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ROCKing resistance: cytoskeletal-mitochondrial synergy in acute myeloid leukemia

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In this issue of Haematologica, Sharma and colleagues present a compelling study titled "Rho kinase (ROCK) inhibitors synergize with venetoclax in therapy of acute myeloid leukemia (AML)[1]," which uncovers a sophisticated link between cytoskeletal dynamics and mitochondrial apoptosis. By demonstrating that Rho kinase (ROCK) inhibition can sensitize AML cells to venetoclax, the authors provide a novel blueprint for overcoming drug resistance in one of the most challenging hematologic malignancies.

Beyond the BCL-2 Horizon: Addressing Venetoclax Resistance

The therapeutic landscape of acute myeloid leukemia (AML) has been radically reshaped by the introduction of venetoclax (VEN), a selective BCL-2 inhibitor[2].When combined with hypomethylating agents or low-dose cytarabine, venetoclax has significantly improved outcomes for elderly or unfit patients. However, the Achilles' heel of this regimen remains the emergence of resistance[3,4]. Conventional research has largely focused on BCL-2 family members—such as the upregulation of MCL-1 or BCL-XL—or the activation of parallel signaling pathways like FLT3 or RAS[5,6].

Sharma et al. pivot away from these established paradigms, focusing instead on the Rho-associated coiled-coil containing protein kinase (ROCK). While ROCK is traditionally recognized for its role in regulating the actin cytoskeleton, cell motility, and adhesion, its involvement in leukemia cell survival and treatment resistance has remained largely enigmatic. The authors’ discovery that ROCK activity is a critical determinant of venetoclax sensitivity opens a new frontier in "cytoskeletal-targeted" leukemia therapy.

Mechanistic Novelty: The Cofilin-Drp1-Mitochondria Axis

The centerpiece of this study is the elucidation of a unique synergistic mechanism

between ROCK inhibitors (e.g., GSK269962A) and venetoclax. The authors demonstrate that inhibiting ROCK leads to the activation of cofilin through dephosphorylation. Under normal conditions, phosphorylated cofilin is inactive; however, its activation triggers F-actin depolymerization and, more importantly, facilitates its interaction with the mitochondrial fission protein Drp1.

This cofilin-Drp1 complex translocates to the mitochondria, promoting mitochondrial outer membrane permeabilization (MOMP). In essence, ROCK inhibition "primes" the mitochondria for death, lowering the threshold for venetoclax-induced apoptosis. This "dual-hit" approach is particularly elegant: while venetoclax removes the "brakes" on apoptosis by neutralizing BCL-2, the ROCK inhibitor actively engages the "accelerator" by driving pro-apoptotic machinery to the mitochondrial surface.

Translational Implications: A Broad-Spectrum Solution?

The clinical appeal of this study lies in its breadth. Sharma et al. validated the GSK+VEN synergy across a diverse array of models, including cell lines, primary patient samples, and in vivo xenografts[1]. Crucially, the combination showed efficacy in AML samples with adverse genetic features, such as TP53 mutations and complex karyotypes, which are notoriously resistant to current standard-of-care treatments.

Furthermore, the study identifies a potential feedback loop: venetoclax treatment can induce caspase-mediated cleavage and activation of ROCK, which may paradoxically foster survival signals in resistant clones. By co-administering a ROCK inhibitor, this escape pathway is blocked, leading to more profound and durable cell death. From a clinical perspective, since several ROCK inhibitors are already utilized in other medical fields (e.g., netarsudil for glaucoma), the path toward "repurposing" or developing leukemia-specific ROCK inhibitors is highly feasible [7,8](Table 1).

Future Directions and Challenges

While the results are promising, several questions warrant further investigation before this strategy reaches the clinic. First, the systemic toxicity of ROCK inhibition must be carefully evaluated; given ROCK's role in vascular tone and smooth muscle contraction, cardiovascular safety will be a primary concern. Second, the optimal scheduling of these agents—whether concurrent or sequential—needs to be refined to maximize the "mitochondrial priming" effect while minimizing off-target effects on normal hematopoiesis.

In conclusion, Sharma et al. have identified a previously unrecognized vulnerability in AML. By bridging the gap between cytoskeletal remodeling and the intrinsic apoptotic pathway, they offer a powerful new strategy to enhance the efficacy of venetoclax. As we move toward an era of increasingly personalized AML therapy, the integration of ROCK inhibitors into the therapeutic armamentarium represents a significant step forward in our quest to "ROCK" the foundation of leukemia resistance.

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Table 1. Comparison of venetoclax monotherapy vs. ROCK inhibitor + venetoclax combination

Feature	Venetoclax Monotherapy	ROCK Inhibitor + Venetoclax Synergy
Primary Target(s)	BCL-2 protein	ROCK1/2 and BCL-2
Cytoskeletal Impact	Negligible	F-actin depolymerization; Cofilin activation
Mitochondrial Effect	Releases pro-apoptotic BH3 proteins	Promotes Cofilin/Drp1 mitochondrial translocation
Apoptotic Trigger	Neutralization of BCL-2	Enhanced MOMP via "Dual-Hit" mechanism
Resistance Mechanism	MCL-1/BCL-XL upregulation; Kinase mutations	Overcomes resistance by bypassing BCL-2 dependency
Clinical Potential	Current Standard of Care	Potential salvage for R/R AML and high-risk subtypes