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Review Article

Defining Mesenchymal Stem Cell (MSC) and Stromal Cells (SC) Within the cellular Stromal Vascular Fraction (cSVF) of Adipose Tissue Complex: Clarifying Definitions, Characterization and Clinical Significance in Biocellular Regenerative Medicine

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Abstract

Background: The cellular Stromal Vascular Fraction (cSVF) of adipose tissue is a heterogeneous, uncultured population of nucleated cells that has become central to Biocellular Regenerative Medicine. Within this compartment, the terms "Mesenchymal Stem Cell (MSC)" and "stromal cell" are frequently used interchangeably in both clinical and investigational literature, obscuring an important biological and regulatory distinction.

Objective: This review clarifies the definitional boundary between MSCs and the broader stromal cell population within cSVF, synthesizes consensus phenotypic criteria and examines the clinical significance of this hierarchy for Regenerative practice.

Methods: A narrative synthesis of foundational and contemporary peer-reviewed literature was performed, incorporating the International Society for Cellular Therapy (ISCT) and International Federation for Adipose Therapeutics and Science (IFATS) consensus position statements, primary immunophenotypic studies and clinical series describing cSVF-based Biocellular therapies.

Results: MSCs represent a multipotent subset of the stromal compartment, defined in cultured form by ISCT minimal criteria (plastic adherence, CD105/CD73/CD90 positivity with CD45/CD34/CD14/CD11b/CD79a/CD19/HLA-DR negativity and trilineage differentiation) and, in their native uncultured state within cSVF, by perivascular identity as pericytes (CD146+) and adventitial cells (CD34+). "Stromal cells" constitute the broader IFATS/ISCT-defined umbrella population that additionally includes fibroblasts, preadipocytes, smooth muscle cells and lineage-committed progenitors lacking full multipotency. Beyond differentiation capacity, both MSCs and non-MSC stromal elements contribute substantially through paracrine secretion of growth factors, cytokines and extracellular vesicles, which underlies much of the observed clinical benefit in cSVF- and Platelet-Rich Plasma (PRP)-based Regenerative applications.

Conclusion: Precise, consensus-based terminology distinguishing MSCs from the broader stromal cell population is essential for reproducible cSVF characterization, accurate reporting of clinical outcomes and continued translational advancement of Biocellular Regenerative Medicine.

Keywords: Mesenchymal Stem Cells; Stromal Vascular Fraction; Adipose-Derived Stem Cells; Perivascular Niche; Biocellular Regenerative Medicine; Paracrine Signaling; ISCT Minimal Criteria; Pericytes; cSVF; tSVF

Introduction

Adipose tissue has become one of the most clinically accessible and abundant sources of regenerative cellular material available to the practicing physician. Zuk, et al., were the first to demonstrate multilineage differentiation capacity from processed human adipose tissue, establishing the biological foundation for adipose-derived cell-based therapies [1]. Gimble, Katz and Bunnell subsequently provided a comprehensive synthesis of this literature, cementing the regenerative medicine potential of adipose-derived stem cells across musculoskeletal, vascular and soft-tissue applications [2].

In clinical and translational practice, adipose tissue is most often processed to yield the cellular Stromal Vascular Fraction (cSVF)- a heterogeneous, uncultured, nucleated cell population isolated from the adipose tissue complex by enzymatic digestion, distinct from tissue-based preparations such as mechanically emulsified Nanofat (tSVF) [3,4]. As the clinical use of cSVF has expanded across testing abilities wthin aesthetic, orthopedic and reparative Regenerative Medicine, the terms "mesenchymal stem cell" and "stromal cell" have too often been used interchangeably, both in practice parlance and in the published literature. This conflation has consequences: it complicates comparison across clinical series, obscures the true multipotent fraction responsible for differentiation-based repair and understates the paracrine contribution of the broader stromal population. This review defines each population, describes the consensus phenotypic and native (in situ) criteria used to identify them within cSVF and discusses the clinical significance of maintaining this distinction in Biocellular Regenerative practice.

Mesenchymal Stem Cells (MSCs) Within cSVF

Mesenchymal Stem Cells (MSCs) within the cellular Stromal Vascular Fraction (cSVF) are multipotent, non-hematopoietic progenitor cells derived from the stromal compartment of adipose tissue [8]. They represent a certain defined subset of the larger stromal cell population and are characterized both by consensus phenotypic criteria established for cultured cells and by native, in situ perivascular identity in uncultured tissue.

