

Review

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Mitochondrial double-stranded RNA escape checkpoints in cancer: immune decoding, immunoediting and therapeutic rewiring

Sajid ALI¹, Wajid ZAMAN²✉

¹Department of Horticulture and Life Science, Yeungnam University, Gyeongsan 38541, Republic of Korea

²Department of Life Sciences, Yeungnam University, Gyeongsan 38541, Republic of Korea

Abstract: Mitochondrial double-stranded RNA (mt-dsRNA) can act as an immune signal; however, its effects in cancer depend on where it is generated, buffered, released, and sensed. Herein, we synthesize evidence for four linked checkpoints: duplex formation and modification, intramitochondrial degradation, membrane escape, and receptor-specific decoding. It is found that human-cell and trafficking studies demonstrate that mitochondrial RNA surveillance constrains mt-dsRNA and that a fraction can reach the cytosol. Cancer studies report distinct outcomes: altered mitochondrial RNA turnover can affect acute myeloid leukemia cell state, tumor-derived mt-dsRNA can remodel B-cell leukemia stroma, and pancreatic cancer-associated sensing supports growth. However, these findings do not establish a pan-cancer dependency; we propose that source, compartment, sensor, recipient cell, and signal duration must be resolved before therapeutic direction is assigned. In addition, we outline assays and biomarkers that distinguish an acute antitumor response from chronic inflammation, tumor-supportive signaling, or normal-tissue toxicity. This framework also guides biomarker selection and treatment scheduling, while the clinical benefit remains to be validated.

Key words: Mitochondrial double-stranded RNA; Viral mimicry; RIG-I-like receptors; Innate immunity; Cancer immunotherapy

1 Introduction

Endogenous double-stranded RNA (dsRNA) can be the result of inverted repeats, transposable elements, mis-spliced transcripts, structured non-coding RNAs, and mitochondrial transcription. The immune effect of dsRNA depends on its structure, subcellular origin, editing, and receptor access; a shared interferon-stimulated gene signature does not identify the initiating ligand (Chen and Hur, 2022; Straub and Sampaio, 2023). The crosstalk between the pattern-recognition receptor and inflammasome provides general innate-immune context (Oh et al., 2025), while nuclear RNA condensates provide a distinct mechanism for controlling nuclear RNA exposure (Ku et al., 2025).

Mitochondrial RNA (mtRNA), for the purpose of this paper, is defined as RNA encoded by mitochondrial DNA (mtDNA), and mitochondrial double-stranded RNA (mt-dsRNA) means complementary duplexes formed within that transcript pool. General reviews place mitochondrial RNA among innate ligands but do not establish cancer-specific effects (Grochowska et al., 2022; Yoon et al.,

✉ Wajid ZAMAN, wajidzaman@yu.ac.kr

 Wajid ZAMAN, <https://orcid.org/0000-0001-6864-2366>

Sajid ALI, <https://orcid.org/0000-0002-0696-3057>

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2023). Direct trafficking experiments show that mt-dsRNA can move to the cytosol (Krieger et al., 2024), while senescent-cell studies reveal that this signal can persist in viable cells and contribute to inflammatory phenotypes (López-Polo et al., 2024). Mitochondrial dynamics can also release RNA and activate innate sensing, although duplex identity must be established for each route (Yasuda et al., 2026). Sequence-level mapping and compartment controls are therefore required before a response is attributed to mt-dsRNA.

The findings of cancer studies point in opposing directions. In acute myeloid leukemia (AML), mitochondrial RNA degradation affects differentiation, stemness and immune sensitivity (Thomas et al., 2026). In B-cell acute lymphoblastic leukemia (B-ALL), tumor-derived mt-dsRNA can reprogram mesenchymal stromal cells toward a cancer-associated fibroblast state (Burt et al., 2024). In pancreatic ductal adenocarcinoma, mt-dsRNA-associated RIG-I/TLR3 inflammation has been linked to tumor growth (Milcarek et al., 2026), whereas non-small-cell lung carcinoma shows intertumoral variation in mt-dsRNA abundance (Krieger et al., 2026). These lineage-specific observations argue for the development of source- and cell-resolved biomarkers rather than histology-wide assumptions.

Therapeutic viral mimicry also requires source attribution. DNA-demethylating drugs can engage OAS–RNase L through endogenous dsRNA (Banerjee et al., 2019), and spliceosome-targeted treatment can provoke antiviral signaling in triple-negative breast cancer (Bowling et al., 2021); however, neither result alone establishes a mitochondrial ligand. Mitochondrial RNA targeting can alter responses to demethylating therapy, showing that nuclear and mitochondrial RNA programs may coexist (Tan et al., 2024). This review evaluates existing evidence from RNA generation through receptor decoding, distinguishes direct causal studies from contextual or associative work, and summarizes experiments needed to assign source, escape, sensor, and biological outcome.

2 The mt-dsRNA rheostat: generation and intramitochondrial buffering

Mitochondrial transcription produces overlapping sense and antisense RNAs, whereas duplex abundance is also shaped by processing, modification and turnover. Non-coding 7S RNA can inhibit mitochondrial RNA polymerase through polymerase dimerization (Zhu et al., 2022), and extramitochondrial RNA-processing systems can alter mitochondrial surveillance and innate immunity (Tjahjono et al., 2022). These findings make mt-dsRNA a regulated pool rather than an inevitable readout of transcription. Foundational human-cell work revealed that the depletion of either SUV3 or PNPase, encoded by PNPT1, permits mt-dsRNA accumulation and MDA5–MAVS signaling (Dhir et al., 2018). This established the link between mitochondrial RNA surveillance and antiviral signaling. Meanwhile, later trafficking studies resolved export as a separate checkpoint, and the evidence does not require describing SUV3 and PNPase as a single stable complex.

RNA chemistry can determine whether mt-dsRNA is degraded or becomes available to cytosolic sensors. NSUN4-associated 5-methylcytosine marks mt-dsRNA for degradation and affects cytosolic release (Kim et al., 2024b). A review of mitochondrial RNA modifications in cancer has provided a broader context but did not prove that every modification changes dsRNA sensing (Wang et al., 2026). Total mtRNA measurements should therefore be paired with duplex-specific and, where relevant, modification-aware assays. Mitochondrial RNA degradation is a major buffer. In AML, disrupting this pathway changes differentiation, stem-like behavior and immune sensitivity, supporting a lineage-specific dependency rather than a universal cancer target (Thomas et al., 2026). Adenosine deaminase acting on RNA 1 (ADAR1) provides a partly independent tolerance node: it can regulate nuclear and mitochondrial dsRNA through editing-dependent and editing-independent mechanisms (Shin et al., 2026), while its loss can expose self-dsRNA sensing in tumors (Ishizuka et al., 2019; Jia et al., 2025). Because ADAR1 loss affects multiple RNA sources, mitochondrial attribution requires source depletion and rescue.

