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An Unusual Ion Channel of the TRP Family TRPV6: A Comment on the Connection of TRPV6 and Mucolipidosis Type II

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Abstract

Mutations in a single TRPV6 allele trigger chronic pancreatitis while loss of both alleles is responsible for skeletal dysplasia in newborns. The latter clinical presentation is accompanied by elevated serum levels of the parathyroid hormone, a condition known as transient neonatal hyperparathyroidism (TNHP). In humans, TRPV6 is abundantly expressed in the primary fetal-maternal interface in the placenta, as well as in pancreatic acini and within a few exocrine glands including salivary and lacrimal glands. However, inconsistent results regarding the cellular localization have complicated elucidation of the exact function within these tissues. We have verified an intracellular localization of TRPV6 within vesicles and identified a sorting motive, a glycosylation site and an ER-retention motive within the sequence, which together account for the observed channel localization. This is in contradiction to postulated functions of TRPV6 being responsible for calcium uptake into epithelial cells, which would require TRPV6 localization within the plasma membrane of expressing cells. We suggest that previous observations which demonstrate TRPV6 expression at the plasma membrane may result from overexpression and do not represent endogenous channel positioning. We showed that normal TRPV6 function requires the action of an enzyme (GNPTAB) and the subsequent interaction with a mannose-6-phosphate receptor to be delivered to endosomes. The GNPTAB enzyme marks proteins with mannose-6-phosphate and is known to be defective in patients suffering from mucolipidosis type II, which also present with skeletal dysplasia with elevated parathyroid hormone. The reliance of TRPV6 on this enzyme for correct localization and therefore function provides a possible explanation why patients suffering from either mucolipidosis type II or TRPV6 malfunction exhibit overlapping symptoms.

Keywords: Ion channel, Mucolipidosis type II, Chronic pancreatitis, Skeletal dysplasia

Special Features of TRPV6

- Highly calcium-selective channel
- Different expression pattern between humans and rodents
- Coupled polymorphisms in humans differentiate two TRPV6 alleles (TRPV6a, TRPV6b)
- Strong selective pressure on the TRPV6b variant (found exclusively in humans)
- N-terminal extension of the TRPV6 protein only in placental animals (TRPV6 expressed in placenta)
- Translation initiated at an ACG triplet
- The initiation triplet (ACG) translated as methionine
- ACG serves as TRPV6 initiation triplet in mammals, except in flying foxes and bats
- N-terminal coding region of the mRNA forms stable stem loop which decreases translation efficiency of the TRPV6 protein
- Contains an atypical ER retention motive
- Overexpressed in prostate, breast and endometrial cancer
- Mutation in a single allele causes chronic pancreatitis (TRPV6 expressed in pancreatic acinus cells)
- Mutation in both alleles causes skeletal dysplasia with increased level of the parathyroid hormone
- Link between TRPV6 and mucolipidosis type II

Commentary

Since the cloning of the TRPV6 cDNA about 25 years ago from rodents and humans [1–4], it has become clear that TRPV6 possesses a few unique features. The family of TRP-channels consists of 28 members [5], most of which are non-selective cation-conducting channels. In contrast, TRPV6 (and TRPV5) is highly selective for calcium [3,6], a property which has been conserved throughout evolution. Evolutionarily old organisms such as echinoderms (starfishes and sea urchins), which are known to have developed more than 600 million years ago [7] have also retained this calcium-selective pore. Using extrapolation and molecular clock mapping, the age of the TRPV6 ancestral gene has been estimated at 730 million years with a relatively constant mutation rate of one amino acid per million years. This has led to a lower sequence identity between human and rodent TRPV6 (~90%) than is observed for other TRP genes such as TRPC4 [7].

