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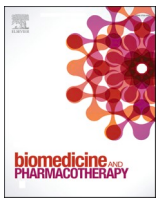

Mitochondrial stress bridge: Could muscle-derived extracellular vesicles be the missing link between sarcopenia, insulin resistance, and chemotherapy-induced cardiotoxicity?

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ABSTRACT

Sarcopenia is currently considered a systemic condition that goes beyond muscle atrophy to include multi-functional metabolic and cardiovascular dysfunction. The mediators between skeletal muscle loss and entire body insulin resistance and increased vulnerability to cardiotoxicity caused by chemotherapy are not clear. We hypothesise that mitochondrial-enriched, muscle-secreted extracellular vesicles (EVs) of mtDNA/mitoproteins, stress-regulated microRNAs (miR-1/133/206; miR-29 family), and ROS-modified damage-associated molecular patterns (DAMPs) are a mitochondrial stress bridge that secretes danger signals from sarcopenic muscle to the liver/adipose and heart. EV cargo mechanistically impairs insulin signaling (IRS-1 → PI3K-AKT → GLUT4) and cardiomyocyte pre-injury (loss of Δpsm, antioxidant repression, apoptosis), increasing the toxicity of doxorubicin. Should this framework be valid, it describes the clustering of sarcopenic patients with metabolic dysfunction and disproportional cardiotoxic incidents throughout cancer therapy and places circulating EV cargo as an indicator of outcomes and therapeutic interventions.

1. Introduction

Progressive loss of skeletal muscle mass and strength Sarcopenia has systemic effects on metabolism, immunity and cardiovascular health as shown in Fig. 1 and Fig. 2 [1,2]. Later onset of insulin resistance (IR) and exposure to cardiotoxicity induced by chemotherapy are some of the severe complications that are associated with mitochondrial dysfunction. EVs (exosomes and microvesicles) released by muscle fibres and satellite cells can reprogram tissues distally in response to their cargo (proteins, miRNAs, metabolites, and mitochondria-derived components) [3–5]. Ageing and sarcopenia cause a shift of EV cargo towards pro-inflammatory/mitochondrial-distress [5,6].

Principle: EV cargo remodelling in the case of sarcopenia is a result of chronic mitochondrial stress in the muscle. These EVs enter the bloodstream, where they suppress insulin receptors in metabolic tissues and precondition cardiomyocytes to withstand a lower injury threshold after chemotherapy (e.g., doxorubicin) is administered.

2. The hypothesis

2.1. Mitochondrial EV cargo and innate immune activation

Mechanistically, sarcopenic skeletal muscle acquires extracellular vesicles (EVs) enriched with pathogenic mitochondrial components, including fragmented mtDNA, cardiolipin, electron transport chain (ETC) subunits, and mitochondrial peptides that activate innate immune sensors like TLR9, cGAS STING, and inflammasomes. These components lead to sterile inflammation, suppression of insulin signaling in hepatic and adipose tissues, and promotion of three distinct effects [5–11].

2.2. MicroRNA-mediated reprogramming

At the same time, the muscle-derived microRNAs have a specific posttranscriptional effect: the miR-29 family suppresses IRS-1 and PI3K-AKT signaling to suppress GLUT4 trafficking, whereas miR-1/133/206 disrupts cardiac calcium homeostasis and cardiomyocyte survival

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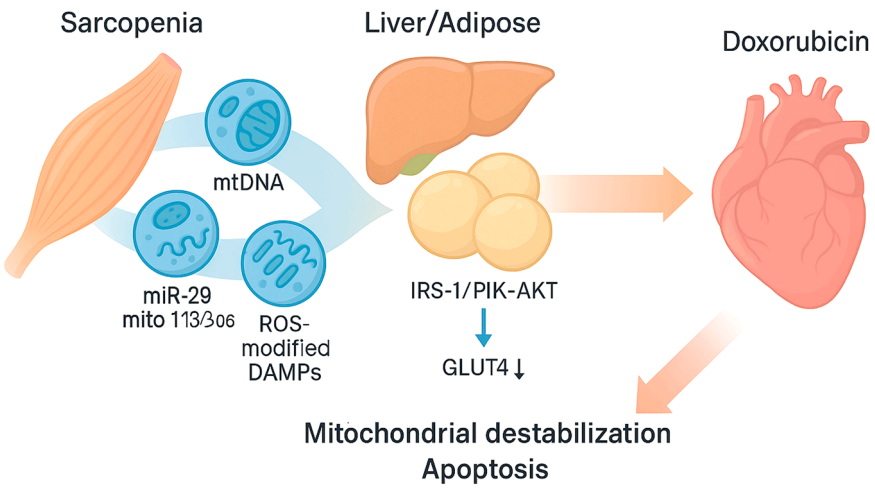

Fig. 1. Muscle-derived EVs act as a mitochondrial stress bridge linking sarcopenia to systemic insulin resistance and chemotherapy-induced cardiotoxicity.

