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EMT in Tumor Metastasis: A Method to the 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 cell acquire the ability to metastasize – *i.e.*, the sixth and final hallmark which is responsible for more than 90 percent of the 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).

EMT was first recognized as a conserved embryonic and developmental process that facilitates the dispersion cells that ultimately lead 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 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, invade and resist anoikis (5,6).

The precise contribution of EMT to tumor metastasis is still a subject of considerable debate in the scientific literature (7). Recent reports of EMT in in-vivo animal models and human studies (8–11), to a certain degree 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

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cancer cells is also fading in light of more and more studies reporting EMT that occurs in normal epithelial cells from various organs in response to injury (8,10,12).

Reports of EMT conferring resistance to certain class of drugs and therapeutic modalities, and correlation of EMT gene signatures with poor outcomes have been described (13–15). These observations, together with the recent finding that EMT may confer stem cell like properties to resulting mesenchymal cells (16) have highlighted the clinical relevance of this process. Consequently, several groups both in the industry and academia are actively pursuing the discovery of novel molecules to target EMT (17).

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 supplement were accepted for publication, and as such, this classification is not used herein. With the exception of the review by Micalizzi et al., the other articles have predominantly discussed what now could be referred to as type III EMT in the new classification system – *i.e.*, EMT in the context of tumor progression. In contrast, the article by Micalizzi et al., describes the regulators of developmental EMT, which now is called 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, Six 1 and Six 4, 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, some of which date as far back as the year 1854. They also presented 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 breast is provided in the article by Wendt et al. lastly, van Zijl et al review the evidence for EMT in hepatocellular carcinoma and discussed its implications for the treatment of these tumors.

Pathways and molecules that distinguish EMT in tumor progression from 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 – *i.e.*, 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 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 the future studies.

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