GOLPH3: a Golgi phosphatidylinositol(4)phosphate effector that directs vesicle trafficking and drives cancer

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Abstract GOLPH3 is a peripheral membrane protein localized to the Golgi and its vesicles, but its purpose had been unclear. We found that GOLPH3 binds specifically to the phosphoinositide phosphatidylinositol(4)phosphate [PtdIns(4)P], which functions at the Golgi to promote vesicle exit for trafficking to the plasma membrane. PtdIns(4)P is enriched at the trans-Golgi and so recruits GOLPH3. Here, a GOLPH3 complex is formed when it binds to myosin 18A (MYO18A), which binds F-actin. This complex generates a pulling force to extract vesicles from the Golgi; interference with this GOLPH3 complex results in dramatically reduced vesicle trafficking. The GOLPH3 complex has been identified as a driver of cancer in humans, likely through multiple mechanisms that activate secretory trafficking. In this review, we summarize the literature that identifies the nature of the GOLPH3 complex and its role in cancer. We also consider the GOLPH3 complex as a hub with the potential to reveal regulation of the Golgi and suggest the possibility of GOLPH3 complex inhibition as a therapeutic approach in cancer.

GOLPH3 (also known as GMx33 and GPP34) was first discovered by proteomic studies of purified Golgi fractions (6, 7). Further investigation revealed GOLPH3 to be a peripheral membrane protein, highly localized to the trans-Golgi and to vesicles budding from the trans-Golgi (6–8). The yeast ortholog of GOLPH3, VPS74, was also found to function at the Golgi (9, 10). However, the mechanism of localization to the Golgi and the purpose of GOLPH3 at the Golgi remained uncertain.

During a genome-wide, proteomic screen for phosphoinositide binding proteins, we identified GOLPH3 as a protein that binds tightly and specifically to PtdIns(4)P (see Fig. 1) (11). We found that GOLPH3 binding to PtdIns(4)P is responsible for its localization to the Golgi in yeast and mammalian cells (11). GOLPH3 is a highly abundant (~10^6 molecules per cell), ubiquitously expressed protein (11, 12). Thus, it is a major effector of PtdIns(4)P at the Golgi.

PtdIns(4)P was already well known to be highly enriched at the trans-Golgi (13–15). From yeast to humans, PtdIns(4)P at the Golgi is required for Golgi-to-plasma membrane trafficking (16–19). Certainly, many effectors of PtdIns(4)P besides GOLPH3 have been described. These have a variety of activities, including several that function as nonvesicular lipid transporters, and have been the subject of many previous reviews (20–22). Two phosphatidylinositols-4-kinases (PI-4-kinases), PI4KIIIα and PI4KIIIβ, localize to the Golgi to produce PtdIns(4)P (13, 14, 23). Currently, we lack a detailed understanding of the differential roles for [PtdIns(4)P]/GOLPH3 complex are oncogenic cancer drivers.

ROLE OF THE PTDINS(4)P/GOLPH3 COMPLEX IN GOLGI FORWARD TRAFFICKING

Cancer involves wholesale production of cellular biomass, and thus we might predict that every part of the cell, and every organelar regulatory pathway, is likely to be involved. Indeed, many organelles, including mitochondria, lysosomes, and the endoplasmic reticulum (ER), have well-established roles in promoting cancer initiation and/or progression (1–5). A role for the Golgi in cancer has been largely speculative until the recent discoveries that components of the Golgi phosphatidylinositol(4)phosphate

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Abbreviations: ER, endoplasmic reticulum; PTP, phosphatidylinositol transfer protein; PtdIns, phosphatidylinositol; PtdIns(4)P, phosphatidylinositol(4)phosphate; PI-4-kinase, phosphatidylinositol-4-kinase.

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these PI-4-kinases in Golgi function. The delivery of PtdIns substrate to these PI-4-kinases appears to be dependent on a family of PtdIns transfer proteins (PITPs) that include PITPα (PITPNA), PITPβ (PITPNB), and PITPNC1 (RdgBβ) (24–29). Early studies proposed a role for the PITPs in nonvesicular transport of PtdIns from the ER to the Golgi (24, 29, 30). More recent studies have provided a more complex interpretation, suggesting a role for PITPs in presenting substrate directly to the PI-4-kinases (30–32).

