

REVIEW

Functional proteomics, human genetics and cancer biology of GIPC family members

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GIPC1, GIPC2 and GIPC3 consist of GIPC homology 1 (GH1) domain, PDZ domain and GH2 domain. The regions around the GH1 and GH2 domains of GIPC1 are involved in dimerization and interaction with myosin VI (MYO6), respectively. The PDZ domain of GIPC1 is involved in interactions with transmembrane proteins [IGF1R, NTRK1, ADRB1, DRD2, TGF β R3 (transforming growth factor β receptor type III), SDC4, SEMA4C, LRP1, NRP1, GLUT1, integrin α 5 and VANGL2], cytosolic signaling regulators (APPL1 and RGS19) and viral proteins (HBc and HPV-18 E6). GIPC1 is an adaptor protein with dimerizing ability that loads PDZ ligands as cargoes for MYO6-dependent endosomal trafficking. GIPC1 is required for cell-surface expression of IGF1R and TGF β R3. GIPC1 is also required for integrin recycling during cell migration, angiogenesis and cytokinesis. On early endosomes, GIPC1 assembles receptor tyrosine kinases (RTKs) and APPL1 for activation of PI3K-AKT signaling, and G protein-coupled receptors (GPCRs) and RGS19 for attenuation of inhibitory G α signaling. GIPC1 upregulation in breast, ovarian and pancreatic cancers promotes tumor proliferation and invasion, whereas GIPC1 downregulation in cervical cancer with human papillomavirus type 18 infection leads to resistance to cytostatic transforming growth factor β signaling. GIPC2 is downregulated in acute lymphocytic leukemia owing to epigenetic silencing, while *Gipc2* is upregulated in estrogen-induced mammary tumors. Somatic mutations of *GIPC2* occur in malignant melanoma, and colorectal and ovarian cancers. Germ-line mutations of the *GIPC3* or *MYO6* gene cause nonsyndromic hearing loss. As GIPC proteins are involved in trafficking, signaling and recycling of RTKs, GPCRs, integrins and other transmembrane proteins, dysregulation of GIPCs results in human pathologies, such as cancer and hereditary deafness.

Experimental & Molecular Medicine (2013) 45, e26; doi:10.1038/emm.2013.49; published online 7 June 2013

Keywords: actin dynamics; cancer antigen; endocytic transport; Frizzled; planar cell polarity; whole-genome sequencing

INTRODUCTION

GIPC1/GIPC (GAIP/RGS19-interacting protein),¹ GIPC2² and GIPC3³ are PDZ domain proteins that constitute the GIPC family.⁴ GIPC1 is also known as TIP2 (Tax-interacting protein 2),⁵ NIP [neuropilin 1 (NRP1)-interacting protein],⁶ GLUT1CBP [GLUT1 (SLC2A1) C-terminal binding protein],⁷ SEMCAP1 [Semaphorin 4C (SEMA4C)-interacting protein 1],⁸ Synectin [Syndecan 4 (SDC4)-interacting protein]⁹ and IIP1 [insulin-like growth factor-1 receptor (IGF1R)-interacting protein 1].¹⁰ GIPC3 is also known as DFNB15, DFNB72, DFNB95 and C19orf64.^{11,12}

Physiological roles of GIPC1 have been well characterized. The PDZ domain in the middle region of GIPC1 is involved in interaction with a variety of PDZ ligands, such as RGS19, NRP1, GLUT1, SEMA4C, SDC4 and IGF1R.^{1,6–10} The N-terminal region of GIPC1 is involved in dimerization, whereas the C-terminal region of GIPC1 is involved in interaction with the retrograde motor protein, myosin VI

(MYO6).^{13–15} On the basis of these protein–protein interactions, GIPC1 functions as an adaptor molecule for loading PDZ-target cargoes on the MYO6 motor protein (Figure 1a).

GIPC family members are evolutionarily conserved with functional similarity.^{1–4,16–24} GIPCs are involved in the trafficking of various transmembrane proteins and regulate a variety of cellular processes, such as proliferation, planar cell polarity, cytokinesis and migration. Pathologies associated with the GIPCs, such as hearing loss^{11,12} and cancer,^{25–34} are emerging topics in the medical sciences. Here, the functional proteomics, evolutionary genetics, human genetics and cancer biology of the GIPC family members will be reviewed, with a focus on recent advances and future directions.