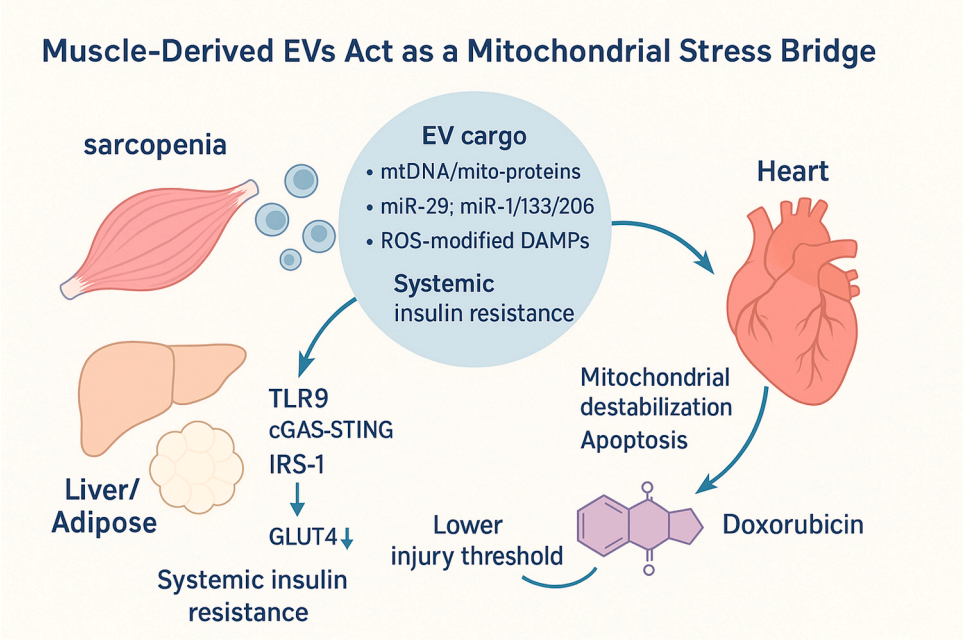

Fig. 2. Muscle-derived EVs Act as a Mitochondrial Stress Bridge.

pathways, inducing mitochondrial instability and apoptosis [6,10,12,13].

2.3. ROS/damp and oxidative amplification

In addition to these processes, the oscillative stress is increased and antioxidant defences decrease throughout tissues by complementing these processes through ROS-modified proteins and other damage-

Table 1
Mechanistic bridge: muscle-derived EV cargo → pathways → outcomes.

EV cargo (class/ examples)	Primary targets	Mechanism/pathways	Molecular effects	Phenotypic outcome	Refs.
mtDNA, cardiolipin, mito-proteins	Hepatocytes, adipocytes, β-cells	TLR9; cGAS–STING; inflammasome	Inflammation ↑; insulin signaling ↓	Insulin resistance; β-cell stress	[5,9,11]
miR-29 family	Liver/adipose	IRS-1/PI3K–AKT targeting	GLUT4 ↓; pAKT (± insulin) ↓	Insulin resistance	[10]
miR-1/miR-133/miR-206	Cardiomyocytes	Pro-apoptotic & Ca^{2+} handling genes; survival pathways ↓	Mito stability ↓; apoptosis ↑	↑ Chemo cardiotoxicity	[6], [13]
ROS-modified proteins/ DAMPs	Systemic (liver/pancreas/ heart)	TLRs; oxidative stress amplification	Antioxidant defenses ↓	IR + chemo sensitivity ↑	[2], [9]
ETC subunits, mito-peptides	Cardiac & metabolic tissues	OXPHOS imbalance; Δψm loss	ATP ↓; ROS ↑	IR + cardiotoxicity ↑	[2], [9]

Table 2
Experiments to test the hypothesis.

