Autophagy

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The nuclear shredder behind PARPi resistance

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PARP inhibitors kill cancer cells by trapping poly(ADP-ribose) polymerase 1 (PARP1) on DNA. A study now shows that cancer cells use a specialized form of autophagy to extract and degrade trapped PARP1, limiting the efficacy of PARP-trapping drugs. Blocking this escape route can re-sensitize resistant tumours.

Over the past two decades, PARP inhibitors (PARPi) have transformed the treatment of certain hereditary cancers. For individuals with mutations in *BRCA1* or *BRCA2* – genes that encode proteins responsible for the high-fidelity DNA repair pathway known as homologous recombination – drugs such as olaparib and talazoparib have emerged as powerful treatment options. These therapies are based on the principle of synthetic lethality, in which cancer cells already compromised in one DNA repair pathway become catastrophically vulnerable when a second pathway is inhibited[1,2]. Six such drugs now carry regulatory approval across breast, ovarian, pancreatic and prostate cancers. Still, for all their promise, PARP inhibitors have a stubborn Achilles' heel: the emergence of resistance. Whether it develops after months of treatment or was present from the start, resistance blunts their efficacy in a notable fraction of patients, and the mechanisms that underlie the resistance remain incompletely understood. Now, a study in this issue of *Nature Cell Biology* by Hoslett et al.[3] shows that cancer cells use a previously unrecognized escape route to dodge the lethal effects of PARP inhibitors: a selective form of autophagy that targets nuclear material for extraction and degradation.

To appreciate the importance of this finding, it helps to understand precisely what PARP inhibitors do. PARP1 is an enzyme that rapidly responds to DNA damage – such as nicks, breaks and stalled replication forks – by binding to affected sites and coating the damaged DNA with chains of poly(ADP-ribose), a signal that recruits and coordinates the repair machinery. Clinically approved PARP inhibitors bind to PARP1 and prevent it from releasing damaged DNA, a phenomenon known as trapping. Trapped PARP1 acts as a physical roadblock on DNA: when the replication machinery encounters it during cell division, the collision can convert a manageable nick into a catastrophic double-strand break. In cancer cells that have already lost the ability to repair such damage via homologous recombination (such as those with *BRCA* mutations), this becomes lethal. The potency of different PARP inhibitors correlates almost perfectly with their trapping ability, rather than their ability to inhibit PARP1 catalytic activity[4]. PARP1 itself is the crucial target: cells that lack PARP1 are resistant to these drugs. Deciphering what happens to trapped PARP1 after it forms is, therefore, central to understanding both how cells die in response to these drugs, and how they survive by developing resistance.

Previous work has shown that cells do not remain passive in the face of PARP1 trapping. The AAA+ ATPase p97, a molecular machine that can unfold and extract proteins from complex assemblies, was shown to pull trapped PARP1 away from chromatin, in a process that requires the protein to first be tagged with SUMO and ubiquitin[5]. In addition, the metalloprotease SPRTN was implicated in the response to trapped PARP1[6]. But what happens to the displaced protein after extraction? Where does it go, and what clears the potentially toxic debris? These questions remained unanswered, until now.

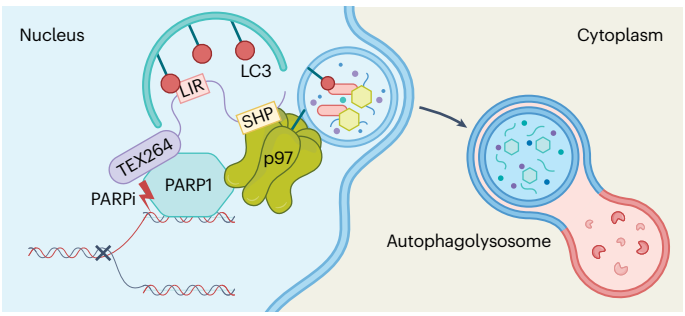

Fig. 1 | Nucleophagy provides an escape route from PARP1 trapping. PARP inhibitors such as talazoparib trap PARP1 on DNA, creating replication-blocking lesions that are lethal in homologous recombination-deficient cancer cells. Cancer cells counteract this by activating nucleophagy. The selective autophagy receptor TEX264, located at the inner nuclear membrane, recognizes trapped PARP1, in cooperation with the p97 AAA+ ATPase. Subsequent nuclear envelope budding enables extraction and export of the toxic PARP1–DNA complexes. The material is then engulfed by autophagosomes and delivered to adjacent lysosomes for degradation. This clearance pathway limits the cytotoxicity of PARP-trapping drugs. Inhibiting key components of the nucleophagic escape route, such as TEX264 or core autophagy factors, re-sensitizes resistant cancer cells to PARP inhibitors.

