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Emerging role of NIK/IKK2-binding protein (NIBP)/Trafficking protein particle complex 9 (TRAPPC9) in nervous system diseases

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Abstract

NFκB signaling and protein trafficking network play important roles in various biological and pathological processes. NIK-and-IKK2-binding protein (NIBP), also known as trafficking protein particle complex 9 (TRAPPC9), is a prototype member of a novel protein family, and has been shown to regulate both NFκB signaling pathway and protein transport/trafficking. NIBP is extensively expressed in the nervous system and plays an important role in regulating neurogenesis and neuronal differentiation. *NIBP/TRAPPC9* mutations have been linked to an autosomal recessive intellectual disability (ARID) syndrome, called NIBP Syndrome, which is characterized by non-syndromic ARID along with other symptoms such as obesity, microcephaly, and facial dysmorphia. As more cases of NIBP Syndrome are identified, new light is being shed on the role of NIBP/TRAPPC9 in the central nervous system developments and diseases. NIBP is also involved in the enteric nervous system. This review will highlight the importance of NIBP/

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TRAPPC9 in central and enteric nervous system diseases, and the established possible mechanisms for developing a potential therapeutic.

Keywords

NIBP; TRAPPC9; NFκB; Neurogenesis; Intellectual Disability; NIBP Syndrome

Introduction

The NIK-and-IKK2-Binding Protein (NIBP) is a protein first discovered in 2005 through a yeast two-hybrid screen that was used to identify molecules involved in the NFκB signaling pathway in the central nervous system (CNS) [1]. The C-terminal portion of NIBP interacts with NFκB-inducing kinase (NIK), and NIBP preferentially binds to IKK2 (IKKβ), not IKK1 (IKKα) or NEMO (IKKγ) [1]. According to the PANTHER classification system (http://www.pantherdb.org), NIBP is classified as a novel family of proteins and is highly conserved amongst species, especially between humans and mice [2].

Trafficking protein particle II (TRAPPII) is one of three TRAPP complexes (TRAPPI, TRAPPII and TRAPPIII) that act as multimeric guanine nucleotide exchange factors (GEFs) to activate certain GTPases, helping regulate vesicular trafficking between organelles. The yeast Trs120 protein was discovered in 2000 [3], and plays an important role in TRAPPII. To identify the subunit of mammalian TRAPPII, Blast analyses showed that NIBP was the closest mammalian homologues of yeast Trs120 [4]. Further experimental evidence proved that NIBP is a Trs120 ortholog of mammalian TRAPPII [5], thus also called trafficking protein particle complex 9 (TRAPPC9) [6–8].

NIBP/TRAPPC9 Gene Characteristics and Expression Patterns

Human *NIBP/TRAPPC9* covers 726.10 kb on the reverse strand of chromosome 8q24.3 [9]. Full length *NIBP/TRAPPC9* consists of 23 exons (Table S1); however, there are 35 distinct introns (34 gt-ag, 1 at-ac) present in the genomic sequence. A total of 17 transcript variants (16 alternatively spliced, 1 unspliced) have been reported in the GenBank database, potentially encoding 13 different protein isoforms (Table S1). *NIBP/TRAPPC9* primarily encodes three isoforms of protein in humans: isoform a (1246 amino acids, aa), b (1148 aa), and c (1139 aa). Isoform a represents the most complete transcript, utilizing a start codon in exon 1, and is normally used when referencing coordinates. However, isoform b is actually found to be more highly expressed, which utilizes a downstream start codon in exon 2 during protein translation. According to the GenBank entry [10] for *NIBP/TRAPPC9 (NM_031466.8)*, the extended 5' coding sequence is not conserved, thus making isoform b the primary isoform expressed in humans. Isoform c uses the same start codon as isoform b but has an alternate splicing pattern resulting in the skipping of exon 5. Exon 5 is the shortest exon of *NIBP/TRAPPC9*, encompassing only 27 nucleotides; the function of this exon-skipping is unknown. These transcripts are highly conserved, as mouse *Nibp/Trappc9 (NM_180662.2*) has a complete 22 exon isoform 2 (encodes a 1139 aa protein; exon 5 is skipped), an isoform 1 that uses a downstream start codon in exon 2 (encodes a 960 aa protein), and an isoform 3 that uses the same start codon as isoform 1 and has a truncated C-

terminus (encodes a 940 aa protein). Different isoforms in other species can be found in Table S1. Northern blot analysis and other experimental evidence suggest that shorter isoforms of NIBP/TRAPPC9 may also be expressed in human tissues such as the kidney and muscles, but the function of these isoforms is unknown [1]. To date, only the larger transcripts have been detected in the human brain [1, 7, 11, 12].

AceView analysis [9] identifies a high level of *NIBP/TRAPPC9* mRNA expression, 2.1 times higher than the average gene. Northern blot analysis of human multiple tissues reveals that the mRNA of *NIBP/TRAPPC9* is abundant in organs such as the heart, kidney, brain, and skeletal muscle, with lower levels in immune tissues like the spleen and thymus [1]. The extensive expression of *NIBP/TRAPPC9* mRNA in brain is also confirmed by *in situ* hybridization of human embryonic brain sections [6]. From the developmental transcriptome data for human brains of BrainSpan (http://www.brainspan.org/), we found that the *NIBP/TRAPPC9* mRNA shows in the top level in cortical plate, no matter the age of the brain. From the microarray data of the Allen Human Brain Atlas (https://human.brain-map.org/), we also found that *NIBP/TRAPPC9* shows strong expression in the cortex and subcortex in 6 donor patients. Immunohistochemical studies demonstrated extensive expression of NIBP protein in brain postmitotic neurons [1, 6], spinal cord motor neurons [1], as well as enteric neurons and enteric neural stem cells [13], all of which suggest specialized functions of NIBP in the nervous system.

The expression of NIBP/TRAPPC9 in the mouse brain was examined by *in situ* hybridization and immunofluorescent analysis. The level of *Nibp/Trappc9* RNA is low in E14 mouse brain, slightly higher in P0 mouse brain, and strong in adult mouse brain [6], indicating accumulation with growth. Confocal microscopy of mouse cortical sections showed that NIBP protein localizes in the cytoplasm, with no localization in the nucleus or any organelles [6]. *In situ* hybridization using *Nibp/Trappc9* RNA probe for mouse brain sagittal sections (male C57BL/6J mouse aged 56 days) from the Allen Mouse Brain Atlas data (https://mouse.brain-map.org/) showed that its expression value (0–5) is highest at 1.12 in hippocampal formation region, second highest at 0.87 in cortical subplate region, 0.4–0.5 in isocortex, thalamus and olfactory areas, and less than 0.2 in other regions.

