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Review Article

Comparative Immunomodulatory Capacity of Adipose- and Umbilical Cord-Derived Mesenchymal Stromal Cells: A Review

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Abstract

Background: Mesenchymal stromal cells (MSCs) suppress immune responses in vitro, and adipose tissue and umbilical cord have largely displaced bone marrow as the source. Whether origin determines potency is contested.

Objective: To review head-to-head comparisons of adipose- and umbilical cord-derived cells, and why they disagree.

Methods: Narrative review of studies comparing MSCs from two or more tissue sources under matched conditions.

Findings: Reported differences are large but inconsistent in direction. In one three-way comparison, unprimed cells at a 1:5 ratio suppressed T-cell proliferation by 51% (bone marrow), 48% (adipose) and 9% (umbilical cord), yet priming with IFN-γ and TNF-α brought all three to comparable potency; another found no difference at all. Suppression is soluble-factor mediated, indoleamine 2,3-dioxygenase dominating in human cells and nitric oxide synthase in murine ones.

Conclusions: Licensing matters more than tissue of origin and collapses most reported source differences. The unresolved problem is the absence of a potency assay predicting clinical effect.

Keywords: mesenchymal stromal cells; adipose tissue; umbilical cord; immunomodulation; potency assay

Introduction

Mesenchymal stromal cells suppress the proliferation of activated T lymphocytes in vitro, and that observation has carried a therapeutic field. The finding is robust — reported for bone marrow stromal cells against both allogeneic and mitogenic stimulation [1] and reproduced widely. The step from there to a product has not been.

Bone marrow was the original source, but aspiration is invasive and yield falls with donor age. Adipose tissue and umbilical cord have displaced it: lipoaspirate is abundant and surgically routine, cord otherwise discarded. Whether they yield cells of equivalent potency is the question here; the literature answers inconsistently enough that the inconsistency is itself the finding.

Throughout, cells are called stromal rather than stem, with the tissue of origin specified, following the International Society for Cellular Therapy [2]. The same body has argued that potency should be assessed with mechanism-matched assays rather than the identity criteria of surface phenotype and trilineage differentiation [3].

Materials and Methods

Studies were retrieved from PubMed, Europe PMC and Crossref for the terms *mesenchymal stromal cell*, *adipose*, *umbilical cord*, *immunomodulation* and *licensing*. Priority went to comparisons under matched culture, ratio and stimulation conditions. Records were confirmed against Crossref or the publisher.

Mechanisms of suppression

Suppression is mostly mediated by soluble factors. Early work implicated transforming growth factor-β1 and hepatocyte growth factor [1] and prostaglandin E2 [4], and indoleamine 2,3-dioxygenase (IDO) inhibited allogeneic T-cell responses through tryptophan degradation [5]. A parallel murine literature attributed the same phenotype to nitric oxide [6].

The contradiction is a species difference: human MSCs use IDO where murine MSCs use inducible nitric oxide synthase [7]. Conclusions from mouse cells do not transfer, leaving much preclinical work weaker than it appears.

MSCs also reprogramme macrophages toward an interleukin-10-producing phenotype through PGE2 [8], inhibit natural killer cell proliferation and cytotoxicity through IDO and PGE2 [9], and secrete programmed death-1 ligands [10]. Regulatory T-cell induction requires contact, PGE2 and TGF-β1 non-redundantly [11], partly by skewing monocytes toward anti-inflammatory macrophages [12]. Extracellular vesicles alone reproduce part of the effect, blunting dendritic cell maturation, cutting IL-12p70 more than a hundredfold and reducing migration toward CCL21 from 73.2 ± 6.4% to 22.4 ± 4.0% [13]. No single mediator accounts for the effect, the first reason one assay does not capture it.

Licensing

MSCs are not constitutively suppressive. They acquire the phenotype on exposure to interferon-γ with tumour necrosis factor-α, and this licensing step is the strongest determinant of measured potency. IFN-γ-licensed cells suppress T-cell effector function partly through IDO-independent pathways [14].

Table 1: Principal effector mechanisms of MSC immunosuppression and the cell populations they act on.

Mediator	Acts on	Note	Ref.
IDO / kynurenine	T cells, NK cells	Dominant pathway in human MSCs	[5,9]
Nitric oxide (iNOS)	T cells	Murine equivalent of IDO; not the human pathway	[6,7]
Prostaglandin E2	T cells, macrophages	Drives IL-10 production by host macrophages	[4,8]
TGF-β1 and HGF	T cells	Among the first mediators identified	[1]
PD-L1 / PD-L2	T cells	Secreted as well as surface-bound	[10]

Mediator	Acts on	Note	Ref.
Contact + PGE2 + TGF-β1	Regulatory T cells	Non-redundant; contact alone is insufficient	[11]
Monocyte skewing	Regulatory T cells	Indirect route via anti-inflammatory macrophages	[12]

Licensing also acts differently by tissue of origin: Wharton's jelly and bone marrow MSCs are differentially influenced by IFN-γ and TNF-α [15]. It is also fragile. Cryopreserved cells mount a heat-shock response and respond poorly to IFN-γ, losing indoleamine 2,3-dioxygenase induction and suppressive activity, both restored by 24 hours of culture after thawing [16]. Any comparison of unlicensed cells therefore measures a baseline state, not the state cells meet in an inflamed recipient — the central problem with this literature.

Comparing sources

Reported differences are large and conflict in direction. Adipose-derived cells have been reported as more immunomodulatory than bone marrow-derived ones [17], and cells from umbilical cord matrix, adipose tissue and bone marrow differ in their capacity to suppress B, natural killer and T cells [18]. Cord blood-derived cells expand further before growth arrest, to passage 14-16 against 11-12 [19]. A review concluded that adipose-derived cells most strongly inhibit interferon-γ secretion and T-cell proliferation, while noting that protocol heterogeneity blurs them [20].

