

ATF4

This [gene](#) encodes a [transcription factor](#) that was originally identified as a widely expressed mammalian DNA binding protein that could bind a tax-responsive enhancer element in the LTR of HTLV-1. The encoded protein was also isolated and characterized as the cAMP-response element binding protein 2 (CREB-2). The protein encoded by this gene belongs to a family of DNA-binding proteins that includes the AP-1 family of transcription factors, cAMP-response element binding proteins (CREBs) and CREB-like proteins. These transcription factors share a leucine zipper region that is involved in protein-protein interactions, located C-terminal to a stretch of basic amino acids that functions as a DNA-binding domain. Two alternative transcripts encoding the same protein have been described. Two pseudogenes are located on the X chromosome at q28 in a region containing a large inverted duplication.

ATF4 transcription factor is also known to play role in osteoblast differentiation along with RUNX2 and osterix.

Terminal osteoblast differentiation, represented by matrix mineralization, is significantly inhibited by the inactivation of JNK. JNK inactivation downregulates expression of ATF-4 and, subsequently, matrix mineralization.

IMPACT protein regulates ATF4 in *C. elegans* to promote lifespan.

Zielke et al. explored the autophagy-inducing mechanisms that underlie the autophagic cell death (ACD)-triggering compound [loperamide](#) (LOP) in [glioblastoma](#) cells. Interestingly, LOP triggers the upregulation of the transcription factor [ATF4](#), which is accompanied by the induction of additional ER stress markers. Notably, knockout of ATF4 significantly attenuated LOP-induced autophagy and ACD. Functionally, LOP also specifically induces the engulfment of large ER fragments within autophagosomes and lysosomes as determined by electron and fluorescence microscopy. LOP-induced reticulophagy and cell death are predominantly mediated through the reticulophagy receptor RETREG1/FAM134B and, to a lesser extent, TEX264, confirming that reticulophagy receptors can promote ACD. Strikingly, apart from triggering LOP-induced autophagy and ACD, ATF4 is also required for LOP-induced reticulophagy. These observations highlight a key role for ATF4, RETREG1 and TEX264 in response to LOP-induced ER stress, reticulophagy and ACD, and establish a novel mechanistic link between ER stress and reticulophagy, with possible implications for additional models of drug-induced ER stress ¹⁾.

¹⁾

Zielke S, Kardo S, Zein L, Mari M, Covarrubias-Pinto A, Kinzler MN, Meyer N, Stolz A, Fulda S, Reggiori F, Kögel D, van Wijk SJL. ATF4 links ER stress with reticulophagy in glioblastoma cells. *Autophagy*. 2020 Oct 28;1-17. doi: 10.1080/15548627.2020.1827780. Epub ahead of print. PMID: 33111629.

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