JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 8, NO. 12, 2023

STATE-OF-THE-ART REVIEW

Biochemical Structure and Function of TRAPP Complexes in the Cardiac System

Peter Papaioannou, BS,[a,b,*] Michael J. Wallace, BS,[a,c,*] Nipun Malhotra, MSc,[a,b] Peter J. Mohler, PhD,[a,c,d] Mona El Refaey, PhD[a,b]

HIGHLIGHTS

- **The majority of TRAPP literature focuses on function in the nervous system. Here, we highlight the molecular pathways of TRAPP in secretion, autophagy, and trafficking to gain insight into potential functions of TRAPP in the heart and beyond. We also discuss cardiac disease states related to trafficking defects in cardiomyocytes, highlighting how TRAPP dysfunction might play potential roles in cardiac dysfunction.**
- **Human variants and/or expression changes in numerous TRAPPC subunits are associated with cardiac dysfunction such as myocardial infarction, stroke, Ca^{2+} handling defects, atrial fibrillation, and others. These individual case reports culminate to validate a role of TRAPPII and TRAPPIII in cardiac function.**
- **TRAPPII is a GEF for Rab1 and Rab11 while TRAPPIII is a GEF for Rab1. Rab1 and Rab11 are GTPases that play roles in expression/localization of cardiac ion channels such as $K_v4.2$ and $K_v1.5$, respectively. Therefore, both TRAPPII and TRAPPIII may play previously unidentified roles in cardiac excitability. Further trafficking mechanistic understanding may drive future therapeutic research.**

SUMMARY

Trafficking protein particle (TRAPP) is well reported to play a role in the trafficking of protein products within the Golgi and endoplasmic reticulum. Dysfunction in TRAPP has been associated with disorders in the nervous and cardiovascular systems, but the majority of literature focuses on TRAPP function in the nervous system solely. Here, we highlight the known pathways of TRAPP and hypothesize potential impacts of TRAPP dysfunction on the cardiovascular system, particularly the role of TRAPP as a guanine-nucleotide exchange factor for Rab1 and Rab11. We also review the various cardiovascular phenotypes associated with changes in TRAPP complexes and their subunits. (J Am Coll Cardiol Basic Trans Science 2023;8:1599-1612) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Frick Center for Heart Failure and Arrhythmia Research, Dorothy M. Davis Heart and Lung Research Institute, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; [b]Division of Cardiac Surgery, Department of Surgery, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; [c]Department of Physiology and Cell Biology, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; and the [d]Division of Cardiovascular Medicine, Department of Internal Medicine, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA. *Mr Papaioannou and Mr Wallace contributed equally to this work.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 3, 2023; accepted March 14, 2023.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2023.03.011

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 8, NO. 12, 2023
DECEMBER 2023:1599–1612

ABBREVIATIONS AND ACRONYMS

ER = endoplasmic reticulum

GEF = guanine nucleotide exchange factor

hiPSC-CM = human induced pluripotent stem cell-derived cardiomyocyte

LGMD = limb girdle muscular dystrophy

LVAD = left ventricular assist device

NIBP = NIK-IKK2-binding protein

RVF = right ventricular failure

TRAPP = trafficking protein particle

Intracellular protein trafficking is essential for delivering proteins to various parts of the cell to perform their designated function and maintain specific protein concentrations in subcellular compartments.[1] The trafficking protein particle (TRAPP) complex serves as a multisubunit protein complex that functions as a tethering factor. Tethering factors facilitate the initial contact between the target membrane and the transport carrier, a complex of proteins that carry cellular products to their destination. As multisubunit tethering factors, TRAPP complexes act as crucial facilitators for transporting protein products. TRAPPIII participates in transport from the endoplasmic reticulum (ER) to the Golgi while TRAPPII participates in transport and secretion within the Golgi apparatus.[1] These processes are vital for maintaining protein-mediated cellular homeostasis, therefore maintaining normal biological activity of various body systems, including the heart and nervous system. In the text, TRAPPI, TRAPPII, TRAPPIII, and TRAPPIV refer to the entire TRAPP structure, including its subunits, while individual subunits within these structures are referred to as TRAPPC# (ie, TRAPPC1, TRAPPC6A, TRAPPC11, etc).

TRAPPII and TRAPPIII are guanine nucleotide exchange factors (GEFs) for Rab11 and Rab1, respectively, and therefore may play an understudied role in modulating the cardiac action potential,[2] although direct studies exploring the relationship between cardiac ion channels and TRAPP have not been conducted.[3,4] Human variants in trafficking regulatory genes cause cardiac dysfunction. For instance, a variant in a trafficking regulatory protein for the voltage-gated sodium channel $Na_v1.5$ was shown to cause Brugada syndrome.[5] Furthermore, mutations in cardiac ion channels at binding sites of trafficking proteins also cause severe cardiac dysfunction in the $K_v11.1$ voltage-activated K^+ channel.[6] Intracellular transport mechanisms for cardiac ion channels have been extensively studied to develop new therapeutic strategies for congenital forms of cardiac dysfunction in which treatment is only limited to control and/or prevent symptoms.[7,8] The voltage-gated K^+ channel $K_v1.5$, and I_{Kur} (ultra-rapid delayed rectifier K^+ current) have garnered attention as potential targets for atrial fibrillation therapy.[9] Knockdown of snorting nexin 17, a regulator of $K_v1.5$ trafficking, increased $K_v1.5$ membrane expression and I_{Kur}, thereby increasing susceptibility to atrial fibrillation in mice, suggesting that trafficking and trafficking regulatory proteins can have robust influences on cardiac phenotype.[10] Therefore, targeting the trafficking pathways for $K_v1.5$ may provide a potential therapeutic strategy. Interestingly, Rab11, a monomeric GTPase, participates in trafficking of $K_v1.5$ ion channels as a driver for $K_v1.5$ endosomal recycling in mouse atrial myocytes.[11] Rab1 GTPases participate in the trafficking of endogenous K^+ channel 4.2 ($K_v4.2$), the main contributor to the $I_{to,f}$ (depolarization-activated fast transient outward K^+ current), within ventricular myocytes.[3] Advancement in the understanding of $K_v1.5$ and $K_v4.2$ trafficking mechanisms, as well as trafficking mechanisms of other cardiac ion channels, may help pave the way for future therapeutic development.

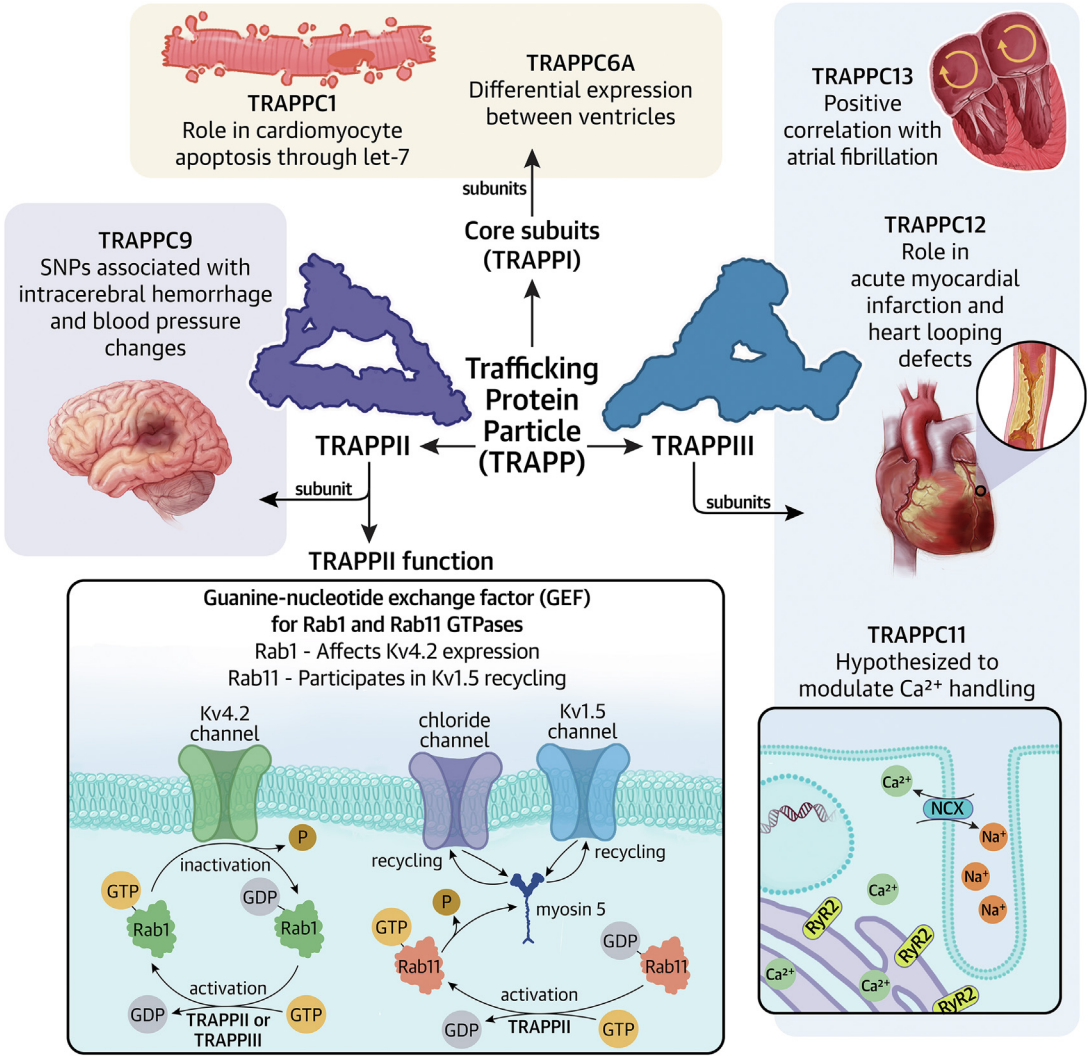
TRAPPC subunits play key roles in brain function and lead to disease in response to reduced or loss of function. For example, a TRAPPC6A and TRAPPC11 variants are associated with intellectual disability, developmental delays, Alzheimer's disease, speech impairment, granule cell hyperplasia, cerebellar atrophy, degeneration and dendrite dystrophy, and Purkinje cell loss.[12,13] However, TRAPPC subunit variants and/or changes in expression have also been recently associated with structural cardiac diseases such as small-vessel stroke, cardiomyocyte apoptosis, heart looping/atrium placement, and coronary artery disease, and electrical cardiac dysfunction such as atrial fibrillation and Ca^{2+} handling defects.[4,14-20]

