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C/EBPα is crucial determinant of epithelial homeostasis by preventing epithelial-to-mesenchymal transition

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Extracellular signals such as transforming growth factor beta (TGF-β) have been shown to influence both tumor initiation and metastasis. TGF-β has been demonstrated to induce epithelial-to-mesenchymal transition (EMT) in cancers of epithelial origin by promoting molecular and phenotypical changes resulting in pro-metastatic characteristics. Using global RNA-sequencing analysis, we identified CCAAT/enhancer binding protein alpha (C/EBPα) as one of most TGF-β-mediated downregulated transcription factors in human mammary epithelial cells. Here, we show that upon TGF-β pathway activation, SMAD3 binding to the *CEBPA* locus is enriched while SMAD3-knockdown cells fail to repress *CEBPA* expression. Constitutive C/EBPα expression impaired TGF-β-driven EMT by inhibiting the expression of known EMT factors including N-cadherin, MMP-2 or ZEB1, and by maintaining E-cadherin expression. Conversely, depletion of C/EBPα expression alone was sufficient to induce mesenchymal-like morphology and molecular features. Moreover, cells that had undergone TGF-β-induced EMT reverted to an epithelial-like state upon C/EBPα re-expression. TGF-β-mediated disruption of epithelial spheroids architecture could also be rescued by the introduction of C/EBPα. By using an established mouse model of breast cancer EMT-driven metastasis, we show that mice injected with tumor organoids constitutively expressing C/EBPα display a dramatic reduction of metastatic lesions in their lungs compared to controls. Taken together, these results show that C/EBPα is required for maintaining epithelial homeostasis by repressing the expression of key mesenchymal markers, thus preventing EMT-mediated tumorigenesis. These data suggest that C/EBPα is an epithelial "gatekeeper" whose expression is required to prevent unwarranted mesenchymal transition, thereby supporting an important role for EMT in mediating breast cancer metastasis.

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