The RNA-seq gene expression profile data across 16 selected tissues shown in NCBI AceView (https://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/), which comes from the Non-Human Primates Reference Transcriptome Resource (http://nhprtr.org/index.html), shows that the expression pattern of *NIBP/TRAPPC9* in non-human primates has some differences compared to that in humans. For example, *NIBP/TRAPPC9* is abundant in human skeletal muscle but scarce in non-human primate skeletal muscle. Moreover, *NIBP/TRAPPC9* is poorly expressed in the spleen, lymph nodes, and thymus of humans, however is abundant in these organs of non-human primates. In other organs and tissues, *NIBP/TRAPPC9* showed similar expression between human and non-human primates.

Experimental evidence using anti-NIBP/TRAPPC9 antibody for Western blot demonstrated the presence of single isoform in human fibroblasts [8] and lymphoblasts [6]. However, several bands of different sizes of NIBP protein were reported in gut tissues [13] and other cells [14–17]. Different sizes of NIBP protein, indicating different isoforms, were also reported in the brain

[13]. The mechanisms underlying the formation of different NIBP isoforms remain elusive, and better antibodies against different NIBP isoforms are still needed. Additionally, CRISPR-mediated tagging of endogenous NIBP at the N-terminal or C-terminal of different isoforms may provide solid experimental evidence for the existence and function of NIBP isoforms[18]. To address this in humans, the induced pluripotent stem cell (iPSC)-derived organoids via CRISPR tagging might be an excellent model[19, 20].

Important Role of NIBP/TRAPPC9 in NFκB Signaling and Protein Trafficking

Regulation of NFκB signaling pathways

The NFκB protein family are transcription factors that are involved in the regulation of many different cellular pathways such as immune responses, cell proliferation and survival, and even memory, neurogenesis, and synaptic plasticity [13, 21]. When NFκB is not activated, it remains in the cytoplasm sequestered by its inhibitor IκB. NFκB is activated if the cell is stimulated, which could be caused by cytokines, antigens, or viruses.

NFκB is activated via three different pathways: classical (canonical), non-classical (non-canonical or alternative), and atypical. The classical pathway can be activated by molecules such as TNFα, IL-1, CD40 ligand, or lymphotoxin-β. In the classical pathway, IKK (composed of 3 subunits: IKK1, IKK2, and regulatory subunit NEMO) is recruited and phosphorylates IκB proteins, leading to the ubiquitination and degradation of IκB via proteasome. With IκB degraded, the NFκB subunit, which classically is a p65 (RelA)/p50 heterodimer, becomes activated and moves from the cytosol to the nucleus to activate transcription. In the non-classical pathway, which can be activated by lymphotoxin-β, CD40 ligand, or B-cell activating factor, NIK is recruited and phosphorylates the IKK complex, which consists of only two IKK1 subunits. The phosphorylated IKK1 then phosphorylates p100 (p52 precursor), causing the transformation of p100 into p52, which forms activated NFκB complex RelB/p52 and moves into the nucleus. Atypical pathways of NFκB activation can be initiated by such causes as UV radiation and oxidative stress. This pathway is atypical because it does not rely on IKK, but the outcome of IκB degradation and NFκB translocation still occurs.

NIBP is involved in both the canonical and non-canonical NFκB activation pathways [1]. NIBP directly interacts with IKK2 of the canonical NFκB pathway and NIK of the non-canonical pathway [1], and enhances cytokine-induced IKK2 kinase activity [1, 2]. These interactions result in the formation of a unique NIK-NIBP-IKK2 complex, which may bridge the canonical and non-canonical NFκB activation pathways (Figure 1). How NIBP balances the canonical and non-canonical NFκB signaling in various physiological and pathological conditions remains largely unknown. When stimulating NIBP-deficient human fibroblast cells with TNFα (a cytokine that strongly activates the canonical NFκB pathway), there was a defect in the degradation of IκB, leading to less activation of NFκB [8]. This indicates that NIBP is required for cytokine-induced canonical NFκB activation in human fibroblast cells [8]. The insufficient NFκB activation induced by human NIBP loss-of-function mutation was confirmed by Mochida *et al.* 2009 and Zahoor *et al.* 2010 [6, 14]. These clinical studies validated the role of NIBP as an enhancer for cytokine-stimulated activation of NFκB signaling[1, 2, 13, 17, 22, 23].

Regulation of protein trafficking

Intracellular protein/membrane trafficking plays a critical role in normal cellular functions and various pathological processes. The proteins and lipids are assembled into vesicles and delivered to their target sites through budding, movement, tethering, docking, and fusion at each organelle. The vesicle or cargo trafficking is mediated mainly by the anterograde secretory/exocytic and the retrograde endocytic transport pathways. The intracellular destinations of the endocytic and exocytic vesicles are determined by the specific coat protein complex (COPI and COPII) that recruit different cargoes. COPI complex coats vesicles transporting proteins from *cis*-Golgi back to the rough endoplasmic reticulum (ER) and between Golgi compartments. COPII complex transports proteins from ER to Golgi. The retromer complex regulates retrograde endocytic trafficking [24, 25], while TRAPP complex generally regulates the anterograde exocytic/secretory trafficking. However, TRAPPI tethers the ER-derived COPII vesicles [26–29], while TRAPPII binds to COPI coatomer and participates in the anterograde transport from *trans*-Golgi network (TGN) to membrane [30, 31] and the retrograde trafficking from endosomes to TGN (Figure 2) [32, 33]. TRAPPIII regulates the trafficking from endosome to TGN and formation of autophagy [34–38].

