

Mitochondrial RNA leakage defines a bounded inflammatory control layer in senescence

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Abstract

Background: Senescent cells can sustain inflammatory secretory programs that contribute to tissue dysfunction during aging. Mitochondrial DNA release through cGAS-STING is established as one route into this phenotype, but recent primary studies identify mitochondrial RNA and mitochondrial double-stranded RNA as additional danger signals.

Objective: This working paper evaluates whether mitochondrial RNA leakage should be treated as a distinct, bounded inflammatory control layer rather than as a generic marker of mitochondrial damage.

Methods: Eight PubMed-indexed primary records published from 2020 through 2026 were verified for DOI, PMID, model system, endpoint class, preprint status, and correction flags. Evidence was coded across four axes: mitochondrial RNA sensor support, mitochondrial dynamics linkage, mitophagy or quality-control restraint, and metabolic permissiveness of inflammatory transcription. Quantitative diagnostics measured weighted axis shares, direct-support counts, core-to-boundary ratios, and leave-one-record-out leverage; descriptive ordinal totals were not used to estimate pooled biological effects.

Results: The strongest support concerned cytosolic mitochondrial RNA or mitochondrial double-stranded RNA activating DDX58, MDA5, and MAVS in senescence or stress models. The mitochondrial RNA axis contributed 10.79 of 28.27 certainty-weighted ordinal units, or 38.2% of all coded support, and remained the top axis after every single-record removal. BAX/BAK-dependent mitochondrial permeabilization linked mitochondrial RNA leakage to earlier mitochondrial DNA findings, while DRP1-loss hyperfusion connected mitochondrial dynamics to RNA-sensing immunity in cancer models. Mitophagy evidence chiefly constrained mitochondrial DNA-cGAS-STING inflammation, and citrate-acetyl-CoA evidence defined a metabolic license for inflammatory gene expression rather than an upstream RNA trigger.

Conclusions: Mitochondrial RNA leakage is best interpreted as a mechanistically specific inflammatory signal that overlaps with, but is not interchangeable with, mitochondrial DNA release. Current evidence supports testable separation of trigger, pore, sensor, quality-control, and chromatin-permissive layers; it does not support broad anti-aging or treatment claims.

Keywords: mitochondrial RNA; senescence; SASP; DDX58; MDA5; MAVS; BAX; BAK; mitochondrial dynamics; mitophagy

1 Introduction

Cellular senescence combines durable growth arrest with a variable senescence-associated secretory phenotype, often abbreviated SASP. The SASP can reinforce tissue repair or tumor suppression in some settings, yet persistent inflammatory SASP activity is also linked to tissue dysfunction during aging. Mitochondria influence this inflammatory program through multiple mechanisms, including reactive oxygen signaling, nucleic-acid release, metabolite supply, and quality-control failure [1-7].

Mitochondrial DNA release has become a central model for mitochondria-driven innate immune activation in senescence. Minority mitochondrial outer-membrane permeabilization can release mitochondrial DNA through BAX and BAK macropores, activating cGAS-STING and inflammatory SASP expression [4]. Age-associated mitophagy responses also appear to restrain cytosolic mitochondrial DNA and cGAS-STING activation in retina and fibroblast contexts [5]. These findings define a DNA-centered axis, but they do not exhaust the possible mitochondrial danger signals.

Recent primary evidence indicates that mitochondrial RNA and mitochondrial double-stranded RNA can enter the cytosol during senescence or mitochondrial stress and activate RNA-sensing pathways. In human senescence systems, mitochondrial double-stranded RNA release was connected to DDX58, MDA5, MAVS, PNPT1, ADAR1, and MFN1-dependent inflammatory output [1]. A separate study found mitochondrial RNA leakage, MAVS aggregation, and BAX/BAK-dependent SASP regulation in human fibroblasts and a mouse liver-disease model [2]. These records raise a practical interpretation problem: mitochondrial RNA leakage may be a specific inflammatory signal, a downstream correlate of broader organelle damage, or one layer of a larger mitochondrial-state checkpoint.

This working paper synthesizes recent primary evidence to define the boundary of that claim. The public objective is to determine whether mitochondrial RNA leakage can be treated as a distinct control layer in senescence-associated inflammation, and to identify the direct tests needed to separate RNA trigger, BAX/BAK pore formation, mitochondrial dynamics, mitophagy restraint, and chromatin-metabolic permissiveness.

