively, the disseminated tumor cells that lodge in the metastatic site can lie 'dormant' until the new microenvironment potentiates the acquisition of traits that enable tumor progression.

(C) The work by Calon et al. (2012) suggests that elevated TGF-β and its downstream products induce changes in the microenvironment of the primary tumor and the metastatic site to facilitate metastatic progression. There are other possibilities mediating metastatic progression including variations and combinations of these three scenarios. The role of the immune system is not accounted for in this assessment.

(2012). The role of the innate immune system in the development of a pre-metastatic niche has been described (Kaplan et al., 2005). However, the detection of TGF-β in circulation in colon cancer metastatic progression in patients supports the role of tumor-derived cytokines in the primary site having long range effects in altering the microenvironment of the metastatic site (Calon et al., 2012). The role of TGF-β in altering the microenvironment of the primary and metastatic sites can be therapeutically leveraged. For example, TGF-β blockade increases chemotherapeutic penetration into tumors by causing perivascular cell activation, leading to increased tumor perfusion and reduced extracellular matrix formation (Liu et al., 2012).

Translational opportunities for the application of these results are dependent on further understanding of the host response to TGF-β signaling. The inhibition of TGF-β signaling at the level of the ligand, receptor-ligand complex, and intracellular signaling molecules are being studied. However, the targeting of downstream paracrine factors, initially thought to be a fools-game of chasing the numerous TGF-β responsive genes, is starting to come down to fewer examples of viable candidates to support greater tumor specificity. Nevertheless, there is an even greater need to understand the metastatic site in order to appropriately determine the TGF-β induced factor(s). Metastatic tropism is reliant on the dynamics of the tumor cell as it attempts to convert its microenvironment to its advantage (Figure 1). Thus, to time the therapeutic window for pharmacological intervention of a metastatic mechanism would be challenging. However, addressing metastasis methods collectively used by heterogeneous tumors may require a multipronged approach that would include targeting the microenvironment at both primary and metastatic sites through a cell type-directed manner.

REFERENCES

Blum, D.L., Koyama, T., M'Koma, A.E., Iturregui, J.M., Martinez-Ferrer, M., Uwamariya, C., Smith, J.A., Jr., Clark, P.E., and Bhowmick, N.A. (2008). Clin. Cancer Res. *14*, 7790–7797.

Budhu, A., Forgues, M., Ye, Q.H., Jia, H.L., He, P., Zanetti, K.A., Kammula, U.S., Chen, Y., Qin, L.X., Tang, Z.Y., and Wang, X.W. (2006). Cancer Cell *10*, 99–111.

Calon, A., Espinet, E., Palomo-Ponce, S., Tauriello, D.V.F., Iglesias, M., Céspedes, M.V., Sevillano, M., Nadal, C., Jung, P., Zhang, X.H.-F., et al. (2012). Cancer Cell *22*, this issue, 571–584.

Jones, S., Chen, W.D., Parmigiani, G., Diehl, F., Beerenwinkel, N., Antal, T., Traulsen, A., Nowak, M.A., Siegel, C., Velculescu, V.E., et al. (2008). Proc. Natl. Acad. Sci. USA *105*, 4283–4288.

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.

Li, X., Sterling, J.A., Fan, K.H., Vessella, R.L., Shyr, Y., Hayward, S.W., Matrisian, L.M., and Bhowmick, N.A. (2012). Mol. Cancer Res. *10*, 494–503.

Liu, J., Liao, S., Diop-Frimpong, B., Chen, W., Goel, S., Naxerova, K., Ancukiewicz, M., Boucher, Y., Jain, R.K., and Xu, L. (2012). Proc. Natl. Acad. Sci. USA *109*, 16618–16623.

Malanchi, I., Santamaria-Martínez, A., Susanto, E., Peng, H., Lehr, H.A., Delaloye, J.F., and Huelsken, J. (2012). Nature *481*, 85–89.

Reticker-Flynn, N.E., Malta, D.F., Winslow, M.M., Lamar, J.M., Xu, M.J., Underhill, G.H., Hynes, R.O., Jacks, T.E., and Bhatia, S.N. (2012). Nat Commun. *3*, 1122.

Stoecklein, N.H., Hosch, S.B., Bezler, M., Stern, F., Hartmann, C.H., Vay, C., Siegmund, A., Scheunemann, P., Schurr, P., Knoefel, W.T., et al. (2008). Cancer Cell *13*, 441–453.