Tier & aim	Model/system	Intervention/arms	Primary endpoints	Assays	Expected result	Notes/controls & falsifiers
Clinical profiling	Humans: sarcopenia vs matched (± chemotherapy)	Stratify by chemo exposure; isolate plasma EVs	EV cargo panel; HOMA-IR; echo/GLS; troponin	miRNA-seq; mtDNA qPCR; proteomics; NTA	Sarcopenia → EV mtDNA↑, miR-133/206↑; correlate with IR & ↓GLS	Age/sex/BMI matched; fasting AM draws; MISEV controls [7,8,14]. **Falsifier:** no cargo differences or no phenotype correlation.
In vitro metabolic	Primary hepatocytes/ adipocytes	EVs sarcopenia vs control; EV-depleted plasma; ± anti-miR-29; ± TLR9 block	pAKT (± insulin); GLUT4; glucose uptake	Western/qPCR; 2-NBDG; Seahorse	EVs blunt AKT; ↓GLUT4; ↓uptake; rescue by anti-miR-29/ TLR9 block	RNase/proteinase controls; uptake inhibitors [9–11]. **Falsifier:** no effect vs control EVs; no rescue.
In vitro cardiac	iPSC-CMs/NRVMs	EVs ± doxorubicin (graded); rescues: antioxidants, TLR9 block, anti-miRs	Δψm, ROS, apoptosis, contractility; LC_{50}	JC-1/TMRE; MitoSOX; TUNEL/caspase; video-contractility	EVs lower doxo LC_{50}; ↑apoptosis/ROS; Δψm loss; rescue reverses	Standardized doxo exposure [12,13]. **Falsifier:** no LC_{50} shift; no rescue.
In vivo	Aged/sarcopenic mice	GW4869 or Rab27a KD; ± doxorubicin	Insulin tolerance; echo/ GLS; troponin; mito assays	GTT/ITT; speckle echo; respirometry; histology	EV inhibition → ↑ insulin sensitivity & ↓ cardiotoxicity	Track EV biodistribution; toxicity screens [11,14]. **Falsifier:** no benefit despite EV reduction.

associated molecular patterns (DAMPs) [2,9].

2.4. Holistic systems behavior, insulin resistance and cardiac priming

Collectively, these EV-induced molecular changes create a pathophysiological environment in which insulin resistance occurs because of innate immune activation and direct damage to insulin signaling; cardiotoxicity is enhanced by mitochondrial priming [12–14].

2.5. Doxorubicin synergy interacts with chemotherapy

In these circumstances, induction of doxorubicin, associated with interference of Top2B and oxidative phosphorylation, triggers early mitochondrial membrane potential (-m) failure and apoptosis and thus enhances chemotherapy-related heart damage [12–14].

Table 1 predicts Table 2: Activation of innate immune sensing (TLR9/cGAS-STING) predicts select readouts: increased circulating and EV-associated mtDNA by qPCR, increased p-TBK1 and interferon-stimulated gene transcripts, increased IL-6/TNF, and a functional impairment of insulin signaling demonstrated through aborted insulin-stimulated phosphorylation of AKT and reduced 2-NBDG glucose uptake. Regulatory miRNA transfer (miR-29 and miR-1/133/206) should cause the downregulation of insulin (pAKT/GLUT4) and mitochondrial destabilisation (lower mitochondrial membrane potential, Δψm, and loss of contractility), which should be repaired by anti-miR treatment. Lastly, the mitopriming condition predicts increased cardiotoxic sensitivity: in the cardiomyocyte, the doxorubicin LC50 moves to the left, mitochondrial ROS (MitoSOX) is enhanced, and apoptotic markers heighten modifications that must be suppressed by TLR9 pathway restraints, antioxidants, or target anti-miRs.

3. Discussion

3.1. Rationale and alternatives

3.1.1. Why we expect these results

Muscle is a bona fide endocrine organ; EV secretion and uptake are robust in exercise, ageing, and disease states [7–9]. Sarcopenia heightens mitochondrial damage, generating EV cargo (mtDNA/mito--proteins/ROS-modified molecules) that is well-positioned to trigger innate sensors (TLR9, cGAS–STING) and repress insulin signaling. Parallelly, cardiac-tropic miRNAs (miR-1/133/206) are abundant in ageing muscle EVs and can target survival/Ca^{2+} pathways in cardiomyocytes, predisposing them to doxorubicin injury [6,13].

3.1.2. What if we're wrong?

3.1.2.1. Falsifiability and boundary conditions.

- **No differential EV cargo**: If sarcopenic vs control EVs do not differ in mtDNA/miRs/proteome (after MISEV-compliant isolation [14]) or differences don't correlate with IR or GLS, the bridge weakens.
- **Decoupled function**: If sarcopenic EVs fail to blunt insulin signaling (pAKT, GLUT4, uptake) or fail to sensitise cardiomyocytes to doxorubicin (no LC_{50} shift, no Δψm loss), the causal link is unlikely.
- **Rescue fails**: If **anti-miR-29** or **TLR9 blockade** fails to restore signaling/mitochondrial stability, then the proposed mediators are not principal.
- **Confounders**: Systemic inflammation, cachexia, or chemotherapy pharmacokinetics could independently explain IR/cardiotoxicity; controlling for these is critical (see Notes/controls in Table 2).