Although TRAPP complexes seemingly have a broad spectrum of roles in the heart, much is still unknown about the extent of influence. The majority of TRAPP complex literature focuses on the nervous system; therefore, we review the role of TRAPP in the brain before delving into its role in the heart. By setting this foundation, a more comprehensive understanding of novel pathways within the heart can be reached, which in turn will provide a platform for others to build upon in future research (**Central Illustration**).

IMPACT OF IMPAIRED TRAFFICKING IN CARDIAC FUNCTION

Protein trafficking within cardiomyocytes is pivotal for establishing proper excitation-contraction within individual myocytes, and for coordinating excitation-contraction coupling across the entire heart. Defects in forward trafficking, membrane organization, and/or internalization/retrograde trafficking are associated with cardiac dysfunction.[21,22] $Na_v1.5$ is the major voltage-gated sodium channel involved in depolarization and initiation of the cardiac action potential.[23] Human variants in *SCN5A*—the gene encoding for $Na_v1.5$—are associated with numerous

CENTRAL ILLUSTRATION **Function of TRAPP Complexes and TRAPPC Subunits in the Cardiovascular System**



Papaioannou P, et al. J Am Coll Cardiol Basic Trans Science. 2023;8(12):1599–1612.

Schematic representation of defined and hypothesized roles of TRAPP complexes and subunits in the cardiovascular system. GDP = guanosine diphosphate; GTP = guanosine triphosphate; NCX = sodium calcium exchanger; RyR2 = ryanodine receptor 2; SNP = single nucleotide polymorphisms.

cardiac diseases including long QT syndrome, Brugada syndrome, cardiac conduction disease, dilated cardiomyopathy, and sudden infant death syndrome.[24] Interestingly, variants in trafficking genes known to associate with $Na_v1.5$ have also been linked with these diseases, such as a dominant-negative variant in MOG1 (E83D), which was identified in a patient with type 1 Brugada syndrome. Adult rat cardiomyocytes transfected with E83D-MOG1 showed abnormal $Na_v1.5$ localization.[5] In addition, dominant-negative SAR1A or SAR1B expression reduces the cell surface expression of $Na_v1.5$ and diminishes the

$I_{Na,peak}$ in neonatal rat cardiomyocytes, while silencing both SAR1A and SAR1B resulted in decreased I_{Na} density.[25] SAR1A and SAR1B are 2 small GTPases that interact with MOG1 and assist in $Na_v1.5$ trafficking. Brugada syndrome, dilated cardiomyopathy, sick sinus syndrome, and atrial fibrillation are all associated with reduced I_{Na},[26] and therefore targeting of the underlying trafficking regulatory proteins such as MOG1, SAR1A, and/or SAR1B can be potential therapies. Indeed, *MOG1* gene therapy using AAV9 vector-mediated delivery was able to reduce the cardiac phenotypes associated with Brugada syndrome in a *Scn5a* mutant mouse model. This approach suggests that modulation of trafficking-associated proteins is sufficient to treat $Na_v1.5$, and other cardiac action potential channel-related diseases/channelopathies.[27]

Human variants in K^+ channels have also been linked to trafficking defects. For example, long-QT syndrome type 2 is caused by loss-of-function variants in *KCNH2* (or *hERG*), which encodes $K_v11.1$.[28] $K_v11.1$ plays a major role in the rapidly activating delayed rectifier K^+ current, and therefore plays a major role in cardiac action potential repolarization.[29] Most disease-causing *hERG* variants instigate trafficking dysfunction.[6] For example, the $K_v11.1$-A561V human variant results in mutant protein degradation by the proteasome. Calnexin/calreticulin is a molecular chaperone that plays a role in the trafficking on $K_v11.1$, and increasing calnexin/calreticulin via ALLN treatment increased $K_v11.1$ maximum peak current density and tail current density.[7] Lumacaftor (10 μm), a drug that acts on $K_v11.1$ protein trafficking, was able to rescue 3 $K_v11.1$ trafficking defect-causing variants in human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs).[8] Between breakthroughs in $Na_v1.5$ and $K_v11.1$ trafficking therapy, the mechanisms of cardiac ion channel trafficking warrant continued research. Although some of these therapies have shown promising results, the ubiquitous nature of trafficking proteins requires further investment and understanding before the science is ready for the patient bedside. As previously mentioned, $K_v1.5$ facilitates I_{Kur}, which participates in the initial phase (phase 1) of the cardiac action potential repolarization. $K_v1.5$ has become a significant therapeutic target for atrial fibrillation. Myosin V motor protein (both MYO5A and MYO5B) was identified to traffic $K_v1.5$ and connexin-43 to the cell surface. Dominant negative expression of MYO5A and MYO5B results in decreased I_{Kur} current density and $K_v1.5$ cell surface levels. Rab11 interacts with and is involved in trafficking of both MYO5A and MYO5B.[30] TRAPPII acts as a GEF for Rab11, and therefore, is potentially a downstream effector on $K_v1.5$, although a direct relationship between the 2 has never been studied.[2]

STRUCTURE OF TRAPP COMPLEXES

Much of the research conducted to understand TRAPP structure has been done through model organisms. While TRAPPI and TRAPPIV have been studied in yeast, TRAPPII and TRAPPIII have been studied in both yeast and metazoan cells. Only TRAPPII and TRAPPIII have been identified in mammalian cells.[31,32] TRAPPI does not exist in the human body on its own but is instead present at the core of other TRAPP complexes. In fact, some have questioned the existence of TRAPPI in living cells at all and have hypothesized that TRAPPI is an in vitro fragment of TRAPPII or TRAPPIII.[33] Furthermore, little is known about TRAPPIV, and currently, it has only been studied in yeast.[34] However, Thomas et al[35] were unable to observe any TRAPPI or TRAPPIV in yeast cells, supporting the existence of only TRAPPII and TRAPPIII in vivo.

TRAPPI is made of 8 types of protein subunits, which are conserved within the core of metazoan TRAPPII and TRAPPIII: TRAPPC1, TRAPPC2, TRAPPC3A/B, TRAPPC4, TRAPPC5, and TRAPPC6A/B.[1] In addition, TRAPPII and TRAPPIII also contain complex-specific subunits, ie, TRAPPC9, TRAPPC10, and TRAPPC14 for the TRAPPII complex and TRAPPC8, TRAPPC11, TRAPPC12, and TRAPPC13 for the TRAPPIII complex.[36-39] For these additional subunits to bind, adaptor proteins are needed at the core. Of the core proteins, TRAPPC2, is considered an adaptor protein and is needed for this association process to form other TRAPP complexes. Another adaptor protein is TRAPPC2L, which interacts with TRAPPC10 to form TRAPPII, and TRAPPC11 to form TRAPPIII.[40,41] There are minor discrepancies in the literature on whether Tca17 (TRAPPC2L homologue) is part of the TRAPPI core or is a TRAPPII accessory subunit.[42] However, recent cryo-electron microscopy structure of metazoan TRAPPIII confirmed the existence of Tca17 in TRAPPIII, therefore suggesting that Tca71 is generally a TRAPPI core subunit.[41] Some of the structural and mechanistic properties of TRAPPII and TRAPPIII were identified using cyro-electron microscopy. These structures were studied in 2 different organisms, with TRAPPII being studied in *Saccharomyces cerevisiae*, containing yeast homologues of the human TRAPPC subunits, while TRAPPIII was examined in *Drosophilia* that has the same TRAPPC subunits with humans. **Table 1** provides a conversion between established yeast and human TRAPPC subunit homologues. In *S. cerevisiae*,

TRAPPII contains the TRAPP core along with the additional Trs120 (TRAPPC9 yeast homologue), Trs130 (TRAPPC10 yeast homologue), and Trs65 (related to TRAPPC13 and 14) subunits, forming a triangular monomer (monomer shown in **Figure 1**). This monomer can bind with an identical monomer via interactions between the TRAPPII-specific subunits (Trs120, Trs130, and Trs65) to form a TRAPPII homodimer that has a single-arch bridge structure. To form this structure, Trs130 binds to the Tca17 adaptor protein at the core, while Trs120 binds at the opposite side to Trs20 and Trs31. Finally, Trs65 binds Trs120 and Trs130 together to close the arch and complete the structure. The monomer exists solely in the closed conformation when bound to Ypt31/Ypt32 (Rab11 yeast homologue), which binds to Trs120 (TRAPPC9 yeast homologue) and Trs31 (TRAPPC5 yeast homologue).[39] Yeast TRAPPII exists exclusively in a dimerized complex, but metazoan TRAPPII lacks a homologue of Trs65—which is essential for the dimerization in yeast[42]—and is monomeric.[36,39,41,43] TRAPPC14 (also referred to as C7orf43) may be the Trs65 orthologue, the same yeast subunit that became the TRAPPC13 subunit in TRAPPIII, although more research must be conducted to determine the validity of these claims.[38,39,41]

