Published in final edited form as:

Nat Med. 2007 November ; 13(11): 1289–1291.

A MSC-ing link in metastasis?

Douglas R Hurst and Danny R Welch

Danny R. Welch is the Leonard H. Robinson Professor of Pathology at the University of Alabama at Birmingham, 1670 University Blvd. VH-G019A, Birmingham, Alabama 35294-0019, USA. e-mail: danwelch@uab.edu

Abstract

Mesenchymal stem cells promote the dissemination of neoplastic cells in a mouse model of breast cancer. The findings sound a cautionary toll for anticancer therapies that rely on these cells and provoke a re-evaluation of how metastases form.

Metastases are derived from distinct subpopulations of cells that exist within a tumor. In a classic example, the melanoma cell subtype B16 can be selected from a primary tumor and enriched for an increased tendency to colonize lung¹. Tumor cell behavior, however, is often quite plastic. The cells have some properties reminiscent of those of cells undergoing epithelial-mesenchymal transition (EMT), a normal developmental process in which embryonic cells temporarily disrupt tissue architecture by disassembling junctional structures and then expressing mesenchymal proteins and migrating². It is hypothesized that in cancers, EMT confers motility by changing cell-cell interactions and adhesive characteristics.

Some researchers hold that the EMT pathway is usurped by tumor cell populations so that they become transiently metastatic³. A recent study in *Nature* by Weinberg and colleagues supports another possible mechanism: mesenchymal stem cells within a primary tumor might elicit a transient enhancement of metastasis⁴.

Metastases develop as the culmination of the so-called ‘metastatic cascade’, a multi-step sequential process in which tumor cells depart the primary tumor, enter the lymphatic system, blood system or body cavity, arrest at nearby or distant sites, and again proliferate to colonize ectopic tissues.

There is a long history of clinical and experimental observations showing that metastases frequently occur at sites of injury. Because stem cells preferentially migrate to tumors and sites of tissue injury⁵, they may prepare the site(s) for subsequent colonization. Once there, hematopoietic stem cells are recruited to a so-called ‘premetastatic niche’, where they reorganize the matrix and establish sites at which tumor cells proliferate more frequently than at other locales to develop *bona fide* metastases⁶. Karnoub *et al*⁴ embarked upon their study to determine whether infiltrating mesenchymal stem cells (MSCs) could alter tumor cell behavior.

The authors showed that weakly metastatic human breast cancer cells acquired an increased ability to disseminate to the lungs when they were mixed with MSCs before being subcutaneously injected⁴. Primary tumor growth was unaffected by the presence of MSC. Because carcinoma cells isolated from secondary tumors in the lungs were no more metastatic than the parental cells, the authors concluded that the enhancement of ‘metastasis’ was transitory. However, markers of EMT were not upregulated in the tumor cells suggesting that other mechanisms for inducing metastasis are operating in this system.

The authors found that tumor cells instead induced expression of the chemokine CCL5 in the MSCs, suggesting that CCL5 may increase the motility of the tumor cells or contribute to

feedback signals sent to the tumor cells via a paracrine or juxtacrine loop⁴. Still, exactly how CCL5 regulates metastasis is uncertain.

The Karnoub *et al.*⁴ study adds to the growing body of evidence that tumor-stromal crosstalk⁷ and genetic background are essential to the behavior of a tumor. But this study is not the first to show that various stem cells and their progeny contribute to invasive and metastatic behavior. Taketo and colleagues recently showed that myeloid stem cells that were recruited to primary colon tumors enhanced the tumors' invasiveness⁸. Others have shown that tumor-elicited macrophages and neutrophils increase metastatic efficiency by enhancing invasion through basement membranes^{9,10}. Additionally, tumor angiogenesis builds or recruits new capillaries through the mobilization of angioblasts, among other processes¹¹. Together, these data highlight how metastatic cells can co-opt other cells to assist them.

Importantly, metastasis is not simply the movement of cells around the body. Clinically relevant secondary tumors must grow to a size that impairs local physiology. In short, to become a *bona fide* metastasis, disseminated cells must colonize ectopic tissues¹². Karnoub *et al.*⁴ used GFP-expressing tumor cells to visualize single cells within tissues. They found that there were more small green foci in the lungs when MSCs were mixed with the cancer cells before injection compared to tumor cells alone⁴. It does not appear, however, that there were substantially more macroscopic tumors (that is, metastases) under these conditions, suggesting that there was increased dissemination of cancer cells, but not necessarily increased metastasis. Notwithstanding this crucial nuance, the data are potentially noteworthy because more disseminated cells should, in theory, translate into increased metastasis. Unfortunately, the measurement of an increased amount of circulating cancer cells has not always correlated with the development of metastasis¹³.

