

## Opinion



# Mitochondrial-derived vesicles: Rethinking a quality control pathway as a therapeutic opportunity

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Mitochondria have long been defined by their role in energy production, yet their capacity to communicate - both within the cell and across tissues - is now recognized as equally fundamental. Far more than mere cellular power plants, they function as dynamic signalling organelles, and their dysfunction underlies a broad spectrum of human diseases, from neurodegeneration to cancer. Among the mechanisms through which mitochondria maintain their own integrity and signal to their environment, mitochondrial-derived vesicles (MDVs) occupy a unique position. First identified in 2008, MDVs are 70–150 nm single- or double-membrane vesicles that bud directly from the mitochondrial surface, selectively incorporating specific protein cargo such as outer membrane translocases, metabolic enzymes, oxidized components, in a process independent of the mitochondrial fission machinery and temporally distinct from mitophagy.<sup>1,2</sup> This selectivity is not incidental: it reflects a precisely regulated quality control decision that allows cells to excise damaged mitochondrial material without committing to wholesale organelle degradation. Under mild stress, MDV formation peaks within 1–3 hours, well before mitophagy, which is typically activated at 12–24 hours, is invoked, establishing these vesicles as a first-line response to mitochondrial stress.<sup>3</sup> Four major subtypes have been identified based on membrane structure and cargo: single-membrane TOMM20-positive (TOMM20<sup>+</sup>), single-membrane TOMM20- and VPS35-positive (TOMM20<sup>-</sup>/VPS35<sup>+</sup>), single-membrane MAPL-positive (MAPL<sup>+</sup>), and double-membrane PDH- or Core2-positive vesicles (PDH<sup>+</sup>/Core2<sup>+</sup>), each directed to distinct degradative destinations including lysosomes, peroxisomes, and multivesicular bodies for potential extracellular release.<sup>2,4</sup> What has changed in recent years is not this basic biology, but our understanding of what MDVs are truly capable of, and that understanding now demands a reconsideration of their therapeutic relevance.

The molecular machinery governing MDV biogenesis is increasingly well characterized. Under basal conditions,

MIRO1/2 GTPases pull thin membrane tubules from mitochondria along microtubules, while DRP1 - recruited by MFF, MID49, and MID51 - executes scission at the tubule tip. Under stress, the PINK1/Parkin pathway shifts cargo selection toward oxidized matrix proteins and activates mitochondrial antigen presentation through RAB9 and SNX9-dependent routes.<sup>1,3,5</sup> Importantly, a subset of MDVs escapes intracellular degradation, fusing with multivesicular bodies and being released into the extracellular space, where they carry disease-specific mitochondrial signatures detectable in plasma and serum.<sup>3,6</sup> This extracellular dimension first suggested diagnostic potential - but a more fundamental discovery has since reshaped the field's understanding of what MDVs are.

For much of their history, MDVs were understood primarily as a mitochondrial waste disposal system. This framing, while accurate, was incomplete. Studies demonstrated that MDVs budding from functional mitochondria selectively incorporate 13 of 17 subunits of the F1F0-ATP synthase complex, retain membrane potential, and autonomously generate ATP. When incubated with respiratory-deficient mitochondria, these MDVs increased ATP production by 560% and transferred their bioenergetic machinery through fusion with recipient organelles - findings validated in human HEK293 cells.<sup>7</sup> This finding reframes MDVs as potential vehicles of mitochondrial rejuvenation, not only damage clearance, and introduces a therapeutic possibility that did not previously exist: using MDV-mediated transfer of functional components to rescue failing mitochondria.

The diseases where this matters most are precisely those defined by progressive mitochondrial dysfunction. In the cardiovascular system, MDV release is amplified under hypoxia and doxorubicin-induced cardiotoxicity; exogenously administered MDVs attenuate cardiomyocyte apoptosis, while adipocyte-derived mitochondrial extracellular vesicles precondition the myocardium against ischemia-reperfusion injury through a Parkin-dependent



mechanism.<sup>3,4,8</sup> In neurodegeneration, PINK1 and Parkin mutations directly impair MDV-mediated mitochondrial antigen presentation, linking vesicle dysfunction to immune dysregulation in Parkinson's disease, while circulating MDVs bearing reduced electron transport chain components serve as measurable indicators of disease progression.<sup>3,6,9</sup> In aging and sarcopenia, MDV cargo molecules distinguish frail older adults from healthy controls in clinical cohorts, positioning circulating MDVs as accessible biomarkers of mitochondrial quality control failure.<sup>3</sup> In cancer, the picture is more complex: MDVs carrying mtDNA activate cGAS-STING innate immune signalling, facilitate tumor immune evasion via macrophage polarization, and transfer chemoresistance between cancer cells, yet in autophagy-deficient malignancies, they simultaneously serve as the primary compensatory quality control mechanism - making the MDV pathway both an oncogenic driver and a targetable vulnerability depending on context.<sup>4,10</sup> Across these disease contexts, MDVs are not merely responsive to pathology but actively shape it.

The therapeutic potential of MDVs is compelling, but critical barriers to clinical translation remain. The isolation of pure MDV populations from biofluids remains technically unresolved: current protocols co-isolate MDVs with other extracellular vesicle subpopulations, and MDV-specific surface markers suitable for immunoaffinity capture have not been fully defined.<sup>3,4</sup> An expanding terminology (including MDVs, mitoEVs, mitovesicles, mitophers) reflects genuine biological heterogeneity across cell types and stress conditions but impedes cross-study comparability and obscures which population carries therapeutic relevance in a given context.<sup>5</sup> Most critically, the evidence base remains almost entirely preclinical; prospective human studies systematically characterizing MDV dynamics in disease onset, progression, or treatment response are largely absent.<sup>6</sup> Addressing these gaps is essential before clinical translation can move forward.

## Conclusion

The extracellular vesicle field has demonstrated that biological complexity need not preclude therapeutic development, with EV-based platforms advancing through clinical trials across oncology, cardiology, and neurology. MDV research now stands at an analogous inflection point. The mechanistic foundation is solid, the disease relevance spans multiple organ systems, and the discovery that MDVs can transfer functional bioenergetic machinery introduces a dimension of therapeutic possibility that demands serious investment. What is required now is the development of MDV-specific isolation and characterization protocols, consensus on a functional classification framework distinguishing vesicle subtype by cargo and biogenetic origin, and human studies capable of establishing MDV signatures as validated

clinical biomarkers. Vesicles that selectively sense mitochondrial damage, transfer functional machinery to damaged organelles, modulate immune responses, and circulate in accessible biofluids represent a therapeutic target of considerable breadth - one that the field is now well-positioned to pursue.

## Authors' Contribution

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## Competing Interests

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