4. Testing the hypothesis

4.1. Clinical profiling (discovery and validation)

4.1.1. Population

The population under study consists of elderly patients with sarcopenia. Age/sex/BMI-matched controls. The patients are categorised based on their exposure to and histories of chemotherapy.

4.1.2. EV methods

Isolation Plasma EV isolation (size-exclusion + density step; detergent controls). The process includes NTA, TEM, and immunocapture of CD9/CD63/CD81.

4.1.3. Cargo assays

The mitochondrial genome undergoes qPCR analysis. The study also utilised miRNA-seq for miR-29 (miR-1/133/206). We use specific proteomics to identify the mitochondrial signature. Cytokine profiling.

4.1.4. Clinical phenotypes

Metabolism: HOMA-IR; OGTT/IKK (where available). Cardiac: echocardiography (GLS); troponin/BNP.

4.1.5. Expectation

Sarcopenia is associated with elevated EV mtDNA and miR-133/206 levels. Insulin resistance and reduced GLS have close relationships with sarcopenia.

4.1.6. Falsifier

There are no significant differences in the EV cargo. Alternatively, it may not be associated with any clinical phenotypes.

4.2. In vitro-metabolic (Causality)

4.2.1. Models

The models include adipocytes and primary human hepatocytes.

4.2.2. Arms

Sarcopenic EVs were compared to control EVs. Inhibitor: ± anti-miR-29. ± TLR9 agonist.

4.2.3. Readouts

pAKT (± insulin). GLUT4 localisation/abundance. 2-NBDG uptake. Seahorse OCR/ECAR.

4.2.4. Expectation

Sarcopenic EVs blunt AKT. GLUT4 and glucose uptake fall. Anti-miR-29 or TLR9 inhibition rescues.

4.2.5. Falsifier

There was no significant difference compared to the control EVs. This condition could potentially be improved by using specific inhibitors.

4.3. In vitro - cardiac (priming and synergy)

4.3.1. Models

The models used were human iPSC-cardiomyocytes and NRVMs.

4.3.2. Arms

The EVs were treated with graded doxorubicin. Rescues: antioxidants (e.g., NAC), TLR9 block, anti-miR-1/133/206.

4.3.3. Readouts

Δψm (TMRE/JC-1). MitoSOX. TUNEL/caspase. Video-based contractility. Doxorubicin LC_{50}.

4.3.4. Expectation

EVs lower LC_{50}. ROS and apoptosis rise. Δψm decreases. The effects are reversed through rescues.

4.3.5. Falsifier

There is no shift in the LC value. The model refutes the existence of mitochondrial instability.

4.4. In vivo mechanism and translatability

4.4.1. Models

The models are based on old or sarcopenic mice, which may be affected by denervation or ageing.

4.4.2. Interventions

The mice undergo GW4869 or Rab27a knockdown. Challenged with doxorubicin.

4.4.3. Readouts

GTT/ITT. Speckle-tracking GLS. Troponin. Tissue respirometry. Histology. The process involves EV biodistribution (DiR). Toxicity screens.

4.4.4. Expectation

EV inhibition enhances insulin sensitivity. EV inhibition decreases the doxorubicin cardiotoxicity.

4.4.5. Falsifier

There is no metabolic or cardiac advantage, even though EV is suppressed.

5. Clinical implications

- **Biomarkers:** Circulating EV **mtDNA**, **miR-133/206**, and mito-proteome signatures to stratify patients for IR and cardiotoxic risk.
- **Therapeutics:** EV-directed strategies (biogenesis inhibition, uptake blockade, anti-miR-29/-1/-133/-206, TLR9 antagonism) to enhance chemotherapy safety in frail patients.
- **Precision medicine:** Integrate EV analytics into oncology/geriatrics workflows to tailor regimens by metabolic/cardiac vulnerability.

6. Limitations & future work

EV heterogeneity remains a challenge; standardized isolation/characterization (MISEV) is essential [14]. Longitudinal human studies must test whether EV signatures precede IR/cardiotoxicity (causal) or merely reflect disease burden (epiphenomenal). Confounders (systemic inflammation, comorbidities, activity/nutrition) require rigorous control.

7. Conclusion

We propose that muscle-derived EVs constitute a mitochondrial stress bridge connecting sarcopenia to systemic insulin resistance and chemotherapy-induced cardiotoxicity. By exporting mitochondrial distress signals and regulatory miRNAs, sarcopenic muscle may drive metabolic impairment and cardiac vulnerability. Validating—and potentially refuting—this model will refine our systemic view of sarcopenia and open biomarker-guided, EV-targeted interventions.