2 Methods

The evidence set was assembled from primary studies centered on mitochondrial RNA or mitochondrial nucleic-acid inflammatory signaling in senescence, aging, mitochondrial dynamics, mitophagy, or SASP execution. Records were verified through PubMed metadata and available abstracts or full text. For every included record, DOI, PMID, publication type, preprint status, and correction or update flags were recorded in `citation_verification.csv`. Reviews and commentary were excluded from the evidence table, although they informed no manuscript claims.

Eligibility required primary experimental evidence with at least one of the following: cytosolic mitochondrial RNA or mitochondrial double-stranded RNA measurement; RNA-sensor or MAVS perturbation; BAX/BAK-linked mitochondrial nucleic-acid release; mitochondrial dynamics perturbation tied to RNA sensing; mitophagy-linked mitochondrial DNA restraint during aging; or metabolic control of SASP transcription. Human cell, mouse, tissue, cancer, liver, retina, and brain-aging models were retained when the model-system boundary could be stated explicitly.

Figure 1 summarizes the implemented workflow from topic scoping, primary-literature search, eligibility screening, evidence coding, ordinal analysis, sensitivity checks, and synthesis.

Each study was coded into one primary endpoint class and four ordinal support axes. The mitochondrial RNA axis captured direct

support for cytosolic mitochondrial RNA or mitochondrial double-stranded RNA activating DDX58, MDA5, MAVS, or related inflammatory signaling. The dynamics axis captured direct DRP1, MFN1, hyperfusion, or morphology-linked evidence. The mitophagy axis captured mitochondrial quality-control restraint of cytosolic nucleic-acid inflammation. The metabolic axis captured mitochondrial metabolite or chromatin-permissive mechanisms that enabled inflammatory gene expression.

Scores ranged from 0 to 3 and were used as descriptive evidence-mapping codes. A certainty weight from 0.82 to 0.95 was assigned from model proximity, directness of perturbation, and correction or context flags. These values are not effect sizes, do not pool heterogeneous endpoints, and do not rank study quality beyond the defined synthesis task. Quantitative evidence-map diagnostics were then computed from the coded matrix: certainty-weighted axis shares, nonzero and direct-support record counts, the ratio of core RNA/dynamics support to boundary mitophagy/metabolic support, and leave-one-record-out leverage for the leading axis. Generated data and figures are reproducible from `analysis.py`.

3 Results

3.1 Evidence synthesis

The evidence matrix is shown in Table 1. Cell-system evidence from Lopez-Polo et al. supports the most direct mitochondrial double-stranded RNA route: senescence increased cytosolic mitochondrial double-stranded RNA, and perturbing mitochondrial RNA polymerase, DDX58/MDA5, MAVS, MFN1, PNPT1, or ADAR1 altered inflammatory SASP expression while broad senescence features remained largely preserved [1]. The endpoint class is mechanistic inflammatory signaling in senescence models; the inference ceiling is not organism-wide aging benefit.

Victorelli et al. extended the RNA-leakage mechanism by showing mitochondrial RNA accumulation in senescent-cell cytosol, DDX58/MDA5 activation, MAVS aggregation, and BAX/BAK dependence in human fibroblasts, with additional liver disease evidence in a mouse metabolic dysfunction-associated steatohepatitis model [2]. This record is especially important because it links RNA leakage to the same BAX/BAK pore family implicated in mitochondrial DNA release [4]. The evidence supports pore-linked necessity in tested systems, not safety or therapeutic sufficiency of blocking BAX/BAK.

Mitochondrial dynamics evidence is strongest in a 2026 Cell Reports study in which DRP1 loss or stress-induced mitochondrial hyperfusion promoted BAX-dependent mitochondrial RNA release and DDX58-MAVS innate immune activation [3]. The functional endpoint included natural killer-cell cytotoxicity and xenograft growth. This is a high-value mechanism study but has a cancer-context boundary; it should not be used alone to claim senescence reversal or normal-aging benefit.

DNA-centered and quality-control studies define adjacent constraints. Minority mitochondrial outer-membrane permeabilization released mitochondrial DNA, activated cGAS-STING, and drove inflammatory SASP features; the PubMed record lists an author correction, which was retained in citation QA [4]. Mitophagy work in aged retina and older-donor fibroblasts linked mitochondrial quality-control responses to cytosolic mitochondrial DNA and cGAS-STING inflammation, but the primary trigger was DNA rather than RNA [5]. These studies show that RNA leakage belongs in a broader mitochondrial nucleic-acid framework, while preserving distinct DNA and RNA sensor boundaries.

