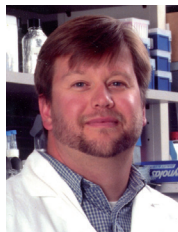


Epithelial–mesenchymal transition in tumor metastasis: a method to the madness



“Dissemination of cancer is not simply a random dispersion of cells, but instead represents an ordered and systematic method to this madness.”

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Were it not for the ability of carcinoma cells to metastasize and colonize distant organs, all solid tumors would present medically as a group of chronic but manageable diseases. There has been significant progress in the understanding of how cancer cells acquire five of the six essential hallmarks proposed for their transformation [1]. Unfortunately, it still remains unclear as to how and when cancer cells acquire the ability to metastasize – that is, the sixth and final hallmark that is responsible for more than 90% of cancer-related mortality [1]. However, it has long been recognized that the dissemination of cancer is not simply a random dispersion of cells, but instead represents an ordered and systematic method to this madness. Indeed, epithelial–mesenchymal transition (EMT) is one such method that has been proposed to initiate the metastasis of carcinoma cells [2].

Epithelial–mesenchymal transition was first recognized as a conserved embryonic and developmental process that facilitates the dispersion of cells that ultimately leads to the generation of distinct tissue types [3]. In undergoing EMT, cells lose their epithelial properties, while acquiring mesenchymal properties that enable transitioned cells to migrate to predetermined destinations [4]. The idea that a similar process is reactivated during tumor progression and other pathologies, including wound healing, tissue regeneration and organ fibrosis, has gained significant ground and acceptance in recent years. Indeed, this fact is readily apparent in the sheer number of publications on this topic, and in the number of EMT-focused sessions and dedicated meetings that have grown exponentially in the last few years. It is now widely accepted that EMT plays an important role during tumor progression and confers certain fundamental abilities to cancer cells that

are essential for tumor metastasis. These include the ability to migrate, resist anoikis and induce immunosuppression [5–7].

The precise contribution of EMT to tumor metastasis is still a subject of considerable debate in the scientific literature [8]. Recent reports of EMT in *in vivo* animal models and human studies [9–12], to a certain degree, have softened the arguments for lack of concrete *in vivo* evidence. However, convincing demonstration of a true phenotypic switch is still yet to come. The other dismissive argument that EMT is simply reflective of genomic instability in cancer cells is also fading in light of increasing numbers of studies reporting EMT that occurs in normal epithelial cells from various organs in response to injury [9,11,13].

Reports of EMT conferring resistance to certain classes of drugs and therapeutic modalities, and correlation of EMT gene signatures with poor outcomes have been described [14–16]. These observations, together with the recent finding that EMT may confer stem cell-like properties to resulting mesenchymal cells [17] have highlighted the clinical relevance of this process. Consequently, several groups, both in industry and academia, are actively pursuing the discovery of novel molecules to target EMT [18].

“...any effort to identify context-specific signals should consider the physiological state of the epithelium in which EMT is taking place – that is, whether it transpires in normal, transformed or injured epithelium...”

Recently, Kalluri and Weinberg proposed to classify EMT into three distinct subtypes based on the biological context in which they

occur [4]. This new terminology was not available at the time the reviews for this special focus issue were accepted for publication, and as such, this classification is not used herein. With the exception of the review by Micalizzi *et al.* [19], the other articles have predominantly discussed what now could be referred to as type III EMT in the new classification system, which is EMT in the context of tumor progression. By contrast, the article by Micalizzi *et al.* describes the regulators of developmental EMT, which now is known as type I EMT in the new classification scheme, and discusses the transcriptional reactivation of type I EMT in the context of type III EMT. Particularly interesting is the discussion of their own work investigating the role of two new players, Six1 and Six4, in the EMT of mouse mammary tumors. Radaelli *et al.* provide a very elegant historical perspective by discussing some of the early descriptions of EMT in mouse tumors [20], some of which date as far back as the year 1854. They also present an interesting comparison of EMT in mouse and human pathologies. A very comprehensive review of the regulatory pathways implicated in TGF- β -induced EMT in normal and malignant cells of the breast is provided in the article by Wendt *et al.* [21], and finally, van Zijl *et al.* [22] review the evidence for EMT in hepatocellular carcinoma and discussed its implications for the treatment of these tumors.

“Given the dramatic changes that take place during EMT, it is wholly reasonable to expect EMT to also elicit powerful alterations within tumor microenvironments, as well as to target the activities and behaviors of various stromal supporting cells.”

Pathways and molecules that distinguish EMT in tumor progression from the other two biological contexts are far from clear. However, any effort to identify context-specific signals should consider the physiological state of the epithelium in which EMT is taking place – that is, whether it transpires in normal, transformed or injured epithelium, and how these unique epithelial states impact the functional consequences of the resulting EMT. Indeed, the vast majority of EMT studies to date have solely focused on assessing the functional consequences of EMT in solely altering the behaviors and functions of tumor cells, not their accompanying stromal components. Given the dramatic changes that take place during EMT, it is wholly reasonable to expect EMT to also elicit powerful alterations within tumor microenvironments, as well as to target the activities and behaviors of various stromal supporting cells. Therefore, the implications of EMT on the interactions of tumor cells with their accompanying stromal and microenvironmental components clearly need to be explored in future studies.

Financial & competing interests disclosure

The research work in Keshamouni's laboratory is supported by grants from Flight Attendant Medical Research Institute, NIH (CA132571), and American Cancer Society (CSM-116801). Dr Schiemann is supported in part by grants from the NIH (CA114039 and CA129359), the DOD (BC084651) and the Komen Foundation (BCTR0706967). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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