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Review article

Vesicle transport through interaction with t-SNAREs 1a (Vti1a)'s roles in neurons

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ABSTRACT

The Soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) family mediates membrane fusion during membrane trafficking and autophagy in all eukaryotic cells, with a number of SNAREs having cell type-specific functions. The endosome-*trans*-Golgi network (TGN) localized SNARE, Vesicle transport through interaction with t-SNAREs 1A (Vti1a), is unique among SNAREs in that it has numerous neuron-specific functions. These include neurite outgrowth, nervous system development, spontaneous neurotransmission, synaptic vesicle and dense core vesicle secretion, as well as a process of unconventional surface transport of the Kv4 potassium channel. Furthermore, the human *VT11A* gene is known to form fusion products with neighboring genes in cancer tissues, and *VT11A* variants are associated with risk in cancers, including glioma. In this review, I highlight VTI1A's known physio-pathological roles in brain neurons, as well as unanswered questions in these regards.

1. Introduction

Vesicle fusion in eukaryotic membrane (or vesicular) traffic is mediated by N-ethylmaleimide-sensitive factor (NSF), Soluble NSF attachment proteins (SNAPs) and SNAP receptors (SNAREs) (Söllner et al., 1993; Weber et al., 1998). These form a distinct physical complex *in vitro* – the 20S complex (Hohl et al., 1998; Zhou et al., 2015). A SNARE protein is membrane associated via a C-terminal transmembrane domain or lipid anchor, and is thus largely cytoplasmically oriented. SNAREs harbor one or two α-helical coiled-coil signature motif known as the SNARE domain (Weimbs et al., 1998). SNARE domains are composed of repeated hydrophobic residues that is interrupted by a charged arginine (R) or glutamine (Q), and thus the basis of classification of SNAREs into R- or Q-SNAREs (Fasshauer et al., 1998; Kloepper et al., 2007). In membrane fusion, SNARE domains belonging to those that are either transport vesicle-associated (v-SNAREs) or target membrane-localized (t-SNAREs) interact spontaneously to form complexes in *trans* with the right composition and stoichiometry (Katz and Brennwald, 2000). In completion of the pairing of the SNARE domain α-helixes, or the formation of multiple ` SNAREpins' (Weber et al., 1998), the energetically favorable SNAREpin formation and clustering at the fusion site provides the biophysical or entropic force required to overcome the electrostatic repulsion and bring about fusion of two negatively charged lipid bilayers (Mostafavi et al., 2017).

In this regard, the fusion between synaptic vesicles and the presynaptic plasma membrane during synaptic vesicle exocytosis in neurons offers a classic example (Südhof, 2014). This action potential-triggered process is highly regulated (Rizo and Xu, 2015), and canonical synaptic vesicle fusion is driven by a trans-SNARE complex formed between the plasma membrane associated Qa-SNARE Syntaxin 1 (STX1A/B) and the Qb-SNARE Synaptosome Associated Protein 25 (SNAP25) with the vesicle-bound R-SNARE Synaptobrevin 2 (Syb2)/-Vesicle-associated membrane protein 2 (VAMP2) (Pevsner et al., 1994; Südhof, 2014). Structural analyses indicate that this synaptic exocytic SNARE complex takes the form of a 4-helix bundle, with leucine-zipper-like layers formed by the SNARE domains at the center (Sutton et al., 1998; Poirier et al., 1998; Katz et al., 1998). Embedded within these leucine-zipper layers is the ionic `zero' layer, consisting of the 1 R (from VAMP2) and 3 Q (1 from STX1A/B and 2 from SNAP25) residues contributed by each of the four SNARE domain α-helices. On the other hand, other SNARE complexes, such as that responsible for endoplasmic reticulum (ER)-Golgi transport, has its 3 Qs contributed by 3

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different t-SNAREs (Xu et al., 2000). This particular `1R + 3Q′ stoichiometric arrangement provides topological constraint (Parlati et al., 2000) and compositional specificity (Yang et al., 2008) for functional membrane fusion, and is likely conserved for all SNARE-mediated membrane fusion in the cell. The unique ionic `zero' layer was shown to be required for eventual dissociation of formed SNARE complex by NSF/α-SNAP (Scales et al., 2001), although mutational analyses in yeast have suggested that the R could also be functionally replaced by a Q (Katz and Brennwald, 2000).

