FOXD3

- Inhibition of FOXD3 O-GlcNAc Modification Ameliorates Spinal Cord Injury by Promoting STUB1-Mediated Ubiquitination Degradation of HMGB1
- LncRNA FOXD3-AS1 Contributes to Glioblastoma Progression Via Sponging miR-3918 to Upregulate CCND1
- LncRNA FOXD3-AS1/miR-128-3p axis-mediated IGF2BP3 in glioma stimulates cancer angiogenesis and progression
- Mutation-derived, genomic instability-associated lncRNAs are prognostic markers in gliomas
- Prognostic value and immune-infiltration pattern of FOXD3-AS1 in patients with glioma
- Specific gene expression signatures of low grade meningiomas
- LncRNA PVT1 Promotes Neuronal Cell Apoptosis and Neuroinflammation by Regulating miR-488-3p/FOXD3/SCN2A Axis in Epilepsy
- Identification of Key Differentially Expressed Transcription Factors in Glioblastoma

FOXD3 (Forkhead Box D3) is a transcription factor belonging to the forkhead family, characterized by a conserved winged-helix DNA-binding domain. It plays pivotal roles in embryonic development, stem cell regulation, and cancer biology.

Biological Functions

1. Transcriptional Regulation FOXD3 functions primarily as a transcriptional repressor. It contains an engrailed homology-1 (eh1) motif that facilitates interaction with co-repressors like Grg4 (Groucho-related gene-4) to modulate gene expression.

2. Stem Cell Pluripotency In embryonic stem cells (ESCs), FOXD3 is crucial for maintaining pluripotency and regulating the transition from the naïve to primed state. It achieves this by modifying chromatin structures, recruiting histone demethylases, and repressing naïve pluripotency genes, thereby preparing enhancers for future activation.

3. Neural Crest Development FOXD3 is essential in neural crest cell development, influencing the fate decisions between Schwann cell progenitors and melanocytes. It helps maintain neural potential while repressing alternative mesenchymal fates .

Clinical Significance

1. Cancer

FOXD3 exhibits tumor suppressor functions in various cancers:

Colorectal Cancer: Frequently methylated, leading to reduced expression and tumor progression.

Ovarian Cancer: Enhances chemosensitivity through the miR-335/DAAM1/myosin II axis.

Esophageal Squamous Cell Carcinoma: Suppresses epithelial-mesenchymal transition by promoting SMAD7 transcription.

Nasopharyngeal Carcinoma: Inhibits cell proliferation and invasion via the PI3K-Akt pathway .

2. Vitiligo Mutations in FOXD3 have been associated with vitiligo, an autoimmune condition characterized by depigmented skin patches . ZFIN

Molecular Interactions

FOXD3 interacts with various proteins and pathways:

PAX3: Collaborates to regulate CXCR4 expression, influencing melanoma cell behavior.

Histone Modifiers: Recruits histone deacetylases and demethylases to modulate chromatin accessibility.

Long Non-Coding RNAs: FOXD3-AS1, an antisense lncRNA, can regulate FOXD3 expression and has been implicated in cancer progression .

FOXD3 Protein Structure

The FOXD3 protein comprises several domains critical for its function:

Forkhead Domain: Responsible for DNA binding.

Engrailed Homology-1 (eh1) Motif: Facilitates interaction with co-repressors like Grg4.

In a study, the interaction between FOXD3 and the STUB1 promoter was analyzed by dual luciferase reporter gene and ChIP assays. O-GlcNAc modification level was significantly elevated in the cell and animal models of Spinal Cord Injury (SCI). O-GlcNAc modification increased both the protein stability and expression of FOXD3. O-GlcNAc modification inhibition or FOXD3 knockdown reduced oxidative stress damage and apoptosis in H2O2-treated PC12 cells. Moreover, FOXD3 mediated transcriptional inhibition of STUB1, and STUB1 induced HMGB1 ubiquitination and degradation in PC12 cells. STUB1 knockdown or HMGB1 overexpression negated the protective effects of FOXD3 knockdown on H2O2-mediated oxidative stress damage and apoptosis in PC12 cells. Inhibiting the O-GlcNAc modification of FOXD3 alleviated oxidative stress damage and apoptosis in nerve cells to mitigate SCI by enhancing STUB1-induced HMGB1 ubiquitination degradation [1)].

The study provides evidence that FOXD3 functions as a pro-damage transcription factor in SCI, mainly through inhibition of a ubiquitination pathway that normally targets the DAMP molecule HMGB1 for degradation.

 Innovation: This is the first study linking O-GlcNAcylation of FOXD3 to SCI pathology, opening therapeutic windows via post-translational modulation.

⚠ Limitation: The direct clinical implications are still distant. While modulation of O-GlcNAc is

pharmacologically feasible, the off-target effects of global inhibition are a concern. Targeted delivery to spinal neurons or cell-specific modulation would be needed for therapeutic translation.

1)

Zhou W, Hei B, Liu Y, Wang C, Wang C, Ding Z. Inhibition of FOXD3 O-GlcNAc Modification Ameliorates Spinal Cord Injury by Promoting STUB1-Mediated Ubiquitination Degradation of HMGB1. Mol Neurobiol. 2025 Apr 24. doi: 10.1007/s12035-025-04954-x. Epub ahead of print. PMID: 40272767.