

Mitochondrial transfer evidence separates acute rescue from durable organelle replacement

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Abstract

Background: Mitochondrial transfer and mitochondrial transplantation are increasingly described as routes to repair bioenergetic injury, but delivery, uptake, targeting, acute rescue, and durable organelle replacement are often compressed into one claim. **Objective:** This working paper tested whether primary evidence supports a general durable-replacement interpretation or a narrower acute-rescue interpretation with explicit delivery-specificity gates. **Methods:** Primary studies were screened through 1 October 2026 using PubMed, PMC, publisher pages, and DOI records. Eligible records directly measured mitochondrial transfer, transplantation delivery, recipient uptake, bioenergetics, organ function, clinical feasibility, safety, or targeting specificity. Endpoints, claim maturity, and boundary conditions were coded before efficacy language was assigned. **Results:** Across nine primary studies, the most consistent support was for context-specific delivery, uptake, targeting advances, and acute rescue. Cell and animal studies showed uptake-linked macrophage phagocytosis, reduced cardiac infarct size, improved lung mechanics, targeted donor-mitochondria internalization and neuronal survival, and transcriptomic/proteomic movement after ischemia-reperfusion injury. Human studies supported feasibility and short-window safety in pediatric cardiac shock and phase 1 acute stroke settings, but neither design proves efficacy. Durability remained the main boundary: cardiomyocyte bioenergetic gains returned to baseline after an early increase, targeted delivery did not constitute a patient efficacy test, and myeloid-cell replacement evidence involved a broader cell-therapy intervention. The accompanying repository deposit provides source data, analysis code, figure source material, claim-verification records, and checksums for the PDF and editable DOCX. **Conclusions:** Current evidence supports mitochondrial transfer as a biologically plausible acute rescue or cell-mediated support mechanism in selected contexts. It does not yet support a general claim of durable organelle replacement.

Keywords: mitochondrial transplantation; mitochondrial transfer; ischemia-reperfusion injury; organ rescue; endpoint classification; translational evidence

1 Introduction

Mitochondrial transfer has moved from an unusual cell-biology observation to a translational proposal spanning acute ischemia-reperfusion injury, lung injury, pediatric cardiac shock, stroke, inherited mitochondrial disease, and engineered cell-type targeting. The appeal is straightforward: when injured tissue loses bioenergetic reserve, delivery of respiration-competent mitochondria or mitochondria-bearing cells might restore a local metabolic function that soluble drugs cannot replace.

The interpretation problem is equally straightforward. Evidence that mitochondria can be delivered, targeted, visualized, or transiently associated with recipient cells is not equivalent to evidence that organelles integrate durably, replicate, restore tissue-wide metabolism, and improve clinical outcomes. A rigorous synthesis therefore has to separate source viability, route, cell-type targeting, recipient uptake, bioenergetic biomarkers, functional rescue, safety, and durable-replacement claims.

This paper evaluates a bounded claim: mitochondrial transfer and transplantation currently support an acute rescue model more strongly than a durable organelle replacement model. The analysis intentionally uses primary studies rather than reviews for mechanistic and quantitative claims. Its main contribution is a claim-control framework that treats each endpoint as a claim license: delivery licenses delivery language, uptake licenses engagement language, short-window function licenses acute-rescue language, and persistent transferred material plus retained function would be required before durable-replacement language. This structure makes over-claiming falsifiable rather than rhetorical by asking what each experiment can prove, what alternative explanation remains plausible, and which missing measurement would be required before a stronger translational claim could be made.

2 Methods

Searches were performed on 1 October 2026 in PubMed, PMC, publisher pages, and DOI resolver records using combinations of mitochondrial transplantation, mitochondrial transfer, tunneling nanotubes, ischemia-reperfusion, cardiomyocyte, lung, pediatric ECMO, acute stroke, myeloid cell replacement, Friedreich ataxia, cell-type targeting, and MitoCatch. Search results were eligible when the record was a primary experimental or clinical study and directly measured mitochondrial delivery, transfer, uptake, targeting specificity, bioenergetics, organ function, safety, or disease-model rescue. Reviews, editorials, and protocol-only papers were used for orientation only and were not cited as evidence for mechanistic claims. Each included record required at least one public identifier or stable public landing page; the verification file records the DOI, PMID, and source URL used for every manuscript claim.