Neurons are polarized cells with rather specific membrane trafficking needs and processes that are exemplified by, but not limited to, synaptic vesicle exocytosis. SNAREs are required in other membrane fusion processes in neurons (Wang and Tang, 2006), including those that are neuron-specific such as neurite outgrowth and neuroendocrine secretion. In this regard, a subset of R-SNAREs known as the longins (as opposed to the brevins) (Filippini et al., 2001; Rossi et al., 2004), have been quite extensively implicated in neuron-specific functions (Rossi et al., 2004; Daste et al., 2015). The longin domain with a profilin-like fold (Gonzalez et al., 2001; Rossi et al., 2004) can be found in the R-SNAREs Sec22b (Gonzalez et al., 2001), Ykt6 (Tochio et al., 2001) and VAMP7 (Proux--Gillardeaux et al., 2007). The multi-functional Ykt6 complexes with several other SNAREs and is shown to be involve in ER-Golgi transport (McNew et al., 1997), Golgi transport (Xu et al., 2002), vacuole targeting (Kweon et al., 2003) and more recently in autophagosome-lysosome fusion (Yong and Tang, 2019; Kriegenburg et al., 2019). However, Ykt6 appears to be specialized for the trafficking of a poorly characterized unique neuronal membrane compartment (Hasegawa et al., 2003). The mammalian Sec22b is involved in ER-Golgi exocytic transport (Hay et al., 1997; Zhang et al., 1999), secretory autophagy (Kimura et al., 2017), ER-plasma membrane (PM) apposition and PM expansion (Petkovic et al., 2014), and has also been implicated in ER-phagosome antigen cross presentation in dendritic cells (Cebrian et al., 2011; Alloatti et al., 2017; Cruz et al., 2020). VAMP7 mediates late endosome-lysosome transport (Advani et al., 1999), TGN-late endosome transport (Pols et al., 2013) and the unconventional process of lysosomal secretion (Sato et al., 2011; Wang et al., 2018). In neurons, VAMP7 is also known to mediate neurite outgrowth (Arantes and Andrews, 2006; Burgo et al., 2009) and spontaneous neurotransmission (Bal et al., 2013).

Orthologue of the SNARE, Vesicle transport through interaction with t-SNAREs 1A (Vti1a), is first identified in yeast (as Vti1p), with functions as an endo-lysosomal SNARE in Golgi retrograde (Lupashin et al., 1997) and Golgi to vacuole transport (Fischer von Mollard and Stevens, 1998). In yeast, Vti1p is the only SNARE of the Qb.IIIb subtype (Kloepper et al., 2007), and two Qb SNAREs with the closest homology to Vti1p in mammals are Vti1a and Vti1b (Fischer von Mollard and Stevens, 1998). The mammalian Vti1a and Vti1b appear to have distinct subcellular localizations, cognate SNARE partners (Kreykenbohm et al., 2002) and trafficking functions. For example, Vti1a functions in insulin-stimulated glucose transport (Bose et al., 2005) and regulated exocytosis in adrenal chromaffin cells, but *VTI1b* null cells show no secretion defects (Walter et al., 2014). Deletion of Vti1b is non-lethal, but rather specifically resulted in reduced amounts of Syntaxin 8 due to enhanced degradation of the latter (Atlashkin et al., 2003). However, they are also likely to have key overlapping functions, as knockout of either of them did not affect viability in mice (Atlashkin et al., 2003; Kunwar et al., 2011), but a double-knockout of both Vti1a and Vti1b resulted in perinatal lethality (Kunwar et al., 2011).