In addition to binding PtdIns(4)P, GOLPH3 tightly interacts with the unconventional myosin, MYO18A (11, 12, 33). MYO18A binds to F-actin, an interaction that is strengthened when MYO18A is bound to GOLPH3 (33–37). The PtdIns(4)P/GOLPH3/MYO18A/F-actin complex applies a tensile force to the Golgi, which is readily observed by the effect of the GOLPH3 complex on the shape of the Golgi. In most mammalian cells, as observed by light microscopy, the Golgi forms a ribbon that extends partially around the nucleus. As observed by electron microscopy, the stacks of Golgi cisternae are highly flattened. However, interference with any part of the GOLPH3 complex [e.g., depletion of PtdIns(4)P, GOLPH3, MYO18A, or F-actin] results in condensation of the Golgi into a compact ball adjacent to the nucleus and rounding of the trans-Golgi cisternae (11, 12, 38–40). These observations suggest that the GOLPH3 complex applies a stretching force to the Golgi that is responsible for its characteristic appearance.

Although the morphological effects are striking, it is unlikely that this is the purpose of the GOLPH3 complex (41). For example, the GOLPH3 complex is conserved and functional in organisms and cell types with dramatically differing Golgi morphology. Rather, we find that the GOLPH3 complex plays a critical role in the exit of vesicles from the Golgi for trafficking to the plasma membrane, and the effect on Golgi shape is a consequence of the mechanism of vesicle budding. Indeed, live imaging reveals that the majority of PtdIns(4)P-positive, cargo-positive vesicles that exit from the Golgi move in a direction parallel to the tensile force, as indicated by the shape of the Golgi (11). Interference with the GOLPH3 complex [e.g., by depletion of PtdIns(4)P, GOLPH3, MYO18A, or F-actin] results in a dramatic reduction in the exit of these vesicles from the trans-Golgi (11). Accordingly, interference with the GOLPH3 complex dramatically reduces Golgi-to-plasma membrane trafficking, as observed by a variety of experiments. Global protein secretion, as measured by 35S-Met pulse/chase and assessment of the appearance of label incorporated into proteins in the media, is inhibited >80% by knockdown of GOLPH3 or MYO18A, similar to the effect of the Golgi poison Brefeldin A (12). Trafficking of VSVG to the plasma membrane is inhibited >50%, with accumulation at the Golgi, by knockdown of GOLPH3 or MYO18A (11, 42). Secretion of hepatitis C virus from infected cells is inhibited >80%, with intracellular accumulation of intact, otherwise fully functional viral particles, upon knockdown of GOLPH3 or MYO18A (43). Taken together, the data suggest that the purpose of the GOLPH3 complex is to apply a tensile force to the trans-Golgi to promote vesicle budding for trafficking to the plasma membrane. The effect of the GOLPH3 complex on Golgi shape is a side effect of the mechanism of trafficking (41).

REGULATION OF THE GOLGI VIA THE GOLPH3 COMPLEX

Until recently, in the scientific literature, the Golgi has been considered as a constitutive organelle, with little known about its regulation in response to extracellular or intracellular signals (20). The discovery of the GOLPH3 complex has provided a framework for understanding regulation of the Golgi. Based on our assumption that the GOLPH3 complex is likely to be regulated, we mapped phosphorylation sites in GOLPH3 (44). One of the sites, Thr143, we found was phosphorylated by the DNA damage-activated protein kinase, DNA-PK. This led to our discovery of the Golgi DNA damage response, a common feature of the cellular response to DNA damage in mammals, whereby the Golgi ribbon fragments into small vesicles that disperse throughout the cytoplasm (44). Briefly, we found that...
phosphorylation of GOLPH3 on Thr143 by DNA-PK in response to DNA damage enhances the interaction with MYO18A, leading to increased vesiculation of the Golgi, resulting in Golgi fragmentation. Ultimately, this hyperactivation of the GOLPH3 complex is required for normal cell survival following DNA damage (44).