Two metabolic records help interpret why nucleic-acid sensing is not sufficient by itself. Mitochondria-to-nucleus retrograde signaling through ROS-JNK promoted cytoplasmic chromatin fragments and SASP activation in senescent cells [6]. A later Nature study reported that mitochondrial citrate export and acetyl-CoA

availability supported histone acetylation at SASP loci, defining a chromatin-permissive metabolic checkpoint [7]. These findings support a two-layer model in which innate immune trigger pathways require permissive transcriptional and chromatin states to produce robust inflammatory output.

Brain-aging evidence adds tissue relevance without removing model boundaries. Li et al. linked mitochondrial double-stranded RNA accumulation to innate immune signaling and cognitive decline-associated phenotypes in brain aging and Alzheimer disease-related contexts [8]. This supports relevance beyond cultured fibroblasts, but organ specificity and disease context prevent generalization to all tissues.

Across the included records, the most consistent causal boundary is perturbation-linked reduction of inflammatory output rather than disappearance of senescence itself. Lopez-Polo et al. reported that reducing mitochondrial double-stranded RNA production or downstream RNA-sensor signaling decreased inflammatory SASP features while leaving broad senescence hallmarks comparatively intact [1]. Victorelli et al. similarly separated mitochondrial RNA leakage and MAVS aggregation from the entire senescence program [2]. This pattern supports a modular model in which mitochondrial RNA sensing tunes the inflammatory arm of senescence more directly than it controls growth arrest.

The BAX/BAK evidence also requires narrow wording. BAX and BAK connect mitochondrial outer-membrane permeabilization to both mitochondrial DNA and mitochondrial RNA leakage, but the published models do not establish a universal pore threshold that selects one nucleic-acid species over another [2,4]. The practical inference is that future studies should assay mitochondrial DNA and mitochondrial RNA in parallel, preferably from matched cytosolic fractions, instead of using one species as a proxy for the other.

The dynamics evidence is mechanistically useful because it provides an upstream organelle-state perturbation. DRP1 loss or stress-induced hyperfusion connected altered morphology to mitochondrial RNA release and DDX58-MAVS signaling in cancer models [3]. MFN1 perturbation modified the mitochondrial double-stranded RNA-SASP axis in senescence models [1]. Together, these findings suggest that mitochondrial shape can influence nucleic-acid containment, but they do not define a simple beneficial direction for fission or fusion. Endpoint class and cell state remain essential to interpretation.

The metabolic evidence sets a separate ceiling on interpretation. Mitochondrial citrate export and acetyl-CoA production affected chromatin acetylation at SASP loci [7], while ROS-JNK retrograde signaling promoted cytoplasmic chromatin fragment formation in senescence [6]. These studies support the idea that inflammatory transcription requires permissive nuclear and metabolic conditions. They do not identify mitochondrial RNA as the initiating signal and should be treated as execution-layer evidence.

