RESEARCH HIGHLIGHT

Nucleophagy repairs toxic DNA lesions

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In a recent study in *Cell*, Lascaux et al. revealed a novel pathway to repair toxic DNA lesions, providing a direct link between nucleophagy, a type of selective autophagy, and the resolution of damaged DNA.

Autophagy is an evolutionarily conserved cellular process that degrades and recycles damaged organelles and proteins to maintain cellular homeostasis.[1,2] Recent studies have established the important role of autophagy in aging, genome stability, and DNA repair.[3] However, until now, no evidence has been found that autophagy directly repairs damaged DNA. Ramadan and colleagues discovered a novel pathway to repair a specific type of DNA lesion, known as DNA–protein crosslinks (DPCs).[4]

DPCs are deleterious DNA lesions caused by metabolic byproducts, environmental agents, and chemotherapeutic drugs.[5] If not properly resolved, DPCs hinder essential processes such as replication and transcription.[6,7] DPC repair is a type of DNA damage repair (DDR) crucial for resolving harmful covalent crosslinks formed between DNA and proteins. Due to the complexity and heterogeneity of DPC lesions, previously known DPC repair mechanisms include: (1) proteolysis-dependent DPC repair, (2) direct crosslink hydrolysis, and (3) nuclease-dependent DPC repair.[5,8] In a recent *Cell* paper, the authors demonstrated that selective autophagy serves as a novel pathway to repair DPCs[4] (Fig. 1). Moreover, the study showed that nucleophagy ensures genomic stability, promotes cell survival, and mediates resistance to topoisomerase 1 (TOP1) inhibitor camptothecin (CPT)-based chemotherapies by removing toxic DNA–TOP1 crosslinking lesions.

The authors explored the role of nucleophagy, a type of selective autophagy, in DDR processes orchestrated by the autophagy receptor TEX264. They showed that CPT-induced DPCs can be directly repaired through TEX264-mediated selective autophagy. An in-depth biochemical investigation revealed crosstalk between autophagy and DNA replication stress upon treatment with nanomolar concentrations of CPT.[9] The study confirmed that TEX264 forms complexes with both replication proteins and autophagy machinery proteins, inducing their lysosomal uptake. Through a series of elaborate experiments, the authors demonstrated that nucleophagy repairs TOP1-DPCs, promoting cell survival and preventing proteotoxic stress caused by the formation of TOP1 protein aggregates.

The study provides evidence that the autophagy receptor TEX264 functions as a specific receptor for resolving TOP1-DPCs. TEX264 interacts through the LIR-motif with LC3 and induces the recruitment of lysosomes to the nuclear sites of DNA replication forks. Uptake of TOP1-DPCs by lysosomes is increased during the S phase of the cell cycle and occurs through an intriguing transient protrusion of the nuclear envelope, allowing cytosolic release of DPCs. Using zebrafish as a model, the authors demonstrated that depletion of tex264 resulted in increased DPC accumulation, reinforcing the evolutionarily conserved role of TEX264-driven selective autophagy across different organisms.

The metalloprotease SPRTN was previously identified as an essential player in DPC proteolysis repair.[10] To determine whether the nucleophagy axis acts in synergy with SPRTN-driven DPC repair, the authors inactivated SPRTN and showed that autophagy pathway does not rely on SPRTN activity for TOP1-DPC resolution. In addition to SPRTN, the proteasome is another degradation system that promotes DPC repair.[11] By inhibiting ubiquitin-proteasome degradation of DPCs, the authors excluded the significance of this pathway in autophagy-driven DPC repair.

The clinical relevance of autophagy-driven DNA repair was further emphasized by showing that the expression levels of TEX264 in primary colorectal cancer tissues correlate with colorectal cancer patients' response to TOP1 inhibitor irinotecan-based chemotherapy. A strong positive correlation between TEX264 protein levels and survival rates of colorectal cancer patients in response to irinotecan-based chemotherapy was observed. Moreover, depletion of TEX264 resulted in genomic instability, suggesting its potentially important role in cancer aggressiveness and resistance to chemotherapies, such as irinotecan, due to increased mutational burden.