GIPC FAMILY

The *GIPC1* gene at human chromosome 19p13.12, the *GIPC2* gene at human chromosome 1p31.1 and the *GIPC3* gene at

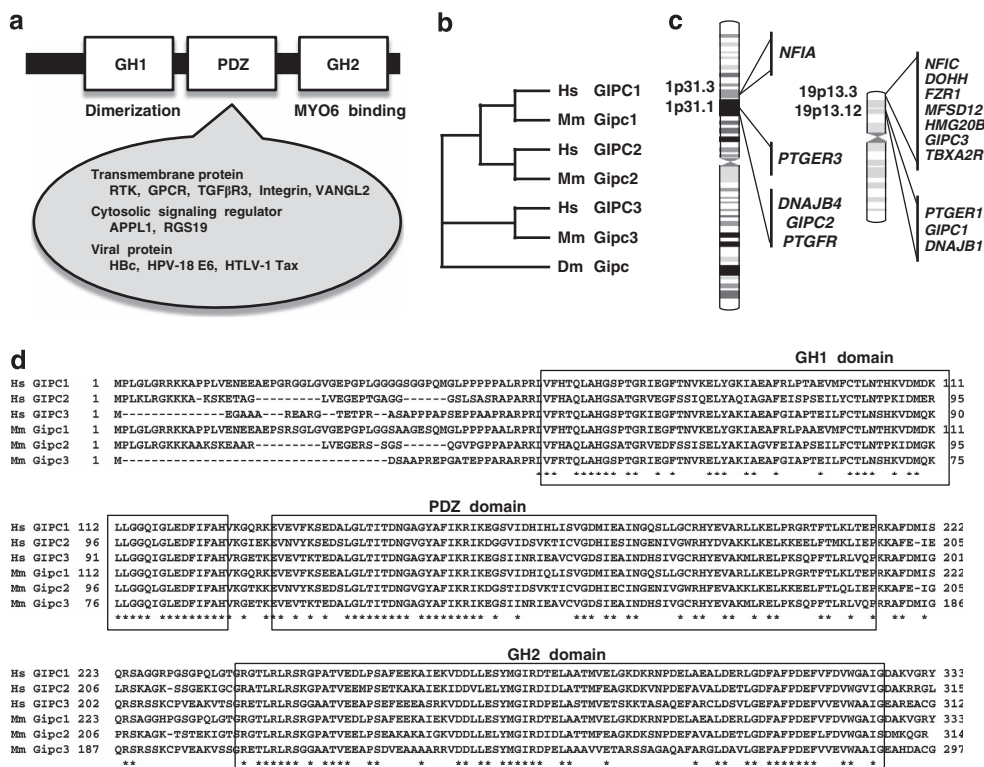


Figure 1 GIPC family. **(a)** Domain architecture of GIPC. GIPC family proteins consist of a GH1 domain, a PDZ domain and a GH2 domain. The regions around the GH1 and GH2 domains of GIPC1 are involved in dimerization and interaction with myosin VI (MYO6), respectively. The PDZ domain of GIPC1 is involved in interactions with transmembrane proteins, cytosolic signaling regulators and viral proteins. **(b)** Phylogenetic analyses of GIPC family proteins. GIPC1 and GIPC2 are more closely related. **(c)** Human chromosomal localization of *GIPC* family genes. **(d)** Alignment of human and mouse GIPC family proteins. The amino-acid position is shown on both sides of the alignment. Conserved amino acids are indicated by an asterisk below the alignment. The GH1 domain in the N-terminal part, PDZ domain in the middle part and GH2 domain in the C-terminal part are well conserved among GIPC family members. Hs, human; Mm, mouse.

human chromosome 19p13.3 constitute the human *GIPC* gene family.⁴ Phylogenetic analysis of human GIPC1 (NP_005707.1), GIPC2 (NP_060125.4), GIPC3 (NP_573568.1), mouse *Gipc1* (NP_061241.1), *Gipc2* (NP_058563.1), *Gipc3* (NP_683753.1) and *Drosophila Gipc* (NP_652028.1) proteins reveals that GIPC1 is the paralog of GIPC2 (Figure 1b). The *GIPC1* gene is located between the *PTGER1* and *DNAJB1* genes; the *GIPC2* gene adjoins the *DNAJB4* gene and lies close to the *PTGER3* gene. The *PTGER1-GIPC1-DNAJB1* and *PTGER3-DNAJB4-GIPC2* loci are paralogous regions in the human genome (Figure 1c).

GIPC family proteins consist of a GIPC homology 1 (GH1) domain, a PDZ domain and a GH2 domain (Figure 1a). The GH1, PDZ and GH2 domains are well conserved among GIPC1, GIPC2 and GIPC3 orthologs (Figure 1d), as previously reported.⁴

PROTEIN-PROTEIN INTERACTIONS OF GIPC1

Protein-protein interactions have been comprehensively characterized for GIPC1, the founding member of the GIPC family (Figure 1a).