Early works have implicated Vti1a in both anterograde (Xu et al., 1998) and retrograde (Mallard et al., 2002) traffic, as well as its enrichment in small synaptic vesicles (Antonin et al., 2000). Vti1a and VAMP4 partners with a number of SNAREs associated with the *trans*--Golgi network (TGN) and the endosome to mediate connecting traffic between the exocytic and endocytic pathways. A SNARE complex formed between Vti1a, Syntaxin 6 (STX6) (Wendler and Tooze, 2001), Syntaxin 16 (STX16) (Simonsen et al., 1998; Tang et al., 1998) and either VAMP3/cellubrevin (McMahon et al., 1993) or VAMP4 (Steegmaier et al., 1999) mediates early/recycling endosome transport of Shiga toxin and TGN46 (Mallard et al., 2002; Kreykenbohm et al., 2002; Laufman et al., 2011). Another related complex, consisting of Vti1a, Syntaxin 10 (STX10) (Wang et al., 2005; Ganley et al., 2008), STX16, and VAMP3, works in mediating Mannose 6-phosphate receptors (MPRs) transport from the endosomes to the Golgi (Ganley et al., 2008). Vti1a, VAMP4 and STX6, in conjunction with Syntaxin 13 (STX13) (Prekeris et al., 1998), forms another complex that mediate homotypic fusion of early endosomes (Brandhorst et al., 2006).

Importantly, Vti1a appears to have specific roles in neuronal processes (Ramirez and Kavalali, 2012; Emperador-Melero et al., 2019), including neuronal development (Kunwar et al., 2011), non-canonical neurotransmission processes (Ramirez et al., 2012; Emperador-Melero et al., 2018), dense core granule secretion (Walter et al., 2014; Emperador-Melero et al., 2018), unconventional transport in neuron (Flowerdew and Burgoyne, 2009), and perhaps also brain malignancy (Kinnersley et al., 2015; Wang et al., 2017; Davidsen et al., 2018). In the paragraphs below, Vti1a's involvement in neuronal development, physiology and pathological processes (summarized in Figure 1) shall be highlighted and discussed.

2. Vti1a/b in neural development

In 2011, von Mollard's group has generated *Vti1a*$^{-/-}$ *Vti1b*$^{-/-}$ double-knockout (DKO) mouse embryos and found somewhat surprisingly that fibroblasts immortalized from embryos exhibit neither obvious aberrance in plasma or endo-lysosomal membrane morphology, nor overt defects in cargo trafficking (Kunwar et al., 2011). However, major neuronal projection tracts and commissures were either absent or reduced in size in E18.5 DKO mice, indicating severely impaired axonal growth. In the DKO embryos, the peripheral ganglia also exhibited varying degrees of neurodegeneration, likely due to neurotrophic deprivation resulting from a lack of axonal targeting and innervation. The DKO animals thus have neuronal trafficking processes that are crucial for axonal growth that was severely defective with the loss of both Vti1a and Vti1b. That defects do not occur in single knockout or double heterozygous mice indicate that Vti1a and Vti1b could compensate for the loss of each other. Notably, the axonal growth phenotype of Vti1a/b DKO in mice is much more severe than those of VAMP7 (Sato et al., 2011; Danglot et al., 2012), although the latter has been implicated in a major neurite outgrowth mechanism involving specific structures known as enlargeosomes (Racchetti et al., 2010; Meldolesi, 2011; Colombo et al., 2014). A more recent study by Verhage's group also showed that Vti1a/Vti1b DKO neurons have diminished viability in culture, are smaller and form fewer synapses (Emperador-Melero et al., 2018). Superficially, the findings would suggest that Vti1a and Vti1b function in a redundant manner in axonal or neurite growth, with the presence of either being sufficient for postnatal survival.