Table 1. Primary-study evidence matrix

Study	Model and perturbation	Key finding	Interpretive limitation
[1]	Human senescence models: IMR-90 fibroblasts, SK-MEL-103 cells, A549 cells; Doxorubicin, palbociclib, or bleomycin-induced senescence; POLRMT, DDX58, MDA5, MAVS, MFN1, PNPT1, and ADAR1 perturbations	Cytosolic mitochondrial double-stranded RNA increased across senescence models; mitochondrial RNA polymerase, DDX58/MDA5, MAVS, and MFN1 perturbations reduced SASP-associated inflammatory expression while preserving broad senescence markers.	Cell-system evidence; the paper supports mt-dsRNA/MAVS control of SASP but does not establish organism-wide aging benefit from pathway inhibition.
[2]	Human MRC5 and IMR90 fibroblasts; mouse metabolic dysfunction-associated steatohepatitis model; Ionizing-radiation senescence; BAX/BAK deletion; RNA-sensor and MAVS interference	Mitochondrial RNA accumulated in senescent-cell cytosol, activated DDX58/MDA5 and MAVS aggregation, and BAX/BAK loss reduced RNA leakage and inflammatory SASP markers in vitro and in liver disease tissue.	The study updates a preprint and supports pathway necessity in tested models; it does not prove selective safety or clinical efficacy of blocking BAX/BAK-linked leakage.
[3]	Human and mouse cancer-cell systems with xenograft testing; DRP1 loss or stress-induced mitochondrial hyperfusion; DDX58, MAVS, and BAX pathway interrogation	Mitochondrial hyperfusion after DRP1 loss or stress was associated with BAX-dependent mitochondrial RNA release and DDX58-MAVS immune activation, with functional links to NK-cell cytotoxicity and xenograft growth.	Cancer-context evidence strengthens dynamics-to-mtRNA plausibility but is not a senescence or normal-aging model.
[4]	Cellular senescence systems and aged mice; Minority mitochondrial outer-membrane permeabilization; BAX/BAK and MOMP inhibition	Sublethal mitochondrial apoptotic stress released mitochondrial DNA through BAX/BAK macropores, activated cGAS-STING, and MOMP inhibition reduced inflammatory markers and improved healthspan readouts in aged mice.	Primary signal is mtDNA/cGAS-STING, not mtRNA; PubMed lists an author correction, so corrected article status must be retained.
[5]	Aged mouse retina, human fibroblasts from older donors, mitophagy-modulation models; Age-associated mitophagy and PINK1/Parkin-linked quality-control analyses	Age-related cytosolic mtDNA and cGAS-STING activation were associated with mitophagy responses, supporting mitochondrial quality control as a restraint on mtDNA-dependent inflammation.	The evidence concerns mtDNA rather than mtRNA; PubMed lists an author correction and tissue scope is retina/fibroblast-centered.
[6]	IMR90 senescence systems; Mitochondrial dysfunction, ROS-JNK retrograde signaling, HDAC-inhibitor rescue	Mitochondrial dysfunction drove ROS-JNK signaling, cytoplasmic chromatin fragment formation, and cGAS-STING-dependent SASP; restoring oxidative phosphorylation gene expression reduced inflammatory features.	Retrograde nuclear chromatin mechanism, not direct mitochondrial RNA release; supports mitochondrial state as an upstream inflammatory license.

Study	Model and perturbation	Key finding	Interpretive limitation
[7]	Senescent-cell metabolic and chromatin systems; Mitochondrial citrate-acetyl-CoA axis; MPC, SLC25A1, and ACLY perturbations	Mitochondrial citrate export and acetyl-CoA availability supported histone acetylation at SASP loci, separating innate immune sensing from epigenetic execution of inflammatory transcription.	Metabolic checkpoint evidence does not identify mitochondrial RNA as the trigger; the published article updates a preprint record.
[8]	Brain aging and Alzheimer's disease-related models; SEC61A1-linked endoplasmic-reticulum-mitochondria contact regulation of mitochondrial nucleic-acid synthesis	Mitochondrial double-stranded RNA accumulated in brain aging and was linked to innate immune signaling and cognitive decline-associated phenotypes.	Neuroaging context supports tissue relevance but should not be generalized to all organs or to treatment claims.

3.2 Evidence-coded sensitivity analysis

Removing the two most direct senescence RNA records leaves the synthesis without sufficient support for mitochondrial RNA leakage as an independent senescence inflammatory layer [1,2]. Removing the cancer dynamics record weakens the bridge from mitochondrial morphology to RNA release but does not eliminate senescence RNA-sensor support [3]. Removing the DNA-centered studies prevents a coherent BAX/BAK and quality-control boundary from being stated, even though RNA-sensor evidence remains [4,5].

The endpoint hierarchy is therefore trigger first, interpretation second. Target engagement is represented by cytosolic mitochondrial RNA or double-stranded RNA, RNA-sensor perturbation, and MAVS aggregation. Biomarker and signaling endpoints include inflammatory gene expression, SASP markers, cGAS-STING mediators, and histone acetylation at SASP loci. Functional endpoints are more limited and model-specific, including xenograft growth, liver disease inflammatory markers, retina aging markers, and brain cognitive phenotypes. No included record supports a generalized clinical intervention claim.

Figure 2 presents the concept-summary model. Solid links identify evidence-supported relations among mitochondrial stress or dynamics imbalance, BAX/BAK pores, cytosolic mitochondrial RNA, DDX58/MDA5-MAVS signaling, and inflammatory SASP output. Dashed links mark hypotheses requiring direct same-sample testing: whether mitophagy and RNA quality control jointly restrain BAX/BAK-linked RNA release, and whether metabolic chromatin licensing quantitatively gates RNA-sensor-driven SASP output.

Figure 3 shows descriptive axis totals generated from the coded evidence table. Mitochondrial RNA sensor support had the highest certainty-weighted ordinal total, followed by mitochondrial dynamics linkage and metabolic licensing. Mitophagy support was lower because most included mitophagy evidence addressed mitochondrial DNA rather than mitochondrial RNA. These values map evidence distribution only and should not be read as pooled effect estimates.