Another example of regulation of the Golgi through the GOLPH3 complex involves growth factor stimulation of an increase in PtdIns(4)P levels at the Golgi (45, 46). Growth factor signaling was found to drive trafficking of the SAC1 PtdIns(4)P-phosphatase from the Golgi to the ER, allowing for elevated levels of PtdIns(4)P at the Golgi. Withdrawal of growth factors leads to an increase in SAC1 at the Golgi and a concomitant decrease in PtdIns(4)P levels at the Golgi, associated with compaction of the Golgi ribbon and reduced Golgi-to-plasma membrane trafficking, the hallmarks of inhibition of the GOLPH3 complex. The mechanism of regulation involves growth factor-stimulated activation of p38/MAPK to regulate SAC1’s interaction with the COPI retrograde trafficking machinery (45, 46).

The activity of the GOLPH3 complex is also differentially regulated during cell-type specification by the selective expression of GOLPH3L in highly secretory cells (12). GOLPH3L is a paralog of GOLPH3 that, like GOLPH3, binds to PtdIns(4)P and localizes to the Golgi. However, unlike GOLPH3, GOLPH3L does not interact with MYO18A. As such, GOLPH3L acts as an endogenous dominant-negative inhibitor of the GOLPH3 complex, with opposite effects on the Golgi compared with GOLPH3 (12, 38). The data indicate that GOLPH3L acts as a throttle in highly secretory cells.

These examples provide a picture of the GOLPH3 complex as a hub for convergent signals for regulation of the Golgi. The old picture of a constitutive Golgi, with little or no regulation, was not biologically plausible. The GOLPH3 complex has provided a conceptual framework to explore and understand regulation of the Golgi, which is likely to be rich and to involve many intracellular and extracellular signaling pathways.

THE GOLPH3 COMPLEX DRIVES CANCER IN HUMANS

Unbiased cancer genome studies have independently identified GOLPH3, MYO18A, and PITPNC1 as drivers of common human cancers. GOLPH3 was found in a genome-wide search for genes that are frequently amplified in human cancers (47). A minimal region of chromosome 5p13, encompassing four genes, was found to be common to all of the amplifications. Of these, GOLPH3 alone was found to have expression levels that correlated with copy number, and its knockdown was found to revert oncogenic transformation in cell culture. The GOLPH3 gene was found to be amplified in 56% of lung carcinomas, 37% of prostate carcinomas, 32% of breast carcinomas, 33% of pancreatic carcinomas, 24% of colon carcinomas, and 57% of ovarian carcinomas. The Cancer Genome Atlas (TCGA) reports rates of amplification of the GOLPH3 gene that are somewhat lower, although still significant, e.g., in 15% of lung squamous cell carcinomas and 10% of lung adenocarcinomas (48, 49). In cell culture and xenograft mouse models, overexpression of GOLPH3 was found to cooperate with HRAS-G12V or BRAF-V600E to cause oncogenic transformation (47). Subsequent studies have demonstrated elevated levels of GOLPH3 mRNA and protein in a variety of cancers compared with adjacent normal tissue. Furthermore, high levels of expression of GOLPH3 correlate with poor patient prognosis in a variety of tumors. Several studies have demonstrated that specific knockdown of GOLPH3 reverts cancer phenotypes and that overexpression of GOLPH3 drives cancer phenotypes in cell culture and xenograft mouse models of cancer (42, 44, 47, 50–54).

Similar results have been observed in a variety of cancer types, as summarized in Table 1. In total, there is quite a lot of support for the idea that GOLPH3 is an oncogene that drives cancer in humans.

MYO18A has also been identified as a cancer driver. Algorithms to analyze genome-wide breast cancer data, including somatic copy number alterations, point mutations, gene expression, and RNA interference screening data, identified 17 drivers of breast cancer in humans, including many expected genes such as ERBB2, CCND1, and MYC (55). Of the novel genes, several of them were validated as oncogenes. Notably, MYO18A was identified in this analysis as a driver of breast cancer. In a separate study of prostate cancer cell lines, elevated expression of MYO18A was found to correlate with increased cell migration and invasion (56). MYO18A has also been found as part of oncogenic fusion proteins created by chromosomal translocations in several myeloid cancers (57–59). Furthermore, TCGA data indicate that the MYO18A gene is amplified at high frequency in a number of cancers, including 11% of metastatic breast cancers (60) and 21% of neuroendocrine prostate cancers (61).

