

Adipose Stromal/Stem Cells: Basic and Translational Advances: The IFATS Collection

In October 2007, the International Federation of Adipose Therapeutics and Science (IFATS), the world's only multidisciplinary society focused on the biology of multipotent stromal/stem cells derived from adipose tissue, as well as applications of these cells for repair and regeneration of tissue injury, met in Indianapolis, Indiana for its fifth Annual Scientific Meeting. This meeting was the occasion for a call for submissions to STEM CELLS of original manuscripts related to these cells. In this issue, STEM CELLS, in collaboration with IFATS, presents a special *IFATS Collection*, peer-reviewed and selected from among those submissions. This issue comprises nine papers; part two of this collection will be forthcoming in another issue of STEM CELLS in the near future.

Multiple Names for Stromal/Stem Cells from Adipose Tissue

The description of a multipotent mesenchymal stromal cell type in adipose tissues and the subsequent work to define the biology as well as develop therapeutic applications of this cell type parallels studies with those derived from bone marrow stroma. Indeed, there are many similarities between these two cell populations and also in two key challenges before the field: **delineating the biological nature and composition of the population(s)**; and agreement upon a **standardized nomenclature** that can be adopted to refer to them. Accordingly, it is helpful to place discussions of these topics in the context of progress being made in the area of non-hematopoietic cells derived from bone marrow. The latter have been designated as MSCs; this acronym was used originally to mean marrow stromal cells [1] and subsequently mesenchymal stem cells [2]. Recently, the International Society for Cellular Therapy (ISCT) produced a position paper which supported the MSC acronym, while recognizing the alternative meanings that it could contain [3]. As the field studying adipose tissue-derived cells is rapidly developing, the expanding number of investigators engaged in research has produced several designations for these cells, as well as several methods for their isolation and characterization. This range of names includes adipose-derived stromal *or* stem cells (ASCs), adipose-tissue derived MSCs (AT-MSCs), and adipose tissue-derived stromal cells (ATSC), among several others that have been described [4]. A symposium was held by the IFATS investigators, during the 2004 IFATS meeting in Pittsburgh, to codify nomenclature, but despite agreement on an inclusive acronym of ASC, which, as indicated above, incorporates a number of descriptive names and parallels the usage of MSCs, there is incomplete adoption of this term.

Multiple Implications of Stromal/Stem Cells from Adipose Tissue

The nine peer-reviewed manuscripts within this installment of the IFATS collection cover a range of topics concerning ASCs and related cells, from cell markers and identity to functional cellular

characteristics to translational experiments. Seven studies involve predominantly ASCs and of these five employ the ASC nomenclature. The article by Minana et al. describes a distinct progenitor population from adipose tissue with the marker profile CD45-/CD105+/KDR+ that possesses hematopoietic activity. This article raises interesting implications based on the concept that adipose tissue supports hematopoietic activity and also points to the emerging understanding that **adipose tissue indeed contains multiple progenitor or stem populations**.

The study by Staszkiwicz et al. on the other hand, describes a population of mesenchymal progenitors that is found in ear tissue rather than adipose tissue per se, and this in turn underscores a second key understanding that the **ASC population in adipose tissue bears much resemblance to other mesenchymal progenitor or stem populations located throughout the body**. Indeed, it was postulated some time ago that MSCs may reside within the connective tissue of many organs [5] and subsequently the cells have been isolated from multiple sources including umbilical cord, umbilical vein, placenta, amniotic fluid, skeletal muscle, synovium, the circulatory system, and dental pulp. Nevertheless, it should be noted that these populations are not functionally equivalent with respect to their differentiation potential, particularly when assayed using stringent *in vivo* assays [6]. Nevertheless, apparent similarities in surface marker profiles, morphology and differentiation potentials assayed *in vitro* has led to suggestions that each of these multipotent cell types arise from a common adult progenitor cell [7] and then may adopt tissue-specific attributes to various degrees according to the particular niche [8].

The progressive realization that healthy adipose tissues, like nearly all tissues so far examined, possesses a population of cells with stem-like properties that are distinguishable from those of committed adipocyte progenitors (e.g., preadipocytes) has sparked considerable interest in better understanding these cells and their potential for therapeutic applications. In particular, a large proportion of this interest stems from the opportunity to readily obtain fresh, uncultured cells in numbers that make point-of-care treatment with autologous preparations feasible (see in this issue, for example, the articles by Ochiya et al. and Fradette et al.).