Mammalian TRPV6 and TRPV5 most likely arose by gene duplication from a common ancestor and as consequence, the genes are localized in tandem on the human chromosome 7q33-34 [2]. TRPV5 is predominantly expressed in epithelial cells of the distal convolute of the kidney where it functions as a calcium re-uptake channel. It has been speculated that the appearance of TRPV5 is connected to the evolution of organisms with a second kidney [8,9], however, TRPV5-like genes can be found in lancelets which developed more than 500 million years ago [7]. Over time, partially loss or doubling of genetic material during evolution has led to organisms with varied numbers of TRPV5 and TRPV6 genes. Birds, for example, have completely lost the TRPV6 gene whereas salmonid fish species possess two TRPV6 copies. A complex model of early doubling events of TRPV5 and TRPV6 genes has been postulated by Flores-Aldama and co-workers [10].

A surprising observation has been described exclusively in placental animals; the TRPV6 protein contains an N-terminal extension of 40 amino acids, corresponding to 120 bases within the mRNA. This relatively rare mechanism does not influence the function of the channel, but greatly reduces the translation effectiveness of the TRPV6 mRNA [11]. Translation is initiated from an ACG triplet at the beginning of this extension which is translated as methionine. Despite the continued presence of an in-frame AUG located downstream in most mammals, we have speculated that the initiator tRNA-Met is placed on the noncanonical ACG codon due to presence of a stabile stem loop structure which prevents the translational machinery from using the standard AUG codon [12]. As overexpression of TRPV6 in conventional cell lines is known to cause dramatic calcium overload, this reduced translation is likely an evolutionary mechanism evolved to prevent toxic calcium overload within the cytosol of TRPV6-expressing cells [13]. Intriguingly, while almost all placental animals initiate translation from this ACG triplet, this is not the case in flying foxes and bats. These animals contain instead a classical AUG triplet at the position corresponding to the upstream ACG codon. Overexpression experiments using chimeras of human and bat TRPV6 show that this modification is responsible for significantly enhanced protein synthesis in these species, speculated to be required to compensate for limited dietary calcium within these animals, especially during pregnancy [12]. One unique mammal, the duck-billed platypus, which does not have a placenta and still lays eggs, possesses only a part of the N-terminal extension, arguing for a role of the extended TRPV6 sequence in placental function [7].

In humans, TRPV6 is abundantly expressed in the placental syncytiotrophoblast – the primary fetal-maternal interface – as well as in pancreatic acini and within a few exocrine glands including salivary and lacrimal glands. Evolutionarily obtained polymorphisms of the TRPV6 gene have been described exclusively in humans, giving rise to two alleles of the TRPV6 gene. Five base changes affecting three amino acid positions within TRPV6 cDNA (C157R, M378V, M681T) have been identified which seem to be genetically linked, leading to an older TRPV6 isoform termed TRPV6a (R157, V378, T681) and a modern variant termed TRPV6b (C157, M378, M681) [3]. The TRPV6a variant is still abundantly present in South-African population (up to 80% of individuals homozygous TRPV6a) whereas the TRPV6b allele is dominant with increasing distance to the African continent (up to 96% homozygous TRPV6b) [14]. Although TRPV6a and TRPV6b channels exhibit similar channel properties [15], the authors suggested that selection pressure may lead to this isoform distribution, but what might drive this selection is still unknown.

Aberrant TRPV6 expression has been connected to several diseases. Carcinomas of the prostate, breast and endometrium overexpress TRPV6 transcripts, whereas the corresponding healthy tissues do not [3,16–22]. In the case of prostate cancer, it was demonstrated that TRPV6 expression is correlated with the malignancy of the cancer cells. Thus, TRPV6-positive tumors were more likely to metastasize beyond the prostate capsule. Based on these data, it was concluded that TRPV6 is a driver for metastatic properties of several malignancies.

Another disease associated with abnormal TRPV6 expression was found to be non-alcohol-dependent chronic pancreatitis [23–27]. Whole exon sequencing revealed several mutations of the TRPV6 gene, which, when overexpressed, dramatically reduced channel activity (<50%). The underlying mechanism for development of this disease is not known but likely reflects disruption of normal TRPV6 function in pancreatic acinus cells. Of note, only one TRPV6 allele was typically mutated in these patients whereas the second allele was still intact.