TRAPPII acts as a COPII-vesicle tether by activating Rab1 GTPase and is needed for docking and fusion of the vesicle with the target membrane [39, 40]. In addition to Rab1 activation, TRAPPII activates Rab18 [17], a key player in regulating the intracellular trafficking and/or dynamics of the cytosolic organelle lipid droplet [41, 42]. NIBP/TRAPPC9 is a key player of TRAPPII [4, 5, 40]. NIBP/TRAPPC9 is essential for lipid droplet homeostasis via interacting with Rab18 in HEK293T cells and hepatocytes [17]. NIBP/TRAPPC9 inactivation by various methods including siRNA depletion and CRISPR/Cas9-mediated deletion induces defective recruitment of Rab18 onto lipid droplet surface, reduces lipolysis and results in aberrantly large lipid droplets [17]. The role of NIBP/TRAPPC9 in neuronal lipid droplets remains to be determined [43, 44].

NIBP/TRAPPC9 protein competitively binds to the dynactin subunit, $P150^{Glued}$, preventing it from binding to Sec23/24, which is needed for the vesicle to move from the ER to the Golgi [15]. This binding allows the uncoupling of the COPII-vesicle from dynactin, allowing for the vesicle to start the docking and fusion process. TRAPPC9 protein contains a Tetratricopeptide Repeat (TPR) domain for protein-protein interactions and 2 ASH (ASPM, SPD-2, Hydin) domains to help localize proteins to the Golgi and help with the interaction of proteins to microtubules [12, 45]. Recently, the TRAPPII complex has been identified as an important regulator of stress granule maturation during the integrated stress response, recruiting COPII to stress granules, which leads to impaired ER export and Golgi fragmentation, thereby halting secretary functions [46]. However, this mechanism is protective to cells, as TRAPPII-depleted cells produce smaller stress granules that cannot properly recruit the signaling proteins RACK1 and Raptor, ultimately making cells less resistant to stress and more prone to apoptosis. Intriguingly, TRAPPII and COPII seem to be recruited only to stress granules in actively proliferating cells in a CDK1/2-dependent manner [46].

NIBP/TRAPPC9 directly binds to TRAPPC2, the mammalian ortholog of Trs20 and part of the core TRAPP complex, and then binds to TRAPPC10, the mammalian ortholog of Trs130

[47] to help form the complete TRAPPII complex. NIBP/TRAPPC9 was found to interact with several additional members of TRAPPII in yeast and Cos-7 cells including Bet3 (TRAPPC3) [5], Trs65 (TRAPPC7), etc [48]. One difference between yeast and mammalian TRAPPII is that there is no mammalian ortholog of Trs65, so TRAPPC6A and TRAPPC6B are required for proper assembly. The STRING interaction network (http://string-db.org/newstring_cgi/show_network_section.pl) identified 14 proteins interacting with NIBP/TRAPPC9, including TRAPPC2, 3, 4, 8, 10, 12. These interactions suggest that NIBP/TRAPPC9 is a critical member of TRAPPII and essentially regulates TGN function.

The molecular mechanisms underlying protein trafficking regulation by NIBP/TRAPPC9 remain largely unclear. NIBP/TRAPPC9 interacts with Rabin8, which is recruited by Rab11 through TRAPPII to the pericentrasomal vesicles and activates Rab8 to promote ciliogenesis [45, 49, 50]. Mutations in the gene *brunelleschi* (*bru*), which encodes the *Drosophila* ortholog of NIBP/TRAPPC9, cause defects in both actomyosin ring constriction and cleavage furrow ingression, indicating the important role of Bru/NIBP/TRAPPC9 in regulating the efficiency of membrane addition to the cleavage furrow, thus promoting cytokinesis in *Drosophila* male meiotic cells [51]. This cytokinetic role results from the genetic interaction of Bru with Rab11 and PI4Kβ in dividing spermatocytes [51–53]. Knockdown of *bru* in circadian neurons resulted in increased locomotor activity and reduced sleep, suggesting the neuronal function of Bru/NIBP/TRAPPC9 in regulating circadian rhythm [54]. Our preliminary studies identified Myo5B as a new partner for NIBP (unpublished data). Myo5B associates with recycling endosomes and triggers rapid spine recruitment of endosomes and local exocytosis in spines upon NMDA receptor-mediated Ca^{2+} influx [55]. Disruption of Myo5B or its interaction with the adaptor Rab11-FIP2 abolishes exocytosis from recycling endosomes and prevents both AMPAR insertion and spine growth [56, 57]. Altogether, NIBP/TRAPPC9 may play important role in meiotic cytokinesis, neuronal polarization and synaptic plasticity via regulating intracellular protein trafficking.

NIBP/TRAPPC9 Loss-of-function Causes Central Nervous System Diseases

NIBP syndrome

A recent review by Mbimba *et al.* has briefly summarized the basic information of NIBP/TRAPPC9 and its association with various human diseases [58]. Here, we focus primarily on the correlation between NIBP/TRAPPC9 mutations and nervous system diseases. Clinically, genetic recessive mutations leading to function-loss of NIBP/TRAPPC9 are associated with non-syndromic autosomal recessive intellectual disability (NS-ARID). The common phenotypes seen within these patients have led clinicians to designate **NIBP syndrome**. The human disease database MalaCards (https://www.malacards.org/) assigned it as “Intellectual Disability-Obesity-Brain Malformations-Facial Dysmorphism Syndrome”. It is also referred to as “Mental Retardation, autosomal recessive 13” (MIM #613192) by the *Mendelian Inheritance in Man* online database [59].

ID affects about 1–3% of the population worldwide and is clinically assessed through the patient’s IQ score below 70 and at least two behavioral issues such as delayed language, impaired social skills, or impaired self-help skills [7, 60, 61]. About 25% of ID genetic causes are due to autosomal recessive mutations, making it a more common cause than X-linked

mutations [8, 47, 62]. The actual number of autosomal genes linked to ID is estimated to be over 2500, with a majority of these being autosomal recessive [47, 54, 63, 64]. This estimate has been further validated by recent large-scale studies identifying 903 ARID candidate genes [65]. It is important to note that genetic heterogeneity makes it difficult to identify causative genes as patients have multiple mutations of unknown effects. With the rise of next generation sequencing, the number of patients diagnosed will likely increase.

