Design and Characterization of Controlled Mitochondrial Eluting Vascular Stents

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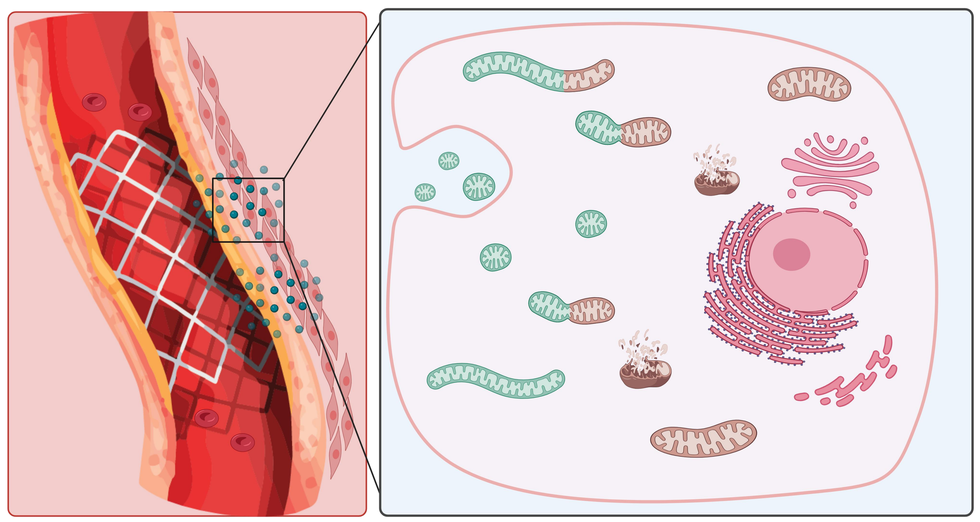
Introduction

- Conventional vascular stents suffer from limitations such as long-term restenosis, increased inflammatory response and side-effect of the eluted drug.
- Mitochondria transplantation have been shown to treat cardiovascular diseases by restoring damaged cardiomyocytes.
- Vascular oxidative stress is majorly regulated by mitochondria. Mitochondrial dysfunction leads to abnormal elevations in ROS levels, and high ROS levels are among the most significant indicators of abnormal EC and VSMC behavior during atherogenesis.



Goal: Develop a novel mitochondrial eluting stents that enable mitochondria target release at atherosclerotic surgery site and restore vascular cells function.

HYPOTHESIS: Utilize the elevated levels of ROS at atherosclerotic sites as a signal for the targeted release of mitochondria; Linking mitochondria to vascular stents using ROS-responsive linkages could enable targeted release of therapeutic mitochondria at sites of dysfunctional cells, helping to treat in-stent restenosis.

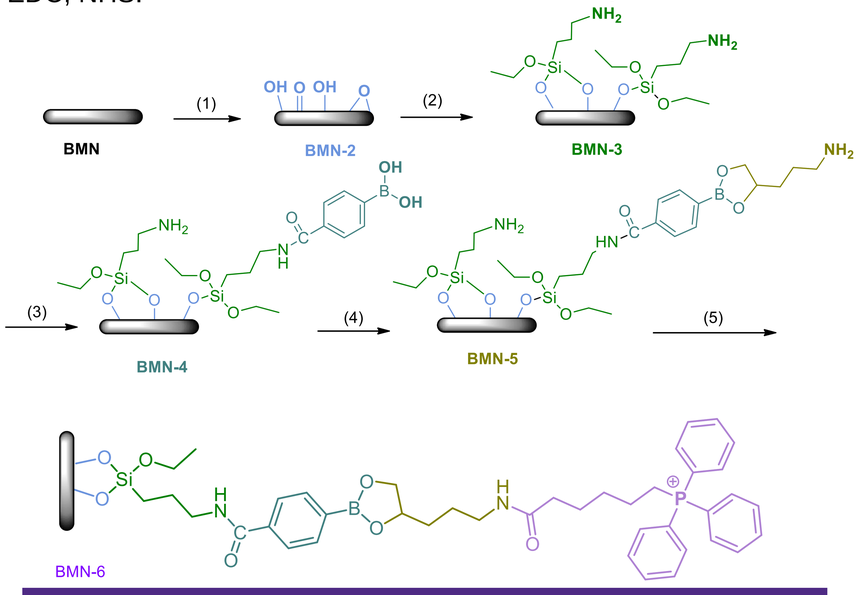
Methods

BMN-6 Preparation

(1) Hydration: H+/OH-;
(2) Amination: APTES;
(3) Amide condensation: CPBA, EDC, NHS;
(4) Dehydration: 3-APD;
(5) Amide condensation: TPP, EDC, NHS.