TRAPPIII has been studied through the arrangement of subunits within the density map of the *Drosophila* TRAPPIII complex. This research found that TRAPPC8 links to both TRAPPC2 and TRAPPC3 at the TRAPP core through the N-terminus while TRAPPC11 binds to TRAPPC2L. Additionally, extending from the core, the C-terminal halves of TRAPPC8 and TRAPPC11 meet at a vertex where TRAPPC12 and TRAPPC13 are present. TRAPPC8 arches over the Rab1 binding site within the core and binds Rab1, thus giving specificity toward the substrate. This conformation shares striking similarities to TRAPPII, and in the same way that TRAPPC14 may be formed through Trs65, TRAPPC13 also seems to have been formed by fungi duplication, followed by budding yeast losing the TRAPPC13 protein. With these similar outcomes in protein changes as well as their placement at the vertex of the TRAPP arms, it is possible that this location is an ideal place for additional subunits, such as TRAPPC12 and TRAPPC13 to bolt onto. Metazoan TRAPPIII is monomeric.[41] **Figure 1** provides a model of the potential morphological structure of TRAPPII and TRAPPIII to better visualize these complexes.

Last, Lipatova et al[34] attributed Trs33 (TRAPPC6A/B yeast homologue) to TRAPPIV, rather than to the TRAPPI core, which is inconsistent with the literature. The authors reached this hypothesis because TRAPPIII or TRAPPIV is required for ypt1-mediated autophagy, yet the presence of Trs33 in the absence of Trs85 (TRAPPC8 homologue, a TRAPPIII-specific subunit) is sufficient alongside the other core TRAPPI subunits for Ypt1-mediated autophagy.[34] Loss of Trs33 was not shown to alter TRAPP assembly, result in cellular growth defects, or abrogate membrane trafficking in yeast, and therefore it is frequently considered nonessential.[44] However, the vast majority of the literature still associates Trs33, or TRAPPC6A/B, with the TRAPPI core.[39,45-47]

TABLE 1 Yeast and Human TRAPP Subunit Homologue Terminology

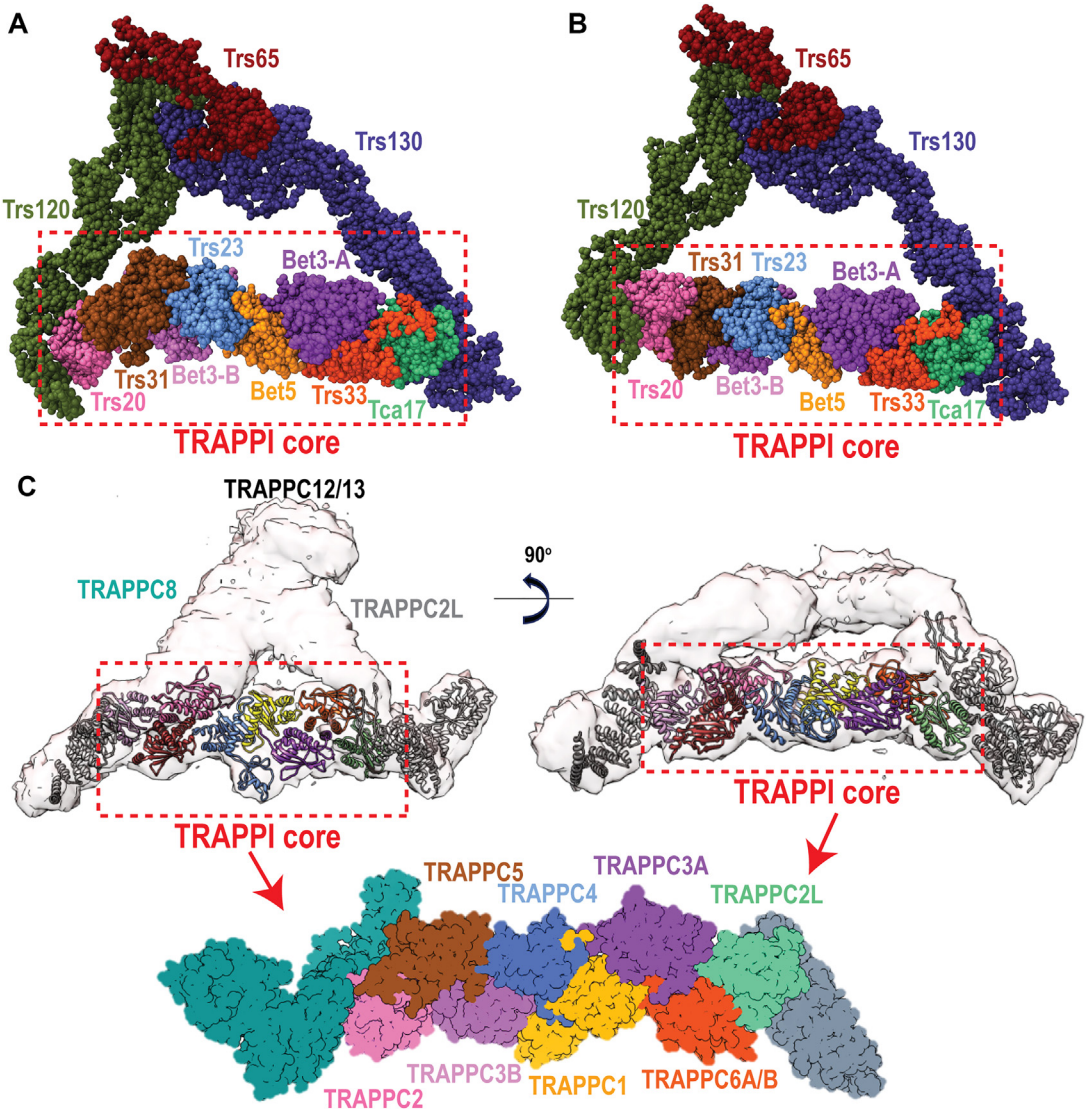
	Yeast TRAPP Subunit[31,45]	Human TRAPP Subunit[31,45]
Core subunit (TRAPPI)	Bet5	TRAPPC1
	Bet3	TRAPPC3
	Trs23	TRAPPC4
	Trs31	TRAPPC5
	Trs33[a]	TRAPPC6A/B[a]
Adaptor proteins	Trs20	TRAPPC2
	Tca17	TRAPPC2L
TRAPPII associated	Trs120	TRAPPC9
	Trs130	TRAPPC10
	Trs65-Related[b]	TRAPPC14[b]
TRAPPIII associated	Trs85	TRAPPC8
	NA	TRAPPC11[c]
	NA	TRAPPC12[c]
	Trs65-Related, but Trs65 is only a TRAPPII subunit in yeast[b]	TRAPPC13[b]

[a]Trs33 and TRAPPC6A/B are TRAPP1-associated subunits. Trs33 is not required for TRAPPI function, and therefore has been proposed as an accessory subunit, potentially for TRAPPIV.[34,45]
[b]Trs65 is speculated to have evolved into TRAPPC14 in TRAPPII and into TRAPPC13 in TRAPPIII, so it is important to note that this is not a yeast homologue as the other subunits are.[38,41] [c]TRAPPC11 and TRAPPC12 are only associated with metazoan TRAPPIII, and therefore have no yeast homologue.[45]
TRAPP = trafficking protein particle.

STRUCTURE AND FUNCTION OF TRAPPC SUBUNITS

TRAPPII and TRAPPIII play essential, well-established roles in human protein trafficking. Comprehensive understanding of interactions within specific TRAPPC subunits may allow for the development of targeted therapies for associated diseases. So far, 3 main TRAPPC subunits have been implicated in heart function: TRAPPC6A (subunit of the TRAPPI core), TRAPPC11, and TRAPPC12 (subunits of TRAPPIII).[41] Although little is known about the specifics of each subunit as it relates to heart function, TRAPPC6A likely plays a role in stabilization of both TRAPPII and TRAPPIII considering its interaction with the adapter subunit TRAPPC2L.[39] TRAPPC11 specifically facilitates isolation membrane elongation in autophagy,[48] while TRAPPC12 plays a role in transport to and within the Golgi.[49] Differential expressions of TRAPPC6A, TRAPPC11, and TRAPPC12

FIGURE 1 Structure of Yeast TRAPPII and Metazoan TRAPPIII



(A) Yeast trafficking protein particle II (TRAPPII) monomer in the closed (PDB ID 7E2D) and (B) open conformation (PDB ID 7E2C) as observed by electron microscopy.[39] Yeast TRAPPC subunits are labeled. (C) Structure of metazoan TRAPPIII[41] in which the TRAPPI core crystallized structure (PDB ID 7B6R) is superimposed on cryo-EM structure of TRAPPIII (EMD 12056) with human TAPPC subunits labeled. TRAPPIII is shown from 2 angles for proper 3-dimensional spatial representation. Corresponding TRAPPI subunits are color-coordinated between TRAPPII and TRAPPIII. Visualized with ChimeraX.[86]

have all been associated with various disease states in the heart.