Quantitative diagnostics strengthened the descriptive interpretation without converting the synthesis into an effect-size meta-analysis. Across 28.27 certainty-weighted ordinal units, mitochondrial RNA sensor support contributed 10.79 units (38.2%), dynamics contributed 8.02 units (28.4%), metabolic licensing contributed 5.91 units (20.9%), and mitophagy restraint contributed 3.55 units (12.6%). The two core axes, mitochondrial RNA sensing and mitochondrial dynamics, therefore carried 1.99-fold more weighted support than the boundary axes of mitophagy restraint and metabolic licensing. Direct senescence RNA records [1,2] accounted for 5.64 of 10.79 weighted units on the mitochondrial RNA axis (52.3%), which prevents the claim from resting mainly on cancer, retina, metabolic, or brain-aging extrapolation.

Leave-one-record-out leverage analysis gave the same ordering constraint. Removing any single included study left mitochondrial RNA sensor support as the highest weighted axis, with remaining totals ranging from 7.94 after removing Victorelli et al. 2025 to 10.79 after removing records that contributed no mitochondrial RNA score [2,5-7]. The closest stress test was removal of Victorelli et al. 2025, after which mitochondrial RNA support remained only 0.87 weighted units above dynamics support. This narrow margin identifies dependence on direct senescence RNA evidence while preserving the conclusion that the RNA-sensor axis is not an artifact of one record.

The sensitivity pattern was robust to removal of adjacent but indirect records. Excluding mitophagy and metabolic-permissiveness studies narrowed the model but did not erase the mitochondrial RNA-sensor core [1,2]. Excluding the dynamics study removed the strongest DRP1-linked bridge but left MFN1 and BAX/BAK evidence as partial morphology and pore constraints [1,2]. In contrast, excluding both direct senescence RNA

studies converted the paper into a mitochondrial DNA and general mitochondrial-stress synthesis, which would no longer answer the stated objective.

The evidence hierarchy therefore places mitochondrial RNA measurement and RNA-sensor perturbation above downstream inflammatory-gene movement. A result that changes IL6, CXCL chemokines, or interferon-stimulated genes without measuring mitochondrial RNA cannot by itself support an RNA-leakage claim. Conversely, a result that detects cytosolic mitochondrial RNA without testing DDX58, MDA5, MAVS, or downstream inflammatory output remains a localization observation rather than a completed mechanism.

Model-system stress testing produced a similar constraint. Fibroblast and cancer-cell studies provide the most direct perturbation experiments [1-3]. Mouse liver, retina, and brain-aging studies provide tissue relevance and aging context [2,5,8]. No included study combines every layer in one organismal aging model. The defensible synthesis is therefore a layered mechanism with clear tissue-transfer limits, not a general intervention framework.

Correction and update flags did not alter the main interpretation, but they affected confidence wording. The Nature minority-MOMP study and the mitophagy-aging study have PubMed-listed author corrections, so claims from those studies were used to define boundaries rather than to expand the mitochondrial RNA core [4,5]. The 2025 mitochondrial RNA leakage article and the 2026 citrate-acetyl-CoA article update earlier preprint records, so the published versions were treated as the citable sources [2,7]. No included PubMed record was flagged as withdrawn.

A denominator stress test was applied to avoid converting many endpoints from the same study into many independent studies. Each included record counted once in the evidence matrix even when it contained multiple cell lines, perturbations, omics assays, or animal readouts. This prevents the two most direct RNA papers from overwhelming the synthesis through internal endpoint multiplicity [1,2]. It also prevents the adjacent DNA and metabolism papers from being counted as direct RNA evidence when their strongest endpoints concerned cGAS-STING, cytoplasmic chromatin fragments, or histone acetylation [4-7].

Endpoint-class separation changed the apparent strength of the concept. The RNA-sensor axis remained strong because it required direct mitochondrial RNA or double-stranded RNA evidence plus RNA-sensing pathway perturbation [1-3,8]. The metabolic axis remained interpretive because citrate export and acetyl-CoA availability support SASP transcriptional execution rather than cytosolic RNA generation [7]. The mitophagy axis remained a restraint axis because the most direct aging evidence measured cytosolic mitochondrial DNA and cGAS-STING activation rather than mitochondrial RNA sensing [5].