Stress can exceed RNA-buffering capacity without a single inherited defect. Mitochondrial dsRNA contributes to chondrocyte stress and osteoarthritis (Kim et al., 2022), while HSP60 can restrict its release in hepatic inflammation (Huang et al., 2022). FARS-1/FARSA also links mitochondrial translation-related homeostasis to mt-dsRNA restraint (Sohn et al., 2026). In childhood Sjögren’s disease, reduced SUV3 in an interferon-enriched monocyte subset was associated with mt-dsRNA accumulation and PKR activation (Yoon et al., 2025). While these non-cancer studies support conserved regulation and identify potential host

liabilities, they do not establish cancer efficacy. Metabolic context is significant, but mitochondrial sirtuin and glutaminolysis studies provide no direct evidence for mt-dsRNA mediation (Lee and Yoon, 2024; Kim et al., 2024a). Fig. 1 summarizes the production and buffering steps that determine whether an escape-competent mt-dsRNA pool forms.

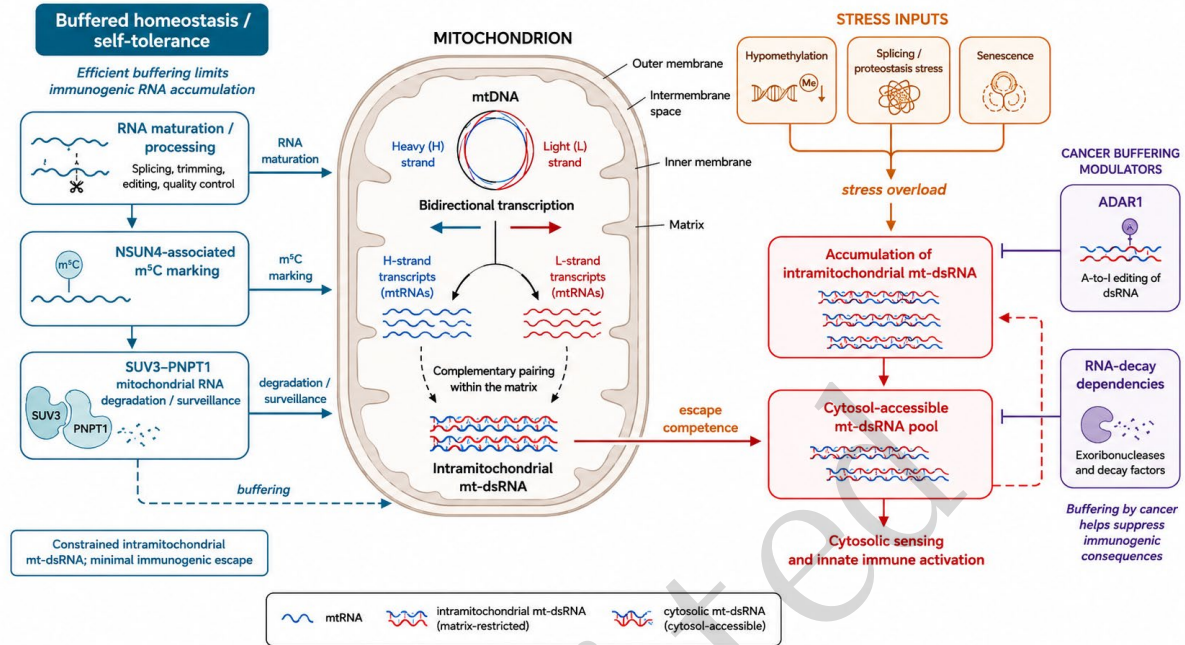


Fig. 1 The mitochondrial double-stranded RNA rheostat. Bidirectional transcription of mitochondrial DNA generates complementary heavy- and light-strand RNA transcripts that can form intramitochondrial double-stranded RNA. RNA maturation, NSUN4-associated RNA methylation, and SUV3/PNPT1-mediated RNA surveillance regulate mitochondrial RNA turnover and limit the accumulation of immunogenic duplexes. Cellular stress, including altered methylation, RNA-processing disturbances, and senescence, may disrupt this balance and increase the pool of mt-dsRNA potentially available for cytosolic escape. ADAR1-dependent regulation and additional RNA-decay mechanisms contribute to the control of endogenous RNA immunogenicity. The model distinguishes total mitochondrial RNA, intramitochondrial mt-dsRNA, and cytosol-accessible mt-dsRNA as separate regulatory pools. Solid arrows indicate regulatory processes or proposed directional relationships, dashed arrows indicate indirect or conditional effects, and blunt-ended lines indicate inhibitory regulation. Abbreviations: ADAR1, adenosine deaminase acting on RNA 1; A-to-I, adenosine-to-inosine; H, heavy strand; L, light strand; m⁵C, 5-methylcytosine; mtDNA, mitochondrial DNA; mt-dsRNA, mitochondrial double-stranded RNA; mtRNA, mitochondrial RNA; NSUN4, NOP2/Sun RNA methyltransferase 4; PNPT1, polyribonucleotide nucleotidyltransferase 1; SUV3, mitochondrial SUV3 RNA helicase.

3 Escape checkpoints: regulated transit from mitochondria to the cytosol

Export is distinct from duplex production. Direct studies have demonstrated the movement of mt-dsRNA from mitochondria to the cytosol and association with cytosolic stress granules, where it can activate type I interferon signaling (Krieger et al., 2024). Measuring matrix and cytosolic mt-dsRNA separately can distinguish increased production from increased escape; however, fractionation requires mitochondrial-contamination controls.

Organelle dynamics provide another route to RNA release. DRP1 loss or mitochondrial stress can promote hyperfusion-associated, BAX-dependent mitochondrial RNA release and RIG-I–MAVS signaling, but these observations do not by themselves prove that the released ligand is dsRNA (Yasuda et al., 2026). BAX/BAK pore studies establish a precedent for mitochondrial nucleic-acid exposure, including infection- and injury-associated mtDNA release (Li et al., 2020; Li et al., 2023b; Cosentino et al., 2022; Yamazaki and Galluzzi, 2022). Broader reviews summarize mtDNA release and sensing as a distinct nucleic-acid pathway (VanPortfliet et al., 2024). Overall, the RNA species and route must be tested directly.

