Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Mini Review

VMP1 (vacuole membrane protein 1)

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Identity

Other names: DKFZp566I133, EPG3, TMEM49

HGNC (Hugo): VMP1

Location: 17q23.1

DNA/RNA

Description

12 exons, spans approximately 133 kb of genomic DNA in the centromere-to-telomere orientation. The translation initiation codon is located to exon 2, and the stop codon to exon 12.

Transcription

mRNA of 2,17 kb.

Protein

Description

The pancreatitis-associated protein vacuole membrane protein 1 (VMP1) is a transmembrane protein of 406 amino-acid length containing 6 putative transmembrane domains and with no known homologues in yeast.

Expression

VMP1 was characterized because is not constitutively expressed in pancreatic acinar cells and it is highly activated early during experimental acute pancreatitis in acinar cells.

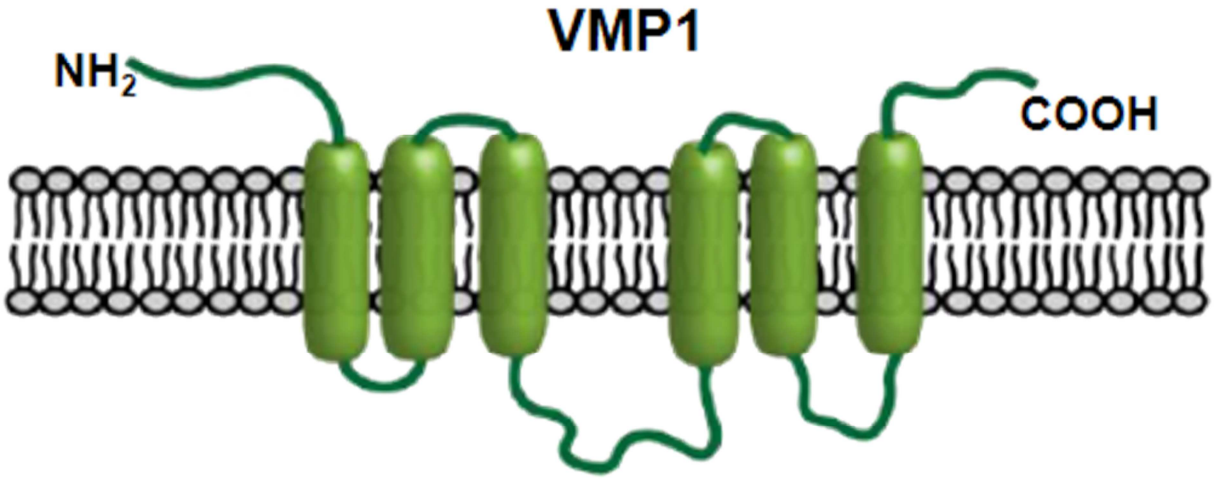
Localisation

Autophagosomal membrane.

Function

VMP1 is an autophagy-related membrane protein. VMP1 expression triggers autophagy, even under nutrient-replete conditions. VMP1 is required for autophagosome development through interaction with Beclin1. Recently, it has been demonstrated that participate in a novel selective form of autophagy, called zymophagy, mediated by VMP1-USP9x-p62 pathway during acute pancreatitis.

Genomic organization of the VMP1/TMEM49 gene.



Schematic representation of VMP1 protein and localization of transmembrane domains.

Implicated in

Pancreatic cancer

Disease

Pancreatic ductal adenocarcinoma is one of the most aggressive human malignancies with a 2-3% 5-year survival rate. This is due to both the aggressive nature of the disease and the lack of specific symptoms and early-detection tools. It is relatively refractory to traditional cytotoxic agents and radiotherapy. Gemcitabine, the standard chemotherapy agent for the treatment of pancreatic cancer, induces autophagy of cancer cells and that this process mediates the cell death-promoting activity of this compound. Early induction of autophagy by gemcitabine leads to cancer cell death and this cellular process is mediated by the activation of VMP1 expression. In PANC-1 and MIAPaCa-2 cells the inhibition of autophagy significantly reduced the percentage of dead cells in response to gemcitabine. In addition, gemcitabine promoted early VMP1 expression, and downregulation of VMP1 expression significantly reduced cell death.