3. Vti1a in spontaneous neurotransmission

Other than action potential-evoked plasma membrane fusion of synaptic vesicles, all synapses exhibit a low background of spontaneous vesicle fusion and action potential-independent miniature neurotransmission (Sutton et al., 2006). Although it has been argued that spontaneous and evoked transmission arise from the same synaptic vesicle pools (Groemer and Klingauf, 2007; Hua et al., 2010; Wilhelm et al., 2010), the notion is controversial and evidence exists for spontaneous fusion being the result of a separate pool of vesicles recycling spontaneously (Sara et al., 2005; Fredj and Burrone, 2009; Andreae et al., 2012; Ramirez et al., 2012). Kavalali's group showed that some synaptic vesicles do recycle when neurons are at rest, and identified by differential tagging of synaptic vesicles a `reluctantly releasable' or `reserved pool' (Sara et al., 2005). Spontaneous, but not evoke transmission, is affected by neurotransmitter depletion at rest rather selectively from the spontaneously fusing vesicles. Also, the pools of activity-dependent and spontaneously

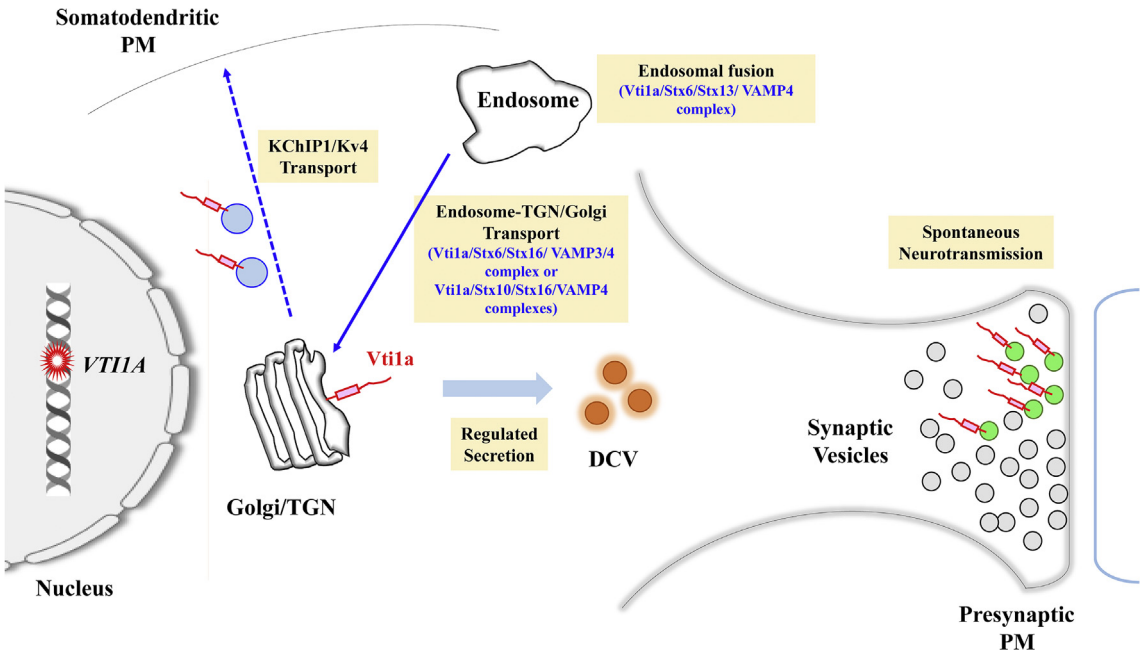

Figure 1. Schematic diagram illustrating the roles of Vti1a in neurons. As in non-neuronal cells, Vti1a is part of a SNARE complexes that mediate endosome-trans-Golgi network (TGN) transport. Vti1a also mediates regulated secretion of dense core vesicles (DCV) and marks a pool of spontaneously fusing synaptic vesicles (green) that recycles at rest and fuse with the axonal presynaptic plasma membrane (PM). Vti1a and VAMP7 (VAMP7) are also involved in Potassium channel interacting protein 1 (KChIP1)/voltage-gated K+ channels (Kv4) to the somatodendritic plasma membrane. Mutations/variants and gene fusion of VTI1A (red star) in neuronal or glia progenitor cells could be oncogenic. See text for more details.

recycling vesicles could become indistinguishable in the absence of Syb2 (Sara et al., 2005).

