ZEB1

Zinc finger E-box-binding homeobox 1 is a protein that in humans is encoded by the ZEB1 gene.

ZEB1 (previously known as TCF8) encodes a zinc finger and homeodomain transcription factor that represses T-lymphocyte-specific IL2 gene expression by binding to a negative regulatory domain 100 nucleotides 5-prime of the IL2 transcription start site.

ZEB1 and its mammalian paralog ZEB2 belongs to the Zeb family within the ZF (zinc finger) class of homeodomain transcription factors. ZEB1 protein has 7 zinc fingers and 1 homeodomain.

Sakamoto et al. previously reported that ETS1 induces expression of the ZEB family proteins ZEB1/δEF1 and ZEB2/SIP1, which are key regulators of the epithelial-mesenchymal transition (EMT), by activating the ZEB1 promoters. They have found that the EHF gene produces two transcript variants, namely, a long-form variant that includes exon 1 (EHF-LF) and a short form variant that excludes exon 1 (EHF-SF). Only EHF-SF abrogates ETS1-mediated activation of the ZEB1 promoter by promoting the degradation of ETS1 proteins, thereby inhibiting the EMT phenotypes of cancer cells. Most importantly, they identified a novel point mutation within the conserved ETS domain of EHF and found that EHF mutations abolish its original function while causing the EHF protein to act as a potential dominant-negative, thereby enhancing metastases in vivo. Therefore, they suggest that EHF acts as an anti-EMT factor by inhibiting the expression of ZEBs and that EHF mutations exacerbate cancer progression [1].

In multiple cancers, ZEB1 serves as a transcription activator to regulate gene expression.

Jiang et al. from the China-Japan Union Hospital of Jilin University, Changchun, China, explored the roles of ZEB1 in HBXIP-induced breast cancer growth.

HBXIP regulation of ZEB1 was evaluated by reverse transcription PCR and immunoblotting. The stimulation of ZEB1 promoter by HBXIP and/or Sp1 was tested using luciferase reporter gene analysis. The alteration of cell proliferation mediated by HBXIP-induced ZEB1 was tested using methyl-thiazolyl-tetrazolium and 5-Ethynyl-2'-deoxyuridine (EdU) incorporation analysis. ZEB1 and HBXIP expression in human breast cancer tissues was analyzed using quantitative real-time PCR. The relationship between HBXIP and ZEB1 was confirmed by Pearson's correlation coefficient.

They observed dose-dependent upregulation of ZEB1 by HBXIP in breast cancer cells. HBXIP can activate the ZEB1 promoter by interacting with transcription factor Sp1. Cell viability and EdU incorporation analysis showed that HBXIP could drive cell proliferation by enhancing ZEB1 in breast cancer. Using quantitative real-time PCR, ZEB1 overexpression and a positive relationship between ZEB1 and HBXIP were observed in clinical breast cancer samples.

Oncogenic HBXIP controls the transcription regulation of ZEB1 by co-activating Sp1, thereby accelerating breast cancer growth [2].

1)
Sakamoto K, Endo K, Sakamoto K, Kayamori K, Ehata S, Ichikawa J, Ando T, Nakamura R, Kimura Y,

Yoshizawa K, Masuyama K, Kawataki T, Miyake K, Ishii H, Kawasaki T, Miyazawa K, Saitoh M. EHF suppresses cancer progression by inhibiting ETS1-mediated ZEB expression. Oncogenesis. 2021 Mar 12;10(3):26. doi: 10.1038/s41389-021-00313-2. PMID: 33712555.
2)

Jiang Y, Wang D, Ren H, Shi Y, Gao Y. Oncogenic HBXIP enhances ZEB1 through Sp1 to accelerate breast cancer growth. Thorac Cancer. 2018 Oct 1. doi: 10.1111/1759-7714.12878. [Epub ahead of print] PubMed PMID: 30273966.