TRAPPC6A. TRAPPC6A is a core subunit required to form TRAPPII and TRAPPIII in humans. This complex consists of 2 isoforms, TRAPPC6A1 and TRAPPC6A2, collectively referred to as TRAPPC6AΔ, with TRAPPC6A2 containing 14 amino acids more than TRAPPC6A1.[1] At the TRAPPI core of TRAPPII and TRAPPIII, TRAPPC6A interacts with TRAPPC3 in a

TABLE 2 Notable TRAPPC Subunits Summarized With Associated Cardiovascular and Nervous System Disorders

TRAPPC Subunit	Role of Subunit	Associated Cardiovascular Disorders	Associated Nervous System Disorders
TRAPPC1	Part of TRAPP core.[45]	May increase in expression in infarcted myocardium in response to let-7a and let-7f dysfunction.[15]	Deficiency results in dysfunctional thymic epithelial cell development.[60]
TRAPPC6A	Part of TRAPP core. TRAPPC6A is a target for ubiquitination, and dysfunction can result in inappropriate protein accumulation.[12]	Trending increases in right ventricular expression have been associated with early stages of right ventricular heart failure.[53]	c.T319A and p.Y107N variants associated with neurological disorders.[12] Aggregation is associated with Alzheimer's disease.[52]
TRAPPC9	Associated with TRAPPII. Trs120, the yeast homologue, is an essential binding site for Ypt32 (Rab11 yeast homologue), and therefore plays a significant role in overall TRAPPII function.[39]	Variant may affect systolic blood pressure in frequent smokers.[17]	Plays a protective role against intracerebral hemorrhage.[16] TRAPPC9 regulates neuronal differentiation, NF-κB signaling, and neurogenesis, and variants are linked to intellectual disability, dysmorphic facial features, brain abnormalities, and speech disorders.[61]
TRAPPC11	Associated with TRAPPIII. TRAPPC11 contains the *foie gras* domain, which is believed to play a vital role in TRAPPIII function.[54] TRAPPC11 participates in autophagy[48] and early-stage anterograde trafficking between the ER and Golgi.[31]	Ingenuity pathway analysis of mRNA from *TRAPPC11* knockdown model predicted deceases in RyR2 and NCX.[4] A TRAPPC11 variant have been associated with small-vessel ischemic stroke.[14]	Numerous recessive variants have been identified limb girdle muscular dystrophy, movement disorder, and intellectual disability.[56]
TRAPPC12	Associated with TRAPPIII. TRAPPC12 plays a role in ER to *cis*-Golgi transport and transport within the Golgi.[49]	Medaka knockout model showed increase in heart rate and abnormal heart looping.[18] TRAPPC12 expression is decreased in acute myocardial infarction.[19]	Variants have been associated with hydrocephalus, intellectual disability, microcephaly, and hearing loss.[49,59]
TRAPPC13	Associated with TRAPPIII. TRAPPC13 is involved in autophagic flux during stress.[62]	TRAPPC13 is positively correlated with atrial fibrillation.[20]	No data.

ER = endoplasmic reticulum; mRNA = messenger RNA; NCX = Na^+/Ca^{2+} exchanger; NF-κB = nuclear factor kappa B; RyR2 = ryanodine receptor 2; TRAPP = trafficking protein particle.

heterodimeric complex.[12] Together, this heterodimer interacts with TRAPPC2L. Although the breadth of TRAPPC6A functions are not yet known, its role in neuronal development and degradation makes it an important topic of future research in neurology. Summaries of TRAPPC subunits associated with cardiovascular diseases are listed in **Table 2**.

TRAPPC6A is also a target for ubiquitination and is rapidly degraded by proteasomes in normal cellular function. Two homozygous *TRAPPC6A* variants (c.T319A and pY107N) were examined to identify the role of *TRAPPC6A*, among other genes, in causing intellectual disability, speech delay, polydactyly, and facial dimorphism. According to a database enriched for patients with neurodevelopmental disorders, the cT319A variant was present in an individual from the Turkish Peninsula, further implying the role TRAPPC6A plays in neurodevelopment. pY107N resulted in a significant reduction in TRAPPC6A expression of wild-type TRAPPC6A, but was offset by the addition of MG132, a proteasome inhibitor. This indicates that TRAPPC6A is a target for ubiquitination that is then degraded by the proteasome. When this process is interrupted, protein buildup may occur and result in neurodevelopmental disorders.[12] Dysfunction in the ubiquitin proteasome system plays a key role in heart failure[50]; therefore, the role of TRAPPC6A and ubiquitination in the heart requires further exploration. Aggregated TRAPPC6A can result in Alzheimer's disease due to a cascading effect that it causes in conjunction with WWOX (WW domain-containing oxidoreductase). WWOX is a risk factor for Alzheimer's disease due to its role in binding tau proteins, which prevents tau protein tangles, a significant component in the onset and progression of Alzheimer's disease.[51,52]

In the heart, *TRAPPC6A* messenger RNA and protein levels are significantly higher in the left ventricle compared with the right ventricle suggesting a different regulatory role of TRAPPC6A in the left ventricle vs the right ventricle. However, TRAPP6CA is potentially differentially expressed during the development of right ventricular failure (RVF).[53] Right ventricular tissue was analyzed for TRAPPC6A expression from left ventricular assist device (LVAD) patients (with left ventricular failure) with varying levels of right ventricular function. LVAD patient samples were then separated into 3 groups: normal right ventricular function, mild RVF, and severe RVF. Through this comparison, TRAPPC6A showed a trending increase in expression in LVAD patients with no RVF and mild RVF compared with healthy control subjects. However, TRAPPC6A RV expression was similar in LVAD patients with RVF to healthy control

hearts.[53] More research needs to be conducted on TRAPPC6A and its function in the heart to confirm the validity of these findings.

TRAPPC11. TRAPPC11 is a 1,133-amino-acid subunit used to form the TRAPPIII complex by binding to TRAPPC2L and TRAPPC3 at the TRAPPI core, and to TRAPPC12 and TRAPPC13 on the opposite vertex in a tong-like conformation.[1,41] Within this subunit, a highly conserved region that spans amino acids 263 to 561, called the *foie gras* domain, is believed to play a vital role in either protein-protein interactions or the general function of the complex. Furthermore, a well-conserved 60-amino-acid domain located near the carboxy terminus, called the gryzun domain, has been identified as a potentially significant contributor to TRAPPC11 function.[54] Despite uncertainty about the full roles or functions of these domains, TRAPPC11 plays several crucial roles in membrane trafficking and may function in more than 1 step of this process.

TRAPPC11 functions upstream of autophagosome sealing in collaboration with TRAPPC12, which functions before autophagosome-lysosome fusion. In this role, TRAPPC11 participates in recruitment of ATG2 (autophagy protein 2) and the PI3P effector WIPI4/WDR45 for isolation membrane expansion, a process required for the engulfment of cytosolic components to subsequently deliver them to the lysosome.[48] Additionally, TRAPPC11 is involved in early-stage anterograde trafficking between the ER and Golgi, as its depletion with TRAPPC12 results in abnormal protein accumulation, forming punctate structures instead of the normal accumulation at perinuclear regions at the Golgi.[31] TRAPPC11 has also been implicated in promoting N-linked glycosylation, and by extension, normal ER function. Variants in *TRAPPC11* result in decreased N-linked protein glycosylation, and it has been hypothesized that this hypoglycosylation results in an unfolded protein response that is indicative of ER dysfunction and fatty liver disease.[55]

Variants in *TRAPPC11* have also been linked to myopathy with intellectual disability and movement disorders as well as limb girdle muscular dystrophy (LGMD). Two population groups, which included a Syrian family that presented with LGMD and Hutterite families that presented with myopathic syndrome (which include infantile hyperkinetic movements, ataxia, and intellectual disability) were studied. Two homozygous variants at the gryzun and *foie gras* domains were found. A missense variant within the gryzun domain (pG980R) was identified in the Syrian family suffering from LGMD while a splice-site variant in the *foie gras* domain (pAla372_Ser420del) was found in the Hutterite family presenting with myopathic syndromes that resulted in a 58-amino-acid in-frame deletion. Marker trafficking experiments for pAla372_Ser420del found that normal ER-to-Golgi trafficking could occur but exit from the Golgi to the cell surface was significantly delayed. Furthermore, both variants resulted in decreased TRAPPC11 binding to other TRAPPC subunits that adversely affected Golgi architecture. Finally, TRAPPC11 dysfunction resulted in an alteration of lysosomal membrane glycoproteins 1 and 2 caused by a defect in secretory protein transport.[56]

In the heart, changes in TRAPPC11 have been linked to deficiencies in RyR2 (ryanodine receptor 2) expression and Ca^{2+} handling, structural markers of left ventricular hypertrophy, and cardiovascular disease. In an African ancestry population, *TRAPPC11* variants were associated with left ventricular hypertrophic traits measured via echocardiogram. Using hiPSC-CMs, a TRAPPC11 knockdown model was generated via gene-specific small interfering RNA to study the pathways affected by reduction in TRAPPC11 expression. *TRAPPC11* hypertrophic gene marker expression profiling found a significant decrease in *MYH7*, a gene that codes for myosin heavy chain beta. Additionally, this down-regulation resulted in secretory transport defects. Ingenuity pathway analysis using hiPSC-CM messenger RNA of this knockdown suggested downregulation of cardiac beta-adrenergic signaling and significant decreases in *RYR2* and *SLC8A1*, a member of NCX (Na^{+}/Ca^{2+} exchanger) that, when combined with protein transport changes, affects Ca^{2+} handling.[4]