Using Syb2, VAMP7 or Vti1a tagged with different fluorescent probes to examine the trafficking and fusion of labeled vesicles both at rest and when stimulated, the group found a population of Vti1-containing vesicles that appear to traffic preferentially at rest (Ramirez et al., 2012). Furthermore, endogenous levels of Vti1a in live neurons correlated with the degree of spontaneous vesicle recycling at individual synaptic termini, and silencing of Vti1a selectively impaired the generation of signals from spontaneous, but not the stimuli-evoked transmission. Conversely, expression of an N-terminally truncated version of Vti1a with a likely disinhibition of Vti1a's SNARE activity, augmented spontaneous neurotransmission. Importantly, this apparently Vti1a-dependent spontaneous vesicle trafficking and fusion still occurs in Syb2-knockout neurons. This latter point is important as it suggests the possibility that Syb2, which is critical for the canonical synaptic vesicle fusion SNARE complex, is not required for functional fusion of the Vti1a-containing vesicles. Vti1a therefore appears to be important for the trafficking and recycling of a rather unique spontaneously-fusing vesicle pool at rest. The questions is whether Vti1a actually participates in the SNARE complex at the final plasma membrane fusion step remains unclear. At first look this notion would appear untenable as the canonical synaptic fusion machinery typically uses the Qb-SNARE SNAP25 (Emperador-Melero et al., 2018), but a non-exclusive role for Vti1a in this regard could not yet be completely ruled out. Notably, the R-SNARE VAMP4, which forms a SNARE complex with Vti1a in mediating endosome-TGN transport (Mallard et al., 2002), also has a pre-synaptic role in maintaining bulk Ca^{2+}-dependent asynchronous neurotransmission that is independent of Syb2-mediated synchronous neurotransmission (Raingo et al., 2012). The role of VAMP4 in this regard is also unclear. VAMP4 has been identified as a component of synaptic vesicle (Raingo et al., 2012; Ramirez and Kavalali, 2012), but there is yet no functional evidence to confirm that VAMP4 directly mediates synaptic vesicle fusion.

In a more recent analysis, Verhage's group found that both synaptic vesicle and dense-core vesicle (DCV) number and secretion were greatly reduced in Vti1a/Vti1b DKO mouse neurons (Emperador-Melero et al., 2018). Whole cell patch clamp recordings indicate that evoked neurotransmitter release upon stimulation was decreased by 80–90%, while frequency of spontaneous fusion events was reduced by 65%. These authors also showed that the Vti1a/b DKO neurons have much reduced levels of proteins important for synaptic vesicle fusion, such as the Qb-SNARE SNAP25, Munc13-1 and Synaptotagmin. There is in general a reduced protein flux into axons and the presynaptic termini, while the somatic Golgi apparatus exhibit distended cisternae and cargo accumulation. These findings indicate that loss of both Vti1a and Vti1b in neurons severely impairs the more upstream event of TGN exocytosis. Vti1a/b DKO neurons also have impaired endosome-Golgi transport as marked by Cholera Toxin subunit-B (Emperador-Melero et al. 2018, 2019). The secretory defects noted in Vti1a/b DKO neurons were rescued almost completely by exogenous expression of Vti1a alone, but some of which (such as total DCV pool and retrograde transport) could only be partially rescue by the expression of Vti1b alone. These findings of Vti1a associated upstream defects makes deciphering of any distinct synaptic role of Vtia difficult. Surprisingly, spontaneous transmission is also not completely abolished in the Vti1a/b DKO neurons, which would suggest that at least some spontaneously fusing vesicles at rest could fuse independently of Vti1a.

