Golgi Feels DNA's Pain

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The Golgi apparatus consists of disc-like cisternae, stretching around the nucleus through forces exerted by F-actin and the Golgi membrane protein GOLPH3. Farber-Katz et al. now report that DNA damage triggers Golgi dispersal and inhibits vesicular transport through DNA-PK-mediated GOLPH3 phosphorylation, thereby linking the DNA damage response to Golgi regulation.

The Golgi apparatus is a eukaryotic organelle essential for secretion, biogenesis and intracellular distribution of a wide range of macromolecules. Bidirectional membrane trafficking exists between the Golgi and the endoplasmic reticulum (ER), which is continuous with the outer nuclear membrane. The Golgi ribbon is stretched around the nucleus, and its characteristic shape is attained by the tensile forces exerted by F-actin and GOLPH3, an effector of the phosphatidylinositol-4-phosphate (Dippold et al., 2009). A report in this issue reveals that Golgi morphology changes dramatically in response to DNA damage, from the typical perinuclear ribbon to punctate fragments dispersed in the cytoplasm (Farber-Katz et al., 2014). Golgi dispersal requires GOLPH3 phosphorylation by DNA-PK, a nuclear protein kinase that is a crucial component of the DNA damage response (DDR) (Figure 1). These findings highlight a link between a key kinase involved in DDR and important cytoplasmic circuits mediating cell trafficking in mammalian cells.

Intriguingly, earlier genetic screens in the yeast *S. cerevisiae* identified mutations in components of the ESCRT complex, involved in vesicle trafficking, that increase the levels of DNA topoisomerase Top1 in a SUMO-dependent manner (Reid et al., 2011). Moreover, mutants of the retromer membrane coat complex, essential for endosome-to-Golgi retrograde protein transport, genetically interact with *YKU70D* strains (Addinall et al., 2011) that lack the gene encoding KU70, a protein involved in telomere capping and, in mammals, a key partner of DNA-PK.

While the exact cellular roles of the Golgi response to DNA damage are not yet fully elucidated, the findings provide tantalizing clues. The DNA-PK-mediated Golgi dispersal persists for weeks after the exposure to DNA damaging agents, raising the possibility that it may represent an adaptive response to genotoxic insults. The authors thus propose that Golgi dispersal might alter the trafficking of key cargoes that influence cell survival under DNA damaging conditions. Another possibility is that such altered trafficking might impact the intracellular pools or the intracellular localization of ubiquitin and sumo, thus influencing the levels or activity of various ubiquitylated and sumoylated proteins involved in the DDR.

Another finding by Farber-Katz et al. that has the potential for great impact is that exposure to genotoxic insults enhances phosphorylation and activity of GOLPH3, which contributes to cell survival. Accordingly, GOLPH3 overexpression also causes Golgi dispersal. Notably, GOLPH3 qualifies as an oncogene and is overexpressed and/or amplified in diverse types of cancer, correlating with poor prognosis (Scott et al., 2009). Given that cancer cells feature enhanced endogenous replication stress and DNA breakage (Halazonetis et al., 2008), the observed overabundance of GOLPH3 in tumors may contribute to their adaptation and survival under such stressful conditions, as well as under radiotherapy or chemotherapy. Consequently, the Golgi dispersal mechanism may have clinical implications, as it likely supports growth of highly genetically unstable tumors and enhances the resistance to DNA damaging treatments used in oncology. Therefore, GOLPH3 might serve as a potential prognostic or even predictive biomarker. Furthermore, considering that neurodegenerative diseases are often caused by alterations in the cell-trafficking apparatus and that genetic syndromes caused by mutations in genes involved in the DDR are commonly associated with neurodegeneration, it is tantalizing to speculate that the link between trafficking and DDR described by Farber-Katz et al. might inspire future studies aimed at understanding the connections between cancer and neurodegeneration.

The upstream mechanism leading to activation and transduction of the process that ultimately causes Golgi dispersal and altered cell trafficking in response to DNA damage is yet to be determined. DNA double-strand break recognition can be mediated by the Ku heterodimer that recruits DNA-PK (Kong et al., 2011) to promote non-homologous-end-joining (NHEJ)-mediated DNA repair. Since the authors find that GOLPH3, in addition to being directly phosphorylated by DNA-PK, also binds to Ku80 and that the DNA damaging agents used to induce Golgi dispersal directly or indirectly cause DNA breaks, it is possible that the process leading to Golgi dispersal is directly triggered by the accumulation of damaged DNA. It would be thus interesting to test whether other types of DNA damaging agents, different from ionizing radiation or radiomimetic drugs, also promote this process. Notably, Golgi dispersal appears

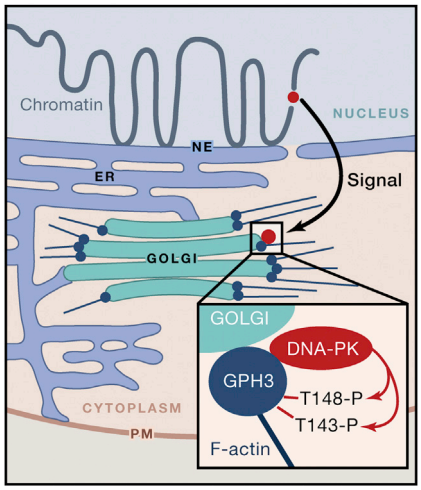

Figure 1. DNA-PK-Mediated Golgi Regulation in Response to DNA Damage

Chromatin is physically connected to the nuclear envelope, which is continuous with the endoplasmic reticulum (ER). Membrane contact sites connect the ER with the Golgi apparatus and with the plasma membrane. GOLPH3 (dark blue shape) is attached to actin (black lines). DNA double-strand breaks generate a signal (red dot) leading to GOLPH3 phosphorylation through a process (arrow) mediated by DNA-PK, inducing Golgi dispersal, impaired intracellular trafficking, and enhanced cell survival. The zoomed-in area depicts DNA-PK-mediated phosphorylation of the critical T143/T148 residues of GOLPH3.

to be independent of ATR and ATM, two other key DDR kinases. It also remains to be elucidated how DNA-PK transduces the signal to a cytoplasmic factor such as GOLPH3. In fact, DNA-PK has been implicated in regulating a variety of cellular pathways, unrelated to DNA repair and nuclear functions, including the inflammatory response and metabolic gene regulation (Kong et al., 2011). Moreover, both DNA-PK and Ku are also associated with cytoplasmic membranes and lipid rafts, microdomains of the plasma membrane that mediate signal transduction events, membrane fluidity, and protein trafficking (Lucero et al., 2003), making the scenario of DNA-PK GOLPH3 activation even more complex. Furthermore, chromatin is physically connected with the nuclear envelope, which is continuous with the ER, and electron microscopy analysis has shown that specific membrane contact sites connect different cellular organelles, including the ER with the Golgi apparatus (Elbaz and Schuldiner, 2011), suggesting physical continuity between the nuclear DNA and the Golgi. An efficient way of signaling across structures that are physically connected by elastic components such as cellular membranes and the chromatin fibers is through mechanotransduction (Wang et al., 2009). The DNA-PK/Ku complex binds both DNA and membranes, representing an ideal scaffold to link mechanical forces and catalytic reactions. Hence, it might be possible that part of the phenomenon observed by Farber-Katz et al. is influenced by mechanotransduction events triggered by chromatin dynamics and involving Golgi shape regulation.

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