Unveiling mitochondrial mysteries to conquering cancer therapy resistance

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An artistic impression illustrating the concept. Similar to the River Styx functioning as a passage for departed souls to the Underworld in Greek mythology, pro-apoptotic BH3 proteins create channels in the mitochondrial membrane for the passage of cytochrome c to the cytoplasm, the biological realm of death in apoptosis. As cancer cells progress through successive lines of therapy, these BH3 protein gateways become less active, making the journey to cell death more challenging; there are fewer entrances to the abyss. However, the identification of targeted drugs that can continue to activate the BH3 protein channels provides an opportunity to exploit these agents. This discovery holds promise for overcoming multi-drug resistance in relapsed or refractory patients with acute myeloid leukemia. Credit: Blood Cancer Discovery

National University of Singapore (NUS) scientists have discovered that the evasion of apoptosis is a key driver of drug resistance in patients with relapsed acute myeloid leukemia (AML), a type of aggressive blood cancer. The results are expected to contribute towards the identification of effective drugs for treating relapsed patients.

Over decades of clinical oncology practice has shown that treating cancer patients upon relapse is increasingly challenging. Relapsed patients not only become resistant to the treatment they receive but also to multiple other agents through a phenomenon called acquired multi-drug resistance—a major cause of treatment failures. Beyond genetic mutations, reliable evidence and available models, particularly *in vivo*, seem insufficient to explain the emergence of multi-drug resistance.

The research team led by Assistant Professor Shruti BHATT from the Department of Pharmacy and Pharmaceutical Sciences, NUS, has identified the potential mechanism behind multi-drug resistance in relapsed AML patients. They also highlighted the effectiveness of a technique, called dynamic BH3 profiling (DBP), in identifying anti-cancer drugs capable of targeting relapsed leukemia cells. The technique

is able to measure the increase in mitochondrial priming, which signifies a higher potential for programmed cell death called apoptosis. This is a collaboration with Dr. Anthony LETAI from the Dana-Farber Cancer Institute, United States of America.

The research findings were published in the journal *Blood Cancer Discovery*.

The research team established *in vivo* models of acquired resistance to a spectrum of clinically relevant anti-cancer drugs using patient-derived xenograft (PDX) models. Subsequently, they conducted a comprehensive analysis encompassing genomics, transcriptomics, and functional studies on drug-resistant AML models. Intriguingly, their investigations revealed a common point for resistance induced by various drugs: the mitochondria. They observed a reduction in mitochondrial apoptotic priming, a phenomenon linked to a decreased tendency for cell death across all their models. This finding suggests that a decline in mitochondrial apoptotic priming is a fundamental mechanism underlying the multi-drug resistance observed in clinical settings, independent of the type of therapy and genetic background of the initial tumor.

Prof Bhatt said, "A key finding was that a reduction in mitochondrial apoptotic priming accompanies acquired resistance to a wide variety of agents, suggesting it as a mechanism for the acquired multi-resistance seen in the clinic."

"One way to battle multi-drug resistance is to develop broadly effective predictive biomarkers to identify drugs with new or persistent activity in resistant tumors," added Prof Bhatt.

To address this challenge, the researchers used dynamic BH3 profiling (DBP), a technique involving short-term treatment of leukemia cells

derived from therapy-resistant preclinical models with a panel of clinically relevant drugs. Mitochondrial apoptotic signaling is then measured to determine drugs capable of overcoming resistance. The researchers implemented DBP across 22 distinct PDX models of AML, and this approach demonstrated remarkable accuracy in predicting the *in vivo* efficacy of drugs with diverse mechanisms of action. DBP's ability to effectively identify exploitable vulnerabilities paves the way for the development of targeted *in vivo* therapeutic strategies.

Prof Bhatt said, "As a next step, we are performing single-cell lineage tracing experiments using barcoding and proliferative index measurements to identify molecular determinants responsible for reduced mitochondrial priming at the minimal residual disease stage."

More information: Elyse A. Olesinski et al, Acquired Multidrug Resistance in AML Is Caused by Low Apoptotic Priming in Relapsed Myeloblasts, *Blood Cancer Discovery* (2024). DOI: 10.1158/2643-3230.BCD-24-0001

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