Ets1 and ESE1 reciprocally regulate expression of ZEB1/ZEB2, dependently on ERK1/2 activity, in breast cancer cells

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The epithelial–mesenchymal transition (EMT) is a crucial morphological event that occurs during progression of epithelial tumors. We reported previously that levels of the EF1 family proteins (ZEB1/ EF1 and ZEB2/SIP1), key regulators of the EMT, are positively correlated with EMT phenotypes and aggressiveness of breast cancer. Here, we show that Ets1 induces ZEB expression and activates the ZEB1 promoter, independently of its threonine 38 phosphorylation status. In the basal-like subtype of breast cancer cells, siRNAs targeting Ets1 repressed expression of ZEBs and partially restored their epithelial phenotypes and sensitivity to anti-tumor drugs. ESE1, a member of the Ets transcription factor family, was originally characterized as being expressed in an epithelial-restricted pattern, placing it within the epithelium-speci c ETS subfamily. ESE1, highly expressed in the luminal subtype of breast cancer cells, was repressed by activation of MEK-ERK pathway, resulting in induction of ZEBs through Ets1 upregulation. Conversely, Est1, highly expressed in the basal-like subtype, was repressed by inactivation of MEK-ERK pathway, resulting in reduction of ZEBs through ESE1 upregulation. ese ndings suggest that ESE1 and Ets1, whose expressions are reciprocally regulated by MEK-ERK pathway, de ne the EMT phenotype through controlling expression of ZEBs in each subtype of breast cancer cells.

Biography

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