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GOLPH3 Links the Golgi, DNA Damage, and Cancer

Matthew D. Buschman[1,2], **Juliati Rahajeng**[1,2], and **Seth J. Field**[1]

[1]Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Diego, La Jolla, CA 92093-0707, USA.

Abstract

GOLPH3 is the first example of an oncogene that functions in secretory trafficking at the Golgi. The discovery of GOLPH3's roles in both cancer and Golgi trafficking raises questions about how GOLPH3 and the Golgi contribute to cancer. Our recent investigation of the regulation of GOLPH3 revealed a surprising response by the Golgi upon DNA damage that is mediated by DNA-PK and GOLPH3. These results provide new insight into the DNA damage response with important implications for understanding the cellular response to standard cancer therapeutic agents.

Keywords

DNA damage; Golgi; GOLPH3; cancer; phosphatidylinositol-4-phosphate

GOLPH3 is an Oncogene

GOLPH3 is an oncogene that functions in secretory trafficking at the Golgi (1–5). Through genome-wide analysis of human cancers, Lynda Chin and colleagues found high frequency of amplification of GOLPH3 in several solid tumor types including 56% of lung cancers, 38% of ovarian cancers, 32% of breast cancers, 33% of pancreatic cancers, 37% of prostate cancers, 32% of melanomas, and 24% of colon carcinomas (5). They then went on to show that GOLPH3 is, in fact, an oncogene, capable of cooperating with other oncogenes to cause transformation in both cell culture and xenograft mouse models. In particular, they observed that overexpression of GOLPH3 could cooperate with B-RAF(V600E) in TERT-immortalized human melanocytes to allow growth in semi-solid media, and with HRAS(G12V) in Ink4a/Arf-deficient primary mouse embryonic fibroblasts to cause focus formation. They also observed that overexpression of GOLPH3 dramatically increased mouse xenograft tumor growth for WM239A melanoma, A549 lung adenocarcinoma, and 1205LU melanoma cell lines. Systematic data from The Cancer Genome Atlas also detect amplification of GOLPH3 in cancers, albeit at lower frequency (e.g., 9.6% of lung adenocarcinomas) (6). The differences in frequency may reflect differences in methods,

Corresponding Author: Seth J. Field, Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Diego, La Jolla, CA 92093-0707, USA. Phone: 858-822-1731; sjfield@ucsd.edu.
[2]These authors contributed equally.

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issues associated with high-throughput screening approaches, or relate to known inconsistencies in the cancer genome datasets (7, 8).

Since the initial publication, over twenty studies have validated GOLPH3 as an oncogene, demonstrating its ability to cause transformation, observing frequent overexpression in a variety of cancers, and showing a correlation between high levels of expression and poor patient prognosis. Evidence of transformation by overexpression of GOLPH3 has been reported in MDA-MB-231 and MCF7 breast cancer cell lines (9–11), and U251 and U87 glioblastoma cell lines (12, 13). Frequent overexpression of GOLPH3 and correlation with poor prognosis have been reported in multiple tumor types including 58–72% of non-small cell lung cancers (14, 15), 52% of breast cancers (11), 70% of prostate cancers (16), 73% of pancreatic ductal adenocarcinomas (17), 65% of hepatocellular carcinomas (18, 19), 55–58% of gastric cancers (20, 21), 53% of renal cell carcinomas (22), 41–53% of glioblastomas (12, 23, 24), 49% of esophageal squamous carcinomas (25), and 45% of ovarian carcinomas (26, 27). Overexpression of GOLPH3 occurs frequently in rhabdomyosarcoma, and knockdown of GOLPH3 in rhabdomyosarcoma cell lines impairs cell proliferation (28). Abnormal expression of microRNA-126 has been associated with increased proliferation, migration, and invasion of esophageal squamous cell carcinoma in a manner that depends on the ability of the microRNA to increase expression of GOLPH3 (29). Taken together, the data argue that overexpression of GOLPH3 is a common feature of many solid tumors that helps drive oncogenic transformation and generally portends poor prognosis.

The Golgi PI4P/GOLPH3/MYO18A/F-Actin Pathway

Working from a different angle, our laboratory discovered GOLPH3 as a novel effector of phosphatidylinositol-4-phosphate (PI4P), playing a critical role in Golgi to plasma membrane trafficking (1). PI4P was known to be highly enriched at the trans-Golgi (30) and to be somehow required for Golgi to plasma membrane trafficking across species (31–33). We found that GOLPH3 binds tightly and specifically to PI4P, resulting in robust localization of GOLPH3 to the trans-Golgi from yeast to humans (1). We further showed that GOLPH3 interacts tightly with an unconventional myosin, MYO18A, recruiting it to the Golgi. MYO18A binds to F-actin and the complex applies a tensile force that pulls on the Golgi membrane. This tensile force deforms the Golgi membrane to participate in the process of vesicle budding for vesicles trafficking from the Golgi to the plasma membrane (1–3).