4. Vti1a/b and secretory granule exocytosis

The first hint that Vti1a could be involved in regulated transport or secretion came from the report which showed that Vti1a regulates insulin-stimulated glucose transport and the secretion of the hormone Adipocyte complement related protein of 30 kD (Acrp30), or adiponectin, in 3T3-L1 adipocytes (Bose et al., 2005). Two studies have since confirmed a role for Vti1a in dense-core vesicle biogenesis and secretion in the endocrine and neuronal systems, respectively (Walter et al., 2014; Emperador-Melero et al., 2018). In the earlier report, Walter and colleagues showed that Vti1a is localized to a subdomain of TGN that appears to be negative for the TGN marker TGN38, but harbors the SNARE Syntaxin 6 (Walter et al., 2014). Analysis of the adrenal glands of Vti1a-null mice showed a reduction in Syb2 levels. The Syb2-positive

large dense-core vesicles (LDCVs) in adrenal chromaffin cells are devoid of Vti1a. However, the Ca^{2+} channel abundance and stimuli-evoked LDCV exocytosis are reduced in Vti1a-null cells. With manipulation of exocytic stimulus, it is shown that despite the secretion defect and the decrease in the number of secretory granules, LDCV secretion in the Vti1a-null cells are unchanged in terms of kinetics and Ca^{2+} sensitivity. The LDCV secretory phenotype is not exhibited by Vti1b-null cells and not exacerbated by a Vti1a/Vti1b DKO, indicating that Vti1b is not involved in, and could not complement Vti1a's role in regulated exocytosis of adrenal chromaffin cells.

As mentioned in the section above, Emperador-Melero and colleagues discovered that, as with synaptic vesicles, DCV number and secretion were also greatly reduced in Vti1a/Vti1b DKO mouse neurons (Emperador-Melero et al., 2018). In the case of neuronal DCV, Vti1b expression could rescue the DCV secretion, but only partially rescue the reduction in total DCV pool. Therefore there appears to be a difference between DCV secretion in neurons and LDCV secretion in adrenal chromaffin cells in terms of Vti1b's ability to compensate for the loss of Vti1a. These results should be interpreted with some caution as compensatory mechanisms that could be activated or engaged by the cells may be different in the case of losing one of the Vti protein as compared to losing both (Villarreal et al., 2013). Born without either Vti1a or Vti1b, different cell types may find different ways to cover for the secretory defect and survive the deficiency.

5. Vti1a in neuronal unconventional exocytic transport

In neurons, the trafficking of voltage-gated Kv4 potassium (K^+) channels to the plasma membrane is dependent on the Potassium channel interacting proteins (KChIPs) (Jerng and Pfaffinger, 2014). The somatodendritic A-type K^+ current underlies neuronal excitability, and KChiPs-modulated Kv4 trafficking is thus important for homeostatic excitability (Wang et al., 2013). KChIP1 is targeted via an N-terminal myristoylation to vesicles that appear to be trafficking intermediates from the ER to the Golgi, but these differ from those conveying conventional ER-Golgi traffic of the classical exocytic cargo marker, Vesicular stomatitis virus G protein (VSVG) (Tang et al., 2005). These require Coat protein I (COPI), but are not COPII-coated and not inhibited by a GTP-locked Sar1 mutant (Hasdemir et al., 2005). These KChIP1-postive vesicles do not have components of the usual ER-Golgi SNARE complexes, but are instead positive for both Vti1a and VAMP7. Silencing of either Vti1a or VAMP7 inhibited the transport of Kv4/KChIP1 to the plasma membrane in HeLa and Neuro2A cells (while not affecting VSVG transport), but not Kv4 transport stimulated by KChIP2 (Flowerdew and Burgoyne, 2009).