The PDZ domain of GIPC1 is involved in direct interactions with a variety of proteins, including adrenergic receptor β1 (ADRB1),³⁵ APPL1,³⁶⁻³⁸ CD93 (C1QR1),³⁹ dopamine receptor D2 (DRD2),⁴⁰ endoglin,⁴¹ GLUT1,⁷ IGF1R,^{10,27} integrin α5,⁴² integrin α6,⁴² luteinizing hormone/choriogonadotropin receptor (LHCGR),⁴³ LRP1,⁴⁴ LRP2 (megalin),⁴⁴ NRP1,^{6,45,46} NTRK1 (TrkA),⁴⁷ RGS19,¹ SDC4,⁹ SEMA4C,⁸ transforming growth factorβ (TGFβ) receptor type III (TGFβR3),⁴⁸⁻⁵⁰ trophoblast glycoprotein (TPBG),⁵¹ TYRP1⁵² and Vang-like 2 (VANGL2 or STB1).⁵³ IGF1R and NTRK1 are receptor tyrosine kinases (RTKs) with a single transmembrane domain; ADRB1, DRD2 and LHCGR are G protein-coupled receptors (GPCRs) with seven transmembrane domains; CD93, endoglin, GLUT1, integrin α5, integrin α6, LRP1, LRP2, NRP1, SDC4, SEMA4C, TGFβR3, TPBG, TYRP1 and VANGL2 are also transmembrane proteins (Figure 2). APPL1 is a scaffold protein, interacting with GIPC1, NTRK1, Rab5, PIK3CA (the catalytic α subunit of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)) and AKT,³⁶⁻³⁸ while RGS19 is a regulator of G protein signaling, interacting with GIPC and G protein α inhibitory subunit 3.¹ APPL1 and RGS19 are

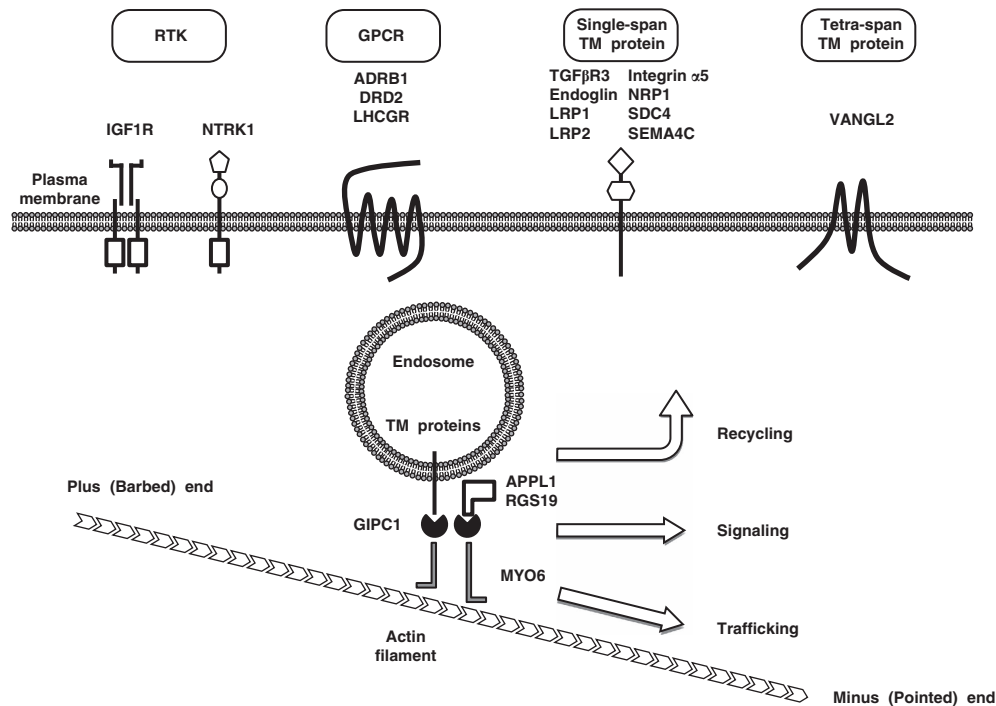


Figure 2 GIPC1–MYO6 complex-dependent trafficking of endocytic vesicles. GIPC1 is an adaptor protein that can interact with trafficking cargoes, while MYO6 is a motor protein that can move along actin filaments from the plus (barbed) end near the plasma membrane to the minus (pointed) end in the cytoplasm. Representative cargoes of the GIPC1–MYO6 complex are classified into receptor tyrosine kinases (RTKs; IGF1R and NTRK1), G protein-coupled receptors (GPCRs; ADRB1, DRD2 and LHCGR), single-span transmembrane (TM) proteins (TGF β R3, endoglin, LRP1, LRP2, integrin α 5, NRP1, SDC4 and SEMA4C), tetra-span TM protein (VANGL2) and cytosolic signaling regulators (APPL1 and RGS19). The GIPC1–MYO6 complex is directly involved in trafficking and signaling and is indirectly involved in the recycling of its cargoes.

cytosolic proteins that regulate intracellular signaling. In addition to the cellular proteins mentioned above, the PDZ domain of GIPC1 directly interacts with viral proteins, such as HBC,⁵⁴ E6⁵⁵ and Tax,⁵ which are derived from the hepatitis B virus, human papillomavirus type 18 (HPV-18) and human T-cell leukemia virus type 1, respectively. The majority of PDZ ligands for GIPC1 are transmembrane proteins, but a minority of them are cytosolic signaling regulators.

