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AUTOPHAGIC PUNCTUM

Mitophagy is a novel protective mechanism for drug-tolerant persister (DTP) cancer cells

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ABSTRACT

Drug-tolerant persister (DTP) cancer cells drive residual tumor and relapse. However, the mechanisms underlying DTP state development are largely unexplored. In a recent study, we determined that PINK1-mediated mitophagy favors DTP generation in the context of MAPK inhibition therapy. DTP cells that persist in the presence of a MAPK inhibitor exhibit mitochondriadependent metabolism. During DTP state development, MYC depletion alleviates the transcriptional repression of *PINK1*, resulting in PINK1 upregulation and mitophagy activation. PINK1-mediated mitophagy is essential for mitochondrial homeostasis in DTP cells. Either knockdown of PINK1 or inhibition of mitophagy eradicates DTP cells and achieves complete responses to MAPK inhibition therapy. This study reveals a novel role of mitophagy as a protective mechanism for DTP development.

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Drug-tolerant persister; MAPK inhibitor; mitophagy; PINK1; quiescent cancer cells

In most cases, cytotoxic anticancer drugs fail to completely eradicate cancers. Resistance inevitably occurs even after initially striking responses and a stable dormant state. DTP cells are acknowledged as key drivers in the dormant state, exhibiting a quiescent or diapauselike phenotype. Therefore, targeting DTP represents a therapeutic opportunity to prevent resistance development. The emergence of DTP highly relies on flexible plasticity to maintain cellular homeostasis and evade death. Autophagy serves as a gatekeeper for cellular homeostasis by eliminating misfolded proteins or damaged organelles. Although autophagy activation enables diapause-like DTP cells to survive, whether specific type of autophagy is involved in DTP development is unknown.

Mitochondria are highly plastic organelles and central in cellular homeostasis maintenance. Mitophagy is one of the mitochondrial plastic behaviors. This process is responsible for eliminating damaged mitochondria and is critical in cell fate determination. For example, in stem cells, mitophagy levels determine whether to remain quiescent or to undergo activation. However, the relationship between mitophagy and the quiescent DTP state has not been explored. In a recent study we report that PINK1-mediated mitophagy favors DTP generation through promoting mitochondrial homeostasis (Figure 1) [1]. This finding provides targeting mitophagy as a therapeutic strategy to eradicate DTP cells.

In the context of lung adenocarcinoma (LUAD) cells and LUAD patient-derived organoids (PDOs), we found that the DTP cells that resist MAPK inhibitor treatment exhibit mitochondria-dependent metabolism. To address how DTP cells accomplish the metabolic reprogramming from glycolysis to mitochondrial respiration and survive under this circumstance, we performed phosphorylated proteomics on the DTP cells. Macroautophagy and mitophagy were enriched in the upregulated phosphoproteins. And phosphorylated ubiquitin (serine 65), a substrate of PINK1, was one of the top candidates for upregulated phosphoproteins. As a sensor for damaged mitochondria, PINK1 plays a central role in mitophagy activation. We further confirmed that PINK1 expression is transcriptionally induced during DTP generation. Upregulated PINK1 promotes mitophagy activation, which is essential for the metabolic switch between aerobic glycolysis and mitochondrial respiration.

In order to shed light on the mechanisms that control PINK1 expression during DTP generation, we examined the potential transcription factors (TF) binding to the *PINK1* promoter. Among these putative TFs, we focused on MYC, which mediates transcriptional repression of the *PINK1* promoter. MYC depletion during DTP generation attenuates the transcriptional repression of *PINK1*, thus inducing PINK1 expression and activating mitophagy. PINK1 expression is usually downregulated in cancer, where aberrant MYC overexpression is common. This finding offers new insight into the biological regulation of PINK1-mediated mitophagy.

