Editorial

Stem Cell INVESTIGATION

Epithelial-mesenchymal transition is predetermined by the epigenetic state of the skin tumor cell of origin

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Epithelial-mesenchymal transition (EMT) signaling has been shown to promote malignancy in epithelial tumors. EMT-targeted therapies may provide new approaches to cancer treatment, hence, understanding the EMT-induction mechanisms is very important. Various types of epithelial cell-derived tumors have different tendencies to induce EMT. Some tumor cells highly express EMT-related genes showing EMT-phenotypes, but other tumor cells express EMT-related genes at a very low level. The factors governing tumor cells, such the EMT-tendency, are largely unknown. Latil and colleagues used skin squamous cell carcinomas (SCCs) mouse models which enabled tracing the cell linage and then they performed chromatin sequencing. They showed that the cell-type-specific chromatin and transcriptional states of cell-of-origin of the tumor affect the EMT-phenotype in primary tumors. Epigenetic properties, including chromatin status and transcriptional profiling, in the SCCs-initiating cells seem to predetermine the EMT-tendency and tumor initiation.

Multipotent or unipotent stem cells, progenitors, and differentiated cells can be the cancer cell of origin. Different cell-of-origin can give rise to tumors having different phenotypes, leading to the generation of heterogeneity in tumors. Such tumor heterogeneity is composed not only of genetic diversity but also phenotypic variation arising from cancer stem cell-based hierarchies and EMT. EMT is a biological process by which polarized epithelial cells lose their polarity and cell-cell adhesion, and gain mesenchymal cell-like phenotypes such as migratory activity and an enhanced production of extracellular matrix (ECM) components. Activation of EMT signals in cancer cells is thought to be associated with cancer invasion, metastasis (1), acquiring stemness (2), and resistance to therapy (3).

The recently developed universal EMT scoring system based on EMT-related gene expression profiles showed that the propensity of EMT differs between cancer types, and furthermore, a wide range of preferences for EMT were observed even in each cancer type (4). According to this scoring system, primarily mesenchymal tumors such as osteosarcoma, neuroblastoma, and glioblastoma show a high and narrow range of scatter plots of the EMT score, but epithelial tumors, so-called cancers, show a variety mean and dispersion of the EMT score. Colorectal cancer has the lowest EMT-rank, whereas the pattern of the EMT score in renal carcinoma is similar to mesenchymal tumors, and other cancers such as bladder, breast, lung, ovarian, and prostate cancers display intermediate mean and wide ranges in the EMT score. What causes such EMT-disposition in cancers? It is believed that the EMT program is triggered by microenvironment factors such as inflammation, macrophages, fibroblasts, and cytokines including transforming growth factor β (TGF-β) (5), and is mediated by the EMT-inducing transcription factors (EMT-TFs) such as Snail, Slug, Twist, ZEB1, and ZEB2 (6). Do only extrinsic factors induce EMT? Latil and colleagues (7) focused on the cancer cell of origin and hypothesized that

EMT-disposition of cancer may reflect intrinsic properties, especially their epigenetic state of the original cell. They used skin SCCs mouse models which enabled tracing the cell linage, and they showed that the cell-type-specific chromatin landscapes and transcriptional states of tumor-initiating cells do affect the EMT-phenotype in primary tumors.

The interfollicular epidermis (IFE) cells and the hair follicles (HF) have been previously identified as the cell of origin of skin SCCs, and it has been demonstrated that oncogenic K-Ras expression combined with p53 deletion in IFE cells as well as in HF lineage leads to the development of different types of invasive SCCs (8). To assess the tumor phenotypes following the same oncogenic mutations, $Kras^{G12D}$, into distinct skin compartments, Latil *et al*. used K14CreER/$KRas^{G12D}$/$p53^{fl/fl}$/Rosa-YFP (K14CreER) mice and Lgr5CreER/$KRas^{G12D}$/$p53^{fl/fl}$/Rosa-YFP (Lgr5CreER) mice. These two transgenic mice developed SCCs by tamoxifen administration. K14CreER targets the IFE and the infundibulum, whereas Lgr5CreER targets HF stem cells and their progeny. The tumors from the K14CreER or Lgr5CreER mice were histologically different. Latil *et al*. found that the SCCs derived from HF are far more prone to undergo EMT and have a greater metastatic potential compared with SCCs derived from IFE. The K14CreER tumors were mostly well-differentiated epithelial SCCs, whereas the Lgr5CreER tumors were heterogeneous; differentiated ($Epcam^+$) SCCs, mesenchymal ($Epcam^-$) SCCs, and mixed SCCs. The mesenchymal components of the Lgr5CreER tumor arose from YFP-labeled tumor cells but not from cancer-associated fibroblasts. They also observed that $Epcam^+$ tumor epithelial cells (TECs) derived from the Lgr5CreER tumors did form mixed tumors containing $Epcam^+$ TECs and $Epcam^-$ tumor mesenchymal cells (TMCs) when they were transplanted into immunodeficient mice. The $Epcam^+$ TEC from the K14CreER tumors and the $Epcam^-$ TMC from the Lgr5CreER tumors formed tumors histologically similar to their primary tumors. These transplanted secondary tumors presented phenotypes of their cell-of-origin. These data indicate that $KRas^{G12D}$ expression and p53 deletion in HF lineages generate SCCs having an intrinsic property to undergo EMT.