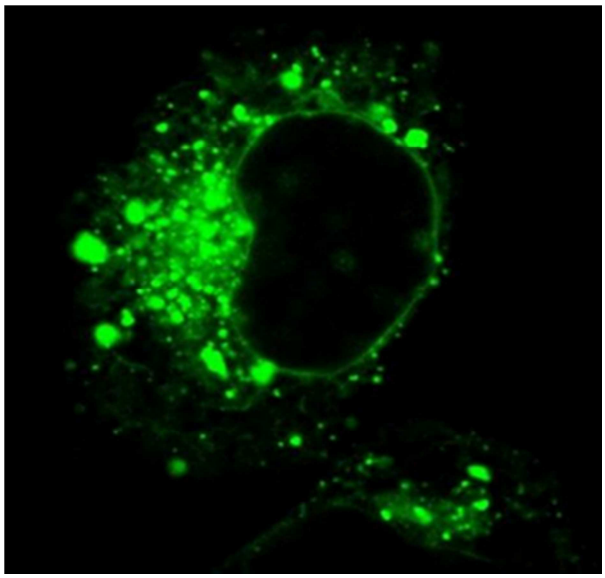
Acute pancreatitis

Disease

VMP1 was characterized because is not constitutively expressed in pancreatic acinar cells and it is highly activated early during experimental acute pancreatitis in acinar cells. VMP1 is an autophagy-related membrane protein involved in the initial steps of the mammalian cell autophagic process. VMP1 is a transmembrane protein that co-localizes with LC3, a marker of the autophagosomes, in pancreas tissue undergoing pancreatitis-induced autophagy. VMP1 interacts with with Beclin1, a mammalian autophagy initiator, to start autophagosome formation. We developed the ElaI-VMP1 mouse in which acinar cell-specific constitutive expression of a VMP1-EGFP chimera induces the formation of autophagosomes. Upon CCK-R hyperstimulation, wild type mice developed acute pancreatitis with high amylase and lipase serum levels.

On the contrary, enzymatic levels in cerulein-treated ElaI-VMP1 mice were significantly lower compared to wild type mice. Consistently, ElaI-VMP1 mouse pancreata showed remarkably less macroscopic evidence of acute pancreatitis compared to wild type animals, which showed marked edema and hemorrhage. Histological analyses displayed a high degree of necrosis as well as infiltration in wild type pancreata with acute pancreatitis. In contrast, neither necrosis nor significant inflammation was seen in cerulein-treated ElaI-VMP1 mice. ElaIVMP1 mice showed secretory granules with normal ultrastructural characteristics CCK-R hyperstimulation in wild type animals induced a markedly altered distribution pattern of the secretory granules. Acinar cells lose their polarity, which results in the relocation of zymogen granules to the basolateral membrane. These alterations in vesicular traffic are known to occur in acinar cells during acute pancreatitis and upon hyperstimulation of their CCK-R with cerulein. ElaI-VMP1 mice subjected to CCK-R hyperstimulation revealed that acinar cells preserve their structure and polarity with negligible or no alteration in vesicular transport. Surprisingly, in pancreata from cerulein-treated ElaI-VMP1 mice, we observed autophagosomes containing zymogen granules displaying a distinct localization to the apical area of the acinar cell. VMP1, the ubiquitin-protease USP9x, and the ubiquitin-binding protein p62 mediate this process. Moreover, VMP1 interacts with USP9x, indicating that there is a close cooperation between the autophagy pathway and the ubiquitin recognition machinery required for selective autophagosome formation. We have coined the term "zymophagy" to refer to this process. Zymophagy is activated by experimental pancreatitis and by acute pancreatitis in humans. Furthermore, zymophagy has

pathophysiological relevance by controlling pancreatitis-induced intracellular zymogen activation and helping to prevent cell death. This new selective autophagy is activated in pancreatic acinar cells during pancreatitis-induced vesicular transport alteration to sequester and degrade potentially deleterious activated zymogen granules.



Confocal microscopy of AR42J cell transfected with pEGFP-VMP1.

Diabetes

Disease

Experimental diabetes activates VMP1 expression and autophagy in pancreas beta cells as a direct response to streptozotocin (STZ). VMP1 mRNA expression is activated after STZ treatment by islet beta cells. Electron microscopy shows chromatin aggregation and autophagy morphology that was confirmed by LC3 expression and LC3-VMP1 co-localization. Apoptotic cell death and the reduction of beta cell pool are evident after 24h treatment, while VMP1 is still expressed in the remaining cells. VMP1-Beclin1 colocalization in pancreas tissue from STZ-treated rats suggests that VMP1-Beclin1 interaction is involved in the autophagic process activation during experimental diabetes. Pancreas beta cells trigger VMP1 expression and autophagy during the early cellular events in response to experimental diabetes.

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