ISCT Minimal Criteria (Phenotypic Definition)

The International Society for Cellular Therapy (ISCT) established three consensus minimal criteria in 2006 for defining multipotent mesenchymal stromal cells in their cultured, plastic-adherent state [5]:

- Plastic-adherence in standard *in-vitro* culture conditions
- Specific surface antigen profile: ≥95% expression of CD105, CD73 and CD90; and <2% expression of CD45, CD34, CD14/CD11b, CD79a/CD19 and HLA-DR
- Trilineage differentiation capacity: *in-vitro* osteogenic, adipogenic and chondrogenic differentiation (Table 1)

Positive Markers (≥95%)	Negative Markers (<2%)	Adipose-Specific Notes
CD105, CD73, CD90	CD45, CD34*, CD14/CD11b	May transiently express CD34; CD36+, CD106-
CD44, CD29	CD79a/CD19, HLA-DR, CD31	CD34 positivity varies by passage
*CD34 negativity is a general criterion; adipose-derived ASCs may be CD34+ depending on donor and passage number [9].		

Table 1: MSC Surface Marker Profile (ISCT Criteria).

Native (In-Situ) State in cSVF-Perivascular Identity

A critical distinction within cSVF is that MSCs exist in a native, uncultured state - they have not undergone *ex-vivo* expansion and their phenotype at isolation therefore differs from that of the culture-expanded cell described by ISCT criteria. Crisan, et al., demonstrated that MSCs across multiple human organs originate from a perivascular niche, residing as pericytes and adventitial cells [6]. Alexander's concise review of Adipose-Derived Stromal Vascular Fraction (AD-SVF) cell biology further characterized this native, uncultured heterogeneous nucleated cell population and its chemical, structural and paracrine components as isolated directly from the adipose tissue complex, without intervening culture or passage [7]. In this *in-situ* configuration, perivascular MSC precursors are identified as:

- Pericytes: CD146+, CD34-, CD31-, CD45- (abluminal capillary and microvessel wall)
- Adventitial cells: CD34+, CD146-, CD31-, CD45- (outer vessel wall)

Because culture expansion alters phenotype and may alter potency, true MSC identification within uncultured cSVF remains presumptive unless confirmed and documented by flow cytometry at the time of isolation [3,5]. This isolation-dependent distinction also differentiates cSVF, obtained through enzymatic digestion to yield a suspension of individually dissociated, uncultured cells, from the tissue Stromal Vascular Fraction (tSVF) produced by mechanical full emulsification (Nanofat) techniques. This protocol preserves native perivascular and extracellular matrix plus stromal architecture rather than a dissociated cell suspension making it unacceptable as a pure cellular source and intravascular delivery [10]. The choice of isolation method therefore directly affects which stromal and MSC populations and in what proportion, are present in the final clinical preparation.

Adipose-Derived MSC Distinguishing Features

Adipose-derived MSCs (ASCs) are distinguished from bone marrow-derived MSCs by positivity for CD36 and negativity for CD106 (VCAM-1). Early-passage ASCs may retain CD34 positivity, a feature of perivascular origin, which is progressively lost with serial passaging [9]. Clinically, this means that freshly isolated, uncultured cSVF preparations should be expected to retain a mixed CD34+/CD34- perivascular population, whereas culture-expanded ASC products used in later-stage research more closely approximate the classic ISCT phenotype.

Stromal Cells in cSVF

The term "stromal cells" within cSVF refers to the broad, heterogeneous population of non-vascular, non-immune connective tissue cells present in the adipose stromal-vascular compartment. Bourin, et al., in a joint IFATS/ISCT statement, provided the foundational definition [11]. "The SVF comprises a heterogeneous mesenchymal population including adipose stromal and hematopoietic stem and progenitor cells, endothelial cells, erythrocytes, fibroblasts, lymphocytes, monocyte/macrophages and pericytes - collectively constituting the stromal compartment" (Table 2) [11].

Cell Populations Encompassed by "Stromal Cells" in cSVF

Cell Type	Key Markers	Multipotency
MSCs / ASCs	CD90+, CD73+, CD105+, CD45-	Full trilineage
Pericytes	CD146+, CD34-, NG2+, PDGFR-β+	MSC precursors
Adventitial cells	CD34+, CD146-, CD31-	Progenitor capacity
Fibroblasts / Fibrocytes	CD90+, CD34 variable, vimentin+	Limited / committed
Preadipocytes	CD34+, FABP4-, perilipin-	Adipogenic lineage
Smooth muscle cells	α-SMA+, calponin+	Mural / contractile

Table 2: Stromal Cell Subtypes Within cSVF.