Of these reported genes linked to NS-ARID, *NIBP/TRAPPC9* is one of the most prevalent. To date (04/2020), there are at least 26 families worldwide, with a total of 55 patients (including 5 cases in the DECIPHER database [66] that have not been included in any published clinical reports to date) (Table 1, Table S2), which have reported homozygous or compound heterozygous mutations in the *NIBP/TRAPPC9* gene. Most of the patients with *NIBP/TRAPPC9* mutations are geographically located in countries where consanguineous families are common, such as Middle Eastern countries, making any autosomal recessive mutations within these families more visible. There are also reports of 4 non-consanguineous families with a total of 6 patients [62, 67].

There are various types of mutations that occur within the *NIBP/TRAPPC9* gene (Table 1 and Table S2). A large majority of these are the truncating nonsense or frameshift mutations, though deleterious missense and splice site mutations have also been reported. In all instances, these recessive mutations lead to the translation of non-functional NIBP/TRAPPC9 proteins (Figure 3). As both alleles are affected either via homozygous or compound heterozygous mutations, little to no functional protein is produced, resulting in NIBP/TRAPPC9 deficiency. Patients with NIBP syndrome exhibit some, if not all, of the following common phenotypical features: moderate to severe ID, speech disorder, postnatal microcephaly, dysmorphic facial features (round face, straight eyebrows, deep set eyes, short philtrum, and thin upper lips), obesity, hypotonia, and brain abnormalities (thin corpus collosum, reduced white matter) [12, 47, 62].

Other NIBP/TRAPPC9-Associated CNS Disorders

While homozygous or compound heterozygous mutations are correlated with the phenotypes associated with NIBP syndrome, a number of heterozygous mutations or copy number variants have been linked to various neurodevelopmental disorders (Table S3). The Simons Foundation Autism Research Initiative (SFARI) Gene database classifies *TRAPPC9* as a strong candidate autism spectrum disorder (ASD) risk gene [68]. A number of studies have identified heterozygous *NIBP/TRAPPC9* mutations in patients with ASD that are considered likely damaging [69–73]. In agreement with this, many NIBP syndrome patients have been reported to have ASD-related features, such as stereotyped/repetitive movements or other behavioral disorders (Table 1). It is also of note that at least two NIBP syndrome patients were originally diagnosed with ASD prior to genomic analysis [74, 75]. One recent report on a patient with a frameshift mutation (c.2415_2416insC, p.His806Profs*9) and a splice site mutation (c.3349C1G>A) showed autistic features and cleft lip, broadening the spectrum of clinical manifestations of TRAPPC9 [74]. It is possible that deficiency of NIBP/TRAPPC9 may be a risk factor for ASD, which would be further exacerbated in cases with homozygous or compound heterozygous mutations. However, as some healthy individuals in

these families have heterozygous mutations and no apparent ASD phenotype, the role of NIBP/TRAPPC9 is likely much more complex.

NIBP/TRAPPC9 mutations and copy number variants have also been linked to schizophrenia [76, 77]. These findings are significant as there is a surprisingly high overlap in risk genes for ASD and schizophrenia [77, 78], as well as overlap for genes related to ID [79]. Recently *NIBP/TRAPPC9* was identified as a potential attention deficit hyperactivity disorder (ADHD) risk gene based on data from large gene studies, which was corroborated using a knockdown *Drosophila melanogaster* model [54]. A probably damaging heterozygous missense mutation of NIBP/TRAPPC9 was discovered in a patient with normosmic hypogonadotropic hypogonadism (nHH)/Kallmann syndrome (KS) [80]. While features related to this disorder have not been reported in any NIBP syndrome patients, it does present a potential role for NIBP/TRAPPC9 in normal hypothalamus function, which may explain the obesity phenotype seen in >60% patients with NIBP syndrome. However, this patient also had a second mutation on another gene (*PDE3A*) of unknown significance that may have contributed to the observed phenotype [80]. NIBP/TRAPPC9 mutations are significantly associated with the prevalence of intracerebral hemorrhage [81]. A study has reported 2 patients that demonstrated prenatal microcephaly [82], however these patients also had a homozygous mutations in *MCPH1* (Microcephaly Primary Hereditary 1) gene that may play a role in this phenotype.

NIBP-NFκB Pathway Involved in CNS Disorders

The causal correlation of NIBP/NFκB recessive mutations with intellectual dysfunction in NIBP syndrome remains elusive. NFκB signaling plays a double-edged sword role after CNS injuries or diseases [83–87]. In most cases, activation of NFκB signaling in immune cells, microglia/macrophage, and astrocytes produces overwhelming inflammatory mediators and neurotoxic molecules, leading to neurodestruction [86, 87]. For example, excess neuroinflammatory responses induced by NFκB overactivation is involved in the development of Alzheimer's disease, Parkinson's disease, and AIDS dementia [8, 88–90]. The expression and function of NIBP in these chronic neurodegenerative diseases have not yet been investigated, although some microarray data was reported in GEO profiles (www.ncbi.nlm.nih.gov/geoprofiles/?term=NIBP). Considering NIBP is an enhancer of cytokine-induced NFκB activation, we speculate that NIBP may be a potential therapeutic target for these neurodegenerative diseases. However, NFκB signaling in neural stem cells, neuron and oligodendrocytes is crucial in regulating neurogenesis, neuronal survival, synaptogenesis, neural plasticity, axonal myelination, learning and memory [84, 86, 87, 91–97]. Thus, disruption of NFκB signaling may contribute to the development of neurodevelopmental disorders. NIBP might be a critical regulator of NFκB signaling during the normal neurodevelopment.

NFκB activation is involved in synaptic plasticity, such as via long-term potentiation (LTP) [1, 13]. Impaired NFκB activation inhibited LTP in the hippocampus and amygdala [98, 99] as well as reduced synapse and dendritic spine number and altered spine morphology [12, 94]. Deletion of NFκB in the forebrain demonstrates impaired spatial memory formation, synaptic transmission, and plasticity [100]. Since NIBP bridges the canonical and non-

canonical NFκB pathways, decreased NIBP expression significantly impairs NFκB activation within neurons. NIBP is highly expressed in neurons of the human brain, and patients with NIBP Syndrome have been shown to have axon connectivity defects [6, 12, 80]. We speculate that loss of NIBP resulting in diminished NFκB activation may lead to decreased gene expression needed for synaptic activity, which could result in the dendritic spine morphological and quantitative changes and lead to impairments in LTP, affecting learning and memory, and contribute to the ID phenotype seen in NIBP Syndrome.

