

A tumor-fighting strategy: turning defeats into victories

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In a study published in *Vita*, Tian *et al.* identify PNPT1 as a key immune checkpoint that suppresses antitumor immunity by degrading immunogenic mitochondrial double-stranded RNA (mt-dsRNA) and restricting its cytosolic release, thereby quelling the mt-dsRNA-mediated danger signaling. Combining PNPT1 inhibitor with BH3-mimetic agent can robustly activate the MAVS pathway, thereby overcoming immunotherapeutic resistance in solid tumors.

Cancer immunotherapy has revolutionized tumor treatment; however, both primary and acquired resistance remain major clinical bottlenecks. Although extensive efforts have focused on targeting the cGAS-STING cytosolic DNA-sensing pathway, repeated clinical setbacks highlight the urgent need to identify more robust and ubiquitously expressed innate immune pathways. Tian *et al.*¹ addressed this critical challenge by unraveling a previously unrecognized mitochondrial RNA (mtRNA)-driven immune axis, and proposing a potent strategy to activate it. The authors demonstrate that targeting the polyribonucleotide nucleotidyltransferase 1 (PNPT1) in combination with agents that promote mitochondrial outer membrane permeabilization (MOMP), can unleash a broad-spectrum antitumor immune response and synergize with standard therapies¹.

A major strength of this study is the identification of a novel antitumor immune pathway centered on mtRNA. It is known that mitochondrial double-stranded RNA (mt-dsRNA) triggers antiviral signaling in humans². Traditional research has largely focused on the cGAS-STING pathway mediated by nuclear or mitochondrial DNA, yet the clinical failures of STING agonists have exposed the limitations of this single-target approach³. In contrast, this study shows that genotoxic chemotherapeutics such as doxorubicin and cisplatin induce the release of mt-dsRNA through Bcl-2-associated X protein (BAX) pores. Acting as a potent damage-associated molecular pattern (DAMP)⁴, mt-dsRNA activates the MAVS signaling cascade⁵, thereby eliciting robust antitumor immunity. More importantly, the widespread expression of MAVS and its upstream receptors across diverse tumor types enables broad immune activation, circumventing the downregulation of STING observed in many tumors⁶. This discovery not only enriches our understanding of endogenous danger signal-mediated antitumor immunity but also identifies a more universally actionable immune activation mechanism.

Equally compelling is the discovery of a tumor-intrinsic counter mechanism that suppresses this immunogenic pathway. Through bioinformatic analyses of chemotherapy-resistant cells and clinical samples, the authors show that PNPT1, a key mediator of tumor immune evasion, is consistently upregulated. PNPT1 degrades immunogenic mt-dsRNA struc-

tures, thereby attenuating MAVS-dependent immune responses. Clinically, elevated PNPT1 expression is associated with poor prognosis and reduced immune cell infiltration across multiple cancer types, establishing PNPT1 as a *bona fide* immune evasion factor. Critically, genetic knockdown of PNPT1 in tumor cells enhances mt-dsRNA accumulation, increases cytokine production, and synergizes with both chemotherapy and anti-PD-1 checkpoint blockade in mouse models, converting immunologically "cold" tumors into "hot" ones. Taken together, these important findings provide a comprehensive framework for understanding the balance between antitumor immunity and immune evasion.

The important translational finding of this study is the pharmacological targeting of the PNPT1-mtRNA axis (Fig. 1). The authors repurposed lanatoside C (also known as isolanid), an FDA-approved cardiac glycoside, with the potent activity to inhibit PNPT1 in cell culture⁷. Recognizing that PNPT1 inhibition alone may be insufficient owing to impaired mt-dsRNA release in apoptosis-resistant tumors, they designed a combination therapy by repurposing lanatoside C with a BH3-mimetic inhibitor (e.g., ABT-263) to directly induce BAX-dependent MOMP⁸. This dual-drug combination simultaneously enhances the generation of immunogenic mt-dsRNA signals via PNPT1 inhibition and promotes its cytosolic release via BH3-mimetics, thereby potently activating antitumor immunity. The combination synergizes with standard therapies, and shows remarkable efficacy in suppressing tumor growth and metastasis in melanoma and hepatocellular carcinoma models, all without significant systemic toxicity.

This work makes several seminal contributions to the field. First, it elevates mt-dsRNA from a relatively underappreciated DAMP to a central mediator of therapy-induced immunity, on par with mitochondrial DNA. Second, it identifies PNPT1 as a previously unrecognized immune checkpoint that regulates ligand availability, analogous to ectonucleotidases such as CD39 and CD73, which degrade extracellular ATP. Third, and most importantly, it proposes an immediately actionable strategy using clinically approved, or late-stage, investigational agents. The incorporation of BH3-mimetics is particularly innovative. Although their efficacy in solid tumors is often limited by compensatory mechanisms and immunosuppressive apoptotic responses, pairing them with an immunostimulatory agent (e.g., lanatoside C) converts potentially tolerogenic cell death into immunogenic cell death.

