ZIP4 signaling pathway

The ZIP4 signaling pathway involves the ZIP4 transporter, a member of the Zrt/Irt-like Protein (ZIP) family encoded by the SLC39A4 gene. ZIP4 plays a central role in zinc uptake, especially in the intestine, but its dysregulation has also been linked to cancer progression, particularly pancreatic cancer and hepatocellular carcinoma.

 Overview of the ZIP4 Signaling Pathway: 1. ZIP4 Function: ZIP4 transports extracellular zinc (Zn^{2+}) into the cytoplasm.

It is upregulated under zinc deficiency.

Located predominantly on apical membranes of intestinal epithelial cells and in cancer cells under pathological conditions.

2. Upstream Regulation: Zinc deficiency or specific transcription factors (e.g., KLF4) can upregulate SLC39A4 gene expression.

Under certain stimuli, ZIP4 can be internalized or stabilized at the membrane.

3. Downstream Signaling Effects: Zinc influx via ZIP4 can activate multiple downstream pathways:

STAT3 (Signal Transducer and Activator of Transcription 3):

Zinc influx leads to STAT3 activation.

This promotes transcription of cell proliferation and survival genes (e.g., cyclin D1, Bcl-2).

CREB (cAMP response element-binding protein):

ZIP4 activation → CREB phosphorylation → transcription of miR-373.

miR-373:

Oncogenic microRNA upregulated by ZIP4 via CREB.

Suppresses LATS2 (a tumor suppressor in the Hippo pathway), enhancing YAP/TAZ oncogenic signaling.

IL-6 and VEGF Upregulation:

ZIP4 signaling increases pro-inflammatory and pro-angiogenic factors like IL-6 and VEGF, contributing to tumor microenvironment remodeling.

⚠ In Disease Context: ZIP4 is overexpressed in several cancers, including:

Pancreatic ductal adenocarcinoma

Hepatocellular carcinoma

Esophageal cancer

In cancer, ZIP4 contributes to:

Enhanced zinc uptake

Increased cell proliferation

Promotion of epithelial-mesenchymal transition (EMT)

Resistance to apoptosis

 Clinical Implications: ZIP4 is a potential biomarker and therapeutic target.

Targeting ZIP4 or its downstream effectors (e.g., STAT3, miR-373) could provide new avenues for anticancer therapies.