NFκB activation leads to anti-apoptotic gene expression, allowing neuronal survival [1, 86, 101]. With the loss of NIBP, NFκB activation in neurons is decreased, which leads to lowered expression of anti-apoptotic genes and, as a result, increased neuronal death. NIBP is expressed in postmitotic neurons [6], therefore, a loss of NIBP may lead to increased postmitotic neuronal death, which may explain why microcephaly in patients with NIBP syndrome is not present at birth, but is developed postnatally, which is called secondary microcephaly [12].

Dysregulation of neurogenesis during the embryonic or neonatal stages has been shown to contribute to ID, epilepsy, autism, and some genetic disorders such as Fragile X and Down's Syndrome [102–104]. NFκB is shown to be involved in regulation of both embryonic and adult neurogenesis, which involves the proliferation, migration, and differentiation of neural stem cells (NSCs) [11, 62, 102, 105, 106]. In order to initiate the early differentiation of NSC, TNFα-induced NFκB activation is required, which downregulates CCAAT/enhancer binding protein beta (C/EBPβ) [95, 102] required for NSC self-renewal. When NFκB activation is blocked, asymmetric cell division of NSC is inhibited and NSC self-renewal is maintained, with the NSC remaining undifferentiated [105]. Impaired neurogenesis has been implicated in the pathogenesis of a wide range of disorders, and therefore is hypothesized to be associated with intellectual disability that is seen in NIBP syndrome.

NFκB regulation of neurogenesis can also be seen as a double-edged sword, with transient NFκB activation regarded as beneficial in neural repair and daily maintenance of neurons while chronic, overactivation of NFκB could lead to a depleted NSC pool and insufficient neurogenesis [102, 107]. In this regard, inhibiting NIBP may be a key to help attenuate NFκB overactivation and help to slow or even treat the implicated neurological deficits. However, caution must be taken since a reduced level of NFκB activation could also lead to insufficient neurogenesis, as seen in NIBP knockdowns, which prevents nerve growth factor (NGF)-induced neuronal differentiation via decreased activation of NFκB and less suppression of C/EBPβ [1, 100, 102, 106]. NIBP may regulate white matter development [100, 106, 108]. Knockdown of NIBP prevents NFκB-regulated axon and dendritic growth, branching, and cell differentiation [1]. In patients with NIBP syndrome, little NIBP expression [6, 8] may result in reduced NFκB-mediated axon growth and less CNS myelination[91], leading to the characteristic white matter hypoplasia seen in these patients.

NIBP/TRAPPC9-Mediated Protein Trafficking in CNS Disorders

Mutations in TRAPP subunits are thought to lead to a build-up of non-functional proteins, which may impair vesicular trafficking, a common biologic defect seen in neurologic

disorders [48, 109]. Mutations in other genes involved in vesicle trafficking, such as Vacuolar Protein Sorting 13 Homolog B (*VPS13B*), GDP Dissociation Inhibitor 1 (*GDI1*), and Tuberous Sclerosis Complex 2 (*TSC2*) have been associated with NS-ARID [12, 110]. Mutations of TRAPP proteins have previously been reported to result in neurologic disorders, which recently have been collectively termed "TRAPPopathies" [111]. For example, mutation of *TRAPPC2* causes X-linked spondyloepiphyseal dysplasia tarda (X-linked SEDT) [16, 112, 113]. Homozygous truncating mutations on *TRAPPC6B* are associated with microcephaly, epilepsy, and NS-ARID [114–116]. A homozygous mutation in *TRAPPC6A* is linked to ID [114], and a separate *TRAPPC6A* mutation is associated with Alzheimer's disease [117]. Mutations in *TRAPPC11* result in neuromuscular and developmental phenotypes [118–120]. A *TRAPPC12* mutation is identified in progressive childhood encephalopathy [121]. Very recently, a homozygous splice variant of *TRAPPC4* is linked to a novel neurodevelopmental disorder marked by severe ID, microcephaly, early-onset epilepsy, and spastic quadriparesis [122]. Since NIBP/TRAPPC9 is a part of a TRAPPII complex, mutations or impairments in expression lead to impairments in TRAPPII complex formation and trafficking [16, 123]. This altered trafficking seen in NIBP/TRAPPC9 mutations may be associated with *TRAPPC9*-associated intellectual disability and neural development [16, 47], suggesting that the trafficking complex TRAPPII may be compromised in NIBP syndrome patients.

NIBP/TRAPPC9 Contribution in Enteric Nervous System Diseases

NIBP may also have a role within the enteric nervous system (ENS), which consists of intrinsic neurons and glial cells and is involved in regulating gut motility, secretion, absorption, and mucosal secretion. In mice, NIBP is expressed in enteric neurons and may be expressed in enteric neural stem cells [13], but is not present in glial cells, colonic smooth muscle cells, or interstitial cells of Cajal [13]. The highest NIBP expression within the ENS is within the myenteric plexus, with different levels of expression in different subpopulations of enteric neurons [13]. This may indicate that NIBP is being trafficked within these neurons or possibly indicates posttranslational modification of NIBP. Future research is needed to get a better understanding of why the different levels of expression exist within these subpopulations. One hypothesized role of NIBP in the ENS is that it regulates the plasticity of the enteric neurons [13]. ENS plasticity, like CNS plasticity, is the strengthening of neuronal connectivity and is believed to be essential for adapting to changes within the environment the nerves are located in. ENS structural and functional changes are a consequence of gut inflammation and can lead to dysfunctional ENS plasticity, which is associated with inflammatory bowel diseases [13, 124]. Experiments using an enteric neural cell line show that a knockdown of NIBP leads to inhibited TNFα-induced NFκB activation and decreased enteric neuronal differentiation, whereas NIBP overexpression promoted NFκB activation and ENS differentiation [13]. Similar to its role in the CNS, NIBP and NFκB may also be involved in neurogenesis within the ENS[125, 126], and decreased expression of NIBP and subsequent inhibition of NFκB activation within these neuronal cells may be associated with inflammation-mediated gastrointestinal disorders. Future research into the function and mechanisms of NIBP within enteric neurons and enteric NSCs is needed for further understanding and treatment of inflammatory bowel diseases and possibly other ENS-related

disorders such as Hirschsprung's Disease, in which NSC transplant is currently being investigated as a treatment option [127, 128].