Finally, a *TRAPPC11* exonic variant has been implicated in contributing to small-vessel ischemic stroke. Using a biracial population-based study of first-ever ischemic stroke cases consisting of Black and White participants 15 to 49 years of age ($n = 723$) along with nonstroke control subjects ($n = 726$), exam-chip genotyping was used to determine genes that significantly contribute to causing small-vessel strokes. Using gene burden tests, *TRAPPC11* was found to be one of a few genes that was identified to have a significant correlation to these types of strokes. Further research analyzing the pathway of over 500 genes that significantly correlated to these strokes found that a *TRAPPC11* missense rs67383011 exonic variant had a near chip-wide significance ($P < 2.05 \times 10^{-7}$) at $P = 5.19 \times 10^{-6}$.[14]

TRAPPC12. TRAPPC12 has a prevalent role in ER to *cis*-Golgi trafficking. TRAPPC12 is necessary for mitosis and proper localization of various kinetochore proteins.[57] *TRAPPC12* is also one of the most consistently expressed genes in the mammalian brain, and

therefore, expression does not vary much from species to species.[58] Homozygous and compound heterozygous variants in the *TRAPPC12* gene have been associated with hydrocephalus, characterized by an abnormal build-up of cerebrospinal fluid in the brain.[59] Unrelated children carrying *TRAPPC12* variants shared striking similarities in condition including intellectual disability, microcephaly, and hearing loss, and displayed fragmented Golgi in fibroblasts.[49]

Medaka with CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9-edited *TRAPPC12* show both structural and functional phenotypes compared with control subjects. Analysis showed a significant percent increase in heart rate (HR) between *TRAPPC12* crispants and control medaka (3.3% increase at 21 °C and 5.2% increase at 28 °C). Furthermore, *TRAPPC12* crispants resulted in morphological heart phenotypes including heart looping defects that caused improper atrium placement compared with the ventricle.[18] TRAPPC12 has also been linked to coronary artery disease, with acute myocardial infarction patients having markedly decreased *TRAPPC12* gene expression compared with patients with normal coronary artery function and intermediate coronary lesions.[19]

ADDITIONAL HEART-RELATED TRAPPC SUBUNITS. In infarcted myocardium, let-7a and let-7f microRNAs were identified as novel factors that were significantly downregulated and were therefore suggested as cardiac protective factors after injury. Through further examination by let-7a and let-7f inhibitors, several genes, including *TRAPPC1*, were found to be significantly upregulated in cardiomyocytes through gene folding increase, indicating that TRAPPC1 may play a downstream role in cardiomyocyte apoptosis when let-7 is dysfunctional.[15] TRAPPC1 deficiency has also been associated with impaired thymic epithelial cell developmental issues, which negatively impacts the immune system.[60]

TRAPPC9 has been associated with intracerebral hemorrhage and blood pressure regulation. By examining the association of genetic variants with subarachnoid or intracerebral hemorrhages among 4,304 Japanese individuals, *TRAPPC9* was determined to be significantly associated with intracerebral hemorrhage through a C-T polymorphism (rs12679196) in intron 21. Through further examination, the T allele of *TRAPPC9* was determined to play a protective role against intracerebral hemorrhage.[16] Another study recorded participant systolic blood pressure based on the average number of cigarette packs smoked per day times the total number of years smoked during one's lifetime (pack-years). The pack-years interaction test found rs7823724, a loci intronic to *TRAPPC9* on chromosome 8, to be significantly correlated with increased systolic blood pressure in smokers ($P = 4.28 \times 10^{-8}$).[17] TRAPPC9 plays significant roles in normal cellular trafficking and nervous system disease development. Interestingly, TRAPPC9 is also referred to as the NIK-IKK2-binding protein (NIBP), which is highly expressed in the nervous system and is important for regulating neuronal differentiation, nuclear factor kappa B signaling, and neurogenesis. As a result, loss-of-function *NIBP/TRAPPC9* variants can lead to NIBP syndrome, a disease characterized by phenotypical features such as severe intellectual disability, dysmorphic facial features, brain abnormalities like reduced white matter and a thin corpus collosum, and speech disorders.[61]

Finally, bioinformatics analysis has indicated that TRAPPC13 is positively correlated with atrial fibrillation, and more specifically, right atrial fibrillation.[20] TRAPPC13 deletion reduces Rab1 activity and impairs autophagy, implicating the TRAPPC13 subunit in autophagic flux which escalates during cellular stress.[62] Overall, TRAPPC subunits seem to play an increasingly significant role in the heart and more research is needed to study the underlying pathways.

FUNCTION OF TRAPP COMPLEXES

ROLE OF TRAPP IN SECRETION. TRAPPII and III play crucial roles in normal cell physiology. The first of these roles are the secretory transport pathways. After proteins are made in the ER, they are shuttled to ER exit sites, followed by the ER-to-Golgi intermediate compartment, Golgi complex, and finally the *trans*-Golgi complex, where proteins can be organized to be sent off in or out of the cell to perform their roles. Within this complex process, Coat Protein I (COPI) and COPII and Rab1/Ypt1 all use TRAPP to effectively execute their duties.[63]

These coat proteins are responsible for selectively transferring macromolecules from one cellular compartment to another by forming small coated vesicles. At the ER exit sites, COPII mediates cargo sorting before being sent off to the Golgi. TRAPPIII, in conjunction with other proteins, act as a membrane trafficking factor to recruit COP II to the ER by promoting outer layer assembly of the COPII coat to conduct its normal processes.[18] COPI mediates a recycling pathway that retrieves proteins from both the Golgi and ER-Golgi intermediate compartment and returns them to the ER. TRAPPI, in conjunction with TRAPPII, helps this intra-Golgi trafficking process function by facilitating COPI.[1,63] TRAPPII

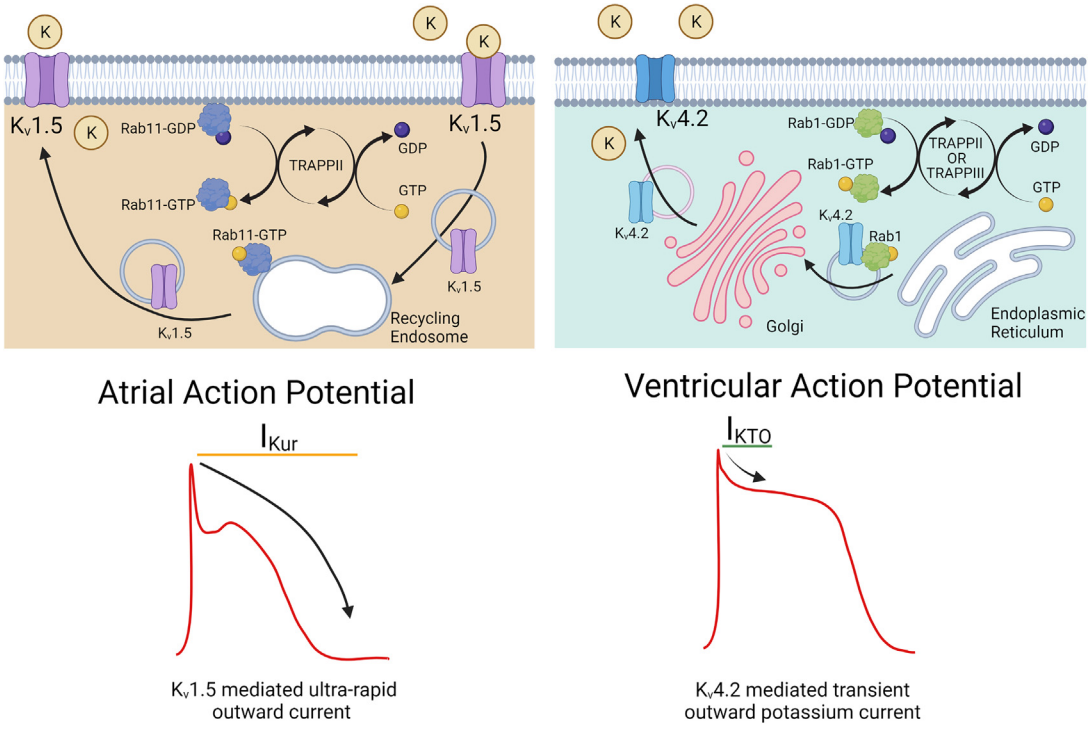
functions in intra-Golgi trafficking, facilitates early Golgi processes, and physically interacts with COPI for vesicle tethering.[1] COPI acts as a mediator for protein and lipid trafficking at the Golgi, allowing for the maintenance of the early secretory pathway and allows for quality control of proteins.[64] Finally, tethering factors are important for allowing vesicles to attach to and interact with various organelles. One of these factors is p115, which is recruited by Rab1 to connect to COPII and potentially COPI.[63] TRAPPIII regulates Rab1 as a GEF, as will be discussed below, and therefore likely regulates this COP tethering process.[65]

