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Linking GOLPH3 and Extracellular Vesicles Content—a Potential New Route in Cancer Physiopathology and a Promising Therapeutic Target is in Sight?

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Abstract

Golgi phosphoprotein 3 (GOLPH3), a highly conserved phosphatidylinositol 4-phosphate effector, is required for maintenance of Golgi architecture, vesicle trafficking, and Golgi glycosylation. GOLPH3 overexpression has been reported in several human solid cancers, including glioblastoma, breast cancer, colorectal cancer, nonsmall cell lung cancer, epithelial ovarian cancer, prostate cancer, gastric cancer, and hepatocellular carcinoma. Although the molecular mechanisms that link GOLPH3 to tumorigenesis require further investigation, it is likely that GOLPH3 may act by controlling the intracellular movement of key oncogenic molecules, between the Golgi compartments and/or between the Golgi and the endoplasmic reticulum. Indeed, numerous evidence indicates that deregulation of intracellular vesicle trafficking contributes to several aspects of cancer phenotypes. However, a direct and clear link between extracellular vesicle movements and GOLPH3 is still missing. In the past years several lines of evidence have implicated GOLPH3 in the regulation of extracellular vesicle content. Specifically, a new role for GOLPH3 has emerged in controlling the internalization of exosomes containing either oncogenic proteins or noncoding RNAs, especially micro-RNA. Although far from being elucidated, growing evidence indicates that GOLPH3 does not increase quantitatively the excretion of exosomes, but rather regulates the exosome content. In particular, recent data support a role for GOLPH3 for loading specific oncogenic molecules into the exosomes, driving both tumor malignancy and metastasis formation. Additionally, the older literature indirectly implicates GOLPH3 in cancerogenesis through its function in controlling hepatitis C virus secretion, which in turn is linked to hepatocellular carcinoma formation. Thus, GOLPH3 might promote tumorigenesis in unexpected ways, involving both direct and indirect routes. If these data are further confirmed, the spectrum of action of GOLPH3 in tumor formation will significantly expand, indicating this protein as a strong candidate for targeted cancer therapy.

Keywords

exosome, excretion, micro-RNA, hepatitis, hepatitis C virus, hepatocellular carcinoma, WNT

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Introduction

The Golgi apparatus acts as a central hub to coordinate endomembrane trafficking with glycoprotein processing, which in turn is crucial to maintain cell homeostasis, cellular migration, and growth in normal cells.[1] Aberrant protein trafficking and secretion has been associated with several disease states including chronic inflammation and cancer.[2] Mutations affecting Golgi resident proteins have been commonly found in human tumors and have been linked to cancer metastasis and poor survival of patients.[3]

Golgi phosphoprotein 3 (GOLPH3) has been defined as a first-in class Golgi oncoprotein and characterized as a peripheral membrane protein mainly enriched in the trans-Golgi network (TGN) and its vesicles by a specific binding to the phosphoinositide phosphatidylinositol 4-phosphate [PI(4)P]. As a PI(4)P effector, GOLPH3 regulates many cellular processes and cell signaling pathways in quiescent and dividing cells.[4–7] Notably, a recent proteomic analysis in

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the model organism *Drosophila melanogaster*, aiming at obtaining the GOLPH3 interactome, revealed additional potential partners not only in vesicle-mediated trafficking, Golgi architecture maintenance, and protein glycosylation, but also in cell proliferation, signaling, and cytoskeleton dynamics.[6]

This review aims to discuss the role of GOLPH3 in controlling the internalization of exosomes and how this function can be related to the cancer phenotypes.