The C-terminal region around the GH2 domain of GIPC1 can directly interact with MYO6, a member of the myosin family of motor proteins.^{13–15} MYO6 moves toward the minus (pointed) end of actin filaments located in the cytoplasm, whereas other myosin family proteins move toward the plus (barbed) end of actin filaments adjacent to the plasma membrane. MYO6 is a retrograde motor protein, involved in various cellular processes such as trafficking of early endosomes, cytokinesis and migration.⁵⁶

The N-terminal region around the GH1 domain of GIPC1 is involved in dimerization.¹³ Because of its dimerization potential, GIPC1 is able to assemble PDZ-binding proteins as cargoes of the MYO6 motor protein in early endosomes (Figure 2).

INTRACELLULAR FUNCTIONS OF GIPC1

Transmembrane proteins on the plasma membrane are internalized and packed into inside-out vesicles as a result of endocytosis.⁵⁷ The endocytic vesicles are initially located in the

periphery of the cytoplasm, beneath the plasma membrane, and are trafficked to early endosomes.⁵⁸ As MYO6 is a motor protein moving along actin filaments from the barbed end near the plasma membrane to the pointed end in the cytoplasm, the GIPC1–MYO6 complex has a pivotal role in the trafficking of transmembrane proteins on endocytic vesicles (Figure 2). Most of transmembrane receptors on the early endosomes are returned to the plasma membrane directly or via recycling endosomes, although some of them are sorted for lysosomal degradation. GIPC1 is necessary for cell-surface expression of transmembrane receptors, such as IGF1R,²⁷ LHCGR⁴³ and TGF β R3.⁴⁸

GIPC1 interacts with integrin α 5 subunit,⁴² which is bound to integrin β subunit to form integrin heterodimers. Integrin α 5 β 1 is trafficked to the early endosomes as a cargo of the GIPC1–MYO6 complex and is then sorted for recycling to the plasma membrane. As integrins are mechano-sensory receptors that bridge extracellular matrix and cytoplasmic adaptor proteins associated with actin filaments, integrin recycling to cell surface is required for the regulation of actin dynamics.^{59,60} Indeed, GIPC1 is required for the trafficking of internalized integrins during cell migration,¹⁹ angiogenesis⁶¹ and cytokinesis.¹⁵

RTKs consist of an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic tyrosine kinase domain. RTKs are receptors for growth factors, such as

epidermal growth factor, IGF1, nerve growth factor and fibroblast growth factor.^{62–64} The binding of ligands to RTKs induces their dimerization and autophosphorylation, which leads to the activation of RAS–ERK, PI3K–AKT, phospholipase C γ (PLC γ) and other signaling cascades. RTKs are internalized as a result of ligand-induced dimerization. RTK signaling occurs from the plasma membrane as well as early endosomes.^{62,63} GIPC1 binds to IGF1R and NTRK1 but not to insulin receptor,^{10,47} and enhanced endosomal signaling occurs from NTRK1 but not from insulin receptor.⁶³ As PI3K and AKT are recruited to the GIPC complex via interactions with APPL1, GIPC1 dimerization induces clustering of RTK and APPL1 complex to early endosomes for the preferential activation of the PI3K–AKT signaling cascade rather than the RAS–ERK signaling cascade.^{36–38} GIPC1 is involved in the endosomal signaling from RTK to the PI3K–AKT signaling cascade (Figure 3a).

GPCRs consist of extracellular ligand-binding regions, seven transmembrane domains and cytoplasmic G protein-binding regions. GPCRs are receptors for a variety of ligands, such as adrenaline (epinephrine), dopamine and WNT.^{65,66} Ligand binding to GPCRs induces dissociation of heterotrimeric G proteins from GPCRs, leading to the activation of G α - and G $\beta\gamma$ -mediated signaling cascades. The G α s subunit activates adenylate cyclase to increase cyclic AMP concentrations. The inhibitory G α (G α i) subunit inhibits adenylate cyclase to decrease cyclic AMP concentrations. The G α q subunit activates PLC β . G α 12/13 subunit activates Rho GTPase. The G $\beta\gamma$ subunit activates PI3K, PLC β and ion channels.⁶⁷ GPCRs are internalized as a result of ligand-induced dissociation of the heterotrimeric G proteins and subsequent association with

β -arrestin. GPCR signaling occurs from the plasma membrane as well as from early endosomes.⁶⁸ As RGS19 functions as a GTPase-activating protein to inactivate G α i, the dimerization of GIPC1 induces clustering of GPCR and RGS19 to the early endosomes for the attenuation of G α i signaling.^{35,40} GIPC1 is involved in the modulation of the endosomal GPCR signaling (Figure 3b).