ROLE OF TRAPP IN AUTOPHAGY. *Autophagy* is a broad term to describe the various processes by which cellular components of the cytoplasm are delivered to the lysosome (animal cells) or vacuole (plant and yeast cells). The lysosome/vacuole is a specific compartment for degradation and recycling of cellular components. Autophagy can be subcategorized into 3 processes: macro-autophagy, micro-autophagy, and chaperone-mediated autophagy. In macro-autophagy, an intermediate organelle called the autophagosome, in which a phagophore (membrane) surrounds the cytoplasmic components, delivers them to the lysosome/vacuole. During micro-autophagy, components are delivered directly to the lysosome/vacuole via inward invagination of the lysosomal membrane. For chaperone-mediated autophagy, proteins deliver soluble cytoplasmic components directly into the lysosome across the membrane without membrane reorganization. Chaperone-mediated autophagy has only been identified in mammals. Cellular stress generally increases autophagy.[66-69] TRAPPIII, and more specifically the Trs85 subunit, participates in the formation of the preautophagosomal structure in macro-autophagy in yeast.[70,71] Ypt1 is required for autophagy, and Trs85 colocalizes and regulates Ypt1 at the pre-autophagosomal structure.[72] Ypt1, the yeast homologue of Rab1, has been shown to directly interact with a crystallized structure of TRAPPI core via Bet5, Trs23, and Bet3. TRAPPIII furthermore has an amphipathic helix within the Trs85 subunit that is necessary for Rab1 activation, while other subunits may act as allosteric regulators of the TRAPP subunits in the Ypt1 binding pocket.[65] Rab1 regulates various membrane trafficking pathways, including COPI-coated vesicle tethering in the early steps of Golgi trafficking.[1] The mammalian homologue of Trs85, TRAPPC8, also has been implicated in autophagy in mammalian cells, but specific role is not clear.[45,73,74] TRAPPIV, which generally has the same subunits as the TRAPPI core as discussed previously, has been identified as a GEF for Ypt1 (a Rab1 yeast homologue).[34] Ypt1 is required for ER-to-Golgi transport in yeast.[75] Apt1 interacts with Atg11 to participate in selective autophagy, which starts with the assembly of the preautophagosomal structure. Ypt1 is necessary to form this structure, and therefore is necessary for autophagy initiation.[72,76] TRAPPIV has been hypothesized as a mediator for Ypt1, and therefore, as a moderator of autophagy.

ROLE OF TRAPP IN RAB GTPase AND TRAFFICKING. TRAPP complexes also play an integral role in Rab GTPase function. Rab GTPases regulate many intracellular trafficking processes. For example, Rab11 is involved in recycling of cell surface proteins such as receptors and adhesion proteins. Specifically, Rab11 builds distinct molecular machinery such as motor protein complexes and exocyst complexes to transport proteins to cell surface.[77] Rab11 is also associated with the Golgi membrane via interactions with PI4KIIIβ.[78] Disruption to Rab function has previously been directly associated with various diseases. During cancer, the small GTPase Rac1 becomes hyperactive, and activates PAK1, which removes E-cadherin from junctions, therefore destabilizing cell-cell contact.[79] TRAPPII is further responsible for helping Rab18 locate onto and help drive lipid droplet production within the membranes of the ER to aid in processes such as lipid storage, metabolism regulation, trafficking, and lipolysis.[80] TRAPPIII has also shown to have GEF activity toward Rab1 in conjunction with TRAPPII and thus is responsible for activating Rab1 to begin this process. It also seems that TRAPPI may be sufficient for Rab1 GEF activity; thus, additional TRAPP subunits likely play assisting roles in this process.[65]

TRAPPII acts with the SH3BP5 protein family as a GEF for Rab11, a GTPase that is associated with endosome recycling, shown in **Figure 2**.[2] Rab11 works with MYO5B to recycle cAMP activated chloride channels and AMPA receptors from recycling endosomes. Through selective Rab11-mediated coupling, Myosin-5B recycles $K_v1.5$-containing endosomes and contributes to the steady-state $K_v1.5$ channel protein cell surface levels. Therefore, Rab11 likely plays a role in native cardiac myocyte electrical excitability.[30] $K_v1.5$ acts as an important voltage-gated K^+ channel underlying the I_{Kur}, the major repolarization current in atrial myocytes. A reduction in outward K^+ current and in $K_v1.5$ expression have both been associated with atrial fibrillation.[30] Cholesterol also modulates cardiac excitability via interactions with $K_v1.5$ and Rab11. Membrane cholesterol depletion via MβCD

FIGURE 2 **Schematic Representation of Rab1 and Rab11 Function**



Rab11 and Rab1 play roles in cardiac myocyte electrical excitability through regulation of the $K_v1.5$ and $K_v4.2$ channels, respectively. Trafficking protein particle (TRAPP) complexes play roles in Rab1 and Rab11 GTPase activity, therefore providing a theoretical mechanism for TRAPPII and TRAPPIII modulation of cardiac excitability. GDP = guanosine diphosphate; GTP = guanosine triphosphate; I_{KTO} = transient outward K+ current; I_{Kur} = ultra-rapid delayed rectifier K^+ current.

increased I_{Kur} in rat adult atrial myocytes, increased the quantity of active $K_v1.5$ channels, and decreased colocalization between $K_v1.5$ and Rab11. MβCD treatment increased I_{Kur} in approximately 7 minutes, which is faster than $K_v1.5$ protein synthesis could occur, suggesting that cholesterol depletion causes increased plasma membrane localization via transport of K_v channels from a submembrane vesicular compartment. Rab11, which is highly expressed in myocytes, is involved in the recycling endosome—a slow recycling pathway—which plays a role in $K_v1.5$ membrane expression. Therefore, cholesterol was hypothesized to regulate exocytosis of $K_v1.5$. Indeed, transfection with Rab11 dominant negative protected $K_v1.5$ from the effects of cholesterol depletion via MβCD. Overexpression of active Rab11, however, reduced I_{Kur}. This result was similar to results achieved when adult atrial rat myocytes were incubated with low-density lipoprotein cholesterol, which reduced outward K^+ current and inward rectifying K^+ current. These data, in summary, suggest that cholesterol modulates $K_v1.5$, and therefore I_{Kur}, by activating Rab11 and the Rab11-associated recycling endosome, therefore causing internalized $K_v1.5$ channels to remain in submembrane storage compartments. Cholesterol depletion may not only increase I_{Kur} via lack of Rab11 activation, but also may induce release of $K_v1.5$ channels from the submembrane storage vesicles.[81,82] Statins, which have cholesterol-lowering abilities, therefore also likely play a role in modulation of the Rab11-$K_v1.5$ pathway. Certain statins also have further non-cholesterol-related effects on Rab5, Rab7, and Rab11 by preventing isoprenylation and inhibiting endosomal localization. Therefore, specific statins could be used as therapies in disease situations in which Rab is upregulated.[83] Although the direct relationship between TRAPPII and atrial fibrillation has never

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 8, NO. 12, 2023
DECEMBER 2023:1599–1612

been studied, the potential downstream role of TRAPPII on $K_v1.5$ provides the framework for a theoretical mechanism that requires further exploration.

Rab1 is also potentially necessary for normal $K_v4.2$ channel trafficking from the ER to the Golgi in the heart. $K_v4.2$ plays a major role in I_{to} in the mammalian heart and is thus crucial for normal heart excitability and function. Rab1 dominant negative expression, which inhibits function of the native Rab1 protein, reduced the $I_{to,f}$ current density by half in adult rat ventricular cardiomyocytes.[3] Therefore, TRAPPII and TRAPPIII may both play an understudied role in $K_v4.2$ expression and overall cardiac excitability. Some have also hypothesized that $K_v4.2$ channel density can also be regulated by internalization/recycling of the channel (controlled by Rab4 and Rab5), and re-delivery of the recycled channel to the membrane (controlled by Rab11 as previously discussed).[3] Finally, Rab1 and its role in cell-growth promotion of neonatal cardiomyocytes has shown that ER-to-Golgi protein transport acts as a regulatory site for cardiomyocyte growth control.[84] Therefore, TRAPPII and TRAPPIII may play various and significant functions in the heart through their role as GEFs. This is also supported by the association of human variants in TRAPPC subunits and changes in TRAPPC subunit expression with cardiovascular disease states. However, future research should be directed into exploring their specific roles in diseased heart.

FUTURE IMPLICATIONS

The TRAPP complex is an evolved, important player in cardiovascular physiology. As a GEF for Rab1 and Rab11 GTPases, TRAPPII/TRAPPIII may regulate expression of $K_v4.2$, and therefore, may influence depolarization-activated transient outward K^+ current in ventricular myocytes. Also, TRAPPII may facilitate the recycling of $K_v1.5$ that conducts the ultra-rapid delayed rectifier current that contributes to action potential repolarization in atrial myocytes. Thus, TRAPPII and TRAPPIII may play a role in the determination of electrical excitability of native cardiomyocytes.[3,30,36] Continued research to better understand this TRAPP-GTPase-ion channel relationship and its impact on the heart function could help determine a novel target to treating arrhythmias and other cardiovascular diseases associated with impaired K^+ channel functioning. Interestingly, Rab11 has been implicated in ENaC (epithelial sodium channel) density. Expression of dominant negative Rab11a or Rab11b significantly decreased Na^+ transport.[85] The relationship of the cardiac sodium channel, $Na_v1.5$, and Rab11 has yet to be explored. $Na_v1.5$ localization has not been shown to be Rab-dependent, but the role of Rab11 in ENaC expression warrants investigation into sodium channels of other cell types, including cardiomyocytes.

Within the TRAPP complex, it is also exceedingly apparent that a large portion of its subunits play a role in heart function. Future studies examining the interactions of these subunits with important myocyte structures will provide more accurately mapped cardiovascular biochemical pathways, which in turn may be used to better treat patients that suffer from these conditions. TRAPPC1 may play a downstream role in cardiomyocyte apoptosis while TRAPPC13 is positively correlated with atrial fibrillation. Additionally, *TRAPPC11* variants have been predicted to result in decreased cardiac beta-adrenergic signaling that cause defects in sarcoplasmic release of stored Ca^{2+} ions and heart contractility while TRAPPC12 facilitates correct heart looping and atrium placement, and may cause coronary artery disease when defective. TRAPPC9 has been associated with intracerebral hemorrhaging and blood pressure regulation.[15-20] Taken together, the current literature on TRAPP complexes and heart function seem like an unrelated assemblage of various cardiac diseases that were associated with *TRAPPC* variants and/or differential TRAPPC expression. More focus on TRAPP complexes in cardiac research is necessary to align and organize the literature. Further understanding of TRAPPC subunits opens up avenues to novel therapeutic targets that can eventually transition to personalized medicine at the patient bedside.

