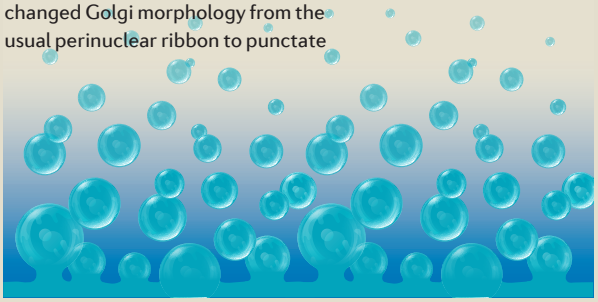
DNA DAMAGE

Dispersing Golgi

The nuclear effects of DNA damage have been well characterized and include cell cycle arrest, changes in transcription and the activation of DNA repair. Field and colleagues now increase our knowledge of the cytoplasmic effect of DNA damage, revealing that it signals directly to the Golgi to cause its dispersal, which enhances cell survival.

The authors observed that treatment of human and mouse cells with agents that induce DNA damage rapidly changed Golgi morphology from the usual perinuclear ribbon to punctate fragments found throughout the cytoplasm.

> DNA-PK phosphorylates GOLPH3 to promote its binding to MYO18A



NPG

Previous studies had shown that the Golgi protein GOLPH3 links Golgi membranes to the unconventional myosin MYO18A and to F-actin, which applies tensile force to the Golgi, stretching the Golgi ribbon around the nucleus, and promoting vehicle budding from it. In this study, siRNA-mediated depletion of GOLPH3 or MYO18A, or F-actin depolymerization, prevented DNA damage-induced Golgi dispersal, indicating that these three factors are implicated in this DNA damage response.

To characterize the link between DNA damage and Golgi dispersal, the authors analysed the role of GOLPH3 phosphorylation at residues Thr143 and Thr148 in a 'TQ' motif, as TQ motifs are known to be substrates of the DNA damage-activated kinases ATM, ATR and DNA-PK. Mutations at Thr143 and Thr148 indicated that their phosphorylation is indeed essential for Golgi dispersal following DNA damage. Moreover, only DNA-PK directly phosphorylated GOLPH3 at Thr143 and Thr148 to mediate this DNA-damage response. Importantly, data suggested that DNA-PK phosphorylates GOLPH3 to promote its binding to MYO18A; this presumably applies a tensile force to the Golgi to promote dispersal.

But what are the functional consequences of Golgi dispersal? The authors found that it was associated with impaired trafficking from the Golgi to the plasma membrane. Moreover, the DNA-PK–GOLPH3–MYO18A pathway increased cell survival upon DNA damage. Thus, a decrease in Golgi–plasma membrane trafficking of specific cargoes may constitute a strategy to improve cell survival following genotoxic stress.

In addition to uncovering a new DNA damage response, these findings may have clinical implications: GOLPH3 is often overexpressed in tumours with poor prognosis and is associated with enhanced cell survival following chemotherapy, making this pathway a potentially useful therapeutic target.

Kim Baumann

ORIGINAL RESEARCH PAPER Faber-Katz, S. E. *et al.* DNA damage triggers Golgi dispersal via DNA-PK and GOLPH3. *Cell* **156**, 413–427 (2014)