The PtdIns transfer protein family member, PITPNC1, has been identified as an oncogene. Investigation of the mechanism of inhibition of metastasis by the microRNA miR-126 identified PITPNC1 as a crucial target that is suppressed by miR-126 (39, 62). Moreover, PITPNC1 is amplified and overexpressed in a high proportion of human breast cancers. Overexpression of PITPNC1 was found to drive increased cancer cell migration, invasion, and metastasis in cell culture and in mouse models of cancer. High levels of PITPNC1 were found to correlate with metastatic progression of breast, melanoma, and colon cancers. Knockdown of PITPNC1 led to impaired migration, invasion, and metastasis of previously aggressive breast and colorectal cancer cell lines. Interestingly, PITPNC1 localizes to the Golgi, and knockdown of it results in compaction of the Golgi, suggesting impaired function of the GOLPH3 complex. Indeed, knockdown of GOLPH3 was able to block the effects of overexpression of PITPNC1, indicating that PITPNC1 acts through GOLPH3 (39).

The Golgi localized PI-4-kinases, PI4KIIα and PI4KIIIβ, have potential links to cancer. PI4KIIα has been found to be overexpressed in a high proportion of breast, melanoma, thyroid, kidney, liver, lung, prostate, colon, uterine,
and pancreatic cancers (63). Overexpression of PI4KIIIβ has been reported in 27% of primary breast cancers (64). However, the implication of these proteins as drivers of cancer remains largely correlative as of yet. Further interventional experiments to test their roles in cancer are needed.

Taken together, amplification or overexpression of GOLPH3, MYO18A, and PITPNC1 (and, perhaps, the PI-4-kinases) occurs at high frequency in cancer. Moreover, even more prevalent in cancer is DNA damage (65). DNA damage is known to activate the GOLPH3 complex through signaling by posttranslational modification of GOLPH3 (44). As discussed above, other signaling pathways, including growth factor signaling, also serve to activate the GOLPH3 complex. Clearly more data are needed, but it seems likely that the GOLPH3 complex is activated in a high proportion of cancers.

MECHANISMS OF ONCOGENESIS BY THE GOLPH3 COMPLEX

Although GOLPH3, MYO18A, and PITPNC1 were found independently to be cancer drivers, the realization that they act together at the Golgi has allowed for powerful insight into several mechanisms by which they promote oncogenic transformation. One role for the GOLPH3 complex in cancer involves the cellular DNA damage response (44). The Golgi DNA damage response, mediated by PtdIns(4)P, GOLPH3, and MYO18A, is required for normal cell survival following DNA damage. Furthermore, overexpression of GOLPH3 drives enhanced cellular survival in the face of DNA damage. Notably, DNA damage is common in cancer cells and plays an important role in cancer progression (65, 66). Moreover, most cancer treatment protocols still rely heavily on DNA-damaging agents. The fact that the GOLPH3 complex [dependent on PtdIns(4)P, GOLPH3, and MYO18A] drives resistance to killing by DNA damage may, in part, explain why high levels of GOLPH3 predict poor prognosis in many cancers.

The GOLPH3 complex has also been found to drive cell migration (42, 50, 51, 67, 68). Cell migration is responsible for cancer invasion and metastasis, the processes that make cancers lethal (69, 70). Several groups found that PtdIns(4)P and GOLPH3 act through the Golgi to promote cell migration (42, 50, 51). We found that PtdIns(4)P and GOLPH3 act through MYO18A to link the Golgi to the actin cytoskeleton (42). This linkage functions to reorient the Golgi toward the cell’s leading edge and to drive trafficking to the leading edge. These activities promote cell migration. Other studies have further implicated MYO18A and PITPNC1 in driving cell migration to promote cancer invasion and metastasis (39, 56). The role of the GOLPH3 complex to drive cell migration is likely important to its ability to drive cancer and to promote a poor prognosis.

When GOLPH3 was first identified as an oncogene, it was observed to be able to drive increased growth factor signaling (47). Numerous studies have corroborated the ability of GOLPH3 to drive increased growth factor signaling, although the mechanism remains uncertain (71–74). Certainly, increasing growth factor signaling is a mechanism to promote oncogenic transformation.