Sublethal escape is evident in senescence: cytosolic mt-dsRNA contributes to the senescence-associated inflammatory phenotype in several human cell models (López-Polo et al., 2024). This result links mitochondrial RNA release to persistent cell-state change, but does not establish that senescence-associated inflammation is always antitumor. Signal duration, cell identity and immune context determine whether the response supports clearance or sustains a tumor-associated niche.

Extracellular transfer introduces an additional checkpoint involving the identity and response of the recipient cell. In B-ALL, tumor-derived mt-dsRNA stimulates mesenchymal stromal cells and promotes a cancer-associated fibroblast phenotype (Burt et al., 2024). Thus, bulk tumor interferon cannot establish whether tumor, stromal or immune cells received the ligand. Spatial or cell-resolved assays are needed to determine whether transfer supports antigen presentation or instead promotes trophic and matrix-remodeling programs. Fig. 2 separates mt-dsRNA accumulation, mitochondrial RNA release and downstream sensing; these events should be measured independently.

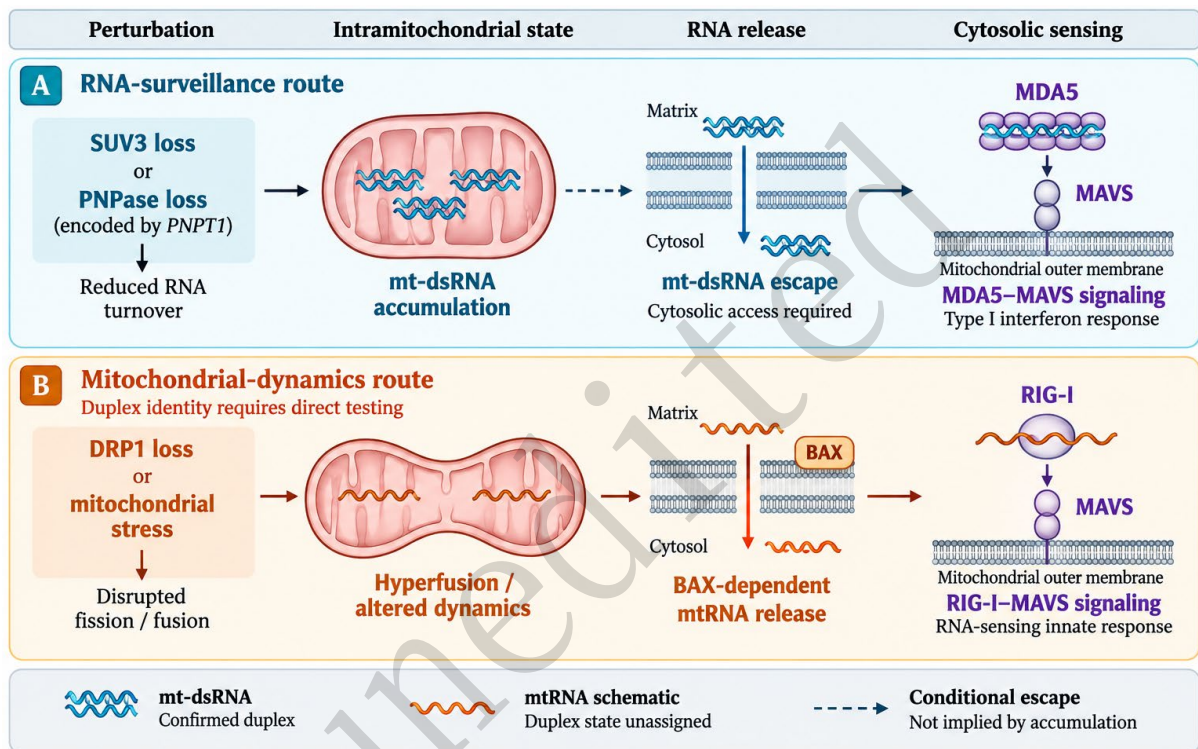


Fig. 2 Distinct routes of mitochondrial RNA escape and cytosolic innate immune sensing. (A) RNA-surveillance pathway. The loss of SUV3 or PNPase/PNPT1-mediated mitochondrial RNA degradation promotes intramitochondrial mt-dsRNA accumulation, which can facilitate cytosolic RNA exposure and activation of MDA5–MAVS signaling, leading to a type I interferon response. (B) Mitochondrial-dynamics pathway. DRP1 deficiency or mitochondrial stress can alter mitochondrial fission–fusion dynamics and promote BAX-dependent mitochondrial RNA release, potentially activating RIG-I–MAVS signaling. However, the double-stranded identity of the released RNA in this pathway requires direct experimental confirmation. The schematic distinguishes RNA accumulation, mitochondrial membrane escape, and downstream receptor activation as separate mechanistic events. Blue paired strands represent confirmed mt-dsRNA, orange strands represent mitochondrial RNA of unassigned duplex identity, and dashed arrows indicate conditional escape that does not necessarily follow RNA accumulation. Abbreviations: BAX, Bcl-2-associated X protein; DRP1, dynamin-related protein 1; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma differentiation-associated protein 5; mt-dsRNA, mitochondrial double-stranded RNA; mtRNA, mitochondrial RNA; PNPase, polynucleotide phosphorylase; PNPT1, polyribonucleotide nucleotidyltransferase 1; RIG-I, retinoic acid-inducible gene I; SUV3, mitochondrial SUV3 RNA helicase.

4 Intracellular and endosomal decoding: sensor routing determines biological meaning

Sensor routing determines the response to escaped mt-dsRNA. RIG-I favors short duplexes with appropriate 5' termini, whereas MDA5 assembles cooperatively on long dsRNA; LGP2 can tune MDA5 recognition (Lei et al., 2022; Duic et al., 2020; Stok et al., 2022). A dominant pathway of a tumor should be

established by receptor loss and rescue rather than inferred from interferon induction. The ligand features, proximal signaling, cancer context, and source limitations are compared in Table 1.