We further characterized the role of PINK1-mediated mitophagy in DTP cells. PINK1 depletion impairs mitochondrial function, disrupts redox homeostasis, and results in extensive apoptosis

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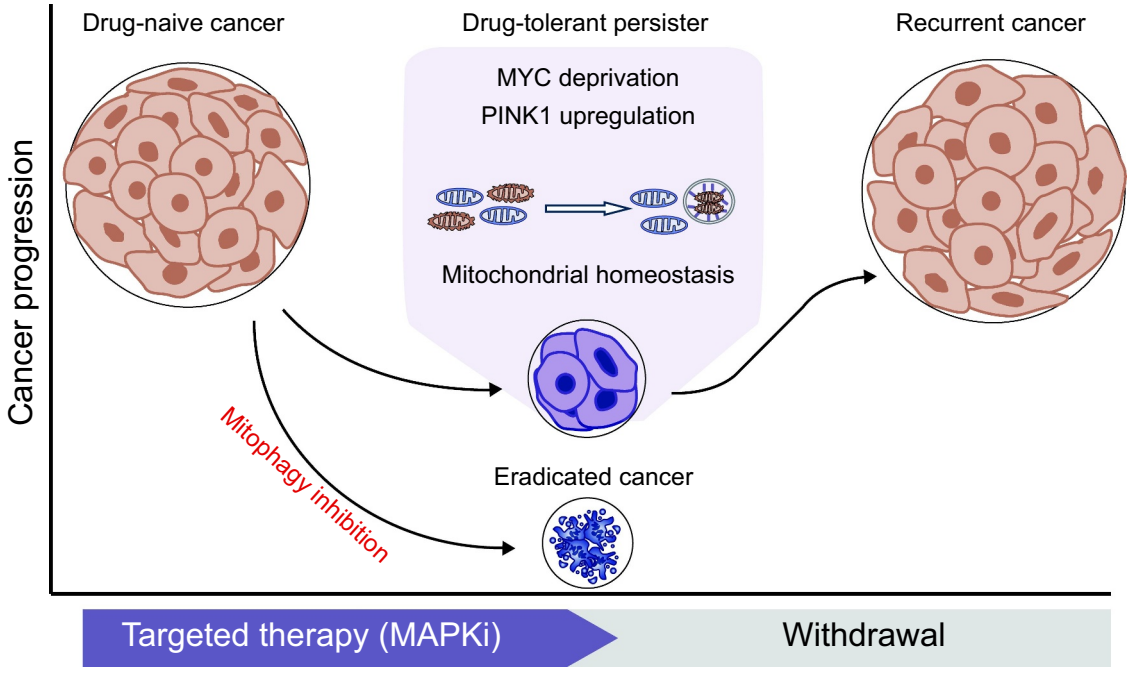

Figure 1. Schematic model showing the process of DTP state development. Cancer cells enter a quiescent DTP state to evade cytotoxic stress from targeted therapy. During this process, MYC deprivation alleviates the transcriptional repression of *PINK1*, resulting in PINK1 upregulation and mitophagy activation. Mitophagy activation enables mitochondrial homeostasis in DTP cells. Mitophagy inhibition eradicates DTP state development and allows complete responses to targeted therapy. MAPKi, MAPK inhibitor.

in DTP cells. Consistent with the contribution of PINK1-mediated mitophagy in DTP generation, PINK1 knockdown leads to durable responses to MAPK inhibition therapy, and decreases tumor regrowth after cessation. We also observed that PINK1 overexpression in LUAD tissues is associated with tumor recurrence and clinical poor prognosis. Besides, when combined with MAPK inhibition therapy, mitophagy inhibition through clinically applicable chloroquine is able to generate cleared tumors that do not relapse after withdrawal.

The DTP state is marked by active mitochondrial metabolism, and PINK1-mediaed mitophagy facilitates resistance to chemotherapy or targeted therapy in various contexts. We provide a novel mechanistic link between these two observations. Due to the alleviation of MYC-engaged transcriptional repression of *PINK1*, PINK1-mediated mitophagy is induced during DTP state development, to maintain a functional mitochondrial network. Our findings provide targeting mitophagy as a novel therapeutic opportunity to eradicate DTP cancer cells.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Reference

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