Grégoire and colleagues compared all three sources in a humanized mouse model of graft-versus-host disease: unprimed cells at a 1:5 MSC:PBMC ratio suppressed T-cell proliferation by 51% for bone marrow, 48% for adipose and 9% for umbilical cord, but after priming with IFN-γ and TNF-α all three reached comparable potency [21]. In vivo the survival benefit was modest and did not separate the sources (hazard ratios 0.63 and 0.56 against control, neither significant).

A more recent three-way comparison found the opposite in vitro: no significant difference between umbilical cord-, bone marrow- and adipose-derived cells in suppressing an allogeneic mixed lymphocyte reaction, in contact or across a transwell — while the same cells differed markedly in proliferation: cumulative population doublings of 46.3 ± 4.5 for umbilical cord against 31.1 ± 7.5 for adipose and 19.3 ± 4.5 for bone marrow [22].

Adipose-derived cells act largely without contact: CD4+ proliferation was inhibited 3.6-fold in direct co-culture and 2.9-fold across a transwell, with IDO elevated three- to 5.5-fold [23].

Donor characteristics are a further confounder that source comparisons rarely control. In adipose-derived cells from cardiac surgery donors, each additional year of donor age was associated with a 0.5% increase in CD4+ proliferation, atherosclerosis with 21.6% and type 2 diabetes with 14.4% [24] — effects that could account for much of the disagreement between laboratories.

The potency problem

Nothing yet predicts suppression in a way that transfers to the clinic. Work optimising an immunomodulatory potency assay found no single readout sufficient, different proliferation indices giving different half-maximal responses on the same cells [25]. The ISCT position is that immune functional assays should serve as release criteria, a matrix rather than one assay [26].

Clinical results are mixed. Bone marrow MSCs produced responses in steroid-resistant acute graft-versus-host disease in a phase II study [27], while an adipose-derived product reached phase III with a positive result in complex perianal fistulas in Crohn's disease [28], though for a local indication. A single-arm phase III of an allogeneic bone marrow product in 54 children with steroid-refractory acute graft-versus-host disease reported a day-28

response of 70.4% against a prespecified control value of 45% [29].

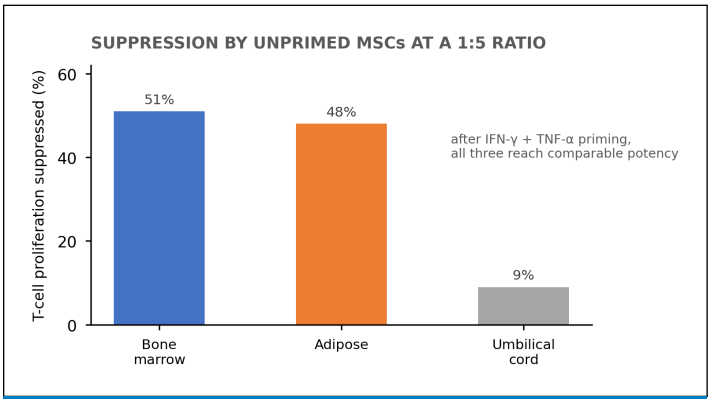

Figure 1: Suppression of T-cell proliferation by unprimed mesenchymal stromal cells from three tissue sources at a 1:5 MSC:PBMC ratio. Priming with IFN-γ and TNF-α abolished the difference. Data from Grégoire et al. [21].

Discussion

Three things follow. First, inflammatory licensing dominates tissue of origin: priming tends to abolish differences seen in resting cells.

Second, the direction of reported differences is not stable across laboratories: ratio, stimulation, passage, readout and donor differences suffice to produce the spread without any real difference between tissues.

Third, what separates the sources reliably is proliferative capacity, not suppression: umbilical cord-derived cells expand further and senesce later, which for manufacturing may matter more.

This is a narrative review; endpoints and ratios differ too widely for quantitative synthesis, and donor and tissue effects are not fully separable.

Conclusion

Adipose- and umbilical cord-derived cells both suppress lymphocyte proliferation in vitro, and the evidence does not support a stable ranking between them or against bone marrow. Licensing state, ratio and assay explain more of the variance than tissue of origin. The limiting problem is not source selection but the absence of a potency measure that predicts clinical response. Studies should report licensing condition, ratio, passage and donor age alongside suppression data, and read murine work with the IDO-versus-iNOS species difference in view.

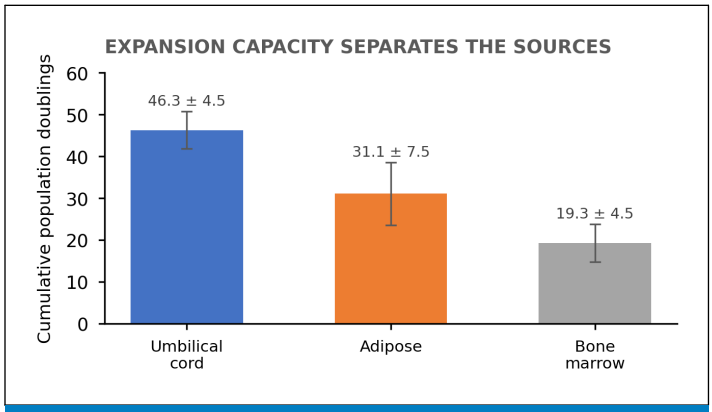

Figure 2: Cumulative population doublings before growth arrest for mesenchymal stromal cells from three tissue sources, mean ± SD. Expansion capacity separates the sources where suppression does not. Data from Hori et al. [22].

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Conflict of Interest

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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