Patients with mutations on both alleles present a reduced calcification of the skeleton at birth accompanied with increased serum levels of the parathyroid hormone [28–32]. The

skeletal dysplasia observed in these patients most likely results from reduced calcium transport through the placenta during the pregnancy coupled with compensatory upregulation of the parathyroid hormone. The mutations identified in these patients typically affect the conductivity of the TRPV6 channel [29]. Since TRPV6 is expressed in the syncytiotrophoblast layer of the placenta, the logical conclusion is that calcium is transported through TRPV6 channels directly. This idea was supported by the finding that TRPV6 overexpression in all cell lines used to date results in calcium influx across the plasma membrane, which could be easily demonstrated by patch clamp or calcium imaging. However, in tissues or cell lines which endogenously express TRPV6, endogenous TRPV6 currents could not be found. TRPV6-like currents have never been measured in syncytiotrophoblast cells and are in addition not detectable in a trophoblast-derived cell line, BeWo, which expresses TRPV6. Also, in two cancer-derived cell lines, T47D and LNCaP, which express the TRPV6-mRNA, no TRPV6 currents could be measured. In addition, HEK293 cells which overexpress a fluorescently-tagged-TRPV6 fusion construct, have no detectable staining at the plasma membrane [11].

Based upon these inconsistent results, we focused on the intracellular destination of TRPV6 and could show that the channel is indeed transported to intracellular vesicles [33]. Firstly, microscopic analysis following transfection of TRPV6 fused to either GFP or RFP confirmed vesicular staining and an absence of signal within the plasma membrane or filopodia. Merged microscopic pictures of TRPV6-GFP and TRPV6-RFP showed that identical vesicles were labelled and staining with Rab5 confirmed these vesicles as early endosomes [34]. Surprisingly, TRPV6 currents were measurable in these cells by patch clamp and calcium imaging, indicating that a small proportion of the TRPV6 protein must reach the plasma membrane under these conditions. Comparative measurements of TRPV6 fused to GFP and wild type TRPV6 cloned in an IRES-GFP plasmid (not fused to the GFP cDNA) showed identical TRPV6 activity and kinetics, indicating that the fusion of GFP or RFP does not influence the activity of TRPV6. In addition, we could show that neither fluorescence tag influenced the intracellular trafficking of TRPV6. We stained pancreatic acini and placenta syncytiotrophoblast with TRPV6-specific antibodies and confirmed the presence of TRPV6-positive vesicles, whereas plasma membrane signal was again not detectable.

A N-glycosylation site (N398), located between the first and second transmembrane domains of TRPV6, is responsible for vesicular transport of TRPV6. To determine this, the localization of the closely related TRPV4 channel, which does not possess an N-glycosylation site at the corresponding position was studied. Overexpression of the TRPV4-GFP fusion construct in cells led to reliable detection of signal within the plasma membrane as well as measurement of TRPV4 currents. A TRPV4 chimera which included the N-glycosylation site of TRPV6 was redirected to intracellular vesicles. When the critical amino acid responsible for the N-glycosylation, asparagine (N), was substituted to alanine in the chimera, this second chimera was localized back in the plasma membrane. These experiments showed that the N-glycosylation site of TRPV6 is responsible for directing the TRPV4-V6 chimera into vesicles and further, that this site underlies vesicular transport of TRPV6.