Kv4/KChIP1 trafficking in neuron may thus occur via a somewhat unconventional exocytic route that is dependent on Vti1a and VAMP7. The precise nature and other membrane trafficking requirements of this route is still unclear. Several routes of unconventional exocytosis in non-neuronal cells have been described (Rabouille et al., 2012; Chua et al., 2012; Ng and Tang, 2016; Rabouille, 2017). However, the SNARE-dependence of KChIP1 vesicle transport does not appear to fit directly with any of these other described modes of unconventional exocytosis. Furthermore, while the trafficking of KChIP1 vesicles does not appear to involve COPII, its requirement of COPI may nonetheless indicate a Golgi-dependent exocytic process. Further work would be required to better decipher the exocytic itinerary and the mechanism of Vti1a-dependent Kv4/KChIP1 surface transport in more detail.

6. Vti1a′s possible connection with brain malignancy

Vti1a's potential involvement in human malignancy is first indicated by the identification of a *VTI1A* gene fusion with a neighboring gene encoding Transcription factor 7-like 2 (TCF7L2)/T-cell transcription factor 4 (TCF4) (Bass et al., 2011). TCF7L2/TC4 is known to co-operate with β-catenin in colorectal carcinogenesis (Morin et al., 1997), but the fusion product lacks the TCF4 β-catenin-binding domain. A more recent analysis has indicated that the Vti1a-TCF4 fusion protein acts as a dominant-negative regulator of Wnt-β-catenin signaling (Davidsen et al., 2018) but the oncogenic role of the fusion protein remains unclear. The genomic region around *VTI1A* appears rather prone to the production of fusion products. Another report has, however, suggested that the high frequency of fusion transcripts between TCF7L2 and its neighboring genes including *VTI1A*, even in non-cancerous tissues, could be due largely to transcription induced chimeras that are expressed at low levels (Nome et al., 2014).

More recent Genome-wide association study (GWAS)-based analysis have also identified colorectal cancer (Wang et al., 2014) and lung cancer (Su et al., 2015) susceptibility locus in *VTI1A*. Moreover, GWAS-based analysis have shown that the *VTI1A* gene harbors risk locus for glioma in a European population (Kinnersley et al., 2015), and the VTI1A-associated single nucleotide polymorphism (SNP) variant rs11196067 is significantly associated with glioma risk in a Chinese population (Wang et al., 2017). A summary of *VTI1A*'s association with cancer is provided in Table 1. A recent meta-analysis of variants reported in the *VTI1A-TCF7L2* region and potential function of these variants using data from the Encyclopedia of DNA Elements (ENCODE) has indicated that the *VTI1A-TCF7L2* region does have a significant role in cancer pathogenesis (Zhang et al., 2018). The generation of oncogenic fusion gene product via chromosomal translocation is well-known, but fusion gene products involving SNAREs are uncommon. In this regard, the fusion of VAMP2 and Neuregulin 1 (NRG1) genes has been found in non-small-cell lung carcinoma and is predicted to be oncogenic (Jung et al., 2015). Likewise, *STX16*'s fusion with Aminopeptidase Like 1 (*NPEPL1*) has been identified in gastrointestinal stromal tumors (Kang et al., 2016).

Our understanding of involvement of membrane trafficking components in human cancer is largely based on the oncogenic roles of Rabs (Chia and Tang, 2009; Tang and Ng, 2009; Wang et al., 2017; Shaughnessy and Echard, 2018). At the moment it is difficult to determine with any certainty how dysregulated or mutated Vti1a could be oncogenic. Given the role of Wnt signaling in brain tumors (McCord et al., 2017; Rajakulendran et al., 2019), it is conceivable that the Vti1a-TCF7L2/TCF4 fusion product may perturb oncogenic signaling in the brain. Furthermore, it is speculatively plausible that the membrane trafficking role of Vti1a may impact on growth receptor signaling, or in some yet undefined manner facilitates migration or metastasis in cancer cells.