ACKNOWLEDGMENTS Molecular graphics and analyses performed with UCSF Chimera, developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California-San Francisco, with support from National Institutes of Health P41-GM103311. The graphical abstract and **Figure 2** were created with BioRender.com.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors are supported by National Institutes of Health grants HL135754 to Dr Mohler and HL146969 to Dr El Refaey, a grant from the Ohio State Frick Center for Heart Failure and Arrhythmia, the Leducq Foundation, and the JB Project. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Mona El Refaey, The Ohio State University College of Medicine, 333 West 10th Avenue, Room 5173, Columbus, Ohio 43210, USA. E-mail: mona.elrefaey@osumc.edu. @drMonaElRefaey.

REFERENCES

1. Sacher M, Shahrzad N, Kamel H, Milev MP. TRAPPopathies: An emerging set of disorders linked to variations in the genes encoding transport protein particle (TRAPP)-associated proteins. *Traffic*. 2019;20:5–26.

2. Riedel F, Galindo A, Muschalik N, Munro S. The two TRAPP complexes of metazoans have distinct roles and act on different Rab GTPases. *J Cell Biol*. 2018;217:601–617.

3. Wang T, Cheng Y, Dou Y, et al. Trafficking of an endogenous potassium channel in adult ventricular myocytes. *Am J Physiol Cell Physiol*. 2012;303:C963–C976.

4. Irvin MR, Aggarwal P, Claas SA, et al. Whole-exome sequencing and hiPSC cardiomyocyte models identify MYRIP, TRAPPC11, and SLC27A6 of potential importance to left ventricular hypertrophy in an African Ancestry population. *Front Genet*. 2021;12:588452.

5. Kattygnarath D, Maugenre S, Neyroud N, et al. MOG1: a new susceptibility gene for Brugada syndrome. *Circ Cardiovasc Genet*. 2011;4:261–268.

6. Anderson CL, Delisle BP, Anson BD, et al. Most LQT2 mutations reduce Kv11.1 (hERG) current by a class 2 (trafficking-deficient) mechanism. *Circulation*. 2006;113:365–373.

7. Wang Y, Shen T, Fang P, et al. The role and mechanism of chaperones Calnexin/Calreticulin in which ALLN selectively rescues the trafficking defective of HERG-A561V mutation. *Biosci Rep*. 2018;38:BSR20171269.

8. O'Hare BJ, John Kim CS, Hamrick SK, Ye D, Tester DJ, Ackerman MJ. Promise and potential peril with lumacaftor for the trafficking defective type 2 long-QT syndrome-causative variants, p.G604S, p.N633S, and p.R685P, using patient-specific re-engineered cardiomyocytes. *Circ Genom Precis Med*. 2020;13:466–475.

9. Borrego J, Feher A, Jost N, Panyi G, Varga Z, Papp F. Peptide inhibitors of Kv1.5: an option for the treatment of atrial fibrillation. *Pharmaceuticals (Basel)*. 2021;14:1303.

10. Geng L, Wang S, Zhang F, et al. SNX17 (sorting nexin 17) mediates atrial fibrillation onset through endocytic trafficking of the Kv1.5 (potassium voltage-gated channel subfamily A member 5) channel. *Circ Arrhythm Electrophysiol*. 2019;12:e007097.

11. McEwen DP, Schumacher SM, Li Q, et al. Rab-GTPase-dependent endocytic recycling of KV1.5 in atrial myocytes. *J Biol Chem*. 2007;282:29612–29620.

12. Mohamoud HS, Ahmed S, Jelani M, et al. A missense mutation in TRAPPC6A leads to build-up of the protein, in patients with a neurodevelopmental syndrome and dysmorphic features. *Sci Rep*. 2018;8:2053.

13. Munot P, McCrea N, Torelli S, et al. TRAPPC11-related muscular dystrophy with hypoglycosylation of alpha-dystroglycan in skeletal muscle and brain. *Neuropathol Appl Neurobiol*. 2022;48:e12771.

14. Jaworek T, Ryan KA, Gaynor BJ, et al. Exome array analysis of early-onset ischemic stroke. *Stroke*. 2020;51:3356–3360.

15. Chen C-Y, Choong OK, Liu L-W, et al. MicroRNA let-7-TGFBR3 signalling regulates cardiomyocyte apoptosis after infarction. *EBioMedicine*. 2019;46:236–247.

16. Yoshida T, Kato K, Yokoi K, et al. Association of genetic variants with hemorrhagic stroke in Japanese individuals. *Int J Mol Med*. 2010;25:649–656.

17. Sung YJ, de Las Fuentes L, Schwander KL, Simino J, Rao DC. Gene-smoking interactions identify several novel blood pressure loci in the Framingham Heart Study. *Am J Hypertens*. 2015;28:343–354.

18. Hammouda OT, Wu MY, Kaul V, Gierten J, Thumberger T, Wittbrodt J. In vivo identification and validation of novel potential predictors for human cardiovascular diseases. *PLoS One*. 2021;16:e0261572.

19. Wang C, Song C, Liu Q, et al. Gene expression analysis suggests immunological changes of peripheral blood monocytes in the progression of patients with coronary artery disease. *Front Genet*. 2021;12:641117.

20. Liu L, Huang J, Wei B, et al. Multiomics analysis of genetics and epigenetics reveals pathogenesis and therapeutic targets for atrial fibrillation. *Biomed Res Int*. 2021;2021:6644827.

21. Xiao S, Shimura D, Baum R, et al. Auxiliary trafficking subunit GJA1-20k protects connexin-43 from degradation and limits ventricular arrhythmias. *J Clin Invest*. 2020;130:4858–4870.

22. Xiao S, Shaw RM. Cardiomyocyte protein trafficking: relevance to heart disease and opportunities for therapeutic intervention. *Trends Cardiovasc Med*. 2015;25:379–389.

23. Marchal GA, Remme CA. Subcellular diversity of Nav1.5 in cardiomyocytes: distinct functions, mechanisms and targets. *J Physiol*. 2023;601:941–960.

24. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace*. 2011;13:1077–1109.

25. Wang Z, Yu G, Liu Y, et al. Small GTPases SAR1A and SAR1B regulate the trafficking of the cardiac sodium channel Na(v)1.5. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864:3672–3684.

26. Wilde AAM, Amin AS. Clinical spectrum of SCN5A mutations: long QT syndrome, Brugada syndrome, and cardiomyopathy. *J Am Coll Cardiol EP*. 2018;4:569–579.

27. Yu G, Chakrabarti S, Tischenko M, et al. Gene therapy targeting protein trafficking regulator MOG1 in mouse models of Brugada syndrome, arrhythmias, and mild cardiomyopathy. *Sci Transl Med*. 2022;14:eabf3136.

28. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell*. 1995;80:795–803.

29. Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. *Cell*. 1995;81:299–307.

30. Schumacher-Bass SM, Vesely ED, Zhang L, et al. Role for myosin-V motor proteins in the selective delivery of Kv channel isoforms to the membrane surface of cardiac myocytes. *Circ Res*. 2014;114:982–992.

31. Scrivens PJ, Noueihed B, Shahrzad N, Hul S, Brunet S, Sacher M. C4orf41 and TTC-15 are mammalian TRAPP components with a role at an early stage in ER-to-Golgi trafficking. *Mol Biol Cell*. 2011;22:2083–2093.

32. Bassik MC, Kampmann M, Lebbink RJ, et al. A systematic mammalian genetic interaction map reveals pathways underlying ricin susceptibility. *Cell*. 2013;152:909–922.

33. Brunet S, Noueihed B, Shahrzad N, et al. The SMS domain of Trs23p is responsible for the in vitro appearance of the TRAPP I complex in Saccharomyces cerevisiae. *Cell Logist*. 2012;2:28–42.

34. Lipatova Z, Majumdar U, Segev N. Trs33-containing TRAPP IV: a novel autophagy-specific Ypt1 GEF. *Genetics*. 2016;204:1117–1128.

35. Thomas LL, Joiner AMN, Fromme JC. The TRAPPIII complex activates the GTPase Ypt1 (Rab1) in the secretory pathway. *J Cell Biol*. 2018;217:283–298.

36. Jenkins ML, Harris NJ, Dalwadi U, et al. The substrate specificity of the human TRAPPII complex's Rab-guanine nucleotide exchange factor activity. *Commun Biol*. 2020;3:735.

37. Zhao S, Li CM, Luo XM, et al. Mammalian TRAPPIII complex positively modulates the recruitment of Sec13/31 onto COPII vesicles. *Sci Rep*. 2017;7:43207.

38. Cuenca A, Insinna C, Zhao H, et al. The C7orf43/TRAPPC14 component links the TRAPPII complex to Rabin8 for preciliary vesicle tethering at the mother centriole during ciliogenesis. *J Biol Chem*. 2019;294:15418–15434.

39. Mi C, Zhang L, Huang G, et al. Structural basis for assembly of TRAPPII complex and specific activation of GTPase Ypt31/32. *Sci Adv*. 2022;8:eabi5603.