Together, these facts indicate that GIPC1 regulates a variety of cellular processes, such as endosomal trafficking, signaling and recycling of RTKs, GPCRs, integrins and other transmembrane proteins.

EVOLUTIONARILY CONSERVATION OF GIPCS

Kermit 1 and Kermit 2 are *Xenopus* orthologs of human GIPC2 and GIPC1, respectively. Kermit 1 interacts with WNT receptors, including Frizzled-3 (Fzd3) and Frizzled-7 (Fzd7), and is required for WNT signaling during neural crest development.¹⁶ Kermit 2 interacts with Igf1r similar to the interaction of human GIPC1 with IGF1R and is required for IGF1 signaling during eye development.¹⁷ Kermit 2 also interacts with the integrin α 5 subunit to regulate endocytosis of α 5 β 1 integrin, which is essential for the lining of the fibronectin matrix on the blastocoel roof during the gastrulation stage of embryogenesis.¹⁹

Zebrafish *Gipc1* genetically interacts with *Neuropilin-2* (*Nrp2*) and *Vegfr3* (*Flt4*), and is involved in lymphangiogenic sprouting during thoracic duct formation.²⁰ Nrp2 functions as a co-receptor for the Vegfr3 ligands, Vegf-c and Vegf-d. Nrp2 and Nrp1 are paralogs, sharing a common domain architecture, especially the C-terminal PDZ-binding site. As

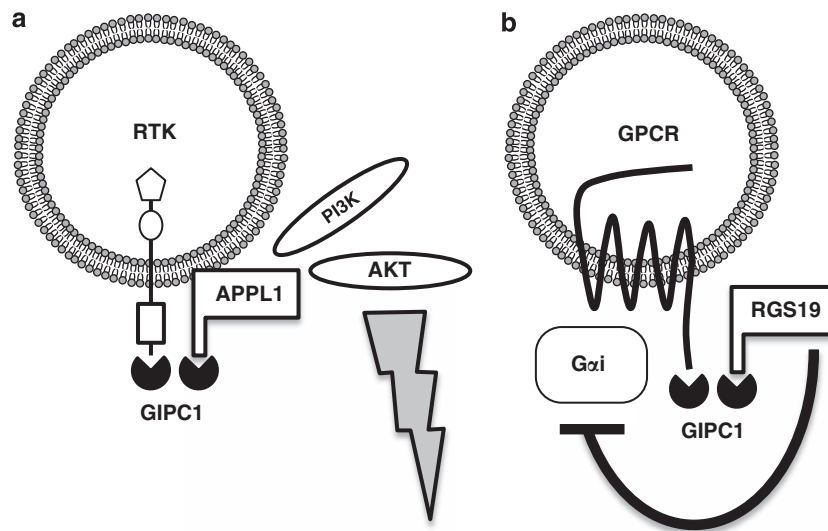


Figure 3 Involvement of GIPC1 in endosomal signaling. (a) GIPC1-mediated early endosomal signaling from receptor tyrosine kinases (RTKs). IGF1R and NTRK1 are GIPC1-interacting RTKs, while APPL1 is a scaffold protein that interacts with GIPC1, RTK, Rab5, PI3K and AKT. GIPC1–RTK and GIPC1–APPL1 complexes are assembled on early endosomes through GIPC1 dimerization or RTK–APPL1 interaction. Internalized RTKs clustered with APPL1 preferentially activate the PI3K–AKT signaling cascade. (b) GIPC1-mediated early endosomal signaling from G protein-coupled receptors (GPCRs). Adrenergic receptor β 1 (ADRB1) and dopamine receptor D2 (DRD2) are GIPC1-interacting GPCRs. ADRB1 transduces signals to G α s and G α i, while DRD2 transduces signals to G α i. RGS19 is a GTPase activating protein that can inactivate G α i. GIPC1–GPCR and GIPC1–RGS19 complexes are assembled on early endosomes through GIPC1 dimerization. RGS19 clustered with internalized GPCRs attenuates G α i signaling.

mouse *Gipc1* directly interacts with the C-terminal tail of Nrp1,⁶ the interaction between *Gipc1* and Nrp2 is thought to be required for lymphangiogenic signaling through the Nrp2–Vegfr3 receptor complex.