Using RNA-sequencing experiments, Hoslett et al.[3] assessed which cellular degradation pathways are upregulated when cancer cells are treated with talazoparib, currently the most potent PARP trapper in clinical use. The results were striking: although proteasome-related genes were barely altered, dozens of genes in the autophagy pathway were significantly upregulated. Going beyond transcriptomics, the authors confirmed that autophagy was not just transcriptionally activated but also functionally enhanced, with a measurable increase in autophagic flux. Moreover, by mining previously published, whole-genome CRISPR screen datasets, they found that genetic loss of core autophagy genes, including *ATG7* and *ULK1*, sensitizes cells to two different PARP inhibitors, across both *BRCA1*- and *BRCA2*-deficient contexts. Notably, proximity labelling mass spectrometry data from the authors' earlier work had placed core autophagy machinery components, such as the autophagosome biogenesis regulators ATG9A and ATG16L1, physically near trapped PARP1 on chromatin. The convergence of these independent lines of evidence is persuasive: autophagy is not just a passive bystander to PARPi treatment; it is induced as an active survival response.

Indeed, boosting autophagy with the mTOR inhibitor torin-1 drove strong talazoparib resistance. By contrast, blocking it with bafilomycin A1 hypersensitized cells. Similarly, genetic depletion of ATG7,

syntaxin-17 or ATG9A, three proteins with distinct roles at different stages of the autophagy pathway, increased sensitivity to talazoparib. Notably, neither torin-1 nor bafilomycin A1 treatment affected cells treated with veliparib, a PARPi that catalytically inhibits PARP1 but traps it only weakly. These experiments paint a coherent picture: autophagy induction after PARPi treatment is a cytoprotective response. This pro-survival mechanism is specifically engaged by PARP1 trapping rather than by PARP inhibition, per se.

The mechanistic core of the study is the identification of the selective autophagy receptor (SAR) responsible for bridging trapped PARP1 to the autophagosome. Hoslett et al.[3] focused on TEX264, a protein that sits at the endoplasmic reticulum and the inner nuclear membrane, which they had previously shown to act as a SAR for topoisomerase 1 cleavage complexes (TOP1ccs), another class of drug-induced protein–DNA adducts that can block replication[7]. TEX264 occupies a structurally interesting position: it carries an LC3-interacting region (LIR) that docks directly onto the autophagosomal membrane protein LC3, and it also contains small heterodimer partner (SHP, also known as NR0B2), motifs that recruit p97 (Fig. 1). TEX264 is essentially a molecular bridge with one foot in the autophagy machinery and one foot in the p97 extraction complex[8]. Using purified recombinant proteins and hydrogen-deuterium exchange mass spectrometry, a technique that detects protein–protein interaction surfaces by measuring solvent accessibility, the authors found that TEX264 binds directly to PARP1 through its C-terminal domain, and that this interaction intensifies under trapping conditions. TEX264-knockout cells accumulated trapped PARP1, were hypersensitive to talazoparib but not veliparib, and could not be rescued by TEX264 variants carrying mutations in either the LIR or the SHP domain alone. Both functions of TEX264, as an autophagy receptor and a p97 co-factor, were required.

To directly demonstrate that trapped PARP1 ends up in lysosomes, the authors used an elegant method called LysoIP, in which lysosomes are rapidly isolated from living cells by exploiting an immunoprecipitation handle on the lysosomal membrane[9]. Under trapping conditions, PARP1 accumulated robustly in lysosomes, and this accumulation was further increased when lysosome acidification was blocked, preventing digestion of the contents. The lysosomal PARP1 signal was strong with potent trappers such as talazoparib and niraparib, weak with the non-trapping veliparib, and essentially absent in cells expressing a trapping-impaired PARP1 mutant. The authors also used a fluorescent reporter, in which PARP1 was tagged with both GFP and mCherry. In the acidic lysosome, GFP fluorescence is quenched whereas mCherry persists, enabling lysosomal delivery to be visualized as a shift from yellow (in the nucleus), to red-only puncta in the cytosol. Remarkably, live imaging captured lysosomes approaching the nuclear periphery, engulfing PARP1-containing material, and eventually dispersing. This process played out within minutes after PARPi treatment and depended on core autophagy factors such as ATG7. These observations indicate that lysosomes are actively recruited to the nucleus to collect their cargo as it exits.

This last point raises a fascinating but unresolved question: how does a large chromatin-associated protein complex cross the nuclear envelope? Hoslett et al.[3] found that blocking nuclear pores with leptomycin B had no effect on lysosomal PARP1 delivery, whereas inhibiting the ATR kinase, which phosphorylates nuclear envelope components in response to DNA damage, significantly impaired it. Recent work suggests that dynamin-family GTPases help to drive the formation of vesicles derived from the nuclear envelope, which can bud off and transport damaged nuclear material to the cytoplasm for clearance via autophagy[10]. Consistent with this model, Hoslett et al.[3] observed nuclear envelope budding under trapping conditions, with PARP1 visibly exiting through these transient membrane protrusions (Fig. 1). This is an elegant solution to a topological problem. Rather than threading a large protein–DNA complex through the nuclear pore, cells seem to use a dedicated nuclear membrane remodelling event to expel damaged chromatin-associated proteins — a mechanism distinct from classical nuclear export. The upstream signals that activate this specific nucleophagic programme, beyond ATR, are not fully characterized. It also remains unclear whether TEX264 targets other types of DNA–protein adduct, beyond TOP1ccs and trapped PARP1, or whether additional SARs contribute to the nuclear clearance of nucleoprotein complexes, under different types of genotoxic stress.