7. Future questions and research directions

In this brief review, the unusually wide and unique roles for the endosomal-TGN SNARE Vti1a in neuron-specific processes are highlighted and discussed. Vti1a appears to function in axonal/neurite outgrowth and thus nervous system development, spontaneous neurotransmission, dense core vesicle exocytosis, and may speculatively have a role in brain malignancy. Our understanding of these Vti1a functions in neurons are in most cases still lacking in mechanistic details, and many important research questions remained. A prominent question would be whether Vti1a could participate directly in a synaptic vesicle SNARE fusion complex, perhaps replacing SNAP25 as a Qb-SNARE. The SNARE complexes formed by VTI1A with other SNAREs in neurons, as well as biochemical and biophysical aspects of their functions in the neuronal processes discussed above, have remained underexplored. Another important question is how does Vti1a's role in endosome-TGN retrograde traffic align with, or explains its apparent role in regulated exocytosis. Little is known about the COPII-independent route of KChIP1 that involves Vti1a. In this regard, does Vti1a have more roles in an unconventional exocytosis involving other cargoes in neurons? Given VTI1A's deciphered role in nervous system development and neurotransmission, it is likely that VTI1A mutations and variants could result in nervous

Table 1. A summary of *VTI1A* and other SNARE family members with known genetic association with various cancers. *VTI1A* - Vesicle transport through interaction with T-SNAREs 1A (Vti1a); *TCF7L2* - Transcription factor 7-like 2; *CFAP46* - Cilia and flagella associated protein 46; *VAMP2* – Vesicle-associated membrane protein 2; *STX16* – Syntaxin 16; *NRG1* – Neuregulin 1; *NPEPL1* – Aminopeptidase-like 1.

Cancer and data type	Vti1a mutation/variant	Reference
Colorectal cancer (CRC) (primary tumor sample and matched adjacent tissues)	*VTI1A-TCF7L2* gene fusion	Bass et al., 2011
CRC cell lines and tissues	Splice variants of *VTI1A-TCF7L2* fusion transcripts	Nome et al., 2014
CRC genome wide association studies (GWAS)	Risk locus at 10q25 (rs12241008, intronic to *VTI1A*)	Wang et al., 2014
Non-small cell lung cancer association	Allele A of *VTI1A* SNP rs7086803	Su et al., 2015
Glioma GWAS	Risk locus at 10q25.2 (rs11196067), near the *VTI1A* gene locus	Kinnersley et al., 2015
CRC GWAS	Risk locus at 10q25.2 (rs10506868)	Zeng et al., 2016
Glioma association	Risk locus rs11196067	Wang et al., 2017
Associations between variants in the *VTI1A-TCF7L2* region and cancer susceptibility	8 common variants of *VTI1A* and *TCF7L2* associated with various cancers	Zhang et al., 2018
Hepatocellular carcinoma (HCC) RNA sequencing	*VTI1A-CFAP46* fusion transcript (from a genomic DNA *VTI1A-CFAP46* translocation event)	Tsuge et al., 2019
Non-small-cell lung adenocarcinoma, whole-transcriptome sequencing	*VAMP2-NRG1* gene fusion	Jung et al., 2015
Gastrointestinal stromal tumors, exome and transciptome sequencing	*STX16-NPEPL1* gene fusion	Kang et al., 2016

system dysfunctions and neurological disorders. This possibility should also be further explored.

With regards to the oncogenic potential of the *VTI1A* locus, an important question would be how do VTI1A variants or mutants, in conjunction with gene fusion products or on their own, drive oncogenesis, particularly those associated with the brain? Forthcoming answers to these questions would undoubtedly enrich our overall fundamental understanding of neuronal physiology and pathology.

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Additional information

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