Interference with GOLPH3 or MYO18A strongly impairs Golgi to plasma membrane trafficking as shown by many different assays, including measurement of vesicular stomatitis virus G glycoprotein trafficking, measurement of total secretory flux by metabolic pulse-chase analysis, live-cell imaging of vesicle exit from the Golgi, and measurement of hepatitis C virus secretion (1–3). We found that the familiar appearance of the Golgi, an extended ribbon observed by light microscopy and flattened stacks observed by electron microscopy, is a consequence of the tensile force applied through the GOLPH3/MYO18A-dependant linkage of the Golgi membrane to the F-actin cytoskeleton. Thus, the shape of the

Golgi is a consequence of the mechanism of trafficking. Furthermore, Golgi morphology serves as a functional readout of the GOLPH3 pathway and Golgi trafficking.

DNA Damage Response and the Golgi

The effect of DNA damage on the Golgi had not been studied previously. While we were studying the regulation of GOLPH3, we found that it is phosphorylated on T143, which we noted to be in the context of Q at the +1 position, forming a TQ motif (4, 34). TQ/SQ is the preferred substrate motif for the DNA damage-activated protein kinases ATM, ATR, and DNA-PK (35, 36). This raised the question of whether there might be a direct signaling pathway from the DNA damage response to GOLPH3 and the Golgi.

We found that exposure of mammalian cells to agents that cause DNA double-stranded breaks (ionizing radiation, camptothecin, or doxorubicin) leads to a significant alteration of Golgi morphology from the normal perinuclear ribbon to a fragmented, punctate Golgi that is dispersed throughout the cytoplasm (see Figure) (4). We found that this dramatic alteration of Golgi morphology is a common feature of the DNA damage response in mammalian cells, including a broad range of cell lines as well as primary mouse and human cells.

We mapped the signaling pathway responsible for DNA damage induced Golgi dispersal (see Figure) (4). We found that DNA-PK (but not ATM or ATR) directly phosphorylates GOLPH3 on the T143 TQ site, and this is required for DNA damage induced Golgi dispersal. We further showed that this phosphorylation of GOLPH3 leads to enhanced interaction between GOLPH3 and MYO18A, resulting in an increased tensile force, and thus increased vesiculation of the Golgi. This vesiculation ultimately causes Golgi fragmentation and dispersal.

The end result of DNA damage induced Golgi dispersal is impaired protein trafficking from the Golgi to the plasma membrane. However, we speculate that the immediate consequence may be an initial burst of anterograde trafficking, which eventually leads to Golgi fragmentation, and subsequently results in impaired Golgi function and reduced trafficking. Future experiments with better temporal resolution will be needed to test this possibility.

While the exact mechanism remains uncertain, it is clear that the DNA-PK/GOLPH3/MYO18A pathway is required for cell survival following DNA damage. Depletion of GOLPH3 or MYO18A results in a significant increase in cellular apoptosis in response to DNA damage. Likewise, depletion of DNA-PKcs (catalytic subunit), GOLPH3, or MYO18A reduces the ability of the cells to survive and proliferate after DNA damage. Furthermore, overexpression of GOLPH3 enhances cell survival in response to DNA damage. This enhanced cell survival due to GOLPH3 overexpression requires both the ability of GOLPH3 to localize to the Golgi and phosphorylation of GOLPH3 on the DNA-PK site. We think it is likely that there exist one or more proteins involved in either survival signaling or death signaling that depend on trafficking from the Golgi to the plasma membrane for their function, and that altered trafficking following DNA damage, by altering the function of these proteins, produces a survival benefit. However, the critical cargoes have yet to be identified.

Logic of the DNA Damage Response

To step back, at the most basic level the DNA damage response has evolved in cells to detect DNA lesions, signal a cellular response, and repair the damaged DNA. The main signaling components in the DNA damage response are the PI3K-like protein kinases ATM, ATR, and DNA-PKcs. The protein kinases ATM and ATR are responsible for the classical DNA damage signaling response, including CHK1/2-dependent cell cycle arrest, activation of DNA repair, and transcriptional regulation of proteins in the DNA damage response (37). ATM and ATR are the more ancient DNA damage response kinases, conserved back to yeast. In a single-celled organism like yeast, every cell attempts to repair the DNA damage to try to survive. By contrast, in higher multicellular organisms each cell must somehow decide whether to repair the DNA damage to allow cellular survival or instead to trigger apoptosis for the benefit of the organism. DNA-PK evolved later, appearing in the genomes of higher multicellular organisms. DNA-PK is a multimeric complex consisting of a catalytic subunit, DNA-PKcs, and the regulatory subunits, Ku70 and Ku80. It plays a critical role in the DNA damage response, particularly in the recognition and repair of double-stranded breaks (38). Cells and mice that lack DNA-PK exhibit increased cell death in response to DNA damage. Interestingly, DNA-PK has a number of diverse and unusual cellular functions.