40. Milev MP, Graziano C, Karall D, et al. Bi-allelic mutations in TRAPPC2L result in a neurodevelopmental disorder and have an impact on RAB11 in fibroblasts. *J Med Genet*. 2018;55:753–764.

41. Galindo A, Planelles-Herrero VJ, Degliesposti G, Munro S. Cryo-EM structure of metazoan TRAPPIII, the multi-subunit complex that activates the GTPase Rab1. *EMBO J*. 2021;40:e107608.

42. Choi C, Davey M, Schluter C, et al. Organization and assembly of the TRAPPII complex. *Traffic*. 2011;12:715–725.

43. Bagde SR, Fromme JC. Structure of a TRAPPII-Rab11 activation intermediate reveals GTPase substrate selection mechanisms. *Sci Adv*. 2022;8:eabn7446.

44. Sacher M, Barrowman J, Wang W, et al. TRAPP I implicated in the specificity of tethering in ER-to-Golgi transport. *Mol Cell*. 2001;7:433–442.

45. Kim JJ, Lipatova Z, Segev N. TRAPP complexes in secretion and autophagy. *Front Cell Dev Biol*. 2016;4:20.

46. Galindo A, Munro S. The TRAPP complexes: oligomeric exchange factors that activate the small GTPases Rab1 and Rab11. *FEBS Lett*. 2023;597(6):734–749. https://doi.org/10.1002/1873-3468.14553

47. Barrowman J, Bhandari D, Reinisch K, Ferro-Novick S. TRAPP complexes in membrane traffic: convergence through a common Rab. *Nat Rev Mol Cell Biol*. 2010;11:759–763.

48. Stanga D, Zhao Q, Milev MP, Saint-Dic D, Jimenez-Mallebrera C, Sacher M. TRAPPC11 functions in autophagy by recruiting ATG2B-WIPI4/WDR45 to preautophagosomal membranes. *Traffic*. 2019;20:325–345.

49. Milev MP, Grout ME, Saint-Dic D, et al. Mutations in TRAPPC12 manifest in progressive childhood encephalopathy and golgi dysfunction. *Am J Hum Genet*. 2017;101:291–299.

50. Brown DI, Parry TL, Willis MS. Ubiquitin ligases and posttranslational regulation of energy in the heart: the hand that feeds. *Compr Physiol*. 2017;7:841–862.

51. Chang JY, Chang NS. WWOX dysfunction induces sequential aggregation of TRAPPC6AΔ, TIAF1, tau and amyloid β, and causes apoptosis. *Cell Death Discov*. 2015;1, 15003-15003.

52. Hsu C-Y, Lee K-T, Sun T-Y, et al. WWOX and its binding proteins in neurodegeneration. *Cells*. 2021;10:1781.

53. Williams JL, Cavus O, Loccoh EC, et al. Defining the molecular signatures of human right heart failure. *Life Sci*. 2018;196:118–126.

54. Milev MP, Stanga D, Schänzer A, et al. Characterization of three TRAPPC11 variants suggests a critical role for the extreme carboxy terminus of the protein. *Sci Rep*. 2019;9:14036.

55. DeRossi C, Vacaru A, Rafiq R, et al. trappc11 is required for protein glycosylation in zebrafish and humans. *Mol Biol Cell*. 2016;27:1220–1234.

56. Bögershausen N, Shahrzad N, Chong Jessica X, et al. Recessive TRAPPC11 mutations cause a disease spectrum of limb girdle muscular dystrophy and myopathy with movement disorder and intellectual disability. *Am J Hum Genet*. 2013;93:181–190.

57. Milev MP, Hasaj B, Saint-Dic D, Snounou S, Zhao Q, Sacher M. TRAMM/TrappC12 plays a role in chromosome congression, kinetochore stability, and CENP-E recruitment. *J Cell Biol*. 2015;209:221–234.

58. Gu X, Ruan H, Yang J. Estimating the strength of expression conservation from high throughput RNA-seq data. *Bioinformatics*. 2019;35:5030–5038.

59. Gass JM, Head BB, Shields SM, Stevenson RE, Louie RJ. Hydrocephaly associated with compound heterozygous alterations in TRAPPC12. *Birth Defects Res*. 2020;112:1028–1034.

60. Dong X, Liang Z, Zhang J, et al. Trappc1 deficiency impairs thymic epithelial cell development by breaking endoplasmic reticulum homeostasis. *Eur J Immunol*. 2022;52:1789–1804.

61. Bodnar B, DeGruttola A, Zhu Y, et al. Emerging role of NIK/IKK2-binding protein (NIBP)/trafficking protein particle complex 9 (TRAPPC9) in nervous system diseases. *Transl Res*. 2020;224:55–70.

62. Ramírez-Peinado S, Ignashkova TI, van Raam BJ, et al. TRAPPC13 modulates autophagy and the response to Golgi stress. *J Cell Sci*. 2017;130:2251–2265.

63. Szul T, Sztul E. COPII and COPI traffic at the ER-Golgi interface. *Physiology (Bethesda)*. 2011;26:348–364.

64. Luo PM, Boyce M. Directing Traffic: Regulation of COPI transport by post-translational modifications. *Front Cell Dev Biol*. 2019;7:190.

65. Joiner AM, Phillips BP, Yugandhar K, et al. Structural basis of TRAPPIII-mediated Rab1 activation. *EMBO J*. 2021;40:e107607.

66. Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. *Cell*. 2011;147:728–741.

67. Kaushik S, Cuervo AM. Chaperone-mediated autophagy: a unique way to enter the lysosome world. *Trends Cell Biol*. 2012;22:407–417.

68. Bejarano E, Cuervo AM. Chaperone-mediated autophagy. *Proc Am Thorac Soc*. 2010;7:29–39.

69. Su T, Li X, Yang M, et al. Autophagy: an intracellular degradation pathway regulating plant survival and stress response. *Front Plant Sci*. 2020;11:164.

70. Meiling-Wesse K, Epple UD, Krick R, et al. Trs85 (Gsg1), a component of the TRAPP complexes, is required for the organization of the preautophagosomal structure during selective autophagy via the Cvt pathway. *J Biol Chem*. 2005;280:33669–33678.

71. Nazarko TY, Huang J, Nicaud JM, Klionsky DJ, Sibirny AA. Trs85 is required for macroautophagy, pexophagy and cytoplasm to vacuole targeting in Yarrowia lipolytica and Saccharomyces cerevisiae. *Autophagy*. 2005;1:37–45.

72. Lipatova Z, Belogortseva N, Zhang XQ, Kim J, Taussig D, Segev N. Regulation of selective autophagy onset by a Ypt/Rab GTPase module. *Proc Natl Acad Sci U S A*. 2012;109:6981–6986.

73. Behrends C, Sowa ME, Gygi SP, Harper JW. Network organization of the human autophagy system. *Nature*. 2010;466:68–76.

74. Zoppino FC, Militello RD, Slavin I, Alvarez C, Colombo MI. Autophagosome formation depends on the small GTPase Rab1 and functional ER exit sites. *Traffic*. 2010;11:1246–1261.

75. Jedd G, Richardson C, Litt R, Segev N. The Ypt1 GTPase is essential for the first two steps of the yeast secretory pathway. *J Cell Biol*. 1995;131:583–590.

76. Weidberg H, Shvets E, Elazar Z. Biogenesis and cargo selectivity of autophagosomes. *Annu Rev Biochem*. 2011;80:125–156.

77. Welz T, Wellbourne-Wood J, Kerkhoff E. Orchestration of cell surface proteins by Rab11. *Trends Cell Biol*. 2014;24:407–415.

78. Burke JE, Inglis AJ, Perisic O, et al. Structures of PI4KIIIβ complexes show simultaneous recruitment of Rab11 and its effectors. *Science*. 2014;344:1035–1038.

79. Erasmus JC, Smolarczyk K, Brezovjakova H, et al. Rac1-PAK1 regulation of Rab11 cycling promotes junction destabilization. *J Cell Biol*. 2021;220:e202002114.

80. Li C, Luo X, Zhao S, et al. COPI-TRAPPII activates Rab18 and regulates its lipid droplet association. *EMBO J*. 2017;36:441–457.

81. Balse E, El-Haou S, Dillanian G, et al. Cholesterol modulates the recruitment of Kv1.5 channels from Rab11-associated recycling endosome in native atrial myocytes. *Proc Natl Acad Sci U S A*. 2009;106:14681–14686.

82. O'Connell KM, Tamkun MM. Targeting of voltage-gated potassium channel isoforms to distinct cell surface microdomains. *J Cell Sci*. 2005;118:2155–2166.

83. Ronzier E, Parks XX, Qudsi H, Lopes CM. Statin-specific inhibition of Rab-GTPase regulates cPKC-mediated IKs internalization. *Sci Rep*. 2019;9:17747.

84. Filipeanu CM, Zhou F, Wu G. Analysis of Rab1 function in cardiomyocyte growth. *Methods Enzymol*. 2008;438:217–226.

85. Butterworth MB, Edinger RS, Silvis MR, et al. Rab11b regulates the trafficking and recycling of the epithelial sodium channel (ENaC). *Am J Physiol Renal Physiol*. 2012;302:F581–F590.

86. Pettersen EF, Goddard TD, Huang CC, et al. UCSF Chimera–a visualization system for exploratory research and analysis. *J Comput Chem*. 2004;25:1605–1612.

KEY WORDS $K_v1.5$, $K_v4.2$, Rab1, Rab11, TRAPP