The clinical relevance of the study becomes clear in the final experiments. Cells that had developed resistance to olaparib after prolonged exposure showed markedly increased autophagy flux compared with drug-naive cells, suggesting that autophagy actively contributes to resistance, rather than merely accompanying it. When TEX264 or ATG7 was depleted in these resistant cells, sensitivity to both talazoparib and olaparib was substantially restored. Consistently, by analysing RNA-seq data from a cohort of nearly 8,000 patients with breast cancer[11], Hoslett et al.[3] found that low *TEX264* expression was associated with approximately 28% better 10-year survival, but only in those with homologous recombination-deficient tumours, not in patients with homologous recombination-proficient disease. As this is a correlational finding, it should be interpreted with appropriate caution. Survival analyses in retrospective cohorts carry well-known confounders, and *TEX264* expression or protein level has not yet been evaluated as a prospective biomarker. The directionality of these findings, however, is exactly what the mechanistic studies would predict. High TEX264 levels indicate more energetic nucleophagy, more efficient clearance of trapped PARP1, and consequently, more survival of cancer cells under PARPi pressure. However, the correlational patient survival data, although in line with the mechanistic model, cannot establish causality. An additional caveat concerns the re-sensitization experiments, which were conducted in cell lines and therefore require validation in more physiologically relevant preclinical models of acquired PARPi resistance. Moreover, resistance in patients is likely to be far more heterogeneous, involving several parallel mechanisms — such as restored homologous recombination through BRCA reversion mutations or stabilization of replication forks — that would not be overcome by TEX264 inhibition alone.

These considerations notwithstanding, the TEX264–p97–nucleophagy axis presents a potential vulnerability of cancer cells, in its own right, and a more surgically precise therapeutic target towards overcoming PARPi resistance, compared with broad autophagy inhibition. Chloroquine derivatives, which block lysosomal acidification and the final degradation of autophagosomal cargo, have shown mixed results in cancer clinical trials, partly because autophagy has opposing tumour-suppressive and tumour-promoting roles at different stages of disease. Hence, non-specific inhibition of autophagy carries considerable tolerability risks[12]. In principle, an inhibitor that targets the TEX264–PARP1 or TEX264–p97 interaction would specifically impair nucleophagy of trapped PARP1, without disrupting the broader autophagy network. Whether such selective inhibitors are chemically tractable remains an open question. However, the structure–function data reported by the authors[3], showing that a specific C-terminal domain of TEX264 mediates PARP1 binding, and point mutations in

either the LIR or SHP domains are each sufficient to disrupt the pathway, provide a useful roadmap. Notably, p97 itself is already the subject of clinical investigation as a cancer target[13], and selective autophagy inhibitors are an active area of pharmaceutical development.

Ultimately, the work of Hoslett et al.[3] not only resolves a long-standing puzzle in cancer biology with unusual mechanistic completeness. It also highlights an increasingly appreciated theme in cell biology: the intimate connections between genome maintenance and protein quality control. DNA repair is often portrayed as a purely nuclear affair, dominated by enzymes that cut, copy and ligate DNA strands. Yet, the dismantling and removal of persistent DNA–protein complexes may require cooperation with cytoplasmic systems normally associated with protein degradation and proteostasis. In that sense, nucleophagy blurs the boundary between nuclear repair and overall cellular housekeeping. In effect, nuclear autophagy acts as a fail-safe system for genome maintenance, eliminating obstacles that would otherwise stall replication and threaten cell survival. For PARP inhibitors, this insight adds an important dimension to our understanding of how these drugs work, and why they sometimes fail. The cancer cell, it turns out, is a far more resourceful adversary than we appreciated. It boasts a nuclear escape hatch, and it is operated by the autophagy machinery.

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References

1. Bryant, H. E. et al. *Nature* **434**, 913–917 (2005).
2. Farmer, H. et al. *Nature* **434**, 917–921 (2005).
3. Hoslett, G. et al. *Nat. Cell Biol.* https://doi.org/10.1038/s41556-026-01961-5 (2026).
4. Murai, J. et al. *Cancer Res.* **72**, 5588–5599 (2012).
5. Krastev, D. B. et al. *Nat. Cell Biol.* **24**, 62–73 (2022).
6. Saha, L. K. et al. *Nucleic Acids Res.* **49**, 10493–10506 (2021).
7. Fielden, J. et al. *Nat. Commun.* **11**, 1274 (2020).
8. Chino, H., Hatta, T., Natsume, T. & Mizushima, N. *Mol. Cell* **74**, 909–921.e906 (2019).
9. Abu-Remaileh, M. et al. *Science* **358**, 807–813 (2017).
10. Aveleira, C. et al. *Nat. Commun.* **17**, 1380 (2026).
11. Staaf, J. et al. *NPJ Breast Cancer* **8**, 94 (2022).
12. Galluzzi, L. et al. *EMBO J.* **34**, 856–880 (2015).
13. Anderson, D. J. et al. *Cancer Cell* **28**, 653–665 (2015).

Competing interests

The author declares no competing interests.