The Road to Metastasis: A Brief Prospective

Richard J Ablin
PhD, DSc (hon)
Associate Editor
E: ablinrj@email.arizona.edu

The majority of deaths in cancer are not from the primary tumour, but from metastasis affecting vital organs. The dogma is that metastasis is a complex multistep linear process culminating in extravasation and colonisation of secondary sites. Current thinking, prompted by the identification of cancer stem cells (CSCs), challenges the dogma and suggests CSCs can self-renew, proliferate, differentiate and even revert back to a stem cell state; they can produce metastatic cells at unexpected stages of disease, ergo, they can arise from transformation of their normal counterparts.

Irrespective of the process of metastasis, epithelial-to-mesenchymal transition (EMT) has a pivotal role. EMT may best be described as a cellular process whereby polygonal appearing epithelial cells acquire a mesenchymal phenotype with a spindly-fibroblastic-like cell morphology with reduced adhesion, increased motility and greater invasivesness [1]. EMT is required for normal embryonic development, organ differentiation and functioning. However, in accord with Grant and Kyprianou [2] EMT is "hijacked" in cancer, by mechanisms that initiate tumour development and progression. This results from transcriptional reprogramming of abnormal survival signals by growth factor receptors affecting the regulation of apoptosis and cytoskeletal organisation [2]. Some of the major factors, beyond specific consideration in this brief commentary, include E-cadherin, β-catenin, TGF-β, Snail, Slug, Twist and Wnt.

While these and other factors have multifaceted and interactive roles, Wnt signaling, for example, is involved in the induction of normal physiological processes, but when it becomes aberrantly activated in carcinogenesis, it induces EMT in tumour cells; it thereby links CSCs and the initiation of EMT – 2 important components in tumour progression [3].

EMT may reflect the ultimate adaptation of cancer cells to survive cytotoxic drugs, thus being responsible for chemoresistance. Given the importance of EMT and its signals initiating tumours and their progression, they conceivably are an ideal target for therapeutic intervention. Hypothetically, such therapeutic approaches might prevent tumour invasion and inhibit metastasis if applied early in tumour growth. However, we are faced with at least 2 conundrums: (i) pathologists rarely see EMT in cancer tissues, wherein invading cells appear epithelial rather than mesenchymal, and usually do not express stem cell markers [4]; and (ii) as yet there is no therapeutic approach that specifically targets EMT, EMT-associated cancer cell migration or invasion [5]. However, Glackin [6] has suggested that targeting EMT by inhibiting Twist and Wnt signaling pathways that mediate EMT may sensitise select cells to further other treatments.

Given the foregoing, the question is whether CSCs arise from the transformation of their normal counterparts producing metastatic cells, rather than from fully differentiated cells through an adaptive trans-differentiation process *ergo*, EMT, then targeting signals promoting EMT and/or EMT-associated cancer cell migration or invasion, may reasonably be insufficient. A *caveat* here will be if cells with an EMT phenotype share molecular characteristics with CSCs; some consider they do, e.g., in epithelial ovarian cancer [7], whereas others opine, for the most part, that they do not [4]. ●

REFERENCES

1. Thiery JP. *Epithelial-mesenchymal transitions in tumour progression.* Nat Rev Cancer 2002;2:442-54.
2. Grant CM, Kyprianou N. *Epithelial mesenchymal transition (EMT) in prostate growth and tumor progression.* Transl Androl Urol 2013;2:202-11.
3. Brabletz T, Jung A, Spaderna S et al. *Migrating cancer stem cells –an integrated concept of malignant tumour progression.* Nat Rev Cancer 2005;5:744-9.
4. Gavert N, Ben-Ze'ev A. *Coordinating changes in cell adhesion and phenotype during EMT-like processes in cancer.* F1000 Biol Rep 2010;2:86.
5. Tiwari N, Gheldof A, Tatari M, Christofori G. *EMT as the ultimate survival mechanism of cancer cells.* Sem Cancer Biol 2012;22:194-207.
6. Glackin CA. *Targeting the Twist and Wnt signaling pathways in metastatic breast cancer.* Maturitas http//dx.doi.org/10.1016/j.maturitis.2014.06.015.
7. Bagnato A, Rosano L. *Understanding and overcoming chemoresistance in ovarian cancer: Emerging role of endothelin axis.* Curr Oncol 2012;19:36-8.