Drosophila gipc mRNA is upregulated during wing development²¹ and its overexpression causes planar cell polarity defects in the wing but not in the eye.²² *Drosophila gipc* does not genetically interact with core planar cell polarity components, such as *frizzled*, *dishevelled*, *flamingo*, *strabismus* (*vang*) and *prickle*; however, it does interact with *jaguar*, which is the *Drosophila* ortholog of human MYO6.

The *Drosophila* *Gipc* protein is expressed in the adult brain, especially in the dopaminergic neurons and glia.²³ *Drosophila gipc* mutants show a reduction of dopaminergic neurons in the dorsomedial regions of the adult brain, which results in locomotor defects and reduced longevity. Although the interaction between *Drosophila* *Gipc* and the dopamine receptor remains unclear, interactions between rat *Gipc* and dopamine receptors suggest that *Drosophila* *Gipc* might also be involved in dopamine signaling.

Schistosoma japonicum is a pathogenic parasite that causes schistosomiasis. The expression level of *S. japonicum gipc* mRNA is relatively higher during the parasitic stages than during the cercarial stage, and *S. japonicum* *Gipc* interacts with the C-terminal tail of the glutamate receptor.²⁴

GIPC proteins are conserved from mammals and other vertebrates to non-vertebrates, such as flies and worms, and some functions of GIPCs are also evolutionarily conserved.

GIPC3 MUTATIONS IN FAMILIAL HEARING LOSS

Germ-line homozygous mutations of human *GIPC3* are associated with familial hearing loss, such as the autosomal

recessive nonsyndromic hearing impairment DFNB15, DFNB72 and DFNB95.^{11,12,69} Human *GIPC3* is almost ubiquitously expressed in adult human tissues, and the expression level of *GIPC3* is relatively high in the small intestine, lymph node, brain parietal lobe, fetal spleen and fetal thymus.³ G46R, M88I and G94D missense mutations are located within the GH1 domain; H170N and R189C missense mutations are located within the PDZ domain; T221I, G256D, L262R missense mutations, W301X nonsense mutation and A229GfsX10 frame-shift mutation are located within the GH2 domain. G46, M88, G94, H170, T221, G256, L262 and W301 amino-acid residues of *GIPC3* are conserved in all human and mouse *GIPC* family members (Table 1).

In line with hereditary deafness caused by mutations of human *GIPC3*, germ-line homozygous G115R mutations of *Gipc3* occur in Black Swiss mice, which manifest progressive sensorineural hearing loss.¹¹ Mouse *Gipc3* mRNA is relatively highly expressed in the brain, lung and testes.⁷⁰ G115 of mouse *Gipc3*, which corresponds to G130 of human *GIPC3*, is located within the PDZ domain. In *Gipc3* mutant mice, the expression levels of the *Gipc3* protein are decreased in the sensory hair cells of Corti's organ and their afferent neurons in the cochlear spiral ganglion, which is accompanied by disorientation and degradation of the stereocilia bundle of sensory hair cells and degradation of sensory neurons in the spiral ganglion, respectively.¹¹

CANCER BIOLOGY OF GIPC FAMILY MEMBERS

GIPC1 is upregulated in human cancers, such as breast cancer,^{25,28,29,32} ovarian cancer^{26,28,34} and pancreatic cancer.^{25,27,31} *GIPC1* is a cancer-associated auto-antigen, as anti-*GIPC1* human monoclonal antibody was established from

Table 1 GIPC mutation spectra

Gene	Type	Mutation	Location	Disease	Conservation	Reference
<i>GIPC1</i>	Somatic	F319L	GH2 domain	HNSCC	GIPC1, GIPC2	76
<i>GIPC2</i>	Somatic	F74Y	GH1 domain	Colorectal cancer	GIPC1, GIPC2, GIPC3	77
	Somatic	G102E	GH1 domain	Ovarian cancer	GIPC1, GIPC2, GIPC3	79
	Somatic	D125N	PDZ domain	Malignant melanoma	GIPC1, GIPC2, GIPC3	78
	Somatic	E216X		Colorectal cancer		77
	Somatic	E288K	GH2 domain	Malignant melanoma	GIPC1, GIPC2	78
	Somatic	R312Q		Colorectal cancer		77
<i>GIPC3</i>	Germ line	G46R	GH1 domain	Familial hearing loss	GIPC1, GIPC2, GIPC3	12
	Somatic	E67K	GH1 domain	Breast cancer	GIPC1, GIPC3	80
	Germ line	M88I	GH1 domain	Familial hearing loss	GIPC1, GIPC2, GIPC3	12
	Germ line	G94D	GH1 domain	Familial hearing loss	GIPC1, GIPC2, GIPC3	12
	Germ line	H170N	PDZ domain	Familial hearing loss	GIPC1, GIPC2, GIPC3	69
	Germ line	R189C	PDZ domain	Familial hearing loss	GIPC3	12
	Germ line	T221I	GH2 domain	Familial hearing loss	GIPC1, GIPC2, GIPC3	12
	Germ line	A229GfsX10	GH2 domain	Familial hearing loss		12
	Germ line	G256D	GH2 domain	Familial hearing loss	GIPC1, GIPC2, GIPC3	12
	Germ line	L262R	GH2 domain	Familial hearing loss	GIPC1, GIPC2, GIPC3	11
	Germ line	W301X	GH2 domain	Familial hearing loss	GIPC1, GIPC2, GIPC3	11