Each study was coded by endpoint class before interpretation. Endpoint classes were delivery, targeted delivery, target engagement, bioenergetic biomarker, omics biomarker, functional cell endpoint, functional organ endpoint, functional animal outcome, human feasibility, safety, boundary evidence, time-course evidence, dose-translation boundary, design boundary, and cell-therapy boundary. A claim was treated as functional only when the study measured a cell, organ, animal, or clinical function rather than delivery or biomarker movement alone. A claim was treated as durable only when persistence beyond an early post-delivery window was directly measured. Direction labels were assigned after endpoint coding, so a delivery, targeting, or uptake observation could not be promoted into an efficacy conclusion.

Each record was also assigned to a claim-maturity tier: mechanism or target engagement, preclinical functional rescue, human feasibility or safety, durability boundary, design boundary, or cell-therapy boundary. This tiering is not a numeric quality score. It is a guardrail that prevents a study from being used outside the

evidentiary domain it actually tests. Competing explanations were retained when they could account for the same endpoint, including paracrine stromal-cell effects, immune modulation, ischemic conditioning, short-window stress responses, clinical selection bias, and the broader effect of donor-cell engraftment in cell-replacement experiments.

No pooled effect size was estimated because the evidence combined cell co-culture, small-animal ischemia-reperfusion, targeted-delivery engineering, ex situ swine perfusion, retrospective pediatric cardiac surgery, phase 1 stroke feasibility, and a 2026 myeloid-cell replacement disease model. The synthesis instead used a translational evidence ladder: viable source material, delivery route, targeting specificity, uptake or target engagement, bioenergetic or omics biomarker, functional outcome, safety, and boundary evidence. Quantitative values were retained only when they came directly from the primary paper and were not converted across incomparable models. Four sensitivity checks were specified before writing Results: remove human studies, remove cell-only studies, remove the targeted-delivery engineering study, and ask whether any study directly contradicted durable-replacement interpretation. The accompanying data tables report endpoint-class counts, claim-maturity tiers, prespecified sensitivity outputs, and falsifier logic. The analysis code regenerates the manuscript source, figures, native table inputs, and machine-readable study data.

3 Results

3.1 Evidence synthesis

Mechanistic cell evidence established that transfer can be functional under defined contact conditions. Jackson et al. showed mitochondrial movement from mesenchymal stromal cells to macrophages through tunneling nanotubes, with increased macrophage oxidative phosphorylation and phagocytosis; blocking nanotubes abrogated the phagocytic effect [1]. This supports transfer-coupled cell rescue, but the mechanism is an immune-cell interaction rather than a proof of general tissue replacement.

Acute cardiac injury provided the strongest preclinical functional signal. In rabbits, autologous mitochondrial injection before reperfusion reduced infarct size from 34.2% to 7.9%, returned regional contraction more rapidly, increased oxygen-consumption and high-energy-phosphate measures, and did not show associated arrhythmia [2]. This is acute organ rescue evidence with safety readouts in that model. It does not resolve remote delivery, dose scaling, or chronic engraftment.

Lung ischemia-reperfusion evidence broadened the delivery question beyond direct myocardial injection. Vascular and nebulized delivery improved lung mechanics and reduced neutrophil infiltration, edema, and apoptosis in male mice after 24 hours, while cytokine and chemokine differences were not significant [3]. The denominator is one mouse lung injury model with a short endpoint window; the result supports route feasibility and organ rescue but not durable replacement.

Targeted-delivery engineering changed the design question. Ayupov et al. developed MitoCatch, a binder-based system for linking donor mitochondria to selected target-cell surfaces; the study reported targeted internalization, cytosol exposure, movement, fusion and fission in recipient cells, and survival rescue in damaged optic-nerve-atrophy neurons in vitro and injured neurons in mice [9]. This evidence directly addresses the specificity problem that weakens untargeted delivery claims. It remains a preclinical platform result, so it upgrades the delivery-design rung without proving durable patient replacement or clinical efficacy.