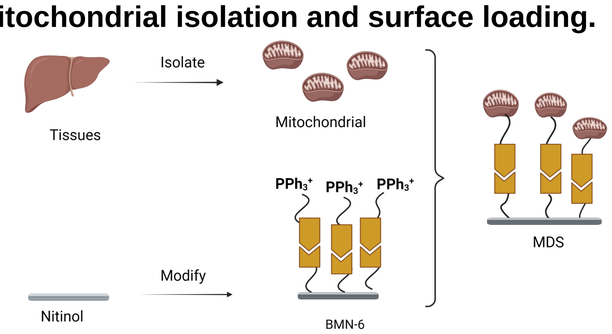
Characterization & verification in-vitro

- SEM, XPS surface modification
- ROS-triggered release mitochondrial
- Size distribution of mitochondria
- Cellular uptake of released mitochondria
- Cellular viability of EC and HASMC

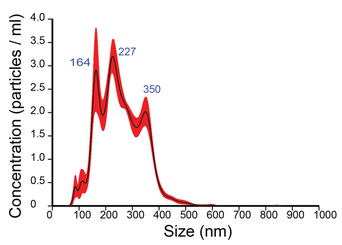


Results

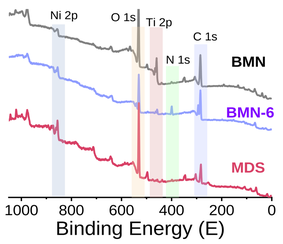
1. Mitochondrial isolation and surface loading.