Interestingly, when the asparagines of the N-glycosylation site (N397A, N398A) in TRPV6 were substituted to alanine, this construct was found exclusively in ER membranes of overexpressing cells. This is in contrast to the localization of TRPV4 which, without a N-glycosylation site, is delivered to the plasma membrane. Therefore, we questioned, whether the TRPV6 sequence contains an ER-retention motive responsible for retaining TRPV6 mutant in the ER. Indeed, TRPV6 contains a C-terminal located RDEL motive, similar to the classical ER retention motive present in soluble ER-proteins (KDEL), within the TRPV6 sequence. A mutation of this motive (RAEL) resulted in plasma membrane staining within TRPV6-RAEL-expressing cells, indicating that this sequence functions as an ER retention signal. This RDEL sequence is located in close proximity to the highly conserved TRP-Box of TRP channels, but is only present in TRPV6 and TRPV5 and none of the other TRP channels. As a consequence, the calcium uptake of TRPV6-RAEL-expressing cells was increased compared to wild type TRPV6.

As described above, patients with one defective TRPV6 allele develop chronic pancreatitis whereas patients with two defective alleles develop a skeletal dysplasia with elevated serum parathyroid levels. In general, TRPV6 mutations have been shown to decrease channel activity to <50%. However, one mutation frequently found in Japanese pancreatitis patients, I223T, still retains normal channel activity [23,33]. Suzuki and co-workers reported a family in which a child carrying the I223T mutation alongside a second TRPV6 mutation R425Q [29] was born with skeletal dysplasia. This raised the question why this seemingly fully-functional channel still manifested in pancreatitis and skeletal dysplasia in these patients. Using TRPV6 containing the R425Q mutation reduced channel activity but co-expression of both cDNAs (TRPV6-I223T and TRPV6-R425Q) demonstrated that the I223T-construct could compensate for the second mutation, fully restoring TRPV6 activity in this scenario [33]. However, we found the TRPV6-I223T-channel is retained in the ER and not transferred to vesicles due to disruption of a sorting motive. We assume that the I223T mutation drives both diseases, chronic pancreatitis and skeletal dysplasia (in combination with the second mutation), due to incorrect localization of TRPV6. We also tested another mutation, G428R, which significantly reduces the TRPV6-activity [29] and co-expressed this mutant with TRPV6-I223T. The decreased activity of the G428R mutation could also be compensated by the I223T mutation (unpublished).

Several case reports show that patients suffering from mucolipidosis type II exhibit overlapping symptoms with TRPV6 deficiency, namely skeletal dysplasia accompanied with elevated parathyroid hormone in the serum at the time of birth [35,36]. Mucolipidosis type II patients exhibit defects in an enzyme (GNPTAB, N-Acetylglucosamine-1-phosphate transferase, [37,38]). This enzyme marks proteins at N-glycosyl side chains with mannose-6-phosphate. Proteins which are mannosylated in this way interact with a mannose-6-phosphate receptor and are delivered to endosomes/lysosomes. It could be shown that TRPV6 interacts with the mannose-6-phosphat receptor (CI-MPR, IGF2R), indicating that TRPV6 is likely mannosylated at the glycosyl side chain and targeted to endosomes. This is consistent with localization experiments showing vesicular staining using a fusion construct of TRPV6-GFP which colocalizes with the endosomal marker Rab5 (**Figure 1**).

The α/β -subunits of GNPTAB are translated from one gene and cleaved by a S1-protease into two independent subunits, a requisite step in generating an active GNPTAB enzyme. Following incubation with an inhibitor of the S1-protease, PF-429242 [39], TRPV6 expression at the plasma membrane increased, supporting a role for GNPTAB in vesicular localization of TRPV6 within the endosome. If the N-glycosylation is completely blocked (by mutation) TRPV6 is retained in the ER. But blocking only the mannosylation leads to increased TRPV6 in the plasma membrane (**Figures 2** and **3**). These results indicate that there is a crosstalk between TRPV6 and GNPTAB and might explain why patients show overlapping symptoms observed in both mucolipidosis type II and TNHP (transient neonatal hyperparathoidism) driven by TRPV6 deficiency.