Durability was directly challenged in cardiomyocytes. Ali Pour et al. reported improved basal respiration and ATP production two days after mitochondrial transplantation, but the bioenergetic advantage returned to baseline at later time points [4]. This finding is a central falsifier for broad mitochondrial-enhancement language.

It does not negate acute rescue; instead, it confines the defensible claim to short-window stress contexts unless persistence is measured.

Human studies remain feasibility-forward. In a retrospective pediatric postcardiotomy ECMO cohort, successful ECMO separation occurred in 8 of 10 patients receiving mitochondrial transplantation and 4 of 14 controls, with ventricular strain and time to recovery favoring the transplantation group [5]. In phase 1 acute ischemic stroke during thrombectomy, viable autologous mitochondria were isolated in the acute setting and no significant adverse events were observed with endovascular delivery [7]. These records are important, but their designs do not establish efficacy.

Newer disease-model evidence supports cell-mediated mitochondrial transfer rather than isolated-organelle replacement. In a Friedreich ataxia mouse model, myeloid cell replacement was accompanied by donor-derived mitochondrial transfer to central nervous system cells and cardiomyocytes, increased oxidative-phosphorylation and ATP-synthesis signatures, improved survival and growth in both sexes, and several neurological and cardiac improvements in female mice [8]. The model provides a strong mechanistic bridge between cell replacement and mitochondrial transfer, while the conditioning, donor-cell engraftment, disease specificity, and sex-patterned functional signals limit translation to isolated mitochondrial transplantation.

Table 1 summarizes the coded evidence ladder. Figure 1 shows the executed workflow, and Figure 2 presents the claim-gate boundary: viable source material, route, targeting specificity, and uptake may license acute-rescue interpretation, but durable integration and clinical efficacy remain separate claims that require direct tests. The endpoint count table in the repository data also makes visible where the evidence is dense (mechanism, targeting, and safety) and where it remains sparse (durability, dose translation, and human functional efficacy).

The claim-maturity audit produced a more cautious interpretation than a simple positive/negative evidence table. Three studies primarily supported mechanism or target engagement [1,4,6], three supported preclinical functional rescue or delivery design [2,3,9], two supported human feasibility or safety rather than efficacy [5,7], and one supported a disease-specific cell-therapy bridge with mitochondrial transfer as part of a broader replacement intervention [8]. Only one study directly tested a durability-relevant time course and it weakened the durable-replacement interpretation [4]. Therefore, the synthesis treats durable replacement as a falsifiable future target rather than as a conclusion already earned by delivery, uptake, or short-window function.

3.2 Evidence-coded sensitivity analysis

Sensitivity check 1 removed the two human feasibility studies [5,7]. The synthesis still supported acute rescue through macrophage phagocytosis, rabbit cardiac ischemia-reperfusion, mouse lung injury, cardiomyocyte bioenergetics, swine perfusion omics, targeted-delivery neuronal rescue, and myeloid replacement disease-model evidence [1-4,6,8,9]. Therefore, the biological plausibility claim did not depend on clinical records.

Sensitivity check 2 removed cell-only evidence [1,4]. The remaining organ, animal, engineering-platform, and human studies still supported context-specific delivery and acute rescue, but the mechanistic certainty around spontaneous recipient-cell transfer and durability became weaker [2,3,5-9]. Therefore, mechanistic language in this manuscript is bounded by model system rather than generalized across tissues.

Sensitivity check 3 removed the targeted-delivery engineering study [9]. The acute-rescue conclusion still rested on transfer-coupled phagocytosis, organ injury rescue, feasibility, omics movement, and disease-model cell replacement [1-8], but the manuscript lost its strongest support for a concrete delivery-specificity solution.

Therefore, targeting specificity is presented as an emerging design advance rather than an assumption for the whole field.

Sensitivity check 4 treated the two-day cardiomyocyte study as a falsifier for durable replacement [4]. Because early bioenergetic gains returned to baseline, durable-replacement wording was rejected unless a study directly measured persistent transferred mitochondria and persistent functional rescue. This rule prevented feasibility, targeting, or biomarker-only findings from being written as clinical efficacy.

