Targeting ELF3-dependent transcription for cancer therapeutics

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Abstract

The transcription factor E74-like factor 3 (ELF3) is inactivated in a range of cancers, including biliary tract cancer. Here, we investigated the tumor-suppressive role of ELF3 in bile duct cells by identifying several previously unknown direct target genes of ELF3 that appear to be implicated in biliary duct carcinogenesis. ELF3 directly repressed ZEB2, a key regulator of epithelial-mesenchymal transition, and upregulated the expression of cingulin, an integral element in lumen formation. Loss of ELF3 led to decreased cell-cell junctions and enhanced cell motility. *ALOX5* and *CXCL16* were also identified as additional direct targets of ELF3; their corresponding proteins 5-lipoxygenase and CXCL16 play a role in the immune response. Conditioned medium from cells overexpressing ELF3 significantly enhanced the migration of natural killer cells and $CD8^+$ T cells toward the conditioned medium. In a biliary tract cancer xenograft model, activation of ELF3 increased expression of ELF3-related genes, enhanced the tubular structure of the tumors, and led to a loss of vimentin. Overall, our results indicate that ELF3 is a key regulator of both epithelial integrity and immune responses in biliary tract cancer.

Background & Results

ELF3 belongs to the E26 transformation-specific family of transcription factors, which plays crucial role in the regulation of homeostasis in epithelial tissues. We had identified *ELF3* with loss-of-function mutations as a novel driver gene in approximately 11% of ampullary carcinomas, implying that it has an inherent tumor suppressor role. Conversely, the amplification and overexpression of *ELF3* have been reported in breast, prostate, colorectal, and lung cancers. Hence, further studies are needed to resolve this apparent contradiction. In the present study, we investigated the tumor suppressive role of ELF3 in normal bile duct epithelial cells, and identified novel direct ELF3 targets through a combination of ChIP-Seq and comprehensive transcriptome analyses. Our results indicate that ELF3 is required for the maintenance of epithelial morphology via the direct negative regulation of ZEB2 and the positive regulation of cingulin in bile duct cells. ELF3 also directly up-regulates the expression of 5-lipoxygenase and CXCL16, and ELF3-deficient cells may escape the attention of immune cells. These findings suggest that the loss of ELF3 is implicated as a driving force for early-onset and progression of disease with epithelial-mesenchymal transition through dampening of host immune defenses in the initial stages of tumor development.

Significance of the research and Future perspective

ELF3 regulates epithelial integrity and host immune responses and functions as a tumor suppressor in biliary tract cancer. Recently, ELF3 and cofactors were identified as an oncogenic super-enhancer in esophageal adenocarcinomas, which strongly drives oncogenic transcription. While further studies will be needed to clarify the tumor suppressive or oncogenic roles of ELF3 in different organ systems, ELF3-dependent transcription might be a driver for cancer progression.

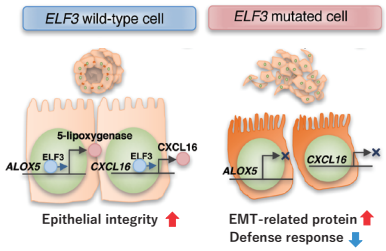

Figure 1: ELF3 regulates cell motility and tumor immunity
ELF3 regulates epithelial integrity and host immune responses and appears to function as a tumor suppressor in biliary tract cancer.

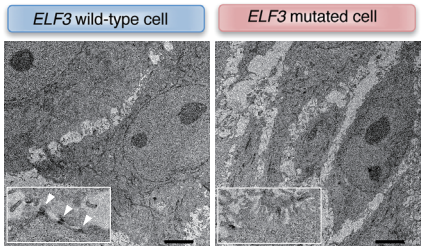

Figure 2: Loss of ELF3 induces the disassembly of cell-cell junctions.
Ultrastructural examination by transmission electron microscopy showed an increased abundance of microvilli in monolayer cultures of *ELF3*-deficient cells, with fewer cell-cell junctions compared to wild-type cells. Arrowheads indicate cell-cell junctions. Scale bars, 5 μm.

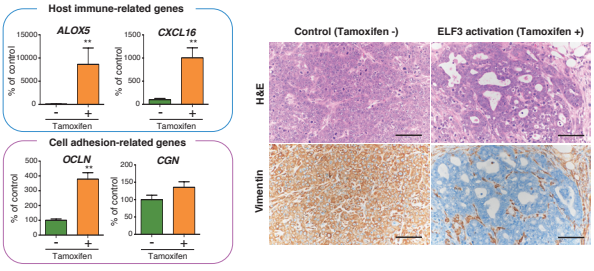

Figure 3: ELF3 activation changes expression of ELF3-related genes in xenograft tumor.
(Left) The elevated expression of ELF3 target genes, *ALOX5* (encoding 5-lipoxygenase), *CXCL16* (encoding C-X-C motif chemokine ligand 16), *OCLN* (encoding occludin) and *CGN* (encoding cingulin), was observed in tamoxifen-treated $HBDEC2^{ELF3-/-}$ EMR ELF3-ERT2 xenograft tumors. (Right) The tubular structure with loss of vimentin was apparently increased in ELF3-activating xenograft tumors.

Patent

Treatise Suzuki, Masami; Saito-Adachi, Mihoko; Arai, Yasuhito et al. E74-like factor is a key regulator of epithelial integrity and immune response genes in biliary tract cancer. Cancer Research. 2021; 82(2): 489-500. doi: 10.1158/0008-5472.CAN-19-2988
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Keyword ELF3, transcription factor, cancer