Based on the results described, TRPV6 is probably an intracellular channel which is endogenously localized within endosomes. We have identified three sequence motives that are thought to prevent TRPV6 from being transported to the plasma membrane (**Figure 3**). We show that mutations within these motives influence the trafficking of the TRPV6 channel

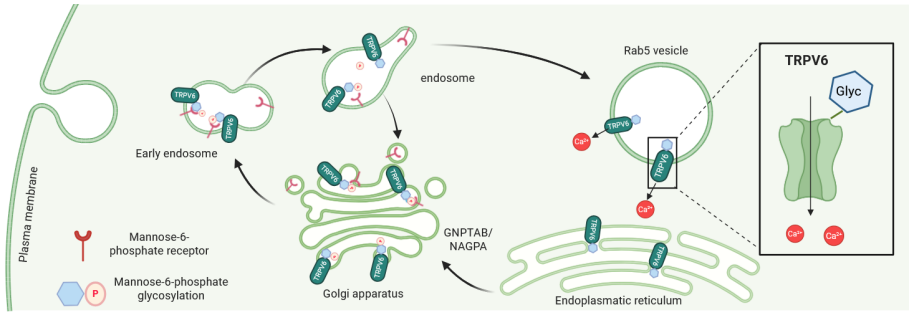

Figure 1. The glycosylation site (N398) is responsible for vesicular localization. The TRPV6 protein is glycosylated and mannosylated with mannose-6-phosphate within the Golgi apparatus and after interaction with a mannose-6-phosphate receptor (CI-MPR/IGF2R) transported to endosomes. TRPV6 is predominantly found in Rab5-positive vesicles (created with Biorender.com).

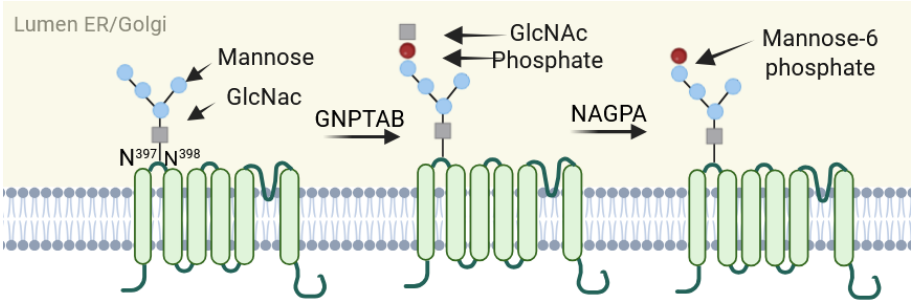

Figure 2. TRPV6 glycosylation occurs at asparagine N398. Through the action of GNPTAB and NAGPA, the glycosyl side chain is labelled with mannose-6-phosphate. GNPTAB consists of α2β2γ2-subunits. For generation of an active GNPTAB enzyme, the cleavage of ab precursor by site1-protease (S1-protease) is required. The activity of GNPTAB can be minimized by blocking the S1-protease with inhibitor PF-429242 (created with Biorender.com).