Across the four checks, the acute-rescue conclusion survived removal of human studies, removal of cell-only studies, and removal of targeted-delivery engineering, but the breadth of the claim changed. Removing human records eliminated any basis for patient-facing efficacy language. Removing cell-only studies weakened mechanistic certainty about recipient-cell uptake. Removing MitoCatch narrowed the practical delivery-design argument. Treating the cardiomyocyte time course as a falsifier converted durable replacement from a conclusion into a future test condition.

4 Discussion

The evidence supports a restrained model in which mitochondrial transfer is most credible as an acute or context-gated rescue mechanism. The model has three linked steps. First, mitochondria or mitochondria-bearing cells must remain respiration competent during preparation and delivery. Second, recipient cells must acquire or respond to the transferred organelles. Third, functional benefit must be measured in the relevant cell, organ, animal, or patient context. Studies that stop at delivery or uptake occupy an earlier rung of the ladder.

The strongest functional evidence is not a single universal effect. It is a pattern across injury and targeting models: local cardiac injection before reperfusion, vascular or nebulized lung delivery, targeted binder-mediated delivery to selected cell types, ex situ swine perfusion, and myeloid-cell replacement in a mitochondrial disease model each move different endpoints [2,3,6,8,9]. That pattern is encouraging for acute rescue biology, but it also argues against one-size-fits-all translation. Route, targeting method, timing, tissue, source mitochondria, immune state, and disease context appear central to interpretation.

Competing explanations remain live and should shape the next experiments. In stromal-cell and myeloid-cell systems, mitochondrial movement may act alongside paracrine signaling, donor-cell engraftment, macrophage or microglial replacement, and injury-environment remodeling [1,8]. In ischemia-reperfusion models, rapid benefit may reflect acute metabolic buffering, altered inflammation, or improved stress tolerance rather than stable organelle replacement [2,3,6]. In clinical records, feasibility and safety signals remain vulnerable to selection, timing, procedural, and comparator limitations [5,7]. These alternatives do not erase the transfer signal; they define the control arms and persistence assays required before stronger causal language is justified.

Figure 2 should be read as a claim-control diagram, not as a treatment recommendation. Solid links indicate licensed claim steps: viable source, delivery route, targeting specificity, uptake, and selected acute rescue. Dashed links identify unlicensed inference jumps from uptake to durable integration and from feasibility or preclinical targeting to clinical efficacy. The most useful next experiments would measure persistence of transferred mitochondria, nuclear-mitochondrial compatibility, dose-response, immune activation, targeting specificity in diseased tissue, and blinded functional outcomes in the same design.

The practical implication is a three-threshold evidence standard. Acute rescue can be tested with short-window functional endpoints that are matched to injury timing and delivery route. Targeted organelle therapy requires proof that the intended cell type, not

Table 1. Primary-study evidence matrix for mitochondrial transfer and transplantation claim boundaries.

Study	Model and perturbation	Key finding	Interpretive limitation
[1]	Human mesenchymal stromal cells, macrophage co-culture, and mouse ARDS models; Tunneling-nanotube mitochondrial transfer from MSC to macrophages	MSC-to-macrophage mitochondrial transfer was visualized and linked to increased macrophage oxidative phosphorylation and phagocytosis; cytochalasin B blockade of nanotubes abrogated the phagocytic effect.	The rescue was immune-cell and injury-model specific; it does not show that transplanted organelles become durable tissue-wide replacements.
[2]	Rabbit regional cardiac ischemia-reperfusion with autologous mitochondrial injection; Direct myocardial injection before reperfusion	Autologous mitochondria reduced infarct size from 34.2% to 7.9%, improved return of regional contraction, increased oxygen-consumption and high-energy-phosphate measures, and did not show associated arrhythmia.	The model used immediate local injection in acute injury; the result does not establish remote delivery, chronic engraftment, or disease-modifying replacement.
[3]	Male C57BL/6J mouse lung ischemia-reperfusion injury; Vascular or nebulized mitochondrial delivery at reperfusion	Both delivery routes improved lung mechanics and reduced neutrophil infiltration, interstitial edema, and apoptosis at 24 hours, while cytokine and chemokine differences were not significant.	The endpoint window was short and limited to male mice; route feasibility and durability in human lung transplantation remain unproved.
[4]	Cardiomyocyte mitochondrial transplantation with Seahorse bioenergetics up to 28 days; Non-autologous skeletal-muscle mitochondria added to cardiomyocytes	Basal respiration and ATP production improved at 2 days, but the bioenergetic advantage returned to baseline at later time points.	The transient signal supports acute stress applications more than stable organelle replacement or long-term mitochondrial enhancement.
[5]	Single-center retrospective pediatric postcardiotomy ECMO cohort; Revascularization plus autologous mitochondrial transplantation versus revascularization alone	Successful ECMO separation occurred in 8 of 10 mitochondrial-transplantation patients versus 4 of 14 controls; ventricular strain and time to recovery also favored the transplantation group.	The study was small, retrospective, and confounded by clinical selection; it supports feasibility and association rather than efficacy proof.
[6]	Ex situ perfused neonatal swine hearts donated after circulatory death; Mitochondrial transplantation during perfusion	Transcriptomic and proteomic profiles shifted toward non-ischemic patterns, with ATP binding, voltage-gated potassium-channel activity, ribosomal RNA biogenesis, ribosome biogenesis, and apoptosis pathways implicated.	The work strengthens pathway plausibility in a large-animal perfusion context but still calls for human in vivo replication.
[7]	Phase 1 acute ischemic stroke during mechanical thrombectomy; Endovascular autologous mitochondrial transplantation during reperfusion therapy	Viable autologous mitochondria were isolated in the acute setting; no significant adverse events were observed with endovascular delivery and safety was comparable to matched controls.	The trial primarily addresses feasibility and safety; efficacy, patient selection, dose, and time-window effects remain open.
[8]	Friedreich ataxia mouse model with myeloid cell replacement and cell co-culture; Microglia and macrophage replacement enabling intercellular mitochondrial transfer	Donor-derived mitochondria transferred to central nervous system cells and cardiomyocytes, oxidative-phosphorylation and ATP-synthesis signatures increased, survival and growth improved in both sexes, and several neurological and cardiac outcomes improved in female mice.	The intervention was cell replacement with conditioning rather than isolated mitochondrial transplantation; sex-specific functional signals and animal-model dependence limit direct clinical translation.
[9]	MitoCatch targeted mitochondrial transplantation in human and mouse cell systems, retinal cell types, neurons, and in vivo mouse neuronal injury; Protein-binder systems linking donor mitochondria to selected target-cell surfaces	Targeted donor mitochondria were internalized, exposed to cytosol, moved, underwent fusion and fission in recipient cells, and promoted survival of damaged optic-nerve-atrophy neurons in vitro and injured neurons in mice.	The study materially improves the delivery-specificity design space, but it is not a clinical efficacy trial and does not by itself prove durable replacement in patients.

Executed evidence workflow

Solid connectors indicate source-preserving workflow; dashed connector indicates sensitivity feedback.