Gene ontology of the genome-wide transcriptional analysis revealed that K14 and Lgr5 derived $Epcam^+$ TECs were enriched for transcripts regulating the epithelial state, whereas TMCs were strongly enriched in secreted molecules and ECM components, and TMCs expressed EMT markers such as EMT-TFs, *Vimentin*, *N-cadherin*, *Cadherin 11*, *Col3a1*, and *Fn1*. Interestingly, Latil *et al*. found that 29% of the genes transcriptionally upregulated in TECs were already upregulated in IFE compared to HF, and 27% of the genes upregulated in $Epcam^-$ *vs.* $Epcam^+$ tumor cells already upregulated in HF versus IFE. These results indicate that transcriptional priming affects the tendency of the cancer cell of origin to undergo EMT during skin tumorigenesis. Next, they determined the changes in the chromatin landscape that occur during skin tumorigenesis. They performed Assay for Transposase-Accessible Chromatin sequencing (ATAC-seq) (9) which enabled them to identify the open chromatin regions and the TFs associated with the remodeling of these chromatin regions. ATAC-seq profiles revealed that K14 and Lgr5 tumor-initiating cells possess distinct chromatin landscapes and gene regulatory networks. In addition to core TFs such as AP1, NF1, and Ets, which commonly promote gene expressions involved in tumorigenesis in both TECs and TMCs, and lineage-specific TFs such as p63 and Klf in TECs, and HLHs and Smad2 in TMCs, which regulate each tumor-phenotype specific gene expression. Lgr5 TECs were sensitive to TGFβ-induced EMT, but K14 TECs were resistant to TGFβ-induced EMT, suggesting that the EMT signal is suppressed in K14 TECs. Lgr5 TECs overexpressing p63 were much more resistant to TGFβ-induced EMT as compared to Lgr5 TECs. Latil *et al*. finally showed that p63 regulates the epigenetic and transcriptional priming of the cancer cell of origin toward well-differentiated SCCs.

EMT in cancer cells has been associated with invasion and metastasis, stemness, and resistant to therapy, and it has been reported recently that EMT also occurs in the early stage of tumorigenesis (2). Latil and colleagues showed that the intrinsic epigenetic state of tumor-initiating cell affects undergoing EMT, which promotes the metastatic potential of tumor cells. These data suggest that the cell-type-specific chromatin and transcriptional states of cell-of-origin of the tumor affect the EMT-phenotype in primary tumors. Epigenetic properties, including chromatin landscapes and gene regulatory networks, in the cell-of-origin of skin SCCs would seem to predetermine the EMT-tendency and tumor phenotypes. It is further necessary to define the relationships between EMT and the epigenetic states of cell-of-origin of other epithelial cell-derived tumors such as breast cancer, prostate cancer, lung cancer, and etc.

Latil *et al*. tried to focus on the intrinsic factors which induce EMT in tumor cells, but their experiments did not

exclude the influence of microenvironmental factors. The changes in gene expression and the epigenetic landscape of tumor cells can also occur as a consequence of regulatory signaling arising from the microenvironment and other extrinsic factors. We need to further understand the mechanisms relating to how the EMT-phenotype is induced in the tumor tissues of cancer patients during progression and/or after therapies. Furthermore, we know that some EMT-TFs, such as Snail, Slug, Twist, ZEB1, and ZEB2 play roles in regulating epigenetic factors, including HDACs, PRC1/2 components, and etc. (10), so further clarification of the molecular mechanism of epigenetic remodeling in cancer cells during EMT is essential.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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