One clearly unique cellular function of DNA-PK is the ability to phosphorylate and activate AKT, observed by Hemmings and colleagues (39). Upon DNA damage DNA-PK phosphorylates AKT on S473, activating its kinase activity. Activation of AKT results in downstream signaling that is well known to enhance cellular survival (40), and thus this is one mechanism by which DNA-PK can generate a survival signal.

DNA-PK also has been shown to play an intriguing role in metabolic gene regulation (41). In response to feeding and insulin signaling, DNA-PK is recruited to transcriptional promoters, where it phosphorylates upstream stimulatory factor (USF-1). The phosphorylation of USF-1 leads to the recruitment of additional transcription factors, including the histone acetyltransferase p300 associated factor (P/CAF), which acetylates USF-1, leading to activation of gene expression. While Sul and colleagues show this unique role of DNA-PK occurs in response to insulin stimulation, it seems likely to be true in response to IGF-1, and perhaps other receptor tyrosine kinases, as well. Notably, the genes that are activated include some that might confer a cellular survival benefit, potentially providing another link from DNA-PK to survival signaling.

Our recent data demonstrate that DNA-PK plays an essential role in regulating the Golgi in response to DNA damage, via the GOLPH3/MYO18A pathway (4). This pathway is required for normal cell survival in response to DNA damage and when enhanced can confer resistance to killing by DNA damaging agents. Here again, we observe a role for DNA-PK in generating a survival signal. Thus, we propose that perhaps DNA-PK evolved in higher multicellular organisms to weigh in on the cellular decision to survive or die following DNA damage. DNA-PK has multiple mechanisms to bias cells toward survival following DNA damage.

Regulation of the Golgi

Previously popular models of Golgi function have failed to provide insight into regulation of the Golgi in response to changes in the status of the cell. This is unexpected, since regulation is the overarching theme in biology. Recent data now demonstrate interesting regulation of the Golgi via the PI4P/GOLPH3/MYO18A pathway. Mayinger and colleagues found that growth factor signaling leads to increased Golgi to plasma membrane trafficking (42). The mechanism involves translocation of the SAC1 PI4P-4-phosphatase away from the Golgi to the endoplasmic reticulum, resulting in a rise in Golgi PI4P levels. The DNA damage response provides another, dramatic example of regulation of the Golgi. In this case, the regulation in response to DNA damage occurs by modulating the strength of the interaction between GOLPH3 and MYO18A (4).

GOLPH3L is a paralog of GOLPH3 that appears late in evolution, restricted to vertebrates, with expression restricted to highly secretory cell types (3). We found that GOLPH3L acts as a dominant-negative inhibitor of the PI4P/GOLPH3/MYO18A pathway. It does so because it is able to bind to PI4P, but is unable to bind to MYO18A. Our data indicate that GOLPH3L acts as a throttle to damp-down secretory trafficking in highly secretory cells. Thus, the PI4P/GOLPH3/MYO18A pathway is emerging as a convergent hub for regulation of the Golgi.

The Role of GOLPH3 and the Golgi in Cancer

The output of the Golgi, chiefly trafficking of proteins to the plasma membrane either to remain there or to be released into the extracellular space, likely has pleiotropic effects on cellular function. Thus, we might expect dysregulation of the Golgi to play a role in common human disease. The fact that GOLPH3 is an oncogene fulfills that prediction, although the mechanism remains poorly understood.

The role of GOLPH3 in the Golgi DNA damage response may provide some insight into the role of GOLPH3 in cancer. We observe that overexpression of GOLPH3, by driving the Golgi DNA damage response, confers resistance to killing by DNA damaging therapeutic agents. Overexpression of GOLPH3 in a variety of clinical cancers has been shown to predict poor prognosis. While poor prognosis can be interpreted in many ways, it definitely means that these patients' cancers have progressed despite standard therapy. Standard therapy relies heavily on DNA damaging chemotherapeutics or radiation. And thus, the fact that overexpression of GOLPH3 can confer resistance to killing by DNA damaging agents may explain its role in determining poor prognosis. Future studies will be needed to determine if overexpression of GOLPH3 is a useful marker for predicting responsiveness to particular therapeutics, and whether inhibition of the GOLPH3 pathway will potentiate standard therapies to provide therapeutic benefit.

