Donor Factors for Allogenic Adipose-Derived Stem Cell Transplantation

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Adipose tissue is a well-known source of adipose-derived stem cells (ADSCs). The current research on adipose stem cell harvest describes quantitative and qualitative differences that could be influenced by different donor conditions and donor sites and could further modify the clinical results.

adipose-derived stem cells | stem cell donor | allogenic stem cells

1. Age

Ageing is known to have a negative impact on all the human tissues and cells, including stem cells. ASCs aging has been demonstrated by differential expression of miRNA in younger (<35 years-old) and older (>60 years-old) donors, and this translated into reduced regeneration capacity [1]. As most of the functions expressed by the ADSCs are cytokine-mediated, a possible alteration of the secretome could lead to further functional changes. It was found that secretory profile of ADSCs is altered in aged donors, with reduced secretion of VEGF, HGF, and SDF-1α, and increased TGF-β production. These findings could further explain the reduced immunomodulatory and angiogenic capacities found in ADSCs from aged donors [2][3][4]. ADSCs are found to express a senescence-associated profile that includes *β*-galactosidase activity, enlarged morphology, and p53 protein upregulation that could explain the decreased proliferation capacity observed in culture media [5][6][7]. However, ageing does not affect equally all ADSC properties, and some contradictory data have been published in the literature. Girolamo et al. showed that cell viability and in vitro adipocytic differentiation were not significantly affected by ageing, whereas osteoblastic differentiation capacity was hampered [8]. On the contrary, other authors did not find any significant donor age-related differences of the osteogenic properties [9][10]. In recent years, numerous studies have been conducted that analyzed the effect of the age of ADSC donors. In 2013, Wu et al. compared cells from infants, adults, and elderly, and demonstrated a loss of viability and regenerative potential associated with increasing donor age [10]. Similar results have been obtained by Zhang et al. in 2018 and Park et al. in 2022 [11][12].

2. Gender

Although earlier studies failed to prove any significant yield and functional differences between male and female ADSCs, more recent research has unveiled this issue by more sophisticated bioinformatic tools, analyzing the molecular and genetic dimorphism that could drive gender-related ADSC differences. Bianconiet al. recently

performed a systematic meta-analysis of hMSC microarrays using the Transcriptome Mapper (TRAM) software [13]. They identified several chromosomal segments and differentially expressed genes in male and female ADSCs related to inflammation, differentiation capacity, and paracrine mechanisms. These findings could be further demonstrated mainly in vitro in other studies, strengthening the conclusion of the gender influence on the ADSC functionality. It was found that female ADSCs have a higher immunosuppression capacity compared to male ADSCs, coordinated by increased levels of anti-inflammatory cytokines IDO1, IL-1RA, and PGE-2, and lower levels of pro-inflammatory cytokines such as G-CSF [14]. The authors found that female (but not male) ADSCs downregulated IL-2 receptor and induced a sustained expression of CD69 in peripheral blood mononuclear cells. On the other hand, their results suggest no need for gender matching, as the immunosuppressive effect of ADSCs remained stable after female-derived ADSCs were co-cultured with peripheral blood mononuclear cells of both sexes. Ogawa et al. found in an in vitro study that ADSCs from female donors have higher adipogenic differentiation capacity than male-derived ADSCs [15]. Gender was also identified to be an important factor that impacts the paracrine, differentiation, and proliferation capacity. In their study, Shu et al. found that ADSCs from female donors exhibit a better ability to differentiate towards bone, fat, and muscle tissue and higher secretion capacity of VEGF and HGF, with a lower apoptotic rate [16]. Although it seems that ADSCs from female donors could be functionally superior, in some studies, male ADSCs, especially from superficial fat tissue, obtained from abdominoplasty specimens proved to be more efficient in achieving osteogenesis [17].

3. Immune Conditions

Having immunomodulatory activity, it seems logical that ADSC's functions could be influenced by certain immune diseases. Crohn's disease is currently one of the main target diseases for stem cell application. However, it has been found in previous studies that autologous ADSCs are less effective in the treatment of perianal fistulae compared to the allogenic ADSCs. Although ADSC yield from inflammatory bowel disease patients was higher [18], an in vitro study of mesenteric and subcutaneous fat tissue from Crohn's disease patients and healthy donors found that Crohn's disease patients' ADSCs expressed more proinflammatory (IL6, TNFA, CCL2, and IL1B), invasive, and phagocytic phenotype and reduced immunosuppressive properties [19]. Similarly, ADSCs derived from ulcerative colitis patients express an altered immunosuppressive profile consisting of lower prostaglandin E2, idoleamine 2, 3-dioxygenase, and TNF-alfa-induced protein 6 [20]. These findings suggest that ADSCs from donors with immune conditions may not be appropriate due to their deficiency in terms of immunomodulatory capacity.