Conclusion and Future Directions

The current understanding of NIBP/TRAPPC9 demonstrates that this protein has both physiologic and pathologic roles and is involved in CNS and ENS. NIBP can potentiate NFκB activation within cells, being beneficial within neuronal cells by inducing neurogenesis, neuronal cell growth, branching, and differentiation, as well as promoting synaptic plasticity, which is associated with learning and memory in the CNS and maintaining gut homeostasis and enteric neuron differentiation within the ENS. NIBP/TRAPPC9 is also a subunit in mammalian TRAPPII complex that is essential for *trans*-Golgi vesicular trafficking important in proper neuronal development.

Decreased expression or functional loss of NIBP/TRAPPC9 in the CNS leads to intellectual disability-obesity-brain malformations-facial dysmorphism syndrome (NIBP syndrome). Mutations of *NIBP/TRAPPC9* should be screened in patients exhibiting similar phenotypic characteristics as seen in NIBP syndrome, especially if they come from a consanguineous family background or if an autosomal recessive mutation is suspected.

Nevertheless, several outstanding questions regarding NIBP/TRAPPC9 and nervous system diseases remain. Whether and how NIBP bridges the classical and non-classical NFκB pathways needs solid experimental evidence. The molecular mechanisms underlying various phenotypic changes such as obesity in NIBP syndrome or those seen in NIBP deficient animal models needs to be explored for potential therapeutic development. How NIBP/TRAPPC9 regulates protein trafficking and whether cell type-dependent difference exists in these regulations also needs more investigation. This protein trafficking is critical for the pathogenesis of diseases like Alzheimer's disease (AD), where trafficking of amyloid precursor protein (APP) and related secretases, in particular the β-site APP cleaving enzyme 1 (BACE1), is essential. As part of TRAPPII, whether and how NIBP/TRAPPC9 regulates APP trafficking and influences AD pathogenesis remains to be discovered. Another area of investigation is whether there are any changes in neurocytological behavior, such as cell structure, axon and cell connection, in NIBP/TRAPPC9 related diseases. Future research is needed to understand the roles and mechanism of NIBP/TRAPPC9 in central and enteric neuropathy diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation

AD	Alzheimer's disease
ADHD	attention deficit hyperactivity disorder
AL	autolysosome
APP	amyloid precursor protein
ASD	autism spectrum disorder
BACE1	β-site APP cleaving enzyme 1
BAFFR	B-cell activating factor receptor
C/EBPβ	CCAAT/enhancer binding protein beta
CNS	central nervous system
COP	coat protein complex
ENS	enteric nervous system
ER	endoplasmic reticulum
GDI1	GDP dissociation inhibitor 11
GEFs	guanine nucleotide exchange factors
ID	intellectual disability
IκB	inhibitor of NFκB
IKK2	IκB kinase 2
IL1R	interleukin-1 receptor
KS	Kallmann syndrome
LTP	long-term potentiation
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NGF	nerve growth factor
nHH	normosmic hypogonadotropic hypogonadism
NIK	NFκB-inducing kinase
NIBP	NIK-and-IKK2-binding protein
NS-ARID	non-syndromic autosomal recessive intellectual disability
NSCs	neural stem cells
SFARI	Simons Foundation Autism Research Initiative

TGN	trans-Golgi network
TLR	toll-like receptor
TNFR	tumor necrosis factor receptor
TPR	Tetratricopeptide Repeat
TRAPP	trafficking protein particle
TRAPPC9	trafficking protein particle complex 9
TSC2	tuberous sclerosis complex 2
VPS13B	vacuolar protein sorting 13 homolog B

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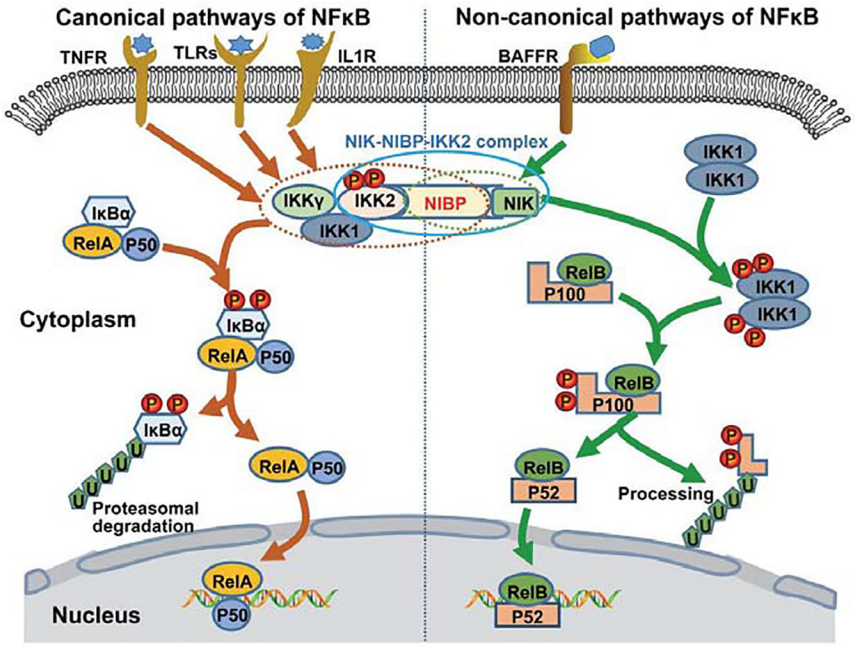

Figure 1. NIBP/TRAPPC9 function within the NFκB activation pathway.

NFκB can be activated via three main pathways: the classical/canonical, alternative/non-canonical, and the atypical pathways. The classical pathway involves a three subunit IKK complex composed of IKK1, IKK2, and regulatory subunit IKKγ, IκB proteins, and the NFκB p65/p50 heterodimer. The alternative pathway involves NIK, a two-subunit IKK complex composed of two IKK1 subunits, p100, and the NFκB RelB/p52 heterodimer. NIBP binds directly to IKK2 and NIK and may bridge both classical and alternative activation pathways together. NIBP may be essential for NFκB activation and its dysregulation may be involved in the pathogenesis of various NFκB-associated disorders. *Notes.* IL1R, interleukin-1 receptor; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor; BAFFR, B-cell activating factor receptor; NIK, NFκB-inducing kinase; IκB, Inhibitor of NFκB; IKK, IκB kinase; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells.