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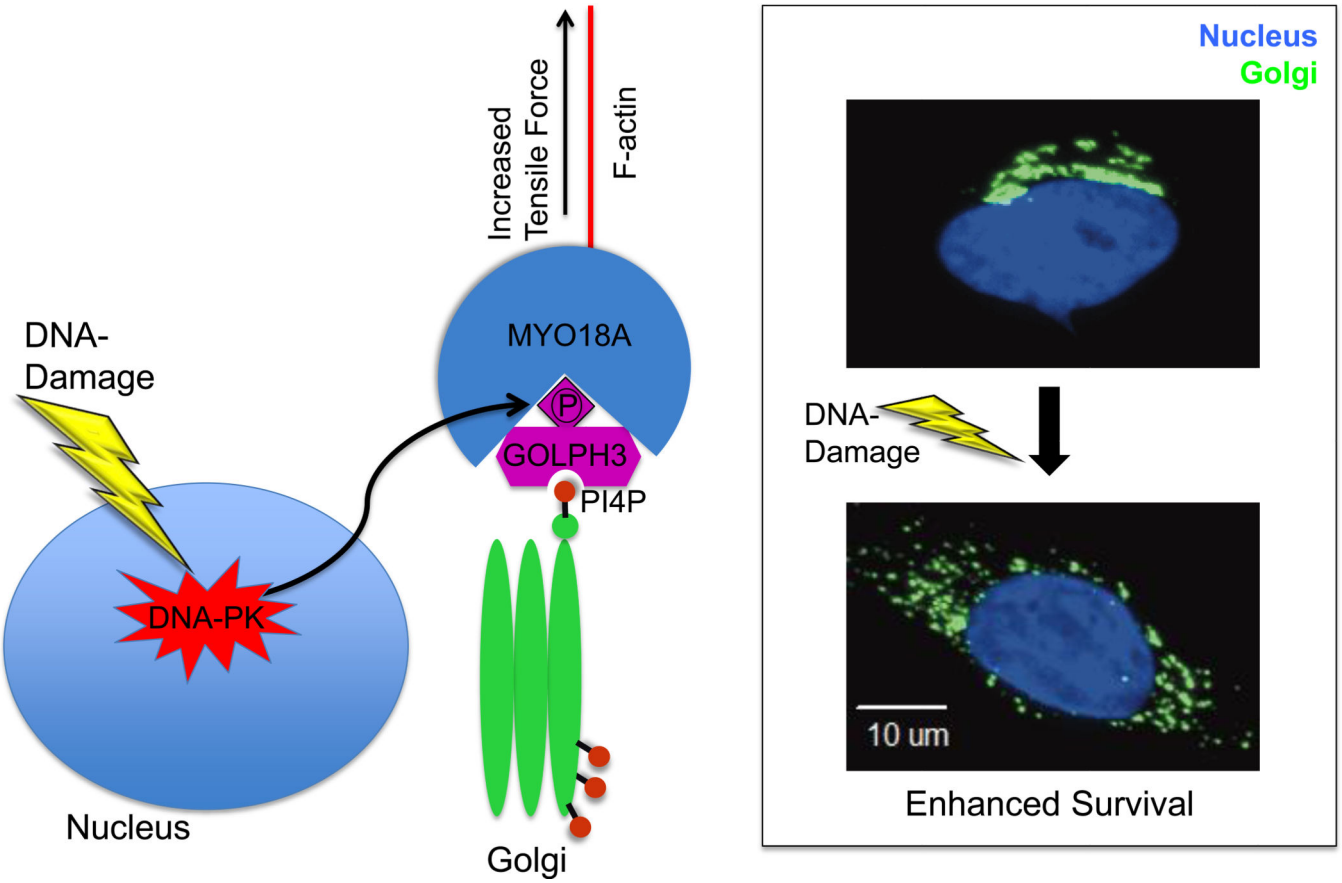

Figure.

Mechanism of DNA damage induced dispersal of the Golgi. In response to DNA damage, DNA-PK is activated and phosphorylates GOLPH3 on the T143 TQ motif. This phosphorylation results in increased GOLPH3 interaction with MYO18A and consequently an increased tensile force on the Golgi, leading to Golgi vesiculation, fragmentation, and dispersal. The DNA-PK/GOLPH3/MYO18A pathway is required for cell survival following DNA damage, and overexpression of GOLPH3 confers resistance to killing by DNA damaging agents.