Table 1 Ligand features, proximal signaling, and cancer-context consequences of major RNA-sensing pathways

Sensor	Ligand/access	Proximal output	Cancer context and limitation	Representative references
RIG-I	Short duplexes; 5'-di/5'-triphosphate ends; cytosolic access.	MAVS–TBK1/IKKε–IRF3/7, NF-κB; interferon, death, cross-priming.	Can support antitumor activity; other ligands, including Y RNAs, also activate it.	(Heidegger et al., 2019; Vabret et al., 2022)
MDA5/LGP2	Long dsRNA; cooperative MDA5 filaments; LGP2 tunes recognition.	MAVS-dependent interferon and inflammation.	Relevant to ADAR1-low tumors; receptor dependence does not identify RNA source.	(Duic et al., 2020; Stok et al., 2022; Ishizuka et al., 2019)
PKR	Structured duplex RNA; PACT and proteotoxic stress also contribute.	eIF2α phosphorylation, translational arrest, stress response.	Can cause stress, death, or adaptation; phospho-PKR is not source-specific.	(Farabaugh et al., 2020; Davidson et al., 2022)
OAS–RNase L	Accessible dsRNA activates OAS; 2'–5' oligoadenylates activate RNase L.	RNA cleavage, translation disruption, secondary signaling.	Can mediate drug-induced cytotoxicity; source still requires testing.	(Koul et al., 2020; Banerjee et al., 2019)
TLR3	Long dsRNA in endosomes, often after uptake or transfer.	TRIF–IRF3 and NF-κB.	Pancreatic cancer study links mt-dsRNA-associated signaling to growth; model-specific.	(Milcarek et al., 2026)
ZBP1	Z-RNA is the defining ligand class, distinct from generic dsRNA.	RIPK1/RIPK3 inflammatory cell death and PANoptosis.	ADAR1 loss may expose this branch; activation does not prove mitochondrial origin (Karki et al., 2021; Zhang et al., 2022).	

RIG-I can connect RNA sensing to tumor-cell death and immune priming. Tumor-intrinsic RIG-I supports response to checkpoint blockade in preclinical models (Heidegger et al., 2019), and RIG-I signaling can cooperate with DNA-repair or IRF1 pathways during genotoxic stress (Guo et al., 2021; Zander et al., 2022). However, endogenous Y RNAs can also activate RIG-I (Vabret et al., 2022); therefore, source-specific depletion is needed before assigning this phenotype to mt-dsRNA. In this regard, reviews of RIG-I-like receptor therapy provide translational context, not proof of a mitochondrial ligand (Jiang et al., 2023).

MDA5 becomes important when ADAR1-mediated self-RNA tolerance fails. The ADAR1-mediated editing of endogenous Z-form RNA limits spontaneous MAVS signaling (Tang et al., 2021), and ADAR1–Z-RNA interactions can restrain MDA5 activation (de Reuver et al., 2021; Nakahama et al., 2021). LGP2 contributes to signaling in ADAR1-deficient states (Stok et al., 2022). Genetic studies have also linked RNA-editing variation to inflammatory-disease risk (Li et al., 2022). These mechanisms explain why MDA5 dependence identifies a long self-dsRNA response but they cannot reveal its mitochondrial or nuclear origin.

PKR translates dsRNA recognition into eIF2α phosphorylation, translational arrest, and integrated stress signaling. The circular-RNA structure can regulate PKR activation (Liu et al., 2019), while PACT and proteotoxic stress can also alter PKR activity (Farabaugh et al., 2020; Davidson et al., 2022). Therefore, PKR phosphorylation is not a source-specific readout. mt-dsRNA can also induce APOBEC3A and nuclear DNA damage, linking RNA sensing to secondary genotoxic stress (Wick et al., 2023); however, whether this promotes killing or sublethal mutagenesis depends on dose and duration.

OAS proteins bind dsRNA and generate 2'–5' oligoadenylates that activate RNase L; this response is influenced by RNA length and structure (Koul et al., 2020; Wang et al., 2020; Schwartz and Conn, 2020). OAS–RNase L mediates cytotoxicity after DNA-demethylating treatment (Banerjee et al., 2019), whereas the presence of gain-of-function OAS1 variants can show the risk of excessive pathway activity (Magg et al., 2021). RNase L can also induce downstream stress and apoptosis programs (Manivannan et al., 2019).

Intronic dsRNA provides a nuclear-source comparator (Chitrakar et al., 2021). These findings support the importance of measuring pathway-specific outputs as well as interferon.

ZBP1 preferentially recognizes Z-RNA and can trigger inflammatory cell death; ADAR1 loss exposes this pathway, but ZBP1 activation does not prove the mitochondrial origin (Herbert, 2019; Nichols et al., 2021; Karki et al., 2021; Zhang et al., 2022). Human and animal studies have further shown that failed ADAR1 restraint can cause severe ZBP1-dependent pathology (Jiao et al., 2022; Hubbard et al., 2022). Endosomal TLR3 can sense transferred dsRNA, and pancreatic cancer data link mt-dsRNA-associated RIG-I/TLR3 inflammation to tumor growth (Milcarek et al., 2026). Fig. 3 emphasizes that the outcome is jointly determined by receptor, recipient cell and duration.