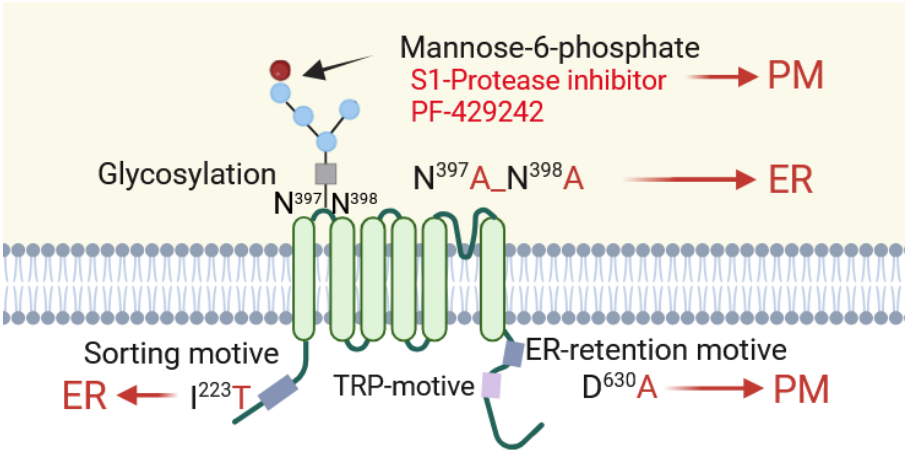

Figure 3. Mutations which affect the localization of TRPV6. A mutation of the sorting motive, I223T, and of the glycosylation site, N397A, N398A, prevent TRPV6 from being transported out of the endoplasmic reticulum. The amount of TRPV6 in the plasma membrane (PM) increases if only the mannosylation with mannose-6-phosphate is blocked by S1-protease inhibitor, PF-429242, or by mutation of the ER-retention motive (D630A) (created with Biorender.com).

but not the function in terms of calcium permeability. Thus, TRPV6-dependent plasma membrane currents may result from spillover effect caused by overexpression, providing an explanation for the inconsistent results described to date. This then raises questions about the actual function of TRPV6 channels within cells. Stainings of placenta syncytiotrophoblast and pancreatic acini with TRPV6 specific antibodies indicate vesicular localization of the channel, which would by definition preclude a role for this channel in the direct transport of calcium, as was supposed [8,40,41]. In addition, low TRPV6 protein levels make it is difficult to imagine how the large amounts of calcium required during late pregnancy (up to 300 mg/day [42]) could be transported via TRPV6 without measurable currents being detectable in the syncytiotrophoblast. However, patients born with skeletal dysplasia as a result of mutated TRPV6 show normalization later in life upon calcium supplementation in the diet, supporting that TRPV6 disruption does indeed perturb transplacental calcium transport in some way but uptake is unaffected [28,43].

In any case, an active uptake system for calcium ions exists in both the small intestine and the syncytiotrophoblast; furthermore, the first TRPV6 mRNA was isolated from the rat small intestine using a functional cloning approach. The expression data, taken together with the properties of the overexpressed channel, were reasonably interpreted to suggest that TRPV6 is a suitable candidate for this function [1,16,44, 45], namely calcium uptake in epithelial cells. The fact that dysfunctional TRPV6 channels lead to skeletal abnormalities in both KO mice and humans also supports the notion that TRPV6 is involved in calcium transport across the placenta [46]. Additionally, TRPV6 expression is found in murine uterine epithelial cells (MEECs) [47]. In these cells, however, only under divalent-free conditions can a very small, TRPV6-mediated transmembrane sodium influx be detected (~2 pA/pF at -80 mV). Since the conductance for Ca^{2+} is approximately 10 times lower than for Na^{+} [3], it can be concluded that even in MEECs, TRPV6 contributes only insignificantly to calcium uptake into these cells. In contrast, intracellular calcium oscillations are significantly reduced in KO cells. Taken together, the results imply that TRPV6 is primarily involved in intracellular calcium signaling and may play only a minor role in the plasma membrane.

TRPV6 expression is observed in glandular tissues (salivary-, lacrimal-gland and pancreatic acinus cells) leading to the speculation that channel function could be connected to secretion processes in these tissues. This finding is supported by TRPV6 mutations which trigger chronic pancreatitis, a disease which occurs if the secretion of zymogens is affected. The syncytiotrophoblast also exhibits features similar to glandular tissues and secretes several hormones which drive placenta differentiation. Thus, if placental differentiation is affected this could alter the surface of the syncytiotrophoblast, thereby influencing transcellular and paracellular Ca^{2+} transport.

In summary we suggest that TRPV6 is involved in the secretory function of these organs and is not primarily involved in Ca^{2+} uptake in epithelial cells. In this respect, the observable deficits in transplacental calcium transport are likely to be attributable to indirect effects.

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