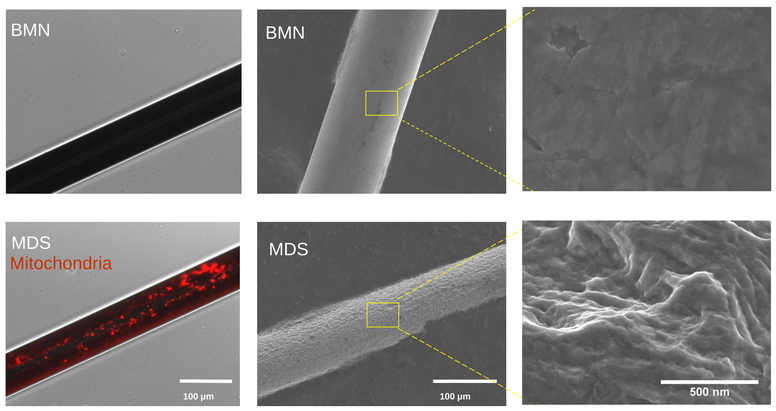


Mitochondria size distribution

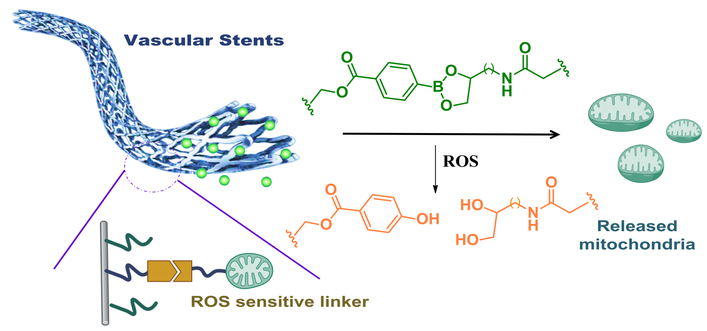


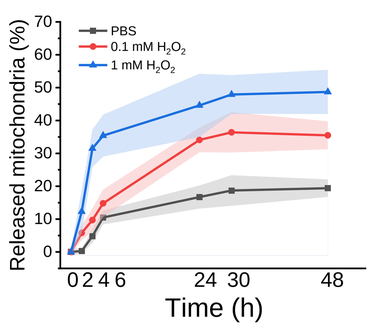
Surface modification XPS



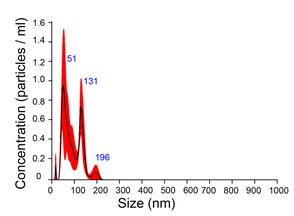


2. Mitochondria ROS-stimulated release

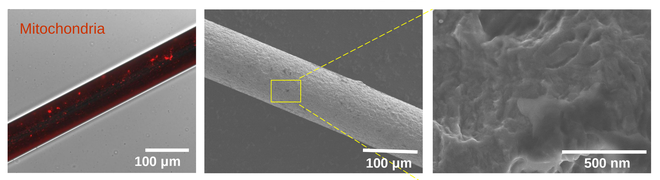




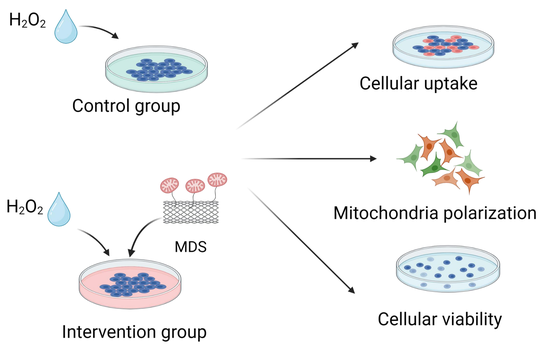
Released at 1 mM H_2O_2 for 48h



Released at 1 mM H_2O_2 for 48h



3. Released mitochondria improved the surrounding cells function



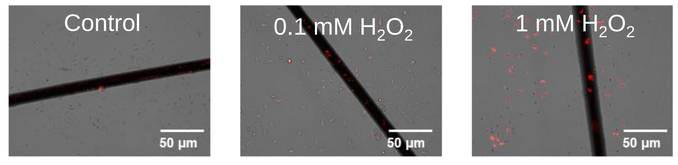
Cell types:

Endothelia cells (EC)
Human artery smooth muscle cells (HASMC)

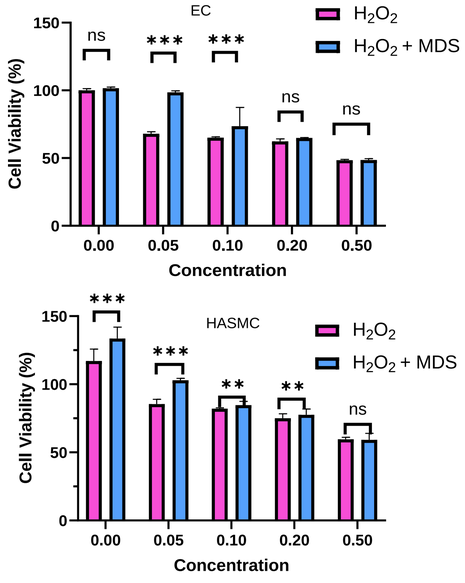
Incubated time: 12h

Stents length: 5cm

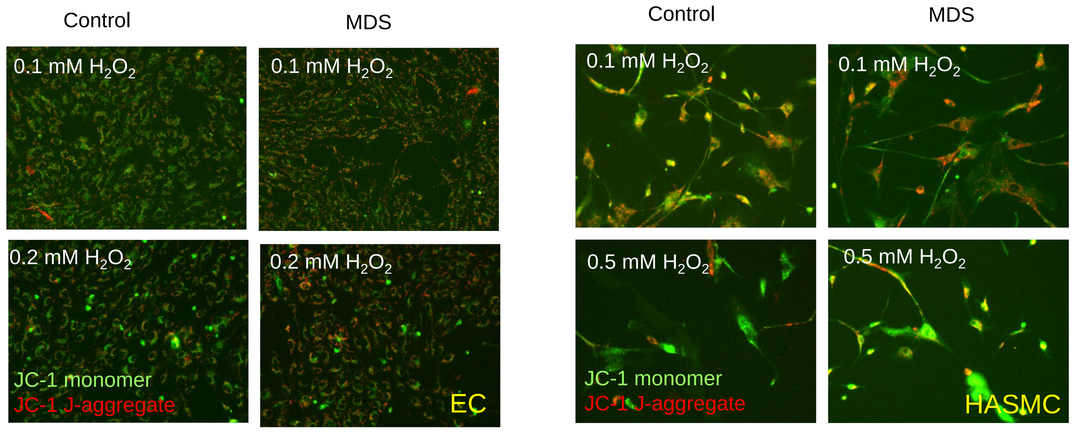
Released mitochondria uptake by surrounding ECs in 4h



MDS mitigates oxidative stress-induced cellular damage



Released mitochondria uptake regulate mitochondrial membrane potential



Conclusions

- This study demonstrates effective modification of ROS-responsive linkage on the surface of vascular stent for targeted and controlled delivery of mitochondria in a ROS-stimulated environment.

References

[1] Paria Ali Pour, et al. Bioenergetics consequences of mitochondrial transplantation in cardiomyocytes. J Am Heart Assoc, 2020, 9, e014501.
[2] Shiqi Hu, et al. Exosome-eluting stents for vascular healing after ischaemic injury. Nat Biomed Eng, 2021, 5, 1174-1188.

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