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Review Article

Extracellular Vesicles from Mesenchymal Stromal Cells and Their Role in Tissue Repair

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Abstract

Background: Mesenchymal stromal cells do not survive long enough after infusion to rebuild tissue, so their benefit is attributed to secreted factors, and increasingly to extracellular vesicles.

Objective: To review the evidence that vesicles mediate repair, the cargo proposed to carry the effect, and the standardisation problems that limit the field.

Methods: Narrative review of biodistribution, preclinical efficacy, cargo and manufacturing studies, and of the position statements on characterisation.

Findings: About 60% of infused cells lodge in the lung within an hour and none are recoverable at 72 hours, which the paracrine account was built to explain. Vesicles reproduce parent-cell effects across cardiac, renal, pulmonary and cutaneous injury. Human evidence is one case and one 40-patient trial whose control arm is reported without numbers.

Conclusions: The paracrine premise is well supported. Dose is reported in incompatible units, no potency assay is agreed, and effect sizes are not poolable.

Keywords: extracellular vesicles; mesenchymal stromal cells; tissue repair; potency; standardisation

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Introduction

For two decades mesenchymal stromal cells were given to patients on the premise that they would engraft and become the tissue that had been lost. The premise did not survive examination. Analysis of tissues from treated patients found limited long-term engraftment and no ectopic tissue formation [1], and tracking studies in mice were blunter still: about 60% of radioactivity was in the lungs an hour after intravenous infusion, viable cells were recoverable from lung cultures only up to 24 hours, and none were detectable at 72 hours or in any other organ at any time [2].

The alternative explanation arrived earlier than the disproof. Conditioned medium from Akt-modified cells protected ischaemic myocardium, which the authors attributed to paracrine action rather than to the cells themselves [3], and medium alone was subsequently shown to reduce infarct size [4]. The active fraction was then narrowed to particles. This review considers what those particles do, what carries the effect, and why the literature remains difficult to aggregate. Cells throughout meet the standard identity criteria [5], with the caveat that those criteria describe the parent cell rather than the product.

Materials and Methods

Records were retrieved from Crossref, OpenAlex and publisher pages for the terms *extracellular vesicle*, *exosome*, *mesenchymal stromal cell*, *tissue repair* and *potency*. Priority was given to primary studies reporting a defined vesicle preparation and to the position statements governing characterisation. Every bibliographic record was confirmed at source; quantitative values not confirmable at source are not reported.

What is being studied, and whether it is comparable

The field's central practical problem is that preparations differ between laboratories and are often not what they are called. That is why three successive position statements exist rather than one. The 2014 statement set minimal experimental requirements for defining vesicles and their functions [6]; MISEV2018 substantially extended it [7]; MISEV2023 revised it again [8]. A separate statement addresses stromal-cell-derived small vesicles specifically, and is the document a manufacturer should work from [9].

The consequence is concrete. A preparation labelled exosome may be a mixed pellet; a dose in micrograms of protein cannot be compared with one in particle number; and biodistribution depends on cell source, route and targeting [10], so a result obtained by one route does not transfer to another.

Cargo, and which cargo matters

Vesicles carry RNA, and the observation that they transfer mRNA and microRNA between cells is what made them interesting [11]. Stromal cells also use vesicles to outsource mitophagy and shuttle microRNAs, and the quantitative detail there is unusually specific: a dose of approximately 3 × 10^11 exosomes containing 40 µg of protein, with miR451a enriched 316-fold and miR21 reduced 91-fold, and significant changes in 50 of 84 Toll-like-receptor-associated transcripts [12]. Whole mitochondria are also transferred, and mitochondrial transfer from stromal cells to alveoli protects against acute lung injury [13].

Whether RNA is the effector is disputed rather than settled. The opposing position holds that stromal-cell exosomes work through a protein-based mechanism [14], and the argument turns on stoichiometry: copy numbers per vesicle for most individual microRNAs are below one, so a transfer model requires many vesicles per recipient cell to deliver a single molecule. Both positions are held by productive groups and neither has been retired.

A third mechanism sits outside the vesicle account altogether. Apoptosis of infused cells induces

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recipient-mediated immunomodulation [15], which means the therapeutic signal may be the cells dying rather than anything they secrete while alive.

Preclinical efficacy

The efficacy literature is broad and directionally consistent. In the heart, exosomes reduced ischaemia-reperfusion injury [16] and raised ATP, lowered oxidative stress and activated PI3K/Akt to limit adverse remodelling [17]. In the kidney, microvesicles protected against acute tubular injury [18] and ischaemia-reperfusion injury [19], and improved survival in a lethal model [20]. In the lung, they treated endotoxin injury [21] and pneumonia [22], and exosomes restored lung function in bronchopulmonary dysplasia through macrophage immunomodulation [23]. In skin, preconditioned cells produced vesicles that shifted macrophage polarisation through let-7b [24].

That last study also reports what a manufacturing yield looks like: approximately 410 µg protein equivalent of exosomes from 80 ml of supernatant from 5 × 10^7 cells, with 37% more total protein after preconditioning [24].

The pattern across these studies is a consistent direction of effect with heterogeneous magnitude, obtained in small, rarely blinded and rarely randomised animal experiments. That is enough to justify continued work and not enough to size a clinical dose.

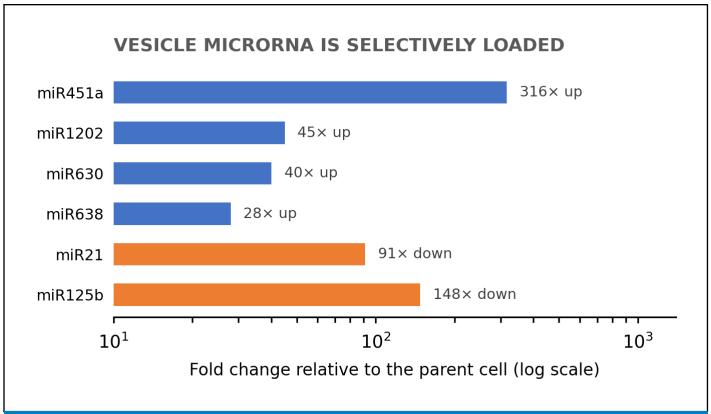

Figure 1: MicroRNA content of stromal cell extracellular vesicles relative to the parent cell, showing the most enriched and most depleted species. Note the logarithmic scale. Data from Phinney et al. [12].

Dose, potency and manufacture

Nothing in the field is harder than saying how much to give. Doses appear as micrograms of protein, as particle counts, or as cell equivalents, and these do not interconvert. There is as yet no agreed potency test for stromal-cell-derived small vesicles, and the considerations for developing one have had to be set out from first principles [25].

Manufacture is further along than potency. Requirements for producing human vesicle therapeutics for clinical use have been described [26], a scalable process was achieved by immortalising the producing cells [27], and the position on applying vesicle therapeutics in trials was set out by the International Society for Extracellular Vesicles [28].

Human evidence

There is very little. A patient with therapy-refractory graft-versus-host disease was treated with stromal-cell-derived exosomes and improved [29]; this is a single case. Forty patients with stage III and IV chronic kidney disease received cord-blood-derived vesicles at 100 µg/kg or placebo, and the treated group showed improvement in estimated glomerular filtration rate from 31.05 ± 4.51 to 47.25 ± 5.14 ml/min at 12 weeks, with serum creatinine falling from 3.44 ± 0.49 to 2.19 ± 0.25

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mg/dl [30]. The control arm is reported as not showing significant improvement, without numbers, which means the comparison cannot be evaluated.

Table 1: Preclinical evidence by organ system, and the preparation used in each case.

Injury model	Preparation	Reported effect	Ref.
Myocardial ischaemia-reperfusion	Exosomes	Reduced injury; raised ATP, lowered oxidative stress	[16,17]
Acute tubular injury	Microvesicles	Protection; improved survival in a lethal model	[18,20]
Renal ischaemia-reperfusion	Microvesicles	Protection acutely and chronically	[19]
Endotoxin lung injury	Microvesicles	Treatment effect in mice	[21]
Severe pneumonia	Microvesicles	Therapeutic effect in mice	[22]
Bronchopulmonary dysplasia	Exosomes	Lung function restored via macrophage immunomodulation	[23]
Chronic cutaneous inflammation	LPS-preconditioned exosomes	Macrophage repolarisation via let-7b	[24]

Discussion

Three conclusions follow. First, the paracrine premise is secure. Cells do not persist, and the effect must therefore be carried by something they release or by their clearance.

Second, the mechanism is genuinely unresolved between RNA transfer and protein cargo, and the stoichiometric objection to the RNA account has not been answered. A review that presents microRNA transfer as established is overstating the position.

Third, the obstacle to translation is metrological rather than biological. Until dose has a unit and potency has an assay, effect sizes cannot be pooled across studies, and a manufacturing change cannot be shown not to matter.

This is a narrative review without systematic search or risk-of-bias assessment. Preclinical studies used different injury models, preparations and doses, and several key quantitative results could not be confirmed at source and are therefore not reported here.

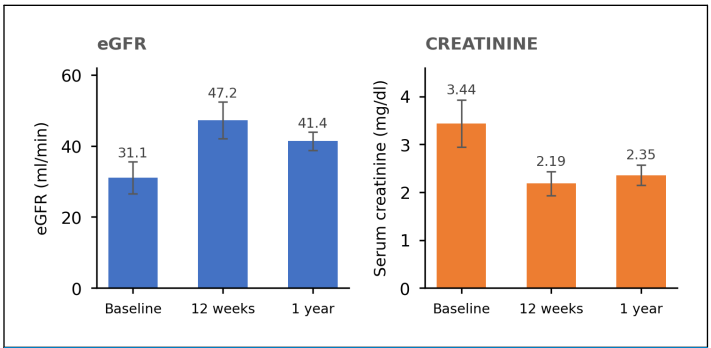

Figure 2: Renal function in the only controlled human trial of mesenchymal stromal cell-derived vesicles, 40 patients with stage III-IV chronic kidney disease given 100 µg/kg. The placebo arm is reported without numbers, so no comparison is drawn. Data from Nassar et al. [30].

Conclusion

Extracellular vesicles from mesenchymal stromal cells reproduce many of the reparative effects attributed to the cells themselves, across cardiac, renal, pulmonary and cutaneous injury, and they do so without the engraftment that the cells were once assumed to achieve. The evidence supporting the paracrine premise is stronger than the evidence identifying the effector, and the human data amount to one case and one small trial with an uninterpretable control arm. Studies should report the preparation method against the current MISEV recommendations, state dose in both particle number and protein mass, and specify the potency measure used, so that the next decade of work can be compared with itself.

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Conflict of Interest

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The authors declare that they have no competing interests relevant to the content of this review.

Ethics Statement

This article reviews previously published studies and contains no new studies with human participants or animals performed by any of the authors. Ethical approval was therefore not required.

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