The falsification threshold is explicit. The proposed control-layer model would be weakened if senescent cells showed inflammatory SASP reduction after DDX58, MDA5, or MAVS perturbation without detectable mitochondrial RNA movement; if mitochondrial RNA moved to the cytosol but failed to alter RNA-sensor signaling under matched conditions; or if BAX/BAK modulation altered inflammatory output entirely through mitochondrial DNA while mitochondrial RNA remained unchanged. These outcomes would favor a DNA-centered or chromatin-centered model over an RNA-leakage model.

The synthesis also remains compatible with parallel mechanisms. Mitochondrial DNA release, cytoplasmic chromatin fragments, mitochondrial metabolite supply, and mitochondrial RNA leakage can operate in the same cell state [4,6,7]. The practical value of separating them is experimental, not semantic: each layer predicts a different rescue experiment and a different failure mode. Same-sample measurement is therefore required before any single layer is described as dominant.

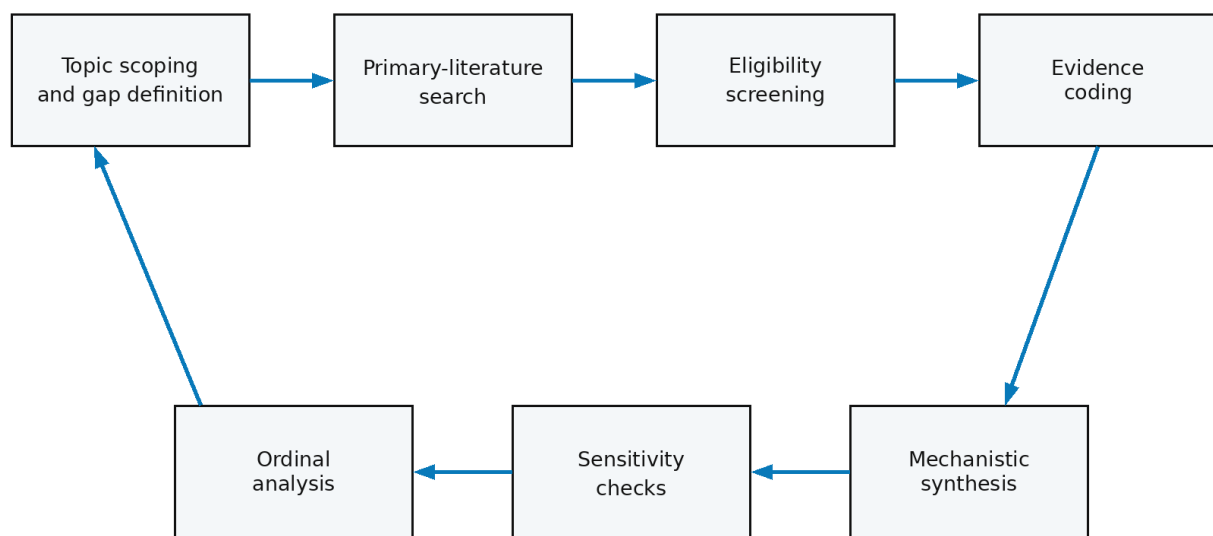


Figure 1. Analysis-process workflow. The public workflow proceeded from topic scoping and primary-literature search through eligibility screening, evidence coding, ordinal analysis, sensitivity checks, and synthesis. Connectors are continuous from source-box boundary to destination-box boundary and indicate executed workflow steps.