CRediT authorship contribution statement

Ugwu Chinyere Nneoma: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology. **Mariam Basajja:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Ugwu Okechukwu Paul-**

Chima: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Conceptualization. **C. Ogenyi Fabian:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology. **Okon Michael Ben:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

[1] J. Dupont, Revised sarcopenia consensus: are we missing the preclinical stage? Online comment on, Age Ageing 48 (1) (2018) 1 (-.).
[2] S.H. Hong, K.M. Choi, Sarcopenic obesity, insulin resistance, and their implications in cardiovascular and metabolic consequences, Int. J. Mol. Sci. 21 (2) (2020) 494.
[3] S. Rome, A. Forterre, M.L. Mizgier, K. Bouzakri, Skeletal muscle-released extracellular vesicles: state of the art, Front. Physiol. 10 (2019) 929.
[4] S. Watanabe, Y. Sudo, T. Makino, S. Kimura, K. Tomita, M. Noguchi, H. Sakurai, M. Shimizu, Y. Takahashi, R. Sato, Y. Yamauchi, Skeletal muscle releases extracellular vesicles with distinct protein and microRNA signatures that function in the muscle microenvironment, PNAS Nexus 1 (4) (2022) pgac173.
[5] A. Picca, R. Beli, R. Calvani, H.J. Coelho-Júnior, F. Landi, R. Bernabei, C. Bucci, F. Guerra, E. Marzetti, Older adults with physical frailty and sarcopenia show increased levels of circulating small extracellular vesicles with a specific mitochondrial signature, Cells 9 (4) (2020) 973.
[6] C. Mytidou, A. Koutsoulidou, M. Zachariou, M. Prokopi, K. Kapnisis, G.M. Spyrou, A. Anayiotos, L.A. Phylactou, Age-related exosomal and endogenous expression patterns of miR-1, miR-133a, miR-133b, and miR-206 in skeletal muscles, Front. Physiol. 12 (2021) 708278.
[7] J. Jia, L. Wang, Y. Zhou, P. Zhang, X. Chen, Muscle-derived extracellular vesicles mediate crosstalk between skeletal muscle and other organs, Front. Physiol. 15 (2025) 1501957.
[8] S. Ma, X. Xing, H. Huang, X. Gao, X. Xu, J. Yang, C. Liao, X. Zhang, J. Liu, W. Tian, L. Liao, Skeletal muscle-derived extracellular vesicles transport glycolytic enzymes to mediate muscle-to-bone crosstalk, Cell Metab. 35 (11) (2023) 2028–2043.
[9] P. D'Acunzo, R. Pérez-González, Y. Kim, T. Hargash, C. Miller, M.J. Alldred, H. Erdjument-Bromage, S.C. Penikalapati, M. Pawlik, M. Saito, M. Saito, Mitovesicles are a novel population of extracellular vesicles of mitochondrial origin altered in Down syndrome, Sci. Adv. 7 (2021) ([Internet]).
[10] L.T. Dalgaard, A.E. Sørensen, A.A. Hardikar, M.V. Joglekar, The microRNA-29 family: role in metabolism and metabolic disease, Am. J. Physiol. Cell Physiol. 323 (2) (2022) C367–C377.
[11] I. Garcia-Martinez, N. Santoro, Y. Chen, R. Hoque, X. Ouyang, S. Caprio, M. J. Shlomchik, R.L. Coffman, A. Candia, W.Z. Mehal, Hepatocyte mitochondrial DNA drives nonalcoholic steatohepatitis by activation of TLR9, J. Clin. Investig. 126 (3) (2016) 859–864.
[12] S. Zhang, X. Liu, T. Bawa-Khalfe, L.S. Lu, Y.L. Lyu, L.F. Liu, E.T. Yeh, Identification of the molecular basis of doxorubicin-induced cardiotoxicity, Nat. Med. 18 (11) (2012) 1639–1642.
[13] C. Tian, Y. Yang, B. Bai, S. Wang, M. Liu, R.C. Sun, T. Yu, X.M. Chu, Potential of exosomes as diagnostic biomarkers and therapeutic carriers for doxorubicin-induced cardiotoxicity, Int. J. Biol. Sci. 17 (5) (2021) 1328.
[14] C. Théry, K.W. Witwer, E. Aikawa, M.J. Alcaraz, J.D. Anderson, R. Andriantsitohaina, A. Antoniou, T. Arab, F. Archer, G.K. Atkin-Smith, D.C. Ayre, Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines, J. Extracell. Vesicles 7 (1) (2018) 1535750.