A role for GOLPH3 has been proposed in cell division, specifically in cytokinesis, in Drosophila (75–77). Knockdown or mutation of GOLPH3 has been observed to result in multinucleate spermatocytes and larval neuroblasts (75). Furthermore, during cytokinesis, during which the Golgi is typically disassembled, partial localization of GOLPH3 in the vicinity of the cleavage furrow has been reported (75, 77). It remains uncertain whether GOLPH3

### TABLE 1. Summary of data examining the GOLPH3 complex in cancer in humans

| Cancer Type | Gene | Gene Amplified | mRNA | Protein | Predicts Poor Prognosis | References |
|-------------|------|----------------|------|---------|-------------------------|------------|
| Lung        | GOLPH3 | 10–56%         | +    | 59–72%  | +                       | (47–49, 80–84) |
| Breast      | GOLPH3 | 32%            | +    | 52–67%  | +                       | (47, 53, 85)  |
|             | MYO18A | 11%            | +    | 46%     | +                       | (55, 60)    |
|             | PITPNC1| 46%            | +    | 52–53%  | +                       | (59)        |
| Colorectal  | GOLPH3 | 24%            | +    | 2%      | +                       | (47, 86–88) |
|             | PITPNC1| 24%            | +    | 42%     | +                       | (39)        |
| Prostate    | GOLPH3 | 37%            | +    | 42%     | +                       | (47, 89)    |
|             | MYO18A | 21%            | +    | 34%     | +                       | (56, 61)    |
|             | PITPNC1| 20%            | +    | 53%     | +                       | (61)        |
| Pancreas    | GOLPH3 | 33%            | +    | 73%     | +                       | (47, 90)    |
| Liver       | GOLPH3 | 29%            | +    | 65%     | +                       | (47, 71, 91, |
|             |         |                |      |         |                         | 92)         |
| Melanoma    | GOLPH3 | 32%            | +    | 63%     | +                       | (47, 93)    |
|             | PITPNC1| 26%            | +    | 52%     | +                       | (39)        |
| Ovary       | GOLPH3 | 38%            | +    | 45–72%  | +                       | (47, 94–96) |
| Esophagus   | GOLPH3 | +              | 49%  | +       | +                       | (72, 97)    |
| Glioma      | GOLPH3 | +              | 41%  | +       | +                       | (54, 98–100) |
| Stomach     | GOLPH3 | +              | 55–60%| +       | +                       | (101, 102)  |
| Kidney      | GOLPH3 | +              | 53%  | +       | +                       | (103)       |
| Bladder     | GOLPH3 | +              | 65%  | +       | +                       | (67, 104)   |
| Myeloid     | MYO18A | +              | +    | +       | +                       | (57–59)     |

Table is organized by cancer type and gene (GOLPH3, MYO18A, or PITPNC1). Where available, listed are the reported rates (or “+” if not quantified) of gene amplification, overexpression of the mRNA or protein relative to adjacent, noncancerous tissue, and correlation between overexpression and clinical prognosis.
has a special role at the cleavage furrow or if its requirement in cytokinesis reflects a need for normal Golgi function for proper cytokinesis (78, 79). Giantsanti and colleagues hypothesize a role for altered cytokinesis in promoting cancer (76). Certainly, such a role would be interesting and novel.

CONCLUSIONS

Despite the dearth of relevant literature in the past, recent studies of the GOLPH3 complex have provided strong support for a role for the Golgi in cancer. Indeed, trafficking from the Golgi to the plasma membrane involves many diverse cargoes, so there are likely to be multiple mechanisms by which activation of secretory trafficking can promote oncogenesis. As described above, a few mechanisms are already known for Golgi/GOLPH3 complex-driven oncogenesis. Several studies have shown that interference with the expression of GOLPH3 or PITPN1 is detrimental to cancer cells (39, 41, 42, 44, 47, 50–54, 62). These studies suggest that inhibitors of the GOLPH3 complex may have value as cancer therapeutic agents. The development of clinically useful inhibitors will depend on determining which parts of the GOLPH3 complex are druggable and whether inhibitors will have a satisfactory therapeutic index. Clearly, drugs that target the Golgi PtdIns(4)P/GOLPH3 complex would represent a novel therapeutic approach, orthogonal to all current treatment approaches to cancer.

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