Precisely because of these advantages, the potential for therapeutic uses is under active investigation and has sparked several ventures to develop self-contained devices that allow processing of adipose in the operating room to yield populations of therapeutic cells for treatment of a wide variety of disorders. The translation of discovery to clinical application is being realized through multiple "first-in-man" Phase I trials, including one testing a partially-purified population of cells from adipose stroma provided to the myocardium of patients with either myocardial infarction or ischemic heart failure [9]. Many other translational applications are under current investigation at the pre-clinical stage, including employing ASCs as biological coatings for implantable devices, as described by Prichard et al. in this issue, and in modulating hepatic injury (Ochiya et al., this

issue) and in creating skin replacements (Fradette et al., this issue). It is interesting to note that perhaps the earliest evaluation of an ASC-containing population for use in a clinical setting occurred more than a decade ago, in the context of cells isolated from fat and placed onto vascular grafts for implantation [10]. While these populations included endothelial cells, it is now clear that the preparative methods utilized would have included ASCs as well.

Multiple Cell Populations from Adipose Tissues

While reading and comparing studies describing cells obtained from adipose tissue, several variables in isolation and identification must be borne in mind. Methods of isolation, which is generally accomplished by collagenase digestion and centrifugal separation, and post-isolation processing, such as substrates for plating and types of media, both differ among investigators. In addition, ASC phenotypes exhibit alteration by culture conditions [11]. Adipose tissue is comprised of adipocytes and a heterogeneous set of cell populations that surround and support them, which are termed the stromal vascular fraction (SVF) upon initial isolation; it appears that this crude isolate includes several major populations with readily distinguishable stem or progenitor characteristics. The SVF includes the stromal cells (ASC) which are characterized as CD45-/CD34+/CD31-; as well as CD45-/CD34+/CD31+ cells from the microvasculature (including endothelial progenitor cells); and CD45-/CD105+/KDR+ cells with hematopoietic progenitor activity. Also present in the SVF are CD45+ leukocytes that may be resident in the parenchyma of adipose tissue. Separation of CD34+ stromal cells can be accomplished, as with bone marrow-derived MSCs, through differential adherence to tissue culture plastic. This adherent fraction is markedly enriched in ASCs which exhibit properties of MSCs; specifically, they possess the ability to differentiate into multiple lineages (including chondrocytes, osteocytes, adipocytes, and (in some clones) myocytes. However, this population is inhomogenous both with respect to differentiation potential [7], and proliferative potential (Merfeld-Clauss et al., unpublished data). In fact, multiparameter flow cytometric analysis demonstrates at least 10 subpopulations of cells to be found in the SVF; these are yet to be fully characterized ([12] and K.L. March, unpublished data). **It is thus crucial to consider carefully the characterization and purity of the cells being characterized in all manuscripts relating to such cells.** Regardless of the complexity of the

populations present, an interesting insight into the natural biology of ASCs has been made by the finding that a major population of these cells bear markers which are hallmarks of pericytes or pre-pericytes ([13] and P.J. Amos et al., this issue) and function to modulate and support vasculature. Furthermore, Rajashekhar et al. also demonstrate an active bidirectional communication between endothelial cells and ASCs that markedly alters the adipogenic potential of ASCs and suggests a strong importance for a vascular niche in determining the fate of ASC differentiation in situ.

Accordingly, in parallel with the development of a nomenclature for these cells, much more work is required to define molecular and phenotypic characterization of these subsets of cells as isolated by various techniques and cultured in a range of media. For example, Kim et al. report on the molecular effects on the differentiation potential of ASCs cultured in the presence of higher than trace levels of selenium. Recently there has been much interest in a progressively detailed examination of the surface phenotype of these cells as a way of more clearly and consistently defining subtypes. Kolonin et al. used a novel approach for identifying ASC surface receptors by selecting out ligands from a randomized library based on binding to the cell surface. Using this approach the authors identified a potentially important ligand/receptor combination that may govern mobilization of ASCs.

There is clearly a need in the medical fields for regenerative therapies. Adipose tissue represents a prime source of cells for addressing this need. It will be very important to understand the mechanisms underlying ASC support of other cells, ASC differentiation into various cell types, and methods to control these processes in defined ways. This work will require the efforts of many laboratories, thus highlighting the importance of developing common standards for preparation of ASCs, under robust and reproducible conditions, that will yield well-defined subsets of cells characterized by biochemical markers and functional behaviors. The compilation of excellent studies in this collection represents the cutting edge of science involving ASCs and provides an impetus for collaborative work in the community to accomplish just these goals.

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