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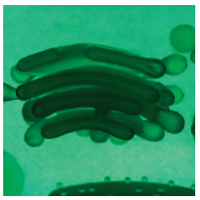
Cell Biology

Major finding: DNA-PK- and GOLPH3-dependent Golgi dispersal is required for cell survival after DNA damage.

Mechanism: GOLPH3 phosphorylation by DNA-PK promotes binding to the unconventional myosin MYO18A.

Impact: Overexpression of GOLPH3 in human cancers may promote chemoresistance.

GOLGI DISPERSAL OCCURS IN RESPONSE TO DNA DAMAGE



DNA damage activates an array of nuclear responses, but cytoplasmic responses to DNA damage and their biologic implications have not been extensively studied. Farber-Katz and colleagues found that diverse DNA damaging agents induced the dispersal of the Golgi throughout the cytoplasm in many cell types, a phenomenon that was unrelated to apoptosis or cell-cycle arrest and persisted long after cells recovered. The Golgi membrane protein GOLPH3, which regulates Golgi morphology by linking trans-Golgi membranes to the actin cytoskeleton through its interaction with the unconventional myosin MYO18A, was required for DNA damage–induced Golgi dispersal. Moreover, the DNA damage–activated protein kinase DNA-PK was specifically required for Golgi dispersal after DNA damage and increased its affinity for MYO18A by directly phosphorylating GOLPH3 on two conserved sites. Consistent with these findings, unphosphorylatable mutants of GOLPH3 failed to rescue DNA damage–induced Golgi dispersal in cells lacking endogenous GOLPH3, implicating direct signaling from DNA-PK to GOLPH3 in the regulation of this process. DNA damage also induced the accumulation of a reporter protein at the Golgi, raising the possibility that Golgi dispersal results in impaired trafficking of proteins from the Golgi to the plasma membrane. Of note, knockdown of DNA-PK, GOLPH3, or MYO18A caused an increase in apoptosis following treatment with DNA-damaging agents, whereas overexpression of GOLPH3, which frequently occurs in human cancers and is correlated with a poor prognosis, conferred a survival advantage that was dependent on both its localization to the Golgi and phosphorylation by DNA-PK. Although further investigation of the mechanism by which impaired protein trafficking confers cellular protection is warranted, these findings identify an important role for the DNA-PK–GOLPH3–MYO18A pathway in regulating Golgi dispersal and cell survival following DNA damage and raise the possibility that GOLPH3 expression may be predictive of responsiveness to chemotherapy. ■

Farber-Katz SE, Dippold HC, Buschman MD, Peterman MC, Xing M, Noakes CJ, et al. DNA damage triggers Golgi dispersal via DNA-PK and GOLPH3. Cell 2014;156:413–27.

Clinical Trials

Major finding: Off-label use of itraconazole reduces Hedgehog pathway activity and proliferation in BCC.

Clinical relevance: Patients who previously received the SMO inhibitor vismodegib did not respond to itraconazole.

Impact: An FDA-approved oral antifungal agent may be a safe and effective treatment for nonadvanced BCC.

ITRACONAZOLE HAS ACTIVITY IN PATIENTS WITH BASAL CELL CARCINOMA

Aberrant activation of the Hedgehog pathway is a hallmark of basal cell carcinoma (BCC). Vismodegib, an antagonist of the Hedgehog component Smoothened (SMO), has been approved by the FDA for treatment of inoperable or metastatic BCC, but some patients have vismodegib resistance. Surgical excision can be used to treat most nonadvanced BCCs but can cause scarring and morbidity. Preclinical studies have identified itraconazole, a widely used, FDA-approved antifungal agent, as a potent Hedgehog pathway antagonist with antitumor activity. Kim and colleagues therefore evaluated the effects of itraconazole on the Hedgehog pathway and tumor growth in an open-label, exploratory phase II trial in 29 patients with nonadvanced BCC. In one cohort, 15 patients received itraconazole tablets twice daily for 1 month, after which tumor size was measured and biopsy samples were analyzed for the proliferation marker Ki-67 and expression of the Hedgehog pathway gene *GLI1*. In a second cohort, 4 patients received a lower dose for approximately twice as long before tumor size was measured. Itraconazole was generally well tolerated, with mild and reversible adverse effects. Compared with baseline levels, itraconazole reduced Ki-67 levels and *GLI1* expression by 45% and reduced tumor size by an average of 24% in vismodegib-naïve tumors. Tumor reductions were comparable between the cohorts, suggesting that lower doses of itraconazole may also be effective. However, cell proliferation, *GLI1* expression, and tumor size were unchanged in untreated patients as well as in patients who had previously received vismodegib, raising the possibility that acquired vismodegib resistance may reduce itraconazole efficacy even though itraconazole and vismodegib inhibit SMO by distinct mechanisms. Although larger, longer studies are required to assess the activity of itraconazole and to compare the efficacy and safety of itraconazole and vismodegib, these results suggest that off-label use of itraconazole may be safe and effective in nonadvanced BCC. ■

Kim DJ, Kim J, Spaunhurst K, Montoya J, Khodosh R, Chandra K, et al. Open-label, exploratory phase II trial of oral itraconazole for the treatment of basal cell carcinoma. J Clin Oncol 2014;32:745–51.

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AACR American Association for Cancer Research

CANCER DISCOVERY

Golgi Dispersal Occurs in Response to DNA Damage

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