SCE 0707 Public Evidence Appendix

Apoptotic-cell mechanisms

Literature review date: September 13, 2026

Controlling principle. Short MSC persistence does not exclude biological activity; in some settings, post-infusion apoptosis followed by host efferocytosis and immune-cell reprogramming may contribute to mechanism, but this must be demonstrated rather than assumed.

Mechanistic evidence map

Domain	What is evaluated	Interpretive boundary
MSC apoptosis after infusion	Post-infusion cell death, timing, pulmonary trapping, route, product dependence, and recipient processing.	Apoptosis may contribute to mechanism but is not necessarily universal, required, or beneficial for every product or indication.
Efferocytosis	Recognition of apoptotic cells, phosphatidylserine exposure, phagocyte identity, engulfment, clearance, and downstream signaling.	Uptake of labeled MSC material alone does not prove regulated efferocytosis.
Macrophage reprogramming	Changes in macrophage/monocyte cytokines, metabolism, antigen presentation, inflammatory tone, and resolution-associated function.	Simplified M1/M2 labels are insufficient; functional reprogramming should be measured directly.
Implications for short cell persistence	Biodistribution, donor-cell survival, host response, persistence, clearance, and downstream biological effects.	Rapid disappearance does not establish biological inactivity; conversely, a plausible host-mediated mechanism does not establish clinical effectiveness.

Key evidence conclusions

Persistence and activity are separate questions. Short donor-cell survival does not necessarily mean that an administered cell product produced no biological effect.

The recipient may be mechanistically active. Monocytes and macrophages can process dying administered cells and translate that interaction into downstream immune signaling.

Product viability and post-infusion fate should not be conflated. High pre-infusion viability remains a manufacturing-quality attribute even when post-administration apoptosis participates in mechanism.

Clinical relevance still requires demonstration. Human apoptosis frequency, dominant phagocyte populations, organ-specific processing, dose-response relationships, biomarkers, safety, and contribution to outcomes remain incompletely defined.

Principal references

1. Galleu A, Riffo-Vasquez Y, Trento C, et al. Apoptosis in mesenchymal stromal cells induces in vivo recipient-mediated immunomodulation. Sci Transl Med. 2017;9:eaam7828.

2. de Witte SFH, Luk F, Sierra Parraga JM, et al. Immunomodulation by therapeutic mesenchymal stromal cells is triggered through phagocytosis of MSCs by monocytic cells. Stem Cells. 2018;36:602-615.

3. Pang SHM, D'Rozario J, Mendonca S, et al. Mesenchymal stromal cell apoptosis is required for their therapeutic function. Nat Commun. 2021;12:6495.

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

5. Relevant contemporary literature concerning MSC apoptosis, efferocytosis, monocyte/macrophage processing, biodistribution, persistence, and host-mediated immunomodulation.