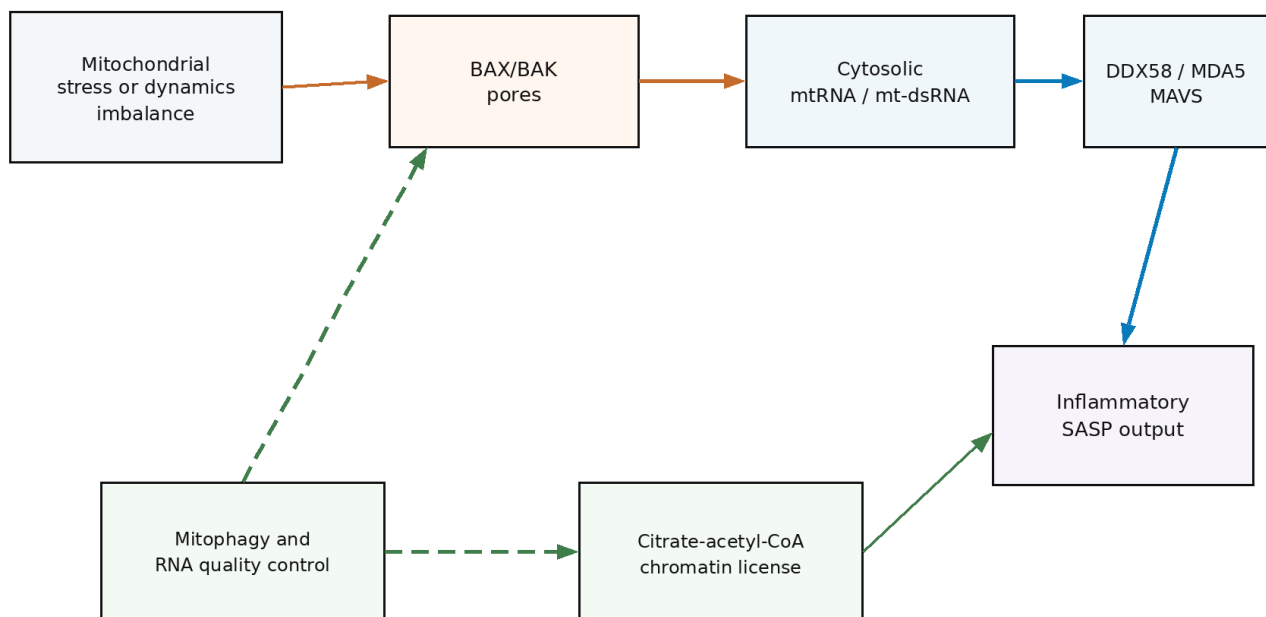


Figure 2. Conceptual summary of mitochondrial RNA leakage as a bounded inflammatory control layer. Solid connectors indicate evidence-supported links in included records; dashed connectors indicate hypotheses requiring same-sample testing. The diagram distinguishes mitochondrial RNA/DDX58-MDA5-MAVS evidence from mitophagy and metabolic-permissiveness boundaries.

Weighted ordinal support by evidence axis

Bars show certainty-weighted ordinal units; labels above bars show raw ordinal totals.