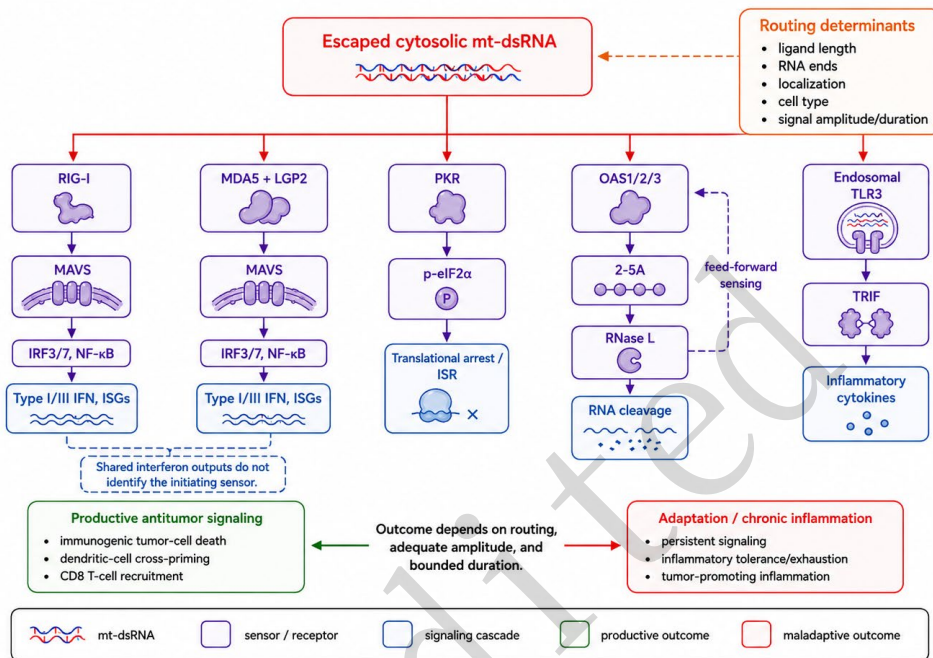


Fig. 3 Cytosolic and endosomal decoding of mitochondrial double-stranded RNA through distinct innate immune sensing pathways. Following mitochondrial escape, mt-dsRNA may activate different RNA-sensing pathways depending on duplex length, terminal structure, subcellular localization, receptor availability, and cellular context. RIG-I and MDA5/LGP2 activate MAVS-dependent signaling, resulting in IRF3/7 and NF-κB activation and the induction of type I and III interferons and interferon-stimulated genes. PKR induces eIF2α phosphorylation, translational arrest, and the integrated stress response, whereas OAS1/2/3 activates RNase L through the generation of 2'-5'-linked oligoadenylates, promoting RNA cleavage and potentially amplifying RNA-sensing responses. TLR3 recognizes dsRNA within endosomal compartments and signals through TRIF to induce inflammatory responses. Although these pathways can produce overlapping immune signatures, their biological outcomes depend on receptor engagement, recipient-cell identity, signal intensity, and duration. Acute, appropriately regulated signaling may promote immunogenic tumor-cell death, dendritic-cell cross-priming, and cytotoxic T-cell recruitment, whereas persistent signaling may contribute to inflammatory adaptation, immune dysfunction, or tumor-promoting inflammation. Purple outlines indicate sensors and proximal signaling components, blue outlines indicate downstream signaling responses, green outlines indicate potentially productive antitumor outcomes, and red outlines indicate maladaptive inflammatory outcomes. Dashed arrows represent regulatory or indirect signaling relationships. Abbreviations: 2-5A, 2'-5'-linked oligoadenylates; CD8, cluster of differentiation 8; dsRNA, double-stranded RNA; eIF2α, eukaryotic translation initiation factor 2 alpha; PKR, double-stranded RNA-activated protein kinase; RIG-I, retinoic acid-inducible gene I; RNase L, ribonuclease L; TLR3, Toll-like receptor 3; TRIF, TIR-domain-containing adaptor-inducing interferon-β.

5 Oncogenic immunoediting and cell-state adaptation

Cancer cells can adapt at several points in the dsRNA circuit. ADAR1 loss can restore tumor sensitivity to checkpoint blockade (Ishizuka et al., 2019), while increased editing supports T-ALL relapse

(Rivera et al., 2024) and ADAR1 loss activates antitumor signaling in lung cancer models (Jia et al., 2025). These effects make ADAR1 a selectable tolerance node instead of a mitochondrial-specific marker. Interferon-induced ADAR1p150 can also create negative feedback, hence treatment history may alter dependence.

ADAR1 restrains several sensor branches through distinct functions. ADAR1p150 limits both MDA5 and PKR activation (Hu et al., 2023), while the disruption of Z-RNA regulation can expose ZBP1-dependent necroptosis or PANoptosis (Karki et al., 2021; Zhang et al., 2022). Severe ADAR1–ZBP1 immunopathology in vivo defines a safety boundary (Jiao et al., 2022; Hubbard et al., 2022). Catalytic inhibition and protein depletion may therefore have different biological effects.

Additional regulatory mechanisms act alongside ADAR1 to control endogenous RNA immunogenicity. For example, SETDB1 suppresses tumor-intrinsic immunogenicity through epigenetic silencing (Griffin et al., 2021); oncogenic KRAS impairs DDX60-dependent dsRNA accumulation in colorectal cancer (Zhou et al., 2024); and XRN1-mediated retroelement decay is cancer dependent (Hosseini et al., 2024). Although these are mainly nuclear-RNA mechanisms, they demonstrate that tumor tolerance is distributed across multiple nodes. Table 2 distinguishes these pathways from mitochondrial RNA surveillance and escape.

Cell state can reverse the effect of endogenous dsRNA. MDA5 signaling supports hematopoietic regeneration after chemotherapy (Clapes et al., 2021), and satellite-repeat RNA is associated with an immunosuppressive phenotype in ovarian cancer (Porter et al., 2022). In breast cancer, DHX9 and ADAR1 loss can induce viral mimicry, whereas epigenetic switching can suppress it in taxane-resistant tumors (Cottrell et al., 2024; Deblois et al., 2020). These model-specific results caution against treating high dsRNA as a universal marker of productive antitumor immunity.

Table 2 Oncogenic control nodes that shape endogenous and mt-dsRNA immunogenicity

Control node	Evidence and level	Interpretation for cancer	Representative references
ADAR1	Self-dsRNA editing/tolerance; tumor checkpoint resistance and T-ALL relapse.	May expose several RNA sources and sensors; mitochondrial share requires depletion controls.	(Ishizuka et al., 2019; Rivera et al., 2024)
SUV3 and PNPase/PNPT1	Mitochondrial RNA surveillance; AML differentiation and immune sensitivity.	Candidate lineage-specific dependency; assess production relative to degradation reserve.	(Dhir et al., 2018; Thomas et al., 2026)
SETDB1	Represses transposable-element-derived immunogenic RNA.	Nuclear-RNA route; source differs from mt-dsRNA.	(Griffin et al., 2021)
KRAS–DDX60	KRAS impairs dsRNA accumulation and viral mimicry in colorectal cancer.	Genotype-specific sensor suppression.	(Zhou et al., 2024)
XRN1	Retroelement RNA decay can be a cancer dependency.	Primarily nuclear/repeat RNA; potential bypass routes include ADAR1.	(Hosseini et al., 2024)
Splicing/hnRNP	Mis-splicing or altered RNA packaging exposes self-dsRNA.	RNA-processing vulnerability; mitochondrial contribution unresolved.	(Bowling et al., 2021; Herzner et al., 2021)
Mitochondrial dynamics	DRP1 loss can release mitochondrial RNA; duplex identity is route-specific.	Test escape separately from RNA accumulation.	(Yasuda et al., 2026)

6 Therapeutic rewiring: inducing a productive pulse rather than maximal dsRNA

Several therapeutic classes induce endogenous RNA sensing, but their primary ligands are often nuclear. DNMT inhibition can trigger OAS–RNase L-dependent cytotoxicity (Banerjee et al., 2019), and selective DNMT1 inhibition has been evaluated in AML (Pappalardi et al., 2021). Furthermore, G9a/DNMT targeting has shown immune-mediated activity in bladder cancer and antitumor effects in cholangiocarcinoma models (Segovia et al., 2019; Colyn et al., 2021). Mitochondrial RNA targeting can

alter response to demethylating agents, so source-resolved measurements are needed during combination treatment (Tan et al., 2024). EGFR inhibition can co-opt antiviral signaling in lung cancer, illustrating that an antiviral program may reflect adaptation rather than tumor killing (Gong et al., 2020).