4. Diabetes

Donor metabolic conditions could also alter the immunomodulatory activity of the ADSCs. Serena et al. found that obesity and Type 2 Diabetes promote the expression of a proinflammatory profile by the ADSCs [21]. Furthermore, Diabetes Mellitus hampers the secretory (through reduced secretion of VEGF, adiponectin, and CXCL-12) and proliferative activity, exhibiting mitochondrial disfunction and senescence phenotype [22]. These findings suggest that ADSCs from diabetic donors should be avoided as their initial characteristics predict altered functionality. However, it seems that ADSCs from different sites are also different in their characteristics. Therefore, not

surprisingly, ADSCs from peripancreatic fat tissue of diabetic patients were found to maintain the migration, immunomodulatory, chondrogenic differentiation capacities, stemness, and vitality as in non-diabetic subjects, while only adipogenic and osteogenic capacity were altered [23]. Osteogenic capacity of ADSCs from diabetic patients is a point of controversy, as other studies have suggested even increased osteogenic potential based on the mRNA level of *BGLAP, ALP,* and *SPP1* [24].

5. Obesity

Obesity is a well-known proinflammatory state [25]. Although some studies have not found differences in the ADSC yields and proliferation capacity [26][27], more recent studies, based on gene expression, have found important alterations. The altered microenvironment in morbidly obese patients, characterized by increased levels of pro-inflammatory cytokines, is found to impact the ADSC functionality [28]. Roldan et al. described a general short-circuit of the stemness gene network of ADSCs from obese donors [29]. Oñate et al. found that ADSCs from morbidly obese patients have a lower proliferation, differentiation, and proangiogenic capacity, as demonstrated by higher TSP-1 and VEGFR1 expression [30]. Although obesity is considered a factor that decreases the immunomodulation capacity of ADSCs [31], in a study of weight-discordant monozygotic twins, it was found that higher weight is related to a lower angiogenic capacity of the ADSCs, but the immunomodulatory activity was stronger, as well as the adipogenic differentiation capacity [32]. Furthermore, ADSCs from obese donors are found to induce an in vitro proinflammatory profile in murine macrophages and microglial cells [33]. ADSCs from obese donors (age and sex matched) produce smaller extracellular vesicles than lean ADSCs, with dysregulation of their miRNA cargo, which alters the cell capacity to modulate injury pathways [34]. These functional alterations caused by obesity seem to be donor site-dependent, as described in the paper of de Girolamo et al., where they found a higher degree of functional and stemness impairment within the visceral fat of obese patient [35]. The presence of metabolic syndrome in those patients could further worsen the ADSC osteogenic and proliferation capacity, which were generally found in obese patients [36][37].

6. Lifestyle Habits

An increasing number of studies are linking different lifestyle habits to the quantity and quality of ADSCs obtained from liposuction. For example, the use of e-cigarettes [38] and tobacco by-products, such as nicotine, have been shown to have a detrimental effect on the obtained ADSCs and their differentiation capacities [39][40][41]. Another example is that regular alcohol consumption induces a lower potential, as well as a decrease in the number of mesenchymal stromal cells [42][43][44].

7. Donor Site

Multiple studies have addressed the search for an optimal donor site to obtain the highest quantity and functionality of ADSCs. Studies oriented towards obtaining of fat grafts for the plastic and esthetic procedure purposes mainly inform on the cellularity and viability, and only some papers study the differentiation capacity. The lower abdomen

and inner thigh seem to yield higher cellularity with greater viability of the cells obtained from the upper abdomen [17][45][46][47], although the outer thigh has also been found to be favorable [48]. This fact itself would not necessarily translate into improved functionality. In fact, Jurgens et al. did not find any osteogenic differentiation capacity differences between different sites [47]. Other studies have found that ADSCs from flanks and thighs express an increased osteogenic and decreased adipogenic capacity compared to ADSCs from the abdomen [49]. ADSCs obtained from thigh subcutaneous fat were also found to have an increased angiogenic potential (higher VEGF, VEGF2, and CD31 expression) compared to abdominal fat tissue [50]. In the same study, the authors describe an increased adipogenic capacity in the thigh-derived ADSCs compared to the abdominal-derived ADSCs, in disