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Tumor Microenvironment Regulates Epithelial – Mesenchymal Transitions in Mestastasis

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Epithelial to mesenchymal transitions in tumor metastasis

Epithelial to mesenchymal transition (EMT), a key developmental process that evokes in tumor cells, has been intensively studied by cancer researchers in the passed decade. It represents one of major mechanisms by which tumor cells gain critical metastatic features including the enhanced mobility, invasion, and resistance to apoptotic stimuli[1,2]. Moreover, through EMT tumor cells acquire cancer stem cell properties with chemo-resistant and secondary tumor initiating capabilities[3–5]. While the EMT process has been well characterized in tumor cells in culture, there is accumulating evidence that EMT is involved in metastasis *in vivo* as well. Taken the advantages of an intravital imaging technique, Giampieri et al. showed that single breast cancer cells gained mobility for hematogenous metastasis by activating EMT-promoting TGFβ-Smad2/3 signaling[6]. Indeed, EMT was also observed during metastasis in spontaneous tumor models in mice. The disseminated tumor cells in the lung of MMTV-PyMT transgenic mice expressed a mesenchymal marker, FSP-1, suggesting EMT in tumor progression[7]. More recently, direct evidence of EMT was also found in Myc-initiated breast tumors[8] and K-ras mediated pancreatic tumors[9] by using lineage specific tracing strategy.

However, the simple EMT model does not explain the observation that metastatic lesions commonly reassemble the epithelial phenotypes of the primary tumors. EMT in tumor cell seems to be transient — once a metastatic cell has invaded a new tissue, the mesenchymal features melt away. For instance, the disseminated MMTV-PyMT tumor cells shifted back to Fsp-1 negative epithelial phenotype as metastatic lesions grew out[7]. Studies with cancer patient samples also showed that metastases in liver, lung and brain expressed epithelial markers as well as the primary breast tumors did[10,11]. Similarly, liver metastases from prostate cancer showed epithelial morphology in most cases[12]. These observations suggest that tumor cells might have revert back to epithelial phenotype during metastatic lesion growth through mesenchymal to epithelial transition (MET).

MET, as the reversal process of EMT, has been characterized as an essential developmental process especially in the organogenesis of kidney. Despite the observations in clinical studies, the evidence of MET in metastasis is very limited. By using experimental metastasis

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model in mice, we found that tail vein injection of a metastatic breast cancer cells (MDA-MB-231), which showed a mesenchymal phenotype with no detectable E-cadherin expression, resulted in E-cadherin+ metastatic lesions in the lung, indicating MET during metastasis formation[13]. Interestingly, recent studies have suggested that MET play an active promoting role in metastasis as well as EMT does. For instance, miR-200 family that enforces the epithelial phenotype by targeting ZEB1/2[14] was surprisingly found to be pro-metastatic. Overexpression of miR-200s is associated with increased risk of metastasis in breast cancer and promotes metastatic colonization in mouse models[15]. On the other hand, tumor cells that were trapped within mesenchymal stage by constitutive activation of TGF-β/Smad2 signaling, failed to develop into metastatic lesions, although they were capable to disseminate in the secondary organs[6]. Taken together, current data suggests that both EMT and MET processes are critical at different stages of tumor metastasis. Tumor cells need to exhibit EMT/MET plasticity to successfully establish metastatic lesions.

Microenvironmental factors regulate EMT/MET process of tumor cells

The EMT/MET plasticity of tumor cells may be regulated by both intrinsic and extrinsic factors. However, genomic analysis of primary tumors and distant metastases have found high degree of similarity at level of global gene copy numbers, loss of heterozygosity and single nucleotide polymorphism[16–18], indicating that intrinsic genomic alterations is not the driver of EMT/MET cascade during metastasis formation. Instead, it is more likely that the metastatic tumor cells exhibit their EMT/MET plasticity to adapt to the changing microenvironment that they encounter at either primary or secondary site.

In the primary tumor, various types of stromal cells especially BM-derived myeloid cells have significant impact on tumor progression by promoting angiogenesis, modulating immune responses, and enhancing recruitment of more inflammatory cells[19]. Their roles in regulating EMT process have started to be unveiled as well. In a spontaneous melanoma model in mice, the recruited myeloid-derived suppressor cells (MDSCs) have been implicated in the EMT promoting microenvironment by producing TGF-β1 and HGF[20]. In addition, tumor associated macrophages (TAMs) that represent the majority of myeloid cells in primary tumors also promote EMT by producing TGF-β1. Analysis of 491 non-small cell lung cancer patients revealed a positive correlation between TAM densities, EMT marker expression, intraepithelial TGF-β1 level and tumor grade[21]. In a spontaneous pancreatic tumor model, EMT was most abundant at inflammatory foci[9]. Treatment with anti-inflammatory drug (dexamethasone) reduced EMT events and abolished dissemination of tumor cells, suggesting the pro-EMT function of the inflammatory cells.

On the other hand, MET of disseminated tumor cells in the metastatic organ was originally considered to be passive due to the lack of EMT-promoting factors. However, our recent studies suggested that the MET process was also actively regulated by microenvironmental factors[13]. In contrast to the TAM in the primary tumor, CD11b+Gr1+ myeloid progenitor cells are the most abundant myeloid cells in the pre-metastatic lung. Interestingly, by secreting versican, an extracellular matrix protein, the CD11b+Gr1+ myeloid cells induced MET of disseminated tumor cells. Selectively depletion of these myeloid cells by anti-Gr1 antibody, or knockdown versican expression in BM-derived cells retarded the MET process

and further inhibited metastatic lesion growth. This study has further supported the reviving "seed and soil" hypothesis of tumor metastasis and characterized a novel pro-MET, pro-metastatic function of BM-derived myeloid cells. Importantly, the identification of the MET inducer that is specifically derived from these myeloid cells may provide us novel opportunities of targeting the MET process in metastasis.

Perspectives

EMT/MET process represents an important hallmark of cancer that is closely related with metastasis, therefore it is an attractive target for cancer therapy. However, several critical questions still need to be addressed before we can translate the findings that both EMT and MET play equivocal roles in tumor metastasis into efficient therapeutic approaches. First, it is still not clear how universal the EMT/MET cascade is applied by tumor cells during metastasis in individual tumors, and among different tumor types. It has been reported that EMT only occurred in myc-initiated but not T antigen or Neu - initiated spontaneous breast cancers in mice[8]. Moreover, in some circumstances EMT was not required for metastasis, since mice bearing Neu- and PyMT-initiated tumors that lacked any evidence of EMT had significant amount of lung metastasis. Therefore, if EMT/MET process is only be required for metastasis by certain types of tumors, specific markers to identify theses tumors will be critical for the development of targeting therapeutic strategies. Second, since both EMT and MET processes play positive roles in tumor metastasis, therapeutic approaches inhibiting one of them is supposed to activate the other one. This may explain the dual roles of EMT and MET inducers in tumor metastasis and the often controversies reported with EMT or MET targeting strategies. For example, the bone morphogenetic protein 7 (BMP7), one of major TGF-β antagonists *in vivo*, has been shown to inhibit metastasis in some models[22], while it promote metastasis by increasing the anchorage-independent cell growth in other models[23,24]. To identify specific mediators of EMT and MET will provide plausible way to address this dilemma. Our new finding that EMT and MET are regulated by different components in according tumor microenvironment provides unique opportunities to target EMT and MET individually or simultaneously. Given that the initial colonization by disseminated tumor cells has occurred in many patients at the time of primary tumor diagnosis, both EMT and MET process might be activated in different tumor lesions in the same patient. The successful therapeutic strategy need to consider both scenarios.

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