Additional epigenetic strategies include PRMT inhibition in triple-negative breast cancer (Wu et al., 2022), EZH2 inhibition with DNMT blockade (Chomiak et al., 2024), and a bifunctional HDAC/DNMT inhibitor (Fan et al., 2024). While these studies provide comparators for acute viral-mimicry responses, they do not establish mt-dsRNA as the ligand. The influenza-triggered mobilization of endogenous retroviral RNA further illustrates how nuclear RNA can produce antiviral signaling (Schmidt et al., 2019).

RNA-processing perturbations can expose additional self-RNA. For instance, spliceosome-targeted treatment induces antiviral responses in triple-negative breast cancer (Bowling et al., 2021); DNMT inhibition can exploit mis-splicing in SETD2-mutant kidney cancer (Li et al., 2023a); and hnRNPC loss can cooperate with ADAR deficiency (Herzner et al., 2021). When mitochondrial and nuclear RNA perturbations are combined, ligand-source depletion and receptor epistasis are needed to identify the contribution of each source.

ADAR1 inhibition may be useful in tumors with substantial self-dsRNA burden and intact downstream sensing, but it can engage MDA5, PKR and ZBP1 simultaneously (Ishizuka et al., 2019; Hu et al., 2023; Jia et al., 2025). Evidence that ADAR1 also regulates mt-dsRNA adds a possible mitochondrial component without removing the need to distinguish nuclear ligands (Shin et al., 2026). A source-resolved biomarker panel should include duplex burden, ADAR1 state, sensor competence, antigen presentation, and cell-death capacity.

Direct dsRNA agonists offer a controllable comparator: the intratumoral poly I:C formulation BO-112 has been tested with anti-PD-1 therapy in refractory tumors (Márquez-Rodas et al., 2020). Tumor-cell IL-7 engineering is a separate immune strategy, not evidence of mt-dsRNA signaling (Shin et al., 2025). Metabolic studies of mitochondrial sirtuins and glutaminolysis provide cancer context only (Lee and Yoon, 2024; Kim et al., 2024a), while $\gamma\delta$ T-cell reviews provide immune-context background (Park and Lee, 2025). Of note, these papers are cited as context, not as direct evidence that mt-dsRNA mediates their effects. Fig. 4 summarizes the design principle, that is to seek a time-bounded, tumor-selective sensing pulse, but not maximal dsRNA accumulation.

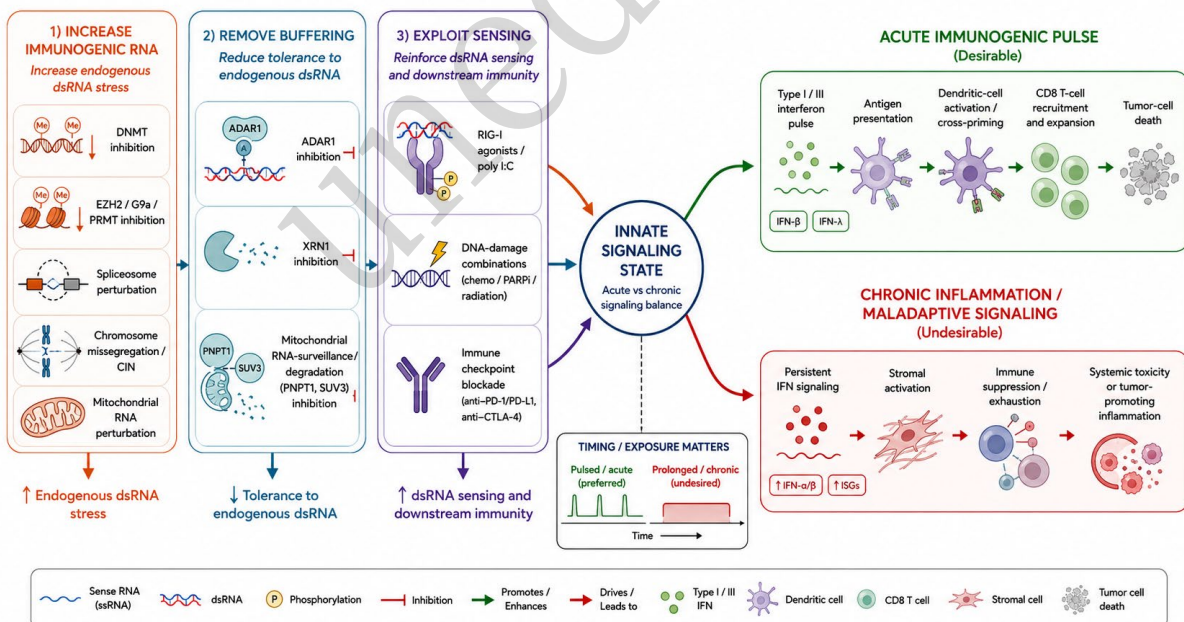


Fig. 4 Therapeutic rewiring of endogenous double-stranded RNA sensing to promote antitumor immunity. The schematic illustrates three complementary strategies for modulating endogenous RNA immunogenicity and downstream innate immune responses. (1) Increasing immunogenic RNA stress through DNA methyltransferase inhibition, histone-modifying enzyme inhibition, spliceosome perturbation, chromosome missegregation, or mitochondrial RNA disruption. (2) Reducing endogenous RNA tolerance through interference with regulatory mechanisms involving ADAR1, XRN1, or mitochondrial RNA-surveillance components, including PNPT1 and SUV3.

(3) Enhancing RNA sensing and downstream immune responses through RNA-sensing agonists, DNA-damaging therapies, or immune checkpoint blockade. These interventions converge on innate immune signaling pathways whose biological consequences depend on the magnitude, duration, and cellular distribution of pathway activation. A transient, appropriately regulated response may promote interferon production, antigen presentation, dendritic-cell cross-priming, cytotoxic T-cell recruitment, and tumor-cell death. Conversely, prolonged or dysregulated signaling may sustain inflammatory stromal activation, immune dysfunction, and tumor-promoting inflammation. The proposed therapeutic strategies and combinations represent a conceptual framework, and their efficacy, selectivity, and safety require validation in relevant cancer models. Green arrows indicate potentially beneficial immune responses, red arrows indicate maladaptive outcomes, blunt-ended lines indicate inhibition, and the circled P denotes phosphorylation. Abbreviations: ADAR1, adenosine deaminase acting on RNA 1; CD8, cluster of differentiation 8; CIN, chromosomal instability; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DNA, deoxyribonucleic acid; DNMT, DNA methyltransferase; dsRNA, double-stranded RNA; EZH2, enhancer of zeste homolog 2; G9a, euchromatic histone lysine methyltransferase 2; IFN, interferon; IFN- α/β , interferon alpha/beta; IFN- β , interferon beta; IFN- λ , interferon lambda; ISGs, interferon-stimulated genes; PARPi, poly(ADP-ribose) polymerase inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PNPT1, polyribonucleotide nucleotidyltransferase 1; poly(I:C), polyinosinic-polycytidylic acid; PRMT, protein arginine methyltransferase; RIG-I, retinoic acid-inducible gene I; RNA, ribonucleic acid; ssRNA, single-stranded RNA; SUV3, mitochondrial SUV3 RNA helicase; XRN1, 5'–3' exoribonuclease 1.