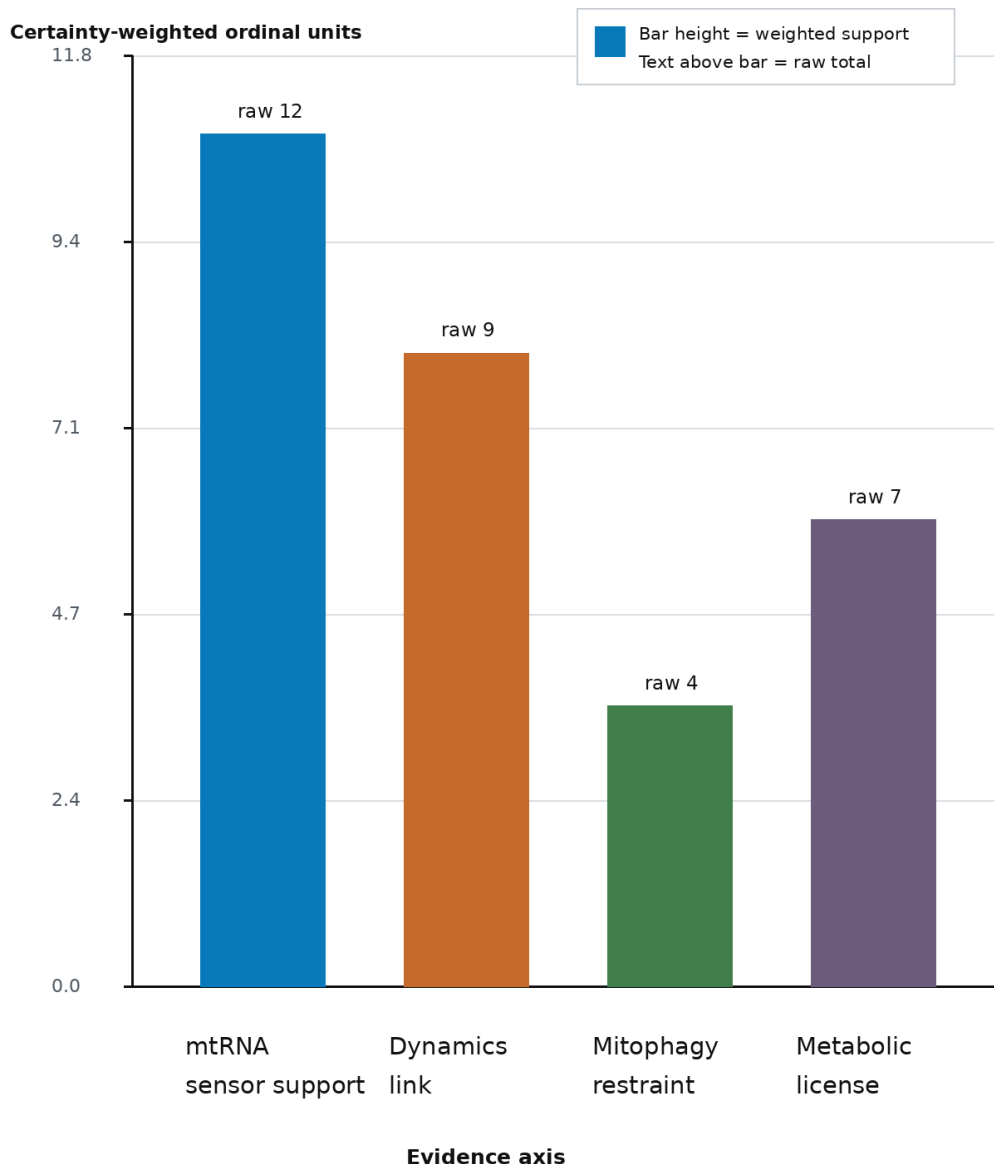


Figure 3. Evidence-axis support totals generated from the coded evidence table. Values are certainty-weighted ordinal synthesis totals from eight primary records and are descriptive evidence-distribution measures, not pooled effect sizes.

4 Discussion

The synthesis supports mitochondrial RNA leakage as a bounded inflammatory control layer in senescence. The core chain is most strongly supported when mitochondrial RNA or mitochondrial double-stranded RNA is measured in cytosolic fractions, RNA sensors are perturbed, MAVS signaling is reduced, and inflammatory SASP output changes without complete loss of senescence identity [1,2]. This separates mitochondrial RNA leakage from broad mitochondrial dysfunction and from DNA-centered cGAS-STING pathways.

The proposed boundary is mechanistic rather than therapeutic. BAX/BAK pores appear in both RNA and DNA release studies, but BAX/BAK biology also belongs to apoptosis and tissue homeostasis [2,4]. MFN1 and DRP1 evidence indicates that mitochondrial morphology can influence RNA release, yet fission-fusion balance is context-specific and may have opposite consequences across cell states [1,3]. A useful model must therefore avoid simple claims that fusion, fission, mitophagy, or RNA sensing is uniformly beneficial or harmful.

The strongest next experiment would combine senescence induction, mitochondrial morphology perturbation, BAX/BAK pore modulation, cytosolic mitochondrial RNA sequencing, DDX58/MDA5/MAVS readouts, mitochondrial DNA-cGAS-STING readouts, and chromatin acetylation at SASP loci in the same cell system. A second experiment should add mitophagy or mitochondrial RNA quality-control perturbations to test whether RNA leakage is prevented upstream or merely buffered downstream. These designs would discriminate trigger, pore, sensor, quality-control, and transcriptional-permissive layers.

5 Limitations

The evidence set is focused and mechanistic rather than systematic in the clinical-review sense. It includes heterogeneous cell types, tissues, perturbations, and endpoints. Several studies are not aging studies, even when they clarify mitochondrial RNA release or mitochondrial dynamics. Ordinal coding was used for transparent evidence mapping and cannot estimate effect size, heterogeneity, publication bias, or causal mediation.

Two included papers have PubMed-listed author corrections, and two published records update earlier preprints [2,4,5,7]. These flags do not invalidate the included findings, but they require citation caution. The synthesis also depends heavily on recent records; replication across independent laboratories and tissues remains incomplete.

6 Conclusions

Mitochondrial RNA leakage should be interpreted as a distinct but bounded inflammatory signal in senescence. The strongest supported claim is that cytosolic mitochondrial RNA or mitochondrial double-stranded RNA can engage DDX58, MDA5, and MAVS to shape inflammatory SASP output in tested systems. Current evidence does not justify broad anti-aging, cognitive, metabolic, or treatment claims. The next evidence threshold is same-sample separation of mitochondrial RNA release from mitochondrial DNA release, mitochondrial dynamics state, mitophagy capacity, and chromatin-metabolic licensing.

Declarations

Data and code availability. The evidence table, machine-readable data, analysis code, figures, and QA record accompany this repository deposit.

Ethics statement. This literature synthesis used no identifiable patient data and required no new human-participant or animal research.

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AI assistance. AI tools assisted literature synthesis, drafting, data visualization, and formatting. Gemini provided an independent critique. Andrew Friedl remains solely responsible for the content and is the sole author.

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