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PREFACE

Soiling the Seed: Microenvironment and Epithelial Mesenchymal Plasticity

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In the past decade we have come to appreciate that the microenvironment has the potential for major influence on the cancer cell. An extreme case for this occurs when the cancer cell changes its environment in the context of metastasis 1, where this may in part underpin the altered biology of cells in metasases. Increasing evidence suggests that changes in the cellular microenvironment contribute to tumourigenesis and metastasis, but the molecular basis of these alterations is not well understood. Reactive stroma provides oncogenic signals to facilitate tumourigenesis and metastasis—co-implantation of normal human epithelial cells *in vivo* with irradiated 2, carcinogen treated 3, 4, or cancer derived fibroblasts 5 leads to the enhancement or formation of malignant tumours 5, 6.

Epithelial mesenchymal plasticity (EMP) is used by normal cells to migrate through the body and facilitates comprehensive tissue remodelling in a non-malignant context7. Cumulative evidence shows that cancers often employ this continuum in a mutation free setting, where it exhibits critical features related to an advanced and lethal cancer phenotype. Epithelial mesenchymal transition (EMT) allows otherwise sessile cells to change their shape, motility, survival, and colony formation potential, all consistent with the assignment of EMT as synonymous to Breast Cancer Stem Cells (BCSC)8. First, through EMT, stationary cells become highly motile and invasive, and can spread to other parts of the body to recolonise into new tissues. Second, EMT endows resistance to therapeutic killing with various insults such as chemotherapy and radiotherapy 8–10, and improves survival in the face of a lack of oxygen 11, integrin signaling 12 or adverse mechanical stress—ultimately it promotes single cell survival. Pathways activated by EMT are now known to drive cell cycle regulation, resistance to apoptosis and avoidance of senescence 13, and may even influence early stage carcinogenesis 14, with implications far beyond (or actually before) the deadly steps of invasion and metastasis. Consequently, EMT is key to the third stage of metastasis, initiation of nascent colonies, following inoculation with small cell numbers, which likely happens after chemotherapy and at the outset of a novel metastatic lesion8.

Consistent with all these features, markers of EMT/BCSCs biology characterise malignancies with worse prognosis. Moreover, as in some abstract level, tumour initiation and carcinogenesis could be seen as similar to an emerging metastatic lesion, dramatically affected by the epithelial EMP (Dubinett, this issue). Recently, the phenotype of cancer stem cell was shown to be under dynamic regulation by the microenvironment 15–17. Similarly, a critical step in the expansion of micrometastatic lesions, which requires cell proliferation, often involves a reverse transition (MET, Wells, this issue). Korpal *et al* 18 recently showed that major EMT drivers such as the transcriptional repressors of E-cadherin like Twist 1/2, Snail 1/2, and Zeb 1/2 are susceptible to cell-cell interaction through EMT-related secretion of proteins like IGFBP4, Tinagl1, and others proteins, which modify metastatic niche formation. Versican production from

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bone marrow-derived cells can also condition the pre-metastatic niche by promoting MET 19. Thus in a Ying-Yan perspective, the grow (epithelial) or go (mesenchymal) dynamics are encompassed in EMP.

Perhaps an objective justification for skepticism of the physiological relevance of EMP comes from the difficulty in detecting epithelial mesenchymal transition of the tumour component *in vivo* in the context of extensive background of stromal mesenchymal gene expression. Novel xenograft analysis tools for Affymetrix *all exon* arrays (Haviv, Purdom, Thompson, unpublished) or RNA-Seq data20, taking advantage of species-specific differences in RNA sequence, will allow such detection. An additional basis for critics of EMP questioned the way EMP presents itself *in vivo*—a stochastic event that would lead to such a coordinated change in many genes at once seemed unlikely. Two hallmarks of wound healing were first appreciated as regulating EMP. First, extracellular remodelling involving proteinases such as MMP3 that can drive EMT 21 involves acute change in the extracellular matrix density, and other mechanical cues, which we now know also control EMP (Nelson, this issue). The second appreciated stromal change is senescent stroma. Consequent to transient proliferative signal of cytokines in the wound healing tissue, and accentuated in a series of chronic inflammatory challenges, the stromal cells exhaust their proliferative license. A significant illumination on this process is that senescent cells become secretory of a number of inflammatory chemokines, which in turn regulate EMP (Desprez, this issue). However, a deeper appreciation of the role of EMP in normal epithelial response to wound healing, combined with the long appreciated notion that cancer microenvironment is constantly in the state of wound healing, suggest that the missing signal for EMP regulation should be sought in the microenvironment. In this model, changes that EMP provides to cancer cells *per se*, such as blocking cell death, increasing migration, and decreasing adhesion to other cells and the extracellular matrix, are consequences of the famous "wound that never heals" nature of cancer. Indeed, TGFβ and EGF, the archetypical regulators of EMT, are major products of the tumour fibroblast (Fisher, this issue) and macrophages 22, respectively. The latter is further accentuated by hypoxia (Pantel, this issue), another feature of the primary and metastatic cancer microenvironment that can regulate EMT, with implications for antiangiogenic therapy 11. Another stromal cell type that could regulate EMP, at least in the context of melanoma, are adipocytes (Núñez, this issue), which has implications for malignant phenotype-affecting lifestyles. Advancing our appreciation of the prevalence of EMP in cancer, this special issue addresses a collection of cancer-host interactions, which culminate in EMP regulation. The cancer-host interaction is bidirectional. For example, both cancer cells, as well as stromal fibroblasts and mast cells, control IL-6 effects within the tumor microenvironment (Hugo, this issue).

In summary, different rate limiting steps of cancer cell phenotype, such as EMP and metastasis, are shown here to be intricately linked with the microenvironment. Considering the remarkable coordinate actions of many cell types at once, and considering the series of cell-cell interactions associated with EMP as summarized here, hopefully the next wave of publications in this field would highlight the potential therapeutic avenues that could utilize EMP in the context of microenvironment and in a personalised medicine approach, minimize effect on normal tissue remodelling, and improve the focus of potential treatment against cancer *per se*.

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