Abbreviations: GH2, GIPC homology 2; HNSCC, head and neck squamous cell carcinoma.

a breast cancer patient.²⁹ Immunohistochemical analyses using the anti-GIPC1 human monoclonal antibody revealed that the GIPC1 protein is overexpressed in primary breast cancer and ovarian cancer.²⁸ *GIPC1* overexpression in ovarian cancer is associated with amplification and overexpression of the *ADRM1* gene, encoding a transmembrane protein that interacts with the UCH37 deubiquitinating enzyme.³⁴ GIPC1, which is involved in IGF1R stabilization, promotes proliferation and survival of pancreatic cancer cells and breast cancer cells.^{27,31,32} GIPC1 knockdown in cancer cells inhibits proliferation and promotes apoptosis. GIPC1 knockdown also results in G2 cell-cycle arrest and decreased motility in MDA-MB231 cells,³³ because GIPC1 is involved in cytokinesis¹⁵ and cell migration.¹⁹ CR1023 (*N*-myristoyl-PSQSSSEA) is a cell-permeable octapeptide corresponding to the IGF1R-binding interface within the PDZ domain of GIPC1 that is able to inhibit the proliferation of IGF1R-dependent cancer cells by downregulating cell-surface IGF1R.^{31,32} CR1166 (*N*-myristoyl-PSQSK(ϵ N-4-bromobenzoyl)SK(ϵ N-4-bromobenzoyl)A) is the most active CR1023 derivative that downregulates both IGF1R and EGFR.⁷¹

GIPC1 is downregulated in cervical cancer associated with HPV-18 infection.⁵⁵ The E6 oncoprotein derived from HPV-18 induces poly-ubiquitination and proteasomal degradation of GIPC1 using mechanisms similar to those observed for p53, Scribbled (SCRIB), MUPP1, MAGI1, MAGI2 and MAGI3. As GIPC1 enhances the cell-surface expression of TGF β 3 and the cellular responsiveness to TGF β ,⁴⁸ E6-mediated GIPC1 downregulation results in decreased sensitivity to cytosolic TGF β signaling.⁵⁵

GIPC2 is upregulated in gastric cancer,⁷² whereas it is downregulated in kidney cancer,² acute lymphocytic leukemia (ALL)³⁰ and adrenocortical carcinoma.⁷³ The CpG island within the promoter region of the *GIPC2* gene is hyper-methylated in all 23 leukemia cell lines, including MOLT4, Jurkat, Peer, T-ALL1, CEM, J-TAG, B-JAB, RS4, ALL1, Raji, REH and Ramos cells of lymphoid origin, as well as K562, BV173, HL60, NB4, THP1, U937, ML1, OCI, HEL, MOLM13 and KBM5R cells of myeloid origin.³⁰ The *GIPC2* promoter is also hyper-methylated in 29 of the 31 cases of ALL. As *GIPC2* repression in MOLT4, Jurkat, CEM, RS4 and Raji cells is restored after 5-aza-2'-deoxycytidine treatment, GIPC2 downregulation in primary ALL cases is predicted to be the result of epigenetic silencing-associated promoter hyper-methylation.³⁰

Mouse *Gipc2* is upregulated in estrogen-induced mammary lesions of *Caveolin-1* knockout mice, which resembles human ductal carcinoma *in situ*.⁷⁴ Mouse *Gipc2* is specifically co-expressed with *Esr1*, which encodes estrogen receptor (ER), and *Keratin 18* (*Krt18*) in the ER⁺ luminal cells of the virgin mammary gland.⁷⁵ These facts suggest the involvement of GIPC2 in human breast cancer of the ER⁺ luminal type.