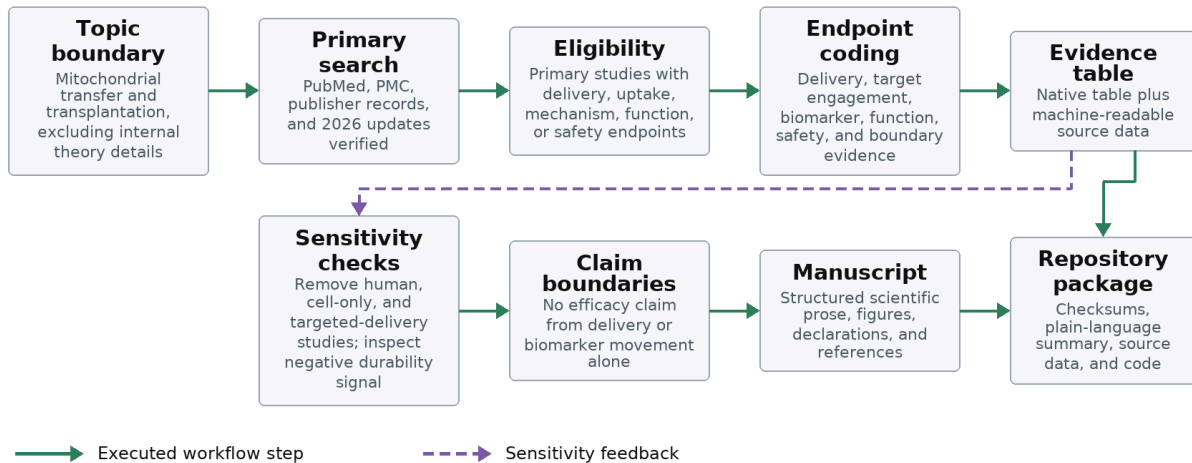


Figure 1. Analysis process. The workflow moved from topic boundary and primary-source search through eligibility screening, endpoint coding, evidence-table construction, sensitivity checks, claim-boundary rules, synthesis, and reproducible bundle assembly. Solid connectors indicate executed workflow steps, and the dashed connector indicates sensitivity feedback.

Claim gates: delivery specificity, rescue, and boundaries

Solid links indicate licensed claims; dashed links mark inference jumps that still need direct tests.

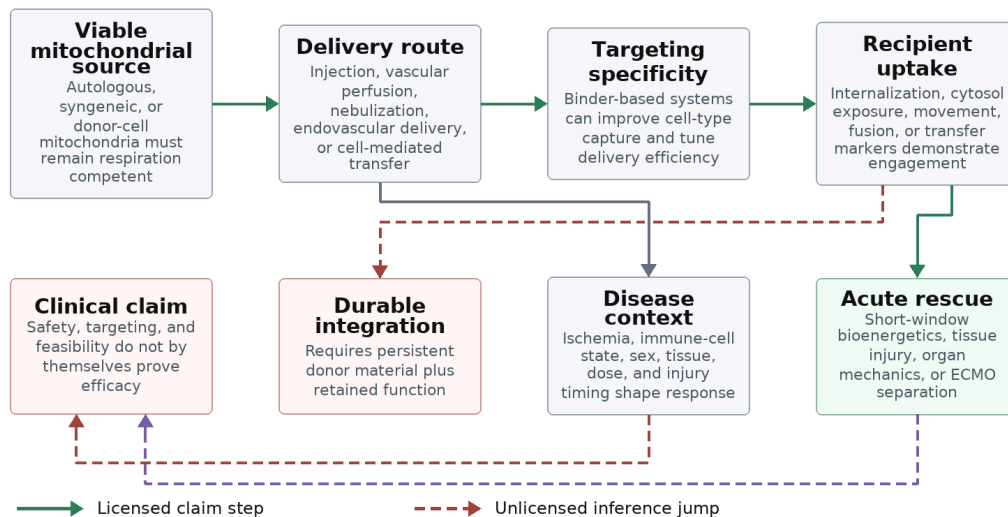


Figure 2. Concept summary. The conceptual map separates respiration-competent mitochondrial source material, delivery route, targeting specificity, recipient uptake, acute rescue, durable integration, disease context, and clinical claim boundaries. Solid connectors indicate licensed claim steps, whereas dashed connectors identify unlicensed inference jumps that require direct persistence or efficacy tests.

merely the tissue compartment, captures and uses the donor mitochondria. Durable replacement requires a harder evidentiary package: persistence of transferred mitochondrial material, retained bioenergetic contribution, absence of maladaptive immune or mitophagy responses, and functional benefit after the acute injury window has closed.

5 Limitations

This working paper is a structured evidence synthesis rather than a systematic review or meta-analysis. The search was current to 1 October 2026 but may miss unpublished negative studies, conference reports, or non-indexed datasets. Heterogeneity across cell systems, animal species, organs, delivery routes, targeting platforms, and clinical designs prevents a pooled estimate. Several important studies come from overlapping research groups, so independent replication remains essential. The manuscript does not evaluate manufacturing, regulatory, or commercial readiness. Evidence grading was intentionally conservative: small clinical feasibility records were not treated as efficacy trials, targeted-delivery engineering was not treated as patient efficacy, and cell-replacement disease-model evidence was not treated as

proof that isolated organelle transplantation would have the same effect.

6 Conclusions

Mitochondrial transfer and transplantation are supported by primary evidence as biologically plausible, context-specific rescue mechanisms. The clearest support is for delivery, targeting advances, uptake, short-window bioenergetic movement, and acute functional improvement in selected experimental systems. Durable organelle replacement and broad clinical efficacy remain unproved and should be stated as hypotheses until directly measured.

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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