Hierarchical Relationship: Stromal Cells vs. MSCs

The critical conceptual distinction is that "all MSCs within cSVF are stromal cells, but not all stromal cells are MSCs". "Stromal cells" is the umbrella designation encompassing more differentiated or lineage-committed cells that lack full plasticity and multipotency. This hierarchy is well established in the IFATS/ISCT joint position statement [11]. In uncultured cSVF, the stromal fraction - defined by IFATS/ISCT as Lin-/CD45-/CD235a-/CD31-/CD34+ for SVF stromal cells and CD45-/CD235a-/CD31-/CD34-/CD73+/CD105+ for ASC-enriched populations provides a practical gating strategy for flow cytometric identification [11].

Paracrine and Regenerative Roles

Beyond differentiation potential, stromal cells particularly MSCs and pericyte/endothelial cells exert regenerative effects primarily through paracrine signaling secretion of anti-inflammatory cytokines, growth factors (VEGF, HGF, IGF-1) and extracellular vesicles [3,7]. Traktuev, et al., demonstrated that CD34+ adipose stromal cells in a periendothelial location stabilize endothelial networks, underscoring the functional importance of the stromal compartment beyond lineage differentiation [12].

Clinically, this paracrine contribution has been leveraged by combining stromal/MSC populations with High-Density Platelet-Rich Plasma (HD-PRP); Sadati, Corrado and Alexander demonstrated that PRP supplementation improves graft volume retention in autologous fat grafting, a clinical outcome attributable in substantial part to the paracrine and matrix-supportive activity of the co-transferred stromal population [13].

Clinical Significance

Maintaining a precise distinction between MSCs and the broader stromal cell population within cSVF has direct clinical relevance. First, regulatory and reporting frameworks increasingly hinge on minimal-manipulation and cell-identity language, making ISCT/IFATS-consistent terminology essential for compliant, defensible clinical documentation [4,5,11]. Second, reproducibility across clinical series depends on consistent characterization of the administered cell population, particularly given that isolation method (enzymatic isolated/concentrated cSVF versus mechanically emulsified tSVF Nanofat) materially changes the proportion of MSCs, stromal cells and retained matrix in the final preparation [10]. Third, recognizing that both the multipotent MSC subset and the broader non-MSC stromal population contribute meaningfully - the former through differentiation, the latter AND the former together function through intercellular communication via paracrine signaling - helps explain the clinical efficacy observed across musculoskeletal, tendon and soft-tissue applications even when only a minority of the transferred cells are true multipotent MSCs [3,4].

This principle is illustrated in clinical series combining cSVF with HD-PRP or bone marrow concentrate. Tate-Oliver and Alexander reported the combined use of autologous adipose-derived tissue stromal vascular fraction with HD-PRP or bone marrow concentrate in the management of Achilles tendon tears, an application in which both the multipotent and the broader paracrine-active stromal populations of the cSVF were considered contributory to the observed clinical outcomes [14]. Such reports underscore why clinicians and investigators reporting cSVF-based Biocellular therapies should specify, wherever possible, the isolation method used and the degree to which ISCT/IFATS phenotypic criteria were confirmed, rather than defaulting to the generic term “stem cells” (Table 3).

MSCs in cSVF	Stromal Cells in cSVF
Subset of stromal cells	Broader umbrella population
Multipotent (trilineage)	Includes committed / differentiated cells
ISCT criteria required for formal designation	Defined by IFATS/ISCT surface gating panel
Native identity: pericytes / adventitial cells	Fibroblasts, preadipocytes, smooth muscle cells, pericytes, ASCs

Table 3: Key Definitional Distinctions: MSCs versus Stromal Cells in cSVF.

Conclusion

MSCs and stromal cells within cSVF exist in a well-defined hierarchical relationship: every MSC is a stromal cell, but the converse does not hold. MSCs may be formally identified either by ISCT minimal criteria in culture or by native perivascular identity (pericyte/adventitial) in uncultured cSVF. This, while the broader stromal population additionally includes fibroblasts, monocytes, T-regulatory (Treg) cells, preadipocytes, smooth muscle cells and other lineage-committed elements defined by the IFATS/ISCT gating framework. Both populations contribute to clinical outcomes in Biocellular Regenerative Medicine, the former principally through multilineage differentiation and the latter, together with the former, through paracrine signaling and matrix support. Continued adoption of consensus, ISCT/IFATS-consistent terminology and transparent reporting of isolation methodology will be essential to advancing reproducible research and clinical practice in cSVF-based Regenerative Medicine [3,4,11].

Conflict of Interest
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement
The project did not meet the definition of human subject research under the preview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement
Not applicable.

Authors' Contributions
All authors contributed equally to this paper.

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