Somatic mutations of *GIPC* family genes have been identified based on whole-exome or whole-genome sequencing. F319L missense mutation of GIPC1 occurs in head and neck squamous cell carcinoma.⁷⁶ F74Y and R312Q missense mutations and E216X nonsense mutation of GIPC2 occur in

colorectal cancer.⁷⁷ D125N and E288K missense mutations of GIPC2 occur in malignant melanoma.⁷⁸ G102E missense mutation of GIPC2 occurs in ovarian cancer.⁷⁹ E67K missense mutation of GIPC3 occurs in breast cancer.⁸⁰ The F74Y, G102E and D125N missense mutations might alter GIPC2 functions, because the F74, G102 and D125 amino-acid residues of GIPC2 are conserved in all human and mouse GIPC family members (Table 1). The E216X nonsense mutation of GIPC2 in colorectal cancer is a deleterious mutation that results in a loss of the MYO6-binding GH2 domain.

CONCLUSION

GIPC proteins function as adaptor molecules that assemble RTKs, GPCRs, integrins, transmembrane proteins and cytoplasmic signaling regulators as cargoes of MYO6-dependent endocytic transport. Germ-line mutations of the *GIPC3* gene occur in nonsyndromic hearing loss. Somatic mutations of *GIPC* family genes occur in several types of human cancers, such as head and neck squamous cell carcinoma, colorectal cancer, malignant melanoma, ovarian cancer and breast cancer. GIPC1 can be oncogenic or tumor suppressive in a context-dependent manner. As GIPCs are involved in trafficking, signaling and recycling of receptors and adhesion molecules, GIPC dysregulation results in a spectrum of human diseases, such as cancer and hereditary deafness.

PERSPECTIVES

Germ-line mutations of the human *GIPC3* gene occur in autosomal recessive nonsyndromic hearing loss, such as DFNB15, DFNB72 and DFNB95,^{11,12,69} while those of human *MYO6* gene occur in other types of familial hearing loss, such as DFNA22 and DFNB37.^{81,82} Mutations of mouse *Gipc3* and *Myo6* are also associated with hereditary hearing loss.^{11,83} GIPC1 interacts with MYO6 using the GH2 domain,^{13–15} which is well conserved between GIPC1 and GIPC3 orthologs (Figure 1d). Taken together, these facts suggest that GIPC3 might directly interact with MYO6 to regulate sensorineural signaling in the cochlea of the inner ear.

It is interesting to ponder what the cargo of the putative GIPC3–MYO6 complex may be. Disorientation of the stereocilia bundle of sensory hair cells in *Gipc3* mutant mice¹¹ is similar to a 'Frizzled' phenotype in the wing hair of *Drosophila*, which is caused by mutations of planar cell polarity genes, such as *frizzled* and *vang*.^{22,84–87} *Xenopus Gipc2* directly interacts with Fzd3 and Fzd7, which are *Xenopus* homologs of *Drosophila* Frizzled.¹⁶ Mouse *Gipc1* directly interacts with Vangl2, which is a mouse homolog of *Drosophila* Vang.^{53,86,88} As the PDZ domain is also well conserved among GIPC family members, Frizzled and Vangl family members might be cargoes of the GIPC3–MYO6 complex. To confirm this, PDZ ligands for GIPC3 in sensory hair cells should be elucidated.

Rat *Gipc1* directly interacts with dopamine receptors, such as DRD2 and DRD3,^{40,89} and *Drosophila Gipc* is expressed in dopaminergic neurons.²³ Germ-line mutations of the human *DRD2* gene occur in myoclonus dystonia,⁹⁰ while allelic

variation of the human *DRD3* gene is associated with schizophrenia⁹¹ and essential tremor.⁹² In addition, as juveniles *Gipc3* mutant mice hyper-react to acoustic stimulation by running around in an uncontrolled manner and having seizures, but they become resistant to loud noise at 6 weeks old, owing to the progression of hearing impairment.¹¹ Germ-line mutations of *GIPC* family genes in neurological diseases, such as myoclonus dystonia, schizophrenia, essential tremor and juvenile epilepsy, might be discovered based on whole-genome or whole-exome sequencing.

GIPC1 upregulation in breast and pancreatic cancers leads to tumor proliferation through IGF1R stabilization and tumor invasion through integrin recycling, whereas GIPC1 down-regulation in cervical cancer results in decreased sensitivity to cytostatic signaling through TGF β R3 destabilization. CR1023 and its derivatives, which block the interaction between GIPC1 and IGF1R, inhibit proliferation of IGF1R-dependent tumors. However, these GIPC1 inhibitors might promote proliferation of TGF β -sensitive tumors. Patients should be rigorously selected for clinical application of GIPC1 inhibitors, including CR1023 and its derivatives. Specific inhibitors of GIPC1 targets, such as the small-molecule IGF1R inhibitor and anti-IGF1R human antibody, might be preferable as therapeutic choices for cancer patients.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported in part by a grant-in-aid for the National Cancer Center Research and Development Fund.

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