ZIP4 Transporter

ZIP4 is a zinc transporter of the SLC39A family that facilitates the import of zinc into the cytoplasm. While essential for zinc homeostasis, overexpression of ZIP4 has been linked to cancer progression, including glioblastoma (GBM).

General Information

- **Full name**: Zrt- and Irt-like Protein 4
- **Gene**: SLC39A4
- **Protein family**: ZIP (Zinc-Iron Permease), also called SLC39A family
- **Function**: Imports extracellular or organellar zinc into the **cytoplasm**
- **Normal expression**: Intestine (especially duodenum), pancreas, brain

Role in Zinc Homeostasis

- Maintains intracellular zinc levels required for:
  - Enzymatic activity
  - Transcription factor function
  - Immune cell signaling
- Mutations in **ZIP4** cause:
  - **Acrodermatitis enteropathica** (rare congenital zinc deficiency)

ZIP4 signaling pathway

ZIP4 signaling pathway

ZIP4 in Glioblastoma (GBM)

ZIP4 in Glioblastoma

—-

General Information

- **Name:** ZIP4
- **Gene:** SLC39A4
- **Family:** ZIP (Zrt/Irt-like Protein) - SLC39 family
- **Function:** Zinc transporter (Zn^{2+} influx into cytoplasm)
- **Location:** Apical membrane of enterocytes (small intestine)

Physiological Role

ZIP4 plays a key role in zinc absorption from the diet. It is especially active during zinc deficiency. It is essential for:

- Maintaining zinc homeostasis
- Growth and development
- Intestinal zinc uptake

ZIP4 is regulated by zinc levels:

- ↓ Zinc → ZIP4 expression ↑ and stabilized on membrane
- ↑ Zinc → ZIP4 internalized and degraded

Clinical Significance

Acrodermatitis Enteropathica

- **Cause:** Loss-of-function mutations in SLC39A4
- **Symptoms:** Skin lesions, diarrhea, immune dysfunction
- **Treatment:** Oral zinc supplementation

Cancer

Overexpression of ZIP4 has been linked to:

- Pancreatic cancer
- Hepatocellular carcinoma
- Esophageal cancer

ZIP4 contributes to:

- Tumor cell proliferation and survival
- Activation of STAT3, CREB
- Upregulation of miR-373 → LATS2 inhibition → oncogenic YAP/TAZ signaling
- Induction of IL-6 and VEGF → tumor progression

Pathways Activated

1. **STAT3** → Cyclin D1, Bcl-2
2. **CREB** → miR-373 → ↓ LATS2
3. **Pro-inflammatory / angiogenic signaling**: IL-6, VEGF

Summary

ZIP4 is a zinc importer with essential physiological roles and important pathological implications,

particularly in hereditary zinc deficiency and oncogenesis.