Editorial

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# Cancer cell of origin controls epithelial-to-mesenchymal transition in skin squamous cell carcinoma

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Epithelial-to-mesenchymal transition (EMT) of cancer is a process wherein epithelial tumor cells lose their differentiated characteristics, such as cell-cell adhesion and apical-basal polarity, and acquire a more motile mesenchymal and invasive/metastatic phenotype (1-3). Although, a minor population of cancer cells acquires EMT, which reflects the intrinsic properties of their cell of origin, the cell of origin of EMT in cancer is largely unknown. The identification of the cell type and the molecular signaling alterations that lead to the EMT process will provide new insights into the regulation of tumor heterogeneity and possible therapeutic interventions(4-6).

Latil and colleagues (7) in the recent issue of *Cell Stem Cell* provides insights into the regulatory process in the cancer cell of origin, promotes and or restricts EMT in primary skin tumors. Latil and colleagues (7) generated mouse models of skin squamous cell carcinoma (SCC) to demonstrate whether the cancer cell of origin controls EMT. SCCs, an ideal model to investigate the origin of EMT, because the skin epidermis is composed of spatially distinct cell lineages including the interfollicular epidermis (IFE), the hair follicle (HF). The tumor phenotypes following KRasG12D expression and p53 deletion either in the IFE using K14CreER mice, preferentially targets the IFE and the infundibulum or in HF using Lgr5CreER mice. Authors observed that HF-originated tumors are favorably primed to undergo EMT as compared to IFE-originated tumors. FACS sorted HF-originated tumor cells shows two types of cells, tumor epithelial cells (TECs) and tumor mesenchymal cells (TMCs). Transplantation study also shows that a single tumor Epcam+ TECs gives rise to a mixed tumor population contains TECs and TMCs, indicate that the cancer cell of origin influences the intrinsic ability of tumor-initiating cells to undergo EMT.

Authors performed microarray analyses in the FACS-isolated YFP+ Epcam+ and Epcam– tumor cells arising from IFE and HF lineages and followed by genome-wide analysis with confirmative quantitative analysis suggested that HF-originated tumors are intrinsically transcriptionally primed to undergo EMT. Furthermore, Gene set enrichment analysis (GSEA), displayed a strong enrichment of IFE genes within the TEC signature and of HF genes within TMC signature supporting their concept that transcriptional priming controls the ability of the cancer cell of origin to acquire EMT during tumorigenesis. Authors found that the primary difference in the expression of genes between IFE and HF lineages determine the acquiescence of EMT. For example IFE lineages are well-differentiated tumors comprised transcription regulators of epidermal differentiation such as Grhl1/3, Cebpa, Klf5, Ovol1, and Pou3f1. However, HF lineages and that are associated with EMT included well-known HF markers such

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as Ltbp2, Grem1, Flstl1, S100A4, Nfatc1, Tbx1, Tcf4, Tcf7l1, and Ctgf. These findings provide support that (I) the transcriptional priming in the HF-lineages is associated with EMT, (II) cancer cell of origin is promoting and restricting EMT in SCCs and (III) EMT tumor cells are highly efficient in secondary tumor formation. However, enhanced tumor metastatic ability of TMCs is unclear and the secondary tumors formed from TMCs *in vivo* are not well recognized with transcriptional alterations priming for metastasis.

The next question asked was how the transcriptional priming in the cell types is regulated in SCCs? Authors identify the critical changes in the chromatin landscape during cancer initiation and EMT process in primary skin SCCs, which provides a novel insight into the mechanism of EMT regulation during tumorigenesis. Tansposase-Accessible Chromatin sequencing assay (ATAC-seq) to map the open chromatin regions on FACS-isolated HF (TECs and TMCs) and IFE consistently showed an upregulated 477 genes with open chromatin regions, irrespective of different tumor population, representing the common genetic alterations occurred in tumor initiation regardless of cancer cell of origin and EMT. Furthermore, motif enrichment analysis of the chromatin regions that opened during tumorigenesis revealed a strong enrichment for the binding site of transcriptional factors such as Jun/AP1 (65%), Ets1 (37%), Runx (29%), Nf-kb (22%), and TEAD (25%). However, open chromatin site for EMT genes Sanil1 and Zeb2 was identified in the HF-TECs, despite the lack of protein expression supporting the notion that the EMT program is epigenetically primed in TECs.

GSEA and gene regulatory network (GRN) analysis between TECs and TMCs from HF tumors revealed that the opening and closing of chromatin is regulated by transcriptional factor motifs regulating EMT on and/or off in primary skin tumors. Thus the motifs with significant upregulation during EMT in TMCs are Jun/AP1 (42%), NF1 (45%), Ets1 (10%), bHLH TFs (20–45%), Nfatc (27%), and Smad2 (37%). Transcriptional factors binding these motifs that are most significantly upregulated in TMCs are Runx1/2, Nfatc1/2, Twist1/2 and Tcf4. Interestingly authors found that the common motifs between IFE and Epcam+ TECs, significantly upregulated during tumorigenesis are Jun/AP1 (58%), p63 (43%), and Klf (22%), suggesting that p63 and Klf5 transcriptional factors contribute to the epigenetic priming to give rise to well-differentiated tumors without EMT initiation upon oncogenic transformation (8). Silencing KLF5 and/or p63 in TECs resulted in the loss of key epidermal factors (Grhl2, Cepba, and p63) and epithelial markers (Ecadh, K5), and thus results in undifferentiated tumors. Finally p63 was overexpressed or silenced in the tumor cells of IFE and TECs to understand its importance regulating TGF-b induced EMT. Authors observed that loss of p63 enhanced TGF-b induced EMT, whereas as gain of p63 opposes TGF-b induced EMT. The data generated and presented by the authors are remarkable and very interesting, although the significance of paracrine, endocrine and autocrine signals in tumor initiation and EMT in SCCs is unclear (9,10). The complexity of the tumor microenvironment and their secreted factors activating EMT in cancer cell of origin, required to be investigated.

The study provides intriguing evidence that p63 functionally acts as a regulator of HF-TECs fate and mediates the IFE cancer cell of origin into well-differentiated SCCs.

Despite the fact that the current therapeutic inhibition of EMT is not effective in impeding tumor metastasis, the control of p63 and/or p63 plus adjuvant therapeutic strategies might help to prevent EMT and associated metastasis, self-renewal, and therapy resistance.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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