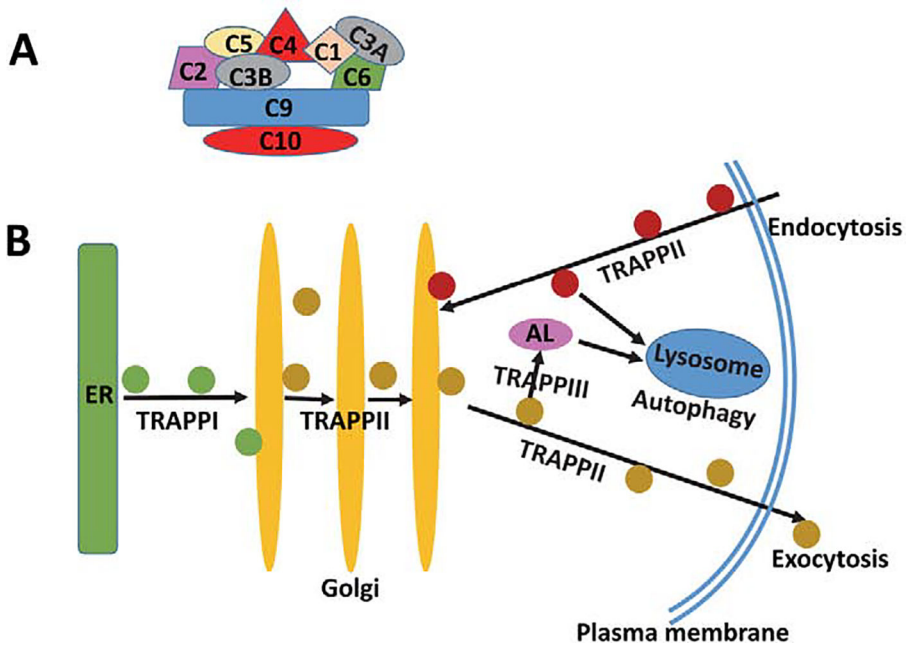

Figure 2. Location and function of NIBP/TRAPPC9 during protein trafficking.

A. Schematic of mammalian TRAPPII complex. TRAPPC9 subunit interacts directly with TRAPPC10, TRAPPC2, and TRAPPC6. **B.** Function of TRAPP complexes. TRAPPI is involved in vesicular transport from ER to Golgi, TRAPPII is involved in *trans*-Golgi, Golgi-to-plasma membrane, and endosome-to-Golgi transport, and TRAPPIII is involved in formation of autolysosome for autophagy.

Notes. ER, endoplasmic reticulum; AL, autolysosome; TRAPP, trafficking protein particle.

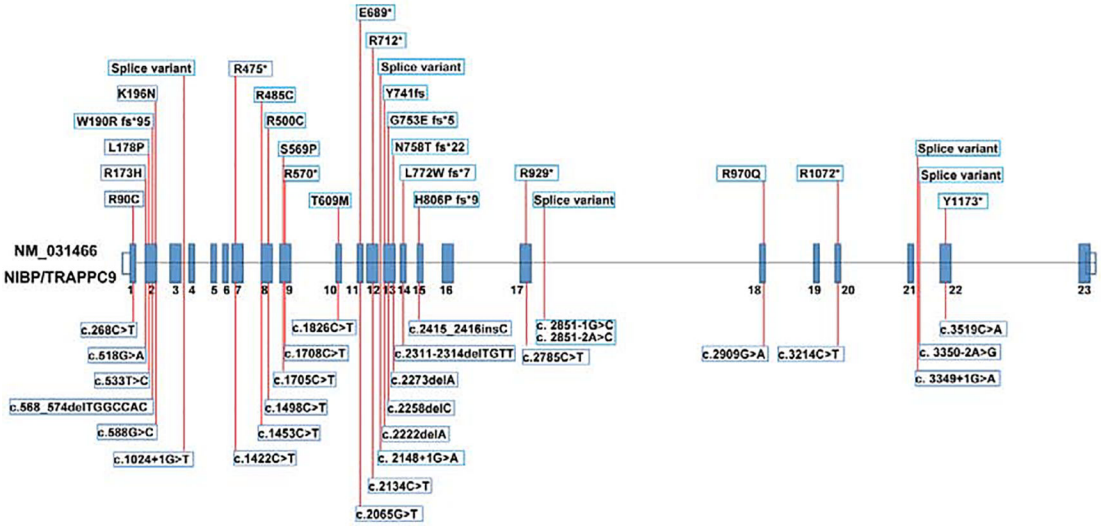

Figure 3. ***NIBP/TRAPPC9*** **gene mutations result in the translation of a truncated, non-functional protein.**

Various genetic mutations within the *NIBP/TRAPPC9* gene have been discovered and affect different exons within the gene. Most genetic mutations reported in this gene lead to a premature stop codon, which results in a truncated NIBP/TRAPPC9 protein. This mutated protein is non-functional and has decreased expression within NIBP Syndrome patients.

Table 1.

Summary of patients with genetic mutations affecting *TRAPPC9* and exhibiting NS-ARID.