Role of GOLPH3 in Tumorigenesis: A Brief Overview of Consolidated Data

GOLPH3 was initially identified in the course of proteomic-based studies of the Golgi[8,9] and subsequently identified as an oncoprotein.[10] Research studies in human cells and model organisms characterized GOLPH3 as a highly conserved protein, which is mainly localized to the TGN, via direct interaction with PI(4)P.[4,11,12] Evidence indicates that GOLPH3 function influences multiple intracellular vesicular routes such as vesicular transport to the plasma membrane, intra-Golgi, and endocytic trafficking.[7] As a PI(4)P effector, GOLPH3 is required for membrane trafficking, Golgi architecture maintenance, and glycosylation.[4,11,12] GOLPH3 has been reported as a broad-spectrum coat protein complex I adaptor with an essential role in enzyme sorting and consequently Golgi glycosylation.[13–17] GOLPH3 has been also involved in endocytic trafficking through the retromer, the endosomal protein sorting machinery which regulates vesicle transport between the endosomes and TGN and between the endosome and the plasma membrane.[12,18]

Increasing evidence links deregulation of intracellular vesicle trafficking to several aspects of cancer biology.[19,20] In the past few years, accumulated evidence has supported the role of GOLPH3 in cancer formation and progression,[5,21] with a special regard to solid tumors. The 5p13 genomic region containing GOLPH3 gene is frequently amplified in several solid tumor types including melanoma, colon adenocarcinoma, and nonsmall cell lung cancer (NSCLC).[18] Moreover, GOLPH3 overexpression correlates with poor prognosis in multiple tumor types including 52% of breast cancers[22] and 41% to 53% of glioblastoma.[23,24] Moreover it has been amply reported that GOLPH3 might exert its oncogenic function by enhancing the mammalian target of rapamycin (mTOR) signaling, although the molecular link remains to be clarified.[18,25–27] It has been suggested that GOLPH3 might promote cellular transformation, by affecting the glycosylation of key cancer relevant glycoproteins or glycolipids.[13] Importantly, aberrant glycosylation such as defective processing of oligomannose glycans, incompletely processed or truncated complex N-glycan and O-glycan, altered sialylation and fucosylation of N-linked and O-linked glycans, are universal features of cancer cells and have been implicated in tumor progression and invasiveness.[28] GOLPH3 also plays a central role to prevent DNA damage and genomic instability, which is a well-known marker of cancer cells.[29] The DNA damage induced by treatment with camptothecin, doxorubicin, and ionizing radiation induces a Golgi shape reorganization for which GOLPH3 action is essential.[30] A similar Golgi reshape occurs in neuroblastoma as a consequence of DNA damage response.[31] GOLPH3 function is also required to prevent tetraploidy and the consequent accumulation of chromosome instability. Indeed, a role for GOLPH3 in preventing cytokinesis failures has been reported in *Drosophila melanogaster* where GOLPH3 accumulates at the cleavage furrow of dividing cells and is required for cytokinesis.[12,32,33] Moreover, a recent GOLPH3 interactome analysis in *Drosophila* has revealed multiple potential molecular partners involved in cytokinesis.[6]

Additional functions of GOLPH3 in tumorigenesis come from numerous sources. Zhou et al[34] showed its role in glioma progression through inhibition of endocytosis and degradation of epidermal growth factor receptor (EGFR). Interestingly, several works accumulated in the past years highlighting the role of GOLPH3 in brain tumors, and in some cases the molecular pathways have been identified, such as those involving mTOR,[23,35] Ak strain transforming (AKT),[35,36] Janus kinase 2 / signal transducer and activator of transcription 3,[37] prohibitin 2,[38] and mitogen-activated protein kinase.[39] Additional signaling pathways influenced by GOLPH3 include myosin XVIIIA (MYO18A) in neuroblastoma,[31] AKT, forkhead Box O1, and activating transcription factor 3 in breast[40,41] and colon[42] cancers, JAK2 and STAT3 in colon cancer,[43,44] Wingless-related integration site (Wnt) in colon[45] and ovary[46] cancers, mTOR—beyond brain tumors—in lung,[47] prostate,[48,49] gastric,[50] ovary,[51] and liver[52] cancers, EGFR in lung cancer,[53] and NACHT-LRR-PYD domains-containing protein 3 in gallbladder carcinoma.[54] Lisanti and coworkers linked GOLPH3 function to cancer metabolism,[55,56] while Rizzo et al[13] showed the central role of GOLPH3 in regulating the cellular sphingolipidome, thus promoting growth factor signaling and cell proliferation. In all cases, a direct correlation could be established between the intracellular amount of GOLPH3 (either by overexpression, gene amplification, or impaired turnover) and cancer aggressiveness.

Recent evidence shows a role of GOLPH3 in cancer development through its role in the control of exosome content, adding a new layer of complexity to the function of this protein. Table 1 shows a summary of what has been discovered in this field so far, while a deeper analysis of exosome-related data is reported below.

Linking GOLPH3 to Hepatocellular Carcinoma via HCV Excretion

According to the January 2022 revision of the American Cancer Society data, more than 800,000 new liver cancer diagnoses are done each year, with a death burden of more than 700,000 patients per year.[63] Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults and the most common cause of death in patients with cirrhosis. This condition can be caused by several factors including chronic liver inflammation caused by liver damage mediated by hepatitis B and C viruses (HBV and HCV, respectively). Indeed, HCV is the leading cause of HCC in North America, Japan, and Europe.[64] HCV is a small enveloped RNA virus

Table 1. Role of GOLPH3 in Exosome Excretion and Cancer.

Cancer Type(s)	Molecular Interactors	Additional Molecules Involved	Exosome Content(s)	Type/Function of Exosome Content(s)	Effects on Cancer Cells	Ref
HCC	MYO18A	nd	HCV	Complete virus	Virus spreading Chronic inflammation	57
HCC	nd	PTEN	miR-494-3p	miR	Angiogenesis Cell migration Apoptosis Sorafenib sensitivity	58
GBM	nd	Various miR	miR-376c-3p	miR	nd	59
BC CRC ME	RAB1B	PITPNC1 14-3-3	HTRA1 MMP1 FAM3C PDGFA ADAM10	Peptidase Peptidase Metabolism Growth factor Peptidase	Tumor invasion Tumor growth	60
GBM	Wls	β-Catenin Wnt	Wnt2b	Wnt signaling	Cell proliferation	61
NSCLC	CKAP4	β-Catenin Wnt	Wnt3A	Wnt signaling	Cell migration Tumor invasion	62

Abbreviations: ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; BC, breast cancer; CRC, colorectal cancer; FAM3C, family with sequence similarity 3C; GBM, glioblastoma multiforme; GOLPH3, Golgi phosphoprotein 3; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HTRA1, high-temperature requirement A serine peptidase 1; ME, melanoma; MMP1, matrix metalloproteinase 1; MYO18A, myosin XVIIIA; nd, not determined; NSCLC, nonsmall cell lung cancer; miR, micro-RNA; PDGFA, plateletderived growth factor subunit A; PTEN, phosphatase and tensin homolog; Wls, Wntless; Wnt, wingless-related integration site.

which completes its life cycle within the cytoplasm of human cells (mainly liver cells, but also lymphocytes, to a lesser extent). After its genome expression occurring at the rough endoplasmic reticulum (ER) and the proteolytic cut of the precursor polypeptide, viral proteins are post-transcriptionally modified in various ways including glycosylation.[65] The final step of the HCV cycle leads to build the lipid envelope, which enables HCV to exit the host cell. These lipoviroparticles mature during an unconventional passage through the Golgi apparatus and a trans-endosomal secretory route.[66] However, an extracellular step is also required to complete HCV maturation.[67] It is well known that PI(4)P is a key molecule for regulating the HCV cycle[68] and that GOLPH3 acts as a PI(4)P effector at the Golgi.[69] Moreover, the release of HCV particles relies on the ER-Golgi secretory trafficking and on the TGN function.[70] The first (and, to date, the only one) direct link between HCV and GOLPH3 was reported 10 years ago.[57] In their work, Bishé et al demonstrated that the interaction between GOLPH3 and the unconventional myosin MYO18A is required for vesicle budding, and that GOLPH3 deficiency dramatically impairs HCV secretion without affecting the virus intracellular replication. Emerging data lead to hypothesize that the HCV-related chronic inflammation possibly leading to HCC might find in GOLPH3 a possible route for tumor formation. This hypothesis foresees that GOLPH3 facilitates virus invasion and—if directly demonstrated—this could allow designing anti-HCV drugs targeting GOLPH3 to inhibit HCV spreading inside the liver. Interestingly, this is not the only link between GOLPH3 and HCC, as illustrated below.

Micro-RNA Excretion in Cancer is Controlled Also by GOLPH3

A recent study in HCC links angiogenesis and sorafenib resistance to upregulation of exosomal miR-494-3p mediated by GOLPH3.[58] Gao et al first demonstrated that downregulation of GOLPH3 expression can suppress angiogenesis and enhance sorafenib sensitivity in HCC. Then, using differential centrifugation, they collected and separated the extracellular vesicles originated by HCC and analyzed their micro-RNA (miR) content. They showed that 13 miRs are differentially expressed between negative control and GOLPH3 knockdown controls. Among these miRs, only one miR—namely, miR-494-3p—showed a direct correlation with GOLPH3. Interestingly, GOLPH3 downregulation did not affect intracellular content of this miR, and GOLPH3 overexpression did not impair the number of exosomes released in HCC cells. Overall, these data indicate that the role played by GOLPH3 in this pathway is essential for regulating the exosome qualitative content, but not the amount of molecules that is loaded into the exosomes. Mechanistically, the authors also showed that upregulation of miR-494-3p expression increased migration rate and capillary tube formation ability of an human umbilical vein endothelial cells cell line, and at the same time upregulated IC_{50} values in seoul national university cell line 449 and metastatic hepatocellular carcinoma cell line 97H cell lines through suppression of apoptosis. The candidate target gene of miR-494-3p was identified as phosphatase and tensin homolog by using an approach based on bioinformatics prediction and dual-luciferase reporter assay.

Additional links between GOLPH3 and the exosome content come from a study performed in glioma by Hu et al.[59] The researchers isolated the exosomes from the supernatant of U251 and U87 human glioblastoma cell lines and then analyzed their content using an approach similar to the abovementioned work of Gao et al. Similar to the previous analysis, this article shows that the effects of GOLPH3 on the exosome content is qualitative and not quantitative, revealing a specific upregulation of tens of miRs in samples with GOLPH3 overexpression. Interestingly, the miR with the higher overexpression value—namely, miR-376c-3p—is a key molecule in the development of HCC[71,72] and in HBV-related HCC.[73]

The Role of GOLPH3 in Proteins Excretion in Cancer

Besides the exosomal miRs, it has also been reported that the exosome protein content is specifically affected by GOLPH3 deregulation. One of the first studies reporting the effects of GOLPH3-mediated protein secretion in cancer is the work of Halberg et al.[60] By using quantitative proteomics, the authors show that the PITPNC (phosphatidylinositol transfer protein cytoplasmic 1)-ras-associated binding 1B GOLPH3 axis drives malignant secretion of growth factors and matrix metalloproteases, which in turn leads to increased cell motility, extracellular matrix remodeling, metastasis, and angiogenesis in breast, melanoma, and colon cancers. Specifically, they show that PITPNC1 binding to PI(4)P via its N-terminal end mediates PITPNC1 localization to the Golgi and enables the recruitment of the small guanosine triphosphatase (GTPase) RAB1B. In turn, the PITPNC1/RAB1B complex allows for the recruitment of GOLPH3 to the *trans*-Golgi compartment which promotes Golgi extension and enhanced release of vesicles in cancer cells. In agreement with this model, proteomic analysis of metastatic cells reveals that PITPNC1 depletion affects the secretion of the pro-invasive and pro-angiogenic mediators high-temperature requirement A serine peptidase 1, matrix metalloproteinase 1, family with sequence similarity 3C, platelet-derived growth factor subunit A, and a disintegrin and metalloproteinase domain-containing protein 10.

Abnormal Wnt/β-catenin signaling in tumorigenesis has also been correlated to GOLPH3 function. The Wnt family of proteins is highly conserved in all metazoans and involved in cancer formation and progression.[74–76] All Wnt ligands are glycosylated in the ER; then, they are transported to the plasma membrane via the Golgi apparatus and finally, in their paracrine action, are excreted in the extracellular space through their incorporation inside exosomes.[75]

Lu et al[61] reported the first direct link between GOLPH3 expression and Wnt2b secretion in glioma progression. They showed that downregulation of Wntless (Wls), the chaperone protein of Wnt secretion and its cargo receptor, partially abolished glioma cell proliferation induced by GOLPH3 overexpression, whereas its overexpression partially rescued the inhibitory effect of GOLPH3 downregulation. This occurs because downregulation of GOLPH3 promotes Wls degradation. Wls is the cargo receptor of Wnt which, in turn, acts on the stability of β-catenin. Consistently, the authors reported that β-catenin is downregulated in a GOLPH3-depleted background, indicating for the first time that the depletion of GOLPH3 impairs Wls recycling and Wnt2b secretion, and consequently decreases the Wnt2b/β-catenin/Cyclin D1 signaling axis in the context of glioma. Thus, the progression of glioma would be (also) driven by the alteration of the Wnt2b pathway, which is due to the decreased loading of Wnt2b protein into the exosomes, in turn affected by GOLPH3-mediated Wls recycling.

Similar results were recently obtained by Song et al[62] in the context of Wnt3A. In their work, the authors studied NSCLC, showing that GOLPH3 overexpression enhances the cell migration and invasion abilities of NSCLC cells. Remarkably, overexpression of GOLPH3 in NSCLC (i) correlates positively with the clinical stage of patients; (ii) causes the enhancement of cell migration and invasion, and a stem cell-like phenotype *in vitro*; (iii) promotes formation of distal metastasis *in vivo*; and (iv) promotes a tumor stemness phenotype in NSCLC cells *in vivo*. To investigate the mechanisms underlying GOLPH3 function in these phenotypes, the authors analyzed the exosomes produced by NSCLC cells demonstrating that *GOLPH3* messenger RNA expression positively correlates with Wnt-activated gene signatures. On the basis of the abovementioned work on glioma,[61] the authors searched in exosomes for members of the Wnt family. Out of 19 members, only 7 Wnt members are expressed in NSCLC and, of them, only Wnt3A shows a positive correlation. They further demonstrated that GOLPH3 does not directly bind Wnt3A, instead it interacts with cytoskeleton-associated protein 4 (CKAP4) and increases CKAP4-containing exosomes which, in turn, binds exosomal Wnt3A to enhance its secretion.

Conclusions

The role of exosomes in cancer formation and progression is widely accepted.[77,78] They promote tumorigenesis through their content, which includes oncogenic proteins and noncoding RNAs such as miR, long non-coding RNA, and circular RNA.[77] Less known is the mechanism by which the exosome content is selected. The role of GOLPH3 in intracellular vesicle trafficking and Golgi function is starting to be elucidated, but a complete understanding of the mechanisms of action of GOLPH3 in cancer development and progression is still far from being fully understood. The sparse bibliography available about GOLPH3 involvement in exosome biology (Table 1) is probably the beginning of a new chapter in understanding tumorigenesis, and it is likely that additional roles of GOLPH3 will be unveiled in the next future. Of course, these findings need further verification. However, the accumulating data support a central role of GOLPH3 in cancer, and strongly candidate this protein as a possible target for cancer therapy, a road that is still largely unexplored.

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