Another minor experimental caveat to the Karnoub *et al.*⁴ study is that they did not test whether the observed high rate of dissemination would occur if the tumor cell injections were done at an orthotopic site (such as a mammary fat pad), where the extracellular milieu is unique and tissue architecture may affect the behavior of the injected cells¹⁴.

Unlike the MSCs in the Karnoub *et al.*⁴ study, stem cells are not always protumorigenic and prometastatic. Khakoo and colleagues showed that MSCs have antitumor effects against Kaposi's sarcoma¹⁵. The knowledge that MSCs localize to sites of tissue injury (as would occur when tumor cells remodel the extracellular matrix) and may have antitumor effects has led many groups to try using MSCs as an anticancer therapy. Whether MSC therapy would apply to all tumor types is unknown. But the data from Karnoub *et al.*⁴ suggest that care should be taken to watch for additional metastases if MSC numbers in the primary tumors are increased.

Ultimately, Karnoub *et al.*⁴ have resurrected the idea of a transiently metastatic cell state and have proposed a potential molecular mechanism. At first glance, the existence of temporarily metastatic cells would seem to undermine the overwhelming body of data supporting a genetically stable metastatic phenotype¹. That conclusion, however, would be overstated. Some tumor cells may be more effective at manipulating host cells to do their bidding at various steps of the metastatic cascade, including the colonization of ectopic tissues. The Karnoub *et al.*⁴ report contributes to the many studies that show how metastatic cells compensate for intrinsic defects or supplement essential pathways by taking advantage of stem cells to assist them in various steps of the metastatic cascade (Fig. 1).

The 'take-home' message from all of these studies is that the most lethal attributes of tumor cells are not going to be neutralized if the research community blindly looks only at the tumor cell or only at the stroma—the interactions between the two are crucial. Although the complexity of these interactions is daunting, the silver lining is that stem cells may provide

researchers with new targets to focus future therapies on. Just as importantly, some of the dusty hypotheses related to mechanisms of metastasis should be revisited because of this new understanding of cellular interactions. As neoplastic cells evolve toward aggressive metastatic behavior, a missing link may now be found in the recruited cell populations.

References

1. Fidler IJ. *Nat New Biol* 1973;242:148–149. [PubMed: 4512654]
2. Thiery JP, Sleeman JP. *Nat Rev Mol Cell Biol* 2006;7:131–142. [PubMed: 16493418]
3. Ling V, Chambers AF, Harris JF, Hill RP. *J Cell Physiol Suppl* 1984;3:99–103. [PubMed: 6589232]
4. Karnoub AE, et al. *Nature* 2007;449:557–563. [PubMed: 17914389]
5. Rafii S, Lyden D. *Nat Med* 2003;9:702–712. [PubMed: 12778169]
6. Kaplan RN, et al. *Nature* 2005;438:820–827. [PubMed: 16341007]
7. Bissell MJ, Radisky D. *Nat Rev Cancer* 2001;1:46–54. [PubMed: 11900251]
8. Kitamura T, et al. *Nat Genet* 2007;39:467–475. [PubMed: 17369830]
9. Welch DR, Schissel DJ, Howrey RP, Aeved PA. *Proc Natl Acad Sci USA* 1989;86:5859–5863. [PubMed: 2762301]
10. Gorelik E, Wiltout RH, Brunda MJ, Holden HT, Herberman RB. *Int J Cancer* 1982;29:575–581. [PubMed: 7095902]
11. Carmeliet P, Jain RK. *Nature* 2000;407:249–257. [PubMed: 11001068]
12. Eccles SA, Welch DR. *Lancet* 2007;369:1742–1757. [PubMed: 17512859]
13. Christiano AP, Yoshida BA, Dubauskas Z, Sokoloff M, Rinker-Schaeffer CW. *Urol Oncol* 2000;5:217–223. [PubMed: 10973711]
14. Weaver VM, Gilbert P. *J Cell Sci* 2004;117:1287–1290. [PubMed: 15020668]
15. Khakoo AY, et al. *J Exp Med* 2006;203:1235–1247. [PubMed: 16636132]

Figure 1.

Bone marrow-derived stem cells have multiple roles in assisting or regulating cancer metastasis. Mobilization of stem cells (blue cells), 1, including hematopoietic or mesenchymal stem cells, is stimulated by tumor cells (yellow cells) through as yet unknown mechanisms. Stem cells have been shown to contribute to angiogenesis, 2, local invasion, 3, and formation of the 'premetastatic niche', 4. Mesenchymal stem cells (MSCs) are recruited to sites of tissue injury, such as that induced by tumor cell modification of the extracellular matrix. Various stem cell populations can potentially complement multiple steps of the metastatic cascade via paracrine or juxtacrine signals.