SCE 0703 Public Evidence Appendix

Tissue protection

Literature review date: September 9, 2026

Controlling principle. Tissue protection preserves threatened cells and function through interacting survival, redox, mitochondrial, autophagic, and metabolic pathways; it is mechanistically distinct from replacing tissue that has already been lost.

Mechanistic evidence map

Domain	What is measured	Interpretive boundary
Antiapoptotic signaling	Cell-death/survival pathways including PI3K-AKT, BCL-2-family signaling and caspase activity.	Reduced apoptosis may be protective in some contexts but is not universally beneficial; direct tissue-specific evidence is required.
Oxidative-stress reduction	Reactive oxygen species, lipid peroxidation, glutathione, antioxidant enzymes and oxidative DNA damage.	A change in one oxidative marker does not establish durable tissue protection or clinical benefit.
Mitochondrial effects	Membrane potential, ATP, respiration, biogenesis, morphology and mitophagy.	Improved mitochondrial biomarkers are mechanistic evidence unless linked to meaningful tissue function.
Autophagy	Autophagosomes, lysosomal processing and autophagic flux.	Static marker levels can misrepresent pathway activity; flux and biological consequences matter.
Cytoprotection	Survival and functional preservation across stressed cell types and tissues.	Cytoprotection preserves threatened tissue; it does not demonstrate replacement of tissue already lost.
Metabolic support	Energy production, substrate use, metabolic flexibility and NAD+/NADH-related homeostasis.	Metabolic changes are context-, dose-, product-, timing- and recipient-dependent.

Key evidence conclusions

Tissue protection and tissue replacement are different. Preserving stressed but viable cells does not imply regeneration of tissue already lost.

The mechanisms interact. Oxidative stress, mitochondrial dysfunction, autophagy/mitophagy, apoptosis, and metabolism form an interconnected network rather than isolated pathways.

Timing matters. Protective effects in acute experimental injury may not translate to established chronic tissue loss or fibrosis.

Surrogate biomarkers are not clinical outcomes. Molecular and cellular measurements can support mechanism, but clinical relevance requires product-specific links to durable tissue function and meaningful patient outcomes.

Principal references

1. Galipeau J, Sensebé L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. Cell Stem Cell. 2018;22:824-833.

2. Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell. 2011;9:11-15.

3. Phinney DG, Pittenger MF. Concise review: MSC-derived exosomes for cell-free therapy. Stem Cells. 2017;35:851-858.

4. Relevant contemporary literature concerning MSC/EV antiapoptotic signaling, oxidative stress, mitochondrial function, autophagy, cytoprotection, and metabolic support.

5. Mechanistic evidence is interpreted separately from indication-specific human clinical efficacy and jurisdiction-specific regulatory status.