7 Cancer-context evidence and biomarker landscape

The strongest cancer-related evidence is lineage-specific. In AML, mitochondrial RNA degradation influences differentiation, stemness and immune sensitivity (Thomas et al., 2026); in B-ALL, mt-dsRNA can reprogram stromal cells (Burt et al., 2024); and in T-ALL, ADAR1-mediated editing supports relapse (Rivera et al., 2024). These results identify different circuit nodes and do not establish one shared dependency across leukemias.

Lung cancer studies report heterogeneous mt-dsRNA levels across NSCLC models, while the proteomic profiling of precancerous lesions links mt-dsRNA-associated signals to immune and stress states (Krieger et al., 2026; Xu et al., 2025). While these data motivate spatial and cell-resolved biomarkers, they remain insufficient to define a treatment threshold. The $\gamma\delta$ T-cell literature also highlights that antitumor immunity depends on recipient-cell composition (Park and Lee, 2025).

The direction can be tumor-promoting: pancreatic cancer data link mt-dsRNA-associated RIG-I/TLR3 inflammation with growth (Milcarek et al., 2026). By contrast, viral-mimicry responses in triple-negative breast cancer and KRAS–DDX60 regulation in colorectal cancer mainly concern endogenous dsRNA whose mitochondrial fraction remains unresolved (Wu et al., 2022; Bowling et al., 2021; Zhou et al., 2024). Table 3 labels these findings by evidence type and candidate biomarker rather than treating them as a pan-cancer effect.

A useful biomarker combines source pressure, escape and decoding, that is, duplex-specific mtRNA burden; mitochondrial contamination-controlled cytosolic signal; buffering reserve; sensor competence; and a cell-resolved death or immune-priming response. Importantly, no single interferon score or J2 image can serve as a stand-alone companion diagnostic.

Table 3 Cancer-context evidence and candidate biomarkers for the mt-dsRNA circuit

Cancer context	Finding	Evidence and direction	Biomarker lead	Representative references
AML	Mitochondrial RNA degradation affects differentiation and immune sensitivity.	Direct causal; potential vulnerability.	mtRNA burden + degradation reserve.	(Thomas et al., 2026)
B-ALL	Tumor mt-dsRNA reprograms mesenchymal stroma.	Direct causal; tumor-supportive niche.	Extracellular mt-dsRNA + stromal response.	(Burt et al., 2024)
T-ALL	ADAR1 editing attenuates dsRNA sensing and supports relapse.	Direct causal; tolerance state.	Editing index + sensor competence.	(Rivera et al., 2024)
NSCLC/lung	mt-dsRNA varies across tumors and precancerous lesions.	Heterogeneous; includes associative signals.	Spatial mt-dsRNA + RIG-I/MDA5.	(Krieger et al., 2026; Xu et al., 2025)

Cancer context	Finding	Evidence and direction	Biomarker lead	Representative references
Pancreatic cancer	mt-dsRNA-associated RIG-I/TLR3 inflammation is linked to growth.	Direct causal in the reported model; potentially tumor promoting.	Receptor topology + cytokine duration.	(Milcarek et al., 2026)
TNBC	PRMT/spliceosome/epigenetic perturbations induce viral mimicry.	Causal for endogenous dsRNA; mitochondrial share unresolved.	Source-resolved dsRNA + sensor status.	(Wu et al., 2022; Bowling et al., 2021)
Colorectal cancer	KRAS impairs DDX60-linked dsRNA accumulation.	Direct causal; immune suppression.	KRAS + DDX60 + dsRNA burden.	(Zhou et al., 2024)

8 The translational boundaries: when mt-dsRNA becomes tumor-promoting or toxic

The first translational boundary is chronicity. Senescent cells can maintain inflammation through cytosolic mt-dsRNA without immediate cell death (López-Polo et al., 2024), and pancreatic cancer provides a model in which mt-dsRNA-associated signaling can support tumor growth (Milcarek et al., 2026). Therefore, a transient interferon pulse followed by tumor-cell death is distinct from persistent signaling without cyto-reduction; to tell them apart, serial pharmacodynamic measurements are needed.

The second boundary is host toxicity. mt-dsRNA contributes to osteoarthritis models (Kim et al., 2022), and mitochondrial RNA polymerase inhibition is being explored to reduce mt-dsRNA-mediated osteoarthritis inflammation (Gao et al., 2026). HSP60 can restrict inflammatory release (Huang et al., 2022), while recent work links mt-dsRNA to aging-associated cognitive decline (Zhang et al., 2026). These findings argue for tumor-localized delivery, pulsed dosing, or tumor-specific dependency rather than assuming that mitochondrial RNA surveillance is cancer-restricted.

The third boundary is source ambiguity. Chromosome missegregation and impaired nuclear RNA export can activate RNA sensing and antitumor immunity (Sasaki et al., 2025; Wang et al., 2025). A mitochondrial claim therefore requires duplex-sequence evidence, clean cytosolic localization, a mitochondrial-source perturbation with rescue, and receptor epistasis; J2 staining or an interferon response alone is insufficient.

The therapeutic order should follow the dominant circuit: amplify a source-resolved, antitumor response when tumor-cell decoding is competent, but suppress a tumor-supportive stromal or TLR3 branch when chronic inflammation dominates. Fig. 5 frames this decision as a therapeutic-window problem involving tumor selectivity, signal duration, and host liability.

