ROCKing resistance: cytoskeletal mitochondrial synergy in acute myeloid leukemia

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In this issue of *Haematologica*, Golla and colleagues present a compelling study examining how Rho-associated coiled-coil containing protein kinase (ROCK) inhibitors synergize with venetoclax (VEN) in the treatment of acute myeloid leukemia (AML).[1] Their study uncovers a sophisticated link between cytoskeletal dynamics and mitochondrial apoptosis. By demonstrating that ROCK inhibition can sensitize AML cells to VEN, the authors provide a novel blueprint for overcoming drug resistance in one of the most challenging hematologic malignancies.

The therapeutic landscape of AML has been radically reshaped by the introduction of VEN, a selective BCL-2 inhibitor.[2] When combined with hypomethylating agents or low-dose cytarabine, VEN 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]

Golla *et al*. pivot away from these established paradigms, focusing instead on 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 VEN sensitivity opens a new frontier in cytoskeletal-targeted leukemia therapy.

The centerpiece of this study is the elucidation of a unique synergistic mechanism between ROCK inhibitors (e.g., GSK269962A) and VEN. 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 VEN-induced apoptosis. This dual-hit approach is particularly elegant: while VEN 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.

The clinical appeal of this study lies in its breadth. Golla *et al*. validated the GSK+VEN synergy across a diverse array of models, including cell lines, primary patient samples, and *in vivo* xenografts.[11] Crucially, the combination showed efficacy in AML samples with adverse genetic features, such

Table 1. Comparison of venetoclax monotherapy *versus* 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

ROCK: Rho-associated coiled-coil containing protein kinase; R/R AML: relapsed/refractory acute myeloid leukemia.

as *TP53* mutations and complex karyotypes, which are notoriously resistant to current standard-of-care treatments. Furthermore, the study identifies a potential feedback loop: VEN 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).

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 the role of ROCK 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, Golla *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 VEN. 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.

Disclosures

No conflicts of interest to disclose.

Contributions

WZ is responsible for the editorial concept, wrote the original draft, and supervised the preparation of the manuscript for publication. SC reviewed and edited the manuscript. ML carried out the literature search and is responsible for formatting.

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