Mutation (GRCh37/hg19)	Mutation Type	Affected Families	Cases, Sex	Consanguineous	Major symptoms
p.Leu178Pro (c.533T>C)	Nonsense homozygous mutation in exon 2	-Moroccan	1 M, 1 F [82]	Likely	Severe ID, congenital microcephaly, severe language and motor delays, MRI findings (white matter abnormalities), hyperkinesia
p.Trp190Argfs*95 (c.568_574delTGGCCAC)	Homozygous 7 nucleotide deletion in exon 2	-Maltese	1 M [75]	No	ID, microcephaly, absence of speech, facial dysmorphia, MRI findings, ASD, stereotypical movements
Splice site defect (c.1024+1G>T)	Homozygous skip of exon 3 or exons 3 and 4	-Pakistani	3 F [129]	Yes	Moderate ID, microcephaly, speech and motor delay
p.Arg475* (c.1423C>T)	Nonsense homozygous mutation in exon 7	-Pakistani -Pakistani -Syrian -Israeli Arab -Egyptian	3 M [12] 1 M, 6 F [7] 3 M, 3 F [130] 3 F [6] 1 F [131] (Decipher ID 296553)	Yes Yes Yes Yes Yes	ID, microcephaly, speech delay Microcephaly, speech and motor delays, mild obesity, MRI findings Severe ID, moderate-severe microcephaly, severe motor and speech delay, hypotonia, severe growth retardation, stereotypic movements Severe ID, microcephaly, speech delay, MRI findings Moderate ID, microcephaly, speech and motor delay, MRI findings, facial dysmorphia, stereotypical movements
p.Arg500Cys (c.1498C>T)	Missense homozygous mutation in exon 8	n/a	1 M (unpublished; Decipher ID 262147)	n/a	Global developmental delay, brachycephaly, delayed speech developmental, mild facial dysmorphia
p.Arg570* (c.1708C>T)	Nonsense homozygous mutation in exon 9	-Tunisian -Tunisian	3 M [8] 1 M, 2 F [67]	Yes Yes	Moderate-Severe ID, speech delay, mild microcephaly, truncal obesity, mild facial dysmorphia, MRI findings Severe ID, microcephaly, obesity, facial dysmorphia
p.Glu689* (c.2065G>T)	Nonsense homozygous mutation in exon 11	-Pakistani	2 M, 1 F [12]	Yes	Severe ID, microcephaly, speech and motor delay
p.Gly753Glufs*5 (c.2258del)	Nonsense homozygous mutation in exon 13	n/a	2 F (unpublished; Decipher ID 284294 and 284295)	n/a	Severe ID, congenital microcephaly, absence of speech, mild facial dysmorphia, stereotypic movements
p.Leu772Trpfs*7 (c.2311-2314delTGTT)	Homozygous out of frame 4 nucleotide deletion in exon 14	-Iranian	3 M [7]	Yes	ID, microcephaly, absence of speech, obesity
p.Arg929* (c.2785C>T)	Nonsense homozygous mutation in exon 19	n/a	1 M [132]	Yes	ID, microcephaly, global developmental delay, abnormal gait, facial

Mutation (GRCh37/hg19)	Mutation Type	Affected Families	Cases, Sex	Consanguineous	Major symptoms
					dysmorphia, MRI findings (including reduced myelination)
p.Thr951Tyrfs*17 (c.2851-2A>C)	Homozygous splice variant causing skip of exon 18 leading to frameshift	-Italian	2 F [62]	No	Severe ID, hypotonia, seizures, microcephaly, facial dysmorphia, speech and motor delay, MRI findings (white matter abnormalities), obesity
p.Arg1072* (c.3214C>T)	Nonsense homozygous mutation in exon 20	-Indian	1 F [133]	Yes	ID, primary microcephaly, Moderate-Severe global developmental delay, truncal obesity, MRI findings, stereotypic movements
8q24.3 microdeletion	Homozygous 141 kb deletion in subtelomeric region of 8q24.3 deleting only *TRAPPC9*	-Filipino	1 F [11]	Yes	Severe ID, microcephaly, MRI findings, facial dysmorphia, severe motor and speech delay, hypotonia, obesity
Intragenic tandem duplication	Homozygous 115 kb intragenic tandem duplication	-Algerian	1 F [67] (Decipher ID 349431)	Yes	Moderate-Severe ID, microcephaly, MRI findings, facial dysmorphia, obesity, stereotypic movements
p.Trp190Argfs*95 (c.568_574delTGGCCAC) and duplication	Maternally inherited 7 nucleotide deletion in exon 2 and paternally inherited 119 kb in-frame intragenic duplication	-Italian	1 F [67] (Decipher ID 314942)	No	Moderate-Severe ID, microcephaly, MRI findings, facial dysmorphia, obesity, stereotypic movements
p.Arg712* (c.2134C>T) and deletion	Paternally inherited heterozygous nonsense variant in exon 12 and maternally inherited 189 kb intragenic deletion	-French	1 F [67]	No	Moderate-Severe ID, microcephaly, MRI findings, facial dysmorphia, obesity, stereotypic movements
p.His806Profs*9 and splice site defect (c.2415_2416insC, c.3349+1G>A)	Compound heterozygous mutations in exon 15 (nonsense) and intron 21 (splice variant)	-Thai	1 M [74] 1 F [74]	No No	ID, developmental delay, microcephaly autism spectrum disorder (ASD), cleft lip
p.Arg475* and splice site defect (c.1423C>T, c.3350-2A>G)	Compound heterozygous mutations in exon 7 (nonsense, maternal) and intron 21 (splice variant, paternal)	-European	1 M [134]	Yes	ID, global developmental delay, speech and motor delays, microcephaly, MRI findings including myelination defects, facial dysmorphia
Compound splice site defects (c.2148+1G>A, c.2851-1G>C)	Compound heterozygous mutations in intron 12 (maternal) and intron 17 (paternal)	n/a	1 F (unpublished; Decipher ID 271665)	n/a	Severe global developmental delay, microcephaly childhood-onset truncal obesity, facial dysmorphia, stereotypic movements
p.Arg570* and p.Arg500Cys (c.1708C>T, c.1498C>T)	Compound heterozygous mutations in exon 9 (nonsense, maternal) and exon 8 (missense, paternal)	n/a	1 M (unpublished; Decipher ID 277516)	n/a	Global developmental delay, absence of speech, facial dysmorphia

Mutation (GRCh37/hg19)	Mutation Type	Affected Families	Cases, Sex	Consanguineous	Major symptoms
p.Ser569Pro, p.Arg570Profs*80; p.Asn758Thrfs*22 (c.1705C>T, c.1708dupC, c.2273delA)	Compound heterozygous nonsense mutations in exon 9 (maternal) and exon 13 (paternal)	-Chinese	1 M [135]	n/a	ID, language delay, abnormal MRI findings including dysplasia of corpus callosum

Note: To date, 26 families with a total of 55 patients have been identified, with most being from consanguineous families. Clinical symptoms seen in all patients include moderate to severe intellectual disability, speech disorder, postnatal microcephaly, dysmorphic facial features, obesity, hypotonia, and brain white matter abnormalities.