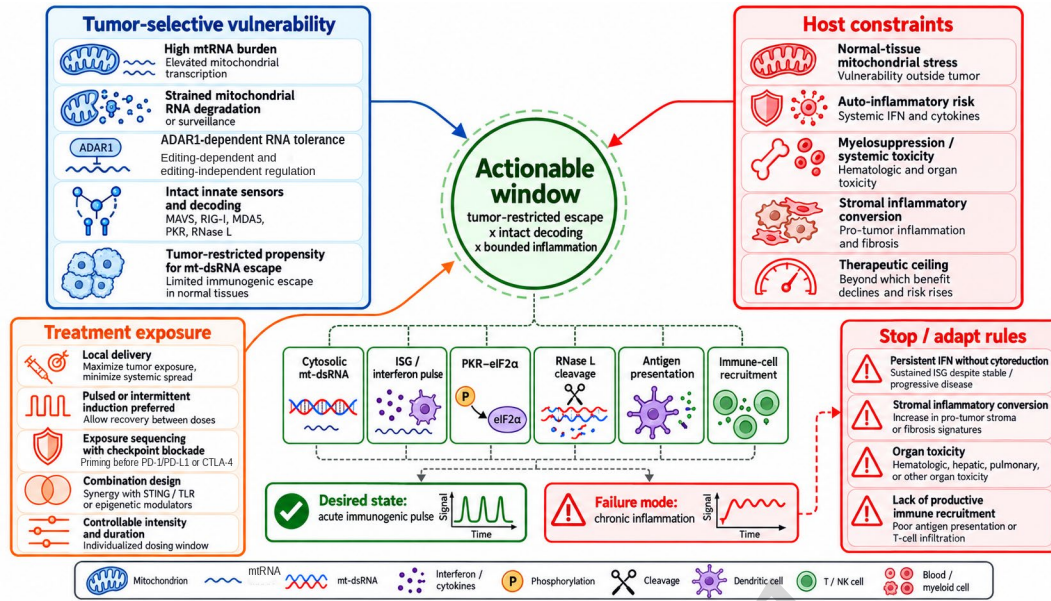


Fig. 5 Translational therapeutic-window model for mt-dsRNA. Whether mt-dsRNA manipulation is useful is jointly determined by tumor-selective vulnerability, treatment exposure, and host constraints. Pharmacodynamic biomarkers should capture cytosolic mt-dsRNA, sensor engagement, cell death, and immune recruitment, while stop/adapt rules should detect persistent interferon without cyto-reduction, stromal inflammatory conversion, and organ toxicity. Abbreviations: ADAR1, adenosine deaminase acting on RNA 1; A-to-I, adenosine-to-inosine; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; eIF2 α , eukaryotic translation initiation factor 2 alpha; IFN, interferon; ISG, interferon-stimulated gene; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma differentiation-associated protein 5; mt-dsRNA, mitochondrial double-stranded RNA; mtRNA, mitochondrial RNA; NK, natural killer; PD-1, programmed cell death protein 1; PKR, double-stranded RNA-activated protein kinase; RIG-I, retinoic acid-inducible gene I; RNase L, ribonuclease L; STING, stimulator of interferon genes; TLR, Toll-like receptor.

9 Experimental roadmap and conclusions

In summary, causal experiments should separate RNA generation, modification, degradation, escape, and sensing. Duplex-specific capture or imaging should be paired with strand-aware, NUMT-aware sequence mapping; cytosolic fractionation should include mitochondrial-contamination markers; and source perturbations need to be rescued. These controls build on published methods for mt-dsRNA analysis (Kim et al., 2023) and on direct trafficking studies (Krieger et al., 2024). The minimum assay and decision criteria are summarized in Table 4.

In terms of sensor loss and rescue, DDX58/RIG-I, IFIH1/MDA5, EIF2AK2/PKR, OAS–RNase L, TLR3, and MAVS contributions should be distinguished. Longitudinal measures should pair cytosolic mt-dsRNA with cell death, antigen presentation, immune recruitment, cytokine persistence, and normal-tissue injury. AML, B-ALL, pancreatic cancer, and NSCLC findings justify model-specific sampling, not histology-wide assumptions (Thomas et al., 2026; Burt et al., 2024; Milcarek et al., 2026; Krieger et al., 2026).

Combination studies should be conducted to demonstrate that adding a mitochondrial perturbation changes the source-resolved ligand pool and improves a functional outcome. To this end, RIG-I/checkpoint combinations and ADAR1-directed strategies offer comparators (Heidegger et al., 2019; Ishizuka et al., 2019; Datta et al., 2024), while BO-112 provides a direct agonist benchmark (Márquez-Rodas et al., 2020).

Table 4. Minimum experimental validation matrix for mt-dsRNA studies.

Question	Assay	Critical control / decision rule
Is the duplex mitochondrial?	Duplex capture + RNase III; strand-aware, NUMT-aware sequencing.	Nuclear-repeat and NUMT controls; mitochondrial reads enriched in RNase III-sensitive duplex fraction.
Has it escaped?	Cytosolic fractionation + RT-qPCR/seq; imaging with organelle masks.	TOMM20/COXIV and integrity controls; cytosolic signal rises without organelle carryover.

Question	Assay	Critical control / decision rule
Which sensor is causal?	Genetic epistasis for RIG-I, MDA5/LGP2, MAVS, PKR, OAS/RNase L, TLR3, ZBP1.	Matched rescue and ligand controls; phenotype collapses in the responsible branch.
Is signaling productive?	Time-resolved death, antigen presentation, dendritic-cell activation, and T-cell recruitment.	Acute signaling couples to killing/priming; persistent interferon without cytoinduction is flagged.
Is the effect selective?	Paired tumor/normal organoids and immune-cell toxicity assays.	Comparable target engagement; therapeutic index retained.
Can resistance emerge?	Longitudinal single-cell RNA/ATAC and dsRNA profiling.	Detect rewiring before relapse; avoid endpoint-only sampling.

The evidence supports a checkpoint model in which transcription and RNA chemistry generate mt-dsRNA, surveillance buffers it, membrane state governs escape, and receptor routing shapes outcome. The therapeutic question is whether a source-resolved, time-limited perturbation can produce tumor-selective killing or immune priming without chronic inflammation, stromal support, or host injury. This model is testable, but its clinical value remains dependent on causal validation in each cancer context.

Data availability statement

Data sharing is not applicable to this review article because no new datasets were generated or analyzed.

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Author contributions

Sajid ALI: Conceptualization, literature investigation and analysis, writing—original draft preparation, visualization, and writing—review and editing.

Wajid ZAMAN: Conceptualization, literature investigation and analysis, writing—original draft preparation, visualization, supervision, and writing—review and editing.

Both authors have read and approved the final manuscript and accept responsibility for its content.

Compliance with ethics guidelines

Conflict of interest

Sajid ALI and Wajid ZAMAN declare that they have no conflicts of interest.

Ethics statement

This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed consent and clinical trial registration

Not applicable.

Declaration on the use of generative AI tools

During the preparation of this manuscript, the authors used OpenAI ChatGPT, Grammarly, and FigureLab for literature organization assistance, language drafting and refinement, and figure conceptualization and formatting, as applicable. During the revision, OpenAI ChatGPT (GPT-4) was used for language refinement and assistance in reviewing conceptual figures. The authors independently reviewed and edited the outputs, verified the scientific content and references, and take full responsibility for the accuracy, originality, integrity, and final content of the manuscript.

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