TMEM97

TMEM97, or Transmembrane Protein 97, is a relatively understudied protein with intriguing roles in cellular biology and potential implications in various diseases. Here's an overview of what is known about TMEM97:

Structure and Localization Transmembrane Nature: As suggested by its name, TMEM97 is a protein that spans the membrane of cells. It is predicted to have multiple transmembrane domains. Cellular Localization: TMEM97 is primarily localized in the endoplasmic reticulum (ER) and Golgi apparatus, but it has also been observed on the plasma membrane in some cell types. Biological Function Role in Cholesterol Homeostasis: TMEM97 has been implicated in cholesterol metabolism. It is thought to interact with NPC1, a protein involved in the transport of cholesterol out of the lysosome. Regulation of LDL Receptors: TMEM97 is also involved in the regulation of low-density lipoprotein (LDL) receptors, affecting cholesterol uptake in cells. Cell Proliferation and Migration: Some studies suggest that TMEM97 may play a role in cell proliferation and migration, potentially by modulating signaling pathways. Disease Associations Cancer: Altered expression of TMEM97 has been noted in various cancers, including breast, liver, and gastric cancers. It may contribute to tumor progression and metastasis. Neurodegenerative Diseases: TMEM97 has been linked to neurodegenerative conditions like Niemann-Pick disease, where cholesterol metabolism is disrupted. Research and Therapeutic Potential Target for Drug Development: Due to its role in cholesterol metabolism and cancer progression, TMEM97 is being investigated as a potential target for therapeutic intervention. Biomarker Potential: Changes in TMEM97 expression could serve as biomarkers for certain diseases, aiding in diagnosis and monitoring of treatment responses. Understanding TMEM97's function and mechanisms more deeply could reveal new therapeutic avenues and improve our knowledge of disease pathogenesis.

Properties

Previous studies have shown that ligands that bind to sigma-2 receptor/TMEM97 (σ2R/TMEM97), a transmembrane protein, have anxiolytic/antidepressant-like properties and relieve neuropathic pain-like effects in rodents. Despite medical interest in σ2R/TMEM97, little affective and pain behavioral characterization has been done using transgenic mice, which limits the development of σ2R/TMEM97 as a viable therapeutic target. Using wild-type (WT) and global Tmem97 knockout (KO) mice, Hong et al. sought to identify the contribution of Tmem97 in modulating affective and pain-like behaviors using a battery of affective and pain assays, including open field, light/dark preference, elevated plus maze, forced swim test, tail suspension test, and the mechanical sensitivity tests. The results demonstrate that female Tmem97 KO mice show less anxiety-like and depressive-like behaviors in light/dark preference and tail suspension tests but not in an open field, elevated plus maze, and forced swim tests at baseline. They next performed spared nerve injury in WT and Tmem97 KO mice to assess the role of Tmem97 in neuropathic pain-induced anxiety and depression. WT mice, but not Tmem97 KO mice, developed a prolonged neuropathic pain-induced depressive-like phenotype when tested ten weeks after nerve injury in females. The results show that Tmem97 plays a role in modulating anxiety-like and depressive-like behaviors in naïve animals with a significant change in the presence of nerve injury in female mice. Overall, these data demonstrate that Tmem97 could be a target to alleviate affective comorbidities of pain disorders.Significance Statement Chronic pain comorbidities, including anxiety and depression, present a significant public health challenge. Pharmacological agents developed to target the sigma-2 receptor/TMEM97 (σ2R/TMEM97) have

demonstrated promising effects in alleviating anxiety, depression, and pain individually.

The work provides insight on the interaction between σ2R/TMEM97 and neuropathic pain-induced affective behaviors using transgenic mice, suggesting its potential as a novel therapeutic target for addressing both the pain and psychiatric components in complex chronic pain disorders [1)]

1)
Hong VM, Rade AD, Yan M, Bhaskara A, Yousuf MS, Chen M, Martin SF, Liebl DJ, Price TJ, Kolber BJ. Loss of sigma-2 receptor/TMEM97 is associated with neuropathic injury-induced depression-like behaviors in female mice. eNeuro. 2024 Jun 12:ENEURO.0488-23.2024. doi: 10.1523/ENEURO.0488-23.2024. Epub ahead of print. PMID: 38866499.