Despite its important advances, this study opens several avenues for future exploration. This study primarily focuses on solid tumors such as melanoma and hepatocellular carcinoma; future work should assess the relevance of the PNPT1-mtRNA axis in hematological malignancies. Identifying tumor types characterized by specific mitochondrial genotypes or

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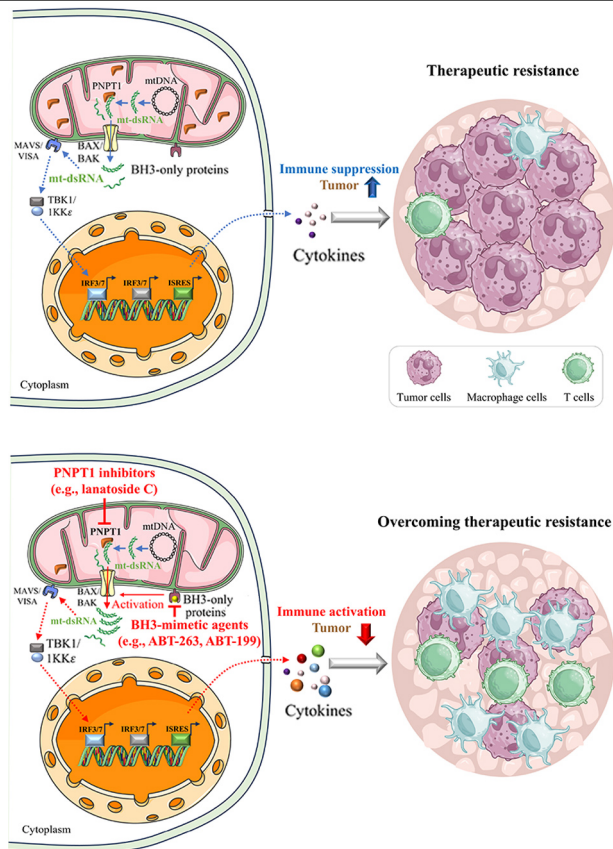


Fig. 1 Schematic illustration of PNPT1-mediated antitumor therapeutic resistance and the mechanistic basis of combining PNPT1 inhibitors with BH3-mimetics to reverse such resistance. PNPT1 exerts dual effects to drive antitumor therapeutic resistance: it directly degrades mt-dsRNA, a critical mediator of antitumor immunity that signals through the MAVS pathway, and restricts the cytosolic release of mt-dsRNA via BAX/BAK-dependent pores. These actions collectively impair tumor immune surveillance, ultimately leading to resistance to antitumor immunotherapy (upper panel). Conversely, cotreatment with PNPT1 inhibitor (e.g., lanatoside C) and BH3-mimetic agent (e.g., ABT-263) robustly potentiates mt-dsRNA-MAVS axis-mediated antitumor immunity, thereby effectively overcoming therapeutic resistance (lower panel).

metabolic states that are most susceptible to this strategy will be crucial for clinical translation. Moreover, the precise mechanisms by which PNPT1 selectively recognizes and degrades mt-dsRNA, as well as potential crosstalk with other immune regulatory pathways, warrant further investigation. Given that lanatoside C has multiple cellular targets⁹, its specificity for PNPT1 in this context should be validated using more selective inhibitors. Because ABT-263 remains an investigative agent in phase 2 studies, the FDA-approved BH3-mimetic venetoclax (ABT-199) could be potentially repurposed⁸. The

potential risk of autoimmunity resulting from chronic mt-dsRNA release also requires careful evaluation, but the acute, therapy-induced nature of the proposed regimen may mitigate this concern. Ultimately, clinical trials are needed to confirm the safety and efficacy of this combination therapy in patients, particularly in subgroups with high PNPT1 expression, to achieve more precise personalized treatment.

In conclusion, this study presents a comprehensive and impactful progression from mechanistic discovery to therapeutic validation. It not only delineates a novel tumor immune evasion pathway but also delivers a pragmatic and promising therapy to overcome it. By shifting the focus from DNA- to RNA-centered innate immune sensing and targeting the enzyme that silences this signal, the authors offer a fresh and compelling approach to reactivate antitumor immunity – one that may bring renewed hope to patients with the spirit to fight against therapy-resistant solid tumors.

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COMPETING INTERESTS

All authors declare no competing interests.

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ADDITIONAL INFORMATION

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