Several research questions emerge from this study. It remains unclear whether other autophagy receptors play any role in resolving DPCs, or TEX264 is the sole autophagy receptor capable of managing DPC repair. Additionally, the precise mechanism by which nuclear envelope alterations facilitate the transport of damaged DNA to lysosomes remains unresolved. More detailed molecular studies are needed to fully understand these dynamics. Moreover, the clinical relevance of TEX264-mediated autophagy in response to irinotecan-based chemotherapy requires orthogonal translational validation to replicate the results. Importantly, the study suggests the use of autophagy modulators, commonly used in other types of cancer, in combination with chemotherapy, might improve treatment outcomes for solid tumors and it is presented as potential translational alternative to cancer therapy.[4,10]

In conclusion, the study demonstrates that selective nucleophagy is an evolutionarily conserved and clinically relevant mechanism for repairing chemotherapy-induced DPCs, independent of the proteasome and SPRTN. TEX264 is the autophagy receptor able to induce the repair of damaged DNA thus maintaining genome stability and promoting cell survival upon exposure to DNA-damaging agents. The study opens new avenues

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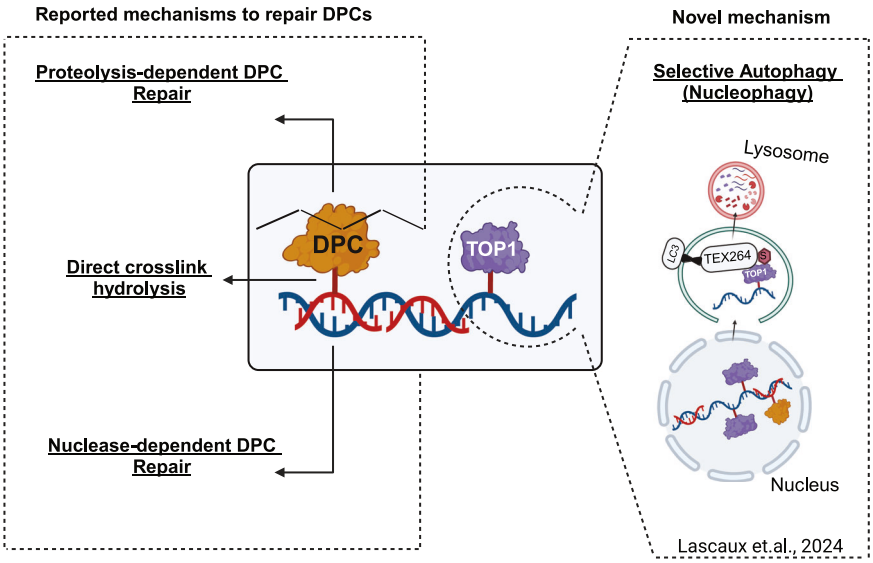

Fig. 1 Overview of the DPC repair pathways, including nucleophagy. Left: Reported mechanisms of DPC repair. (1) Proteolysis-dependent DPC repair, orchestrated by proteasome and proteases, acts on the protein level of DNA–protein crosslink. (2) Direct crosslink proteolysis resolves DNA–protein crosslinks on the level of crosslink/covalent bond. (3) In nuclease-dependent DPC repair, DPCs are processed by nucleotide excision repair and homologous recombination. Right: Nucleophagy — a novel mechanism of DPC repair. A type of selective autophagy, nucleophagy, is orchestrated by TEX264. Selective autophagy processes nuclear TOP1-DPCs induced by low-dose CPT-based therapy that facilitates the aggregate formation of TOP1. Created with BioRender.com.

for understanding autophagy's role in DNA repair and it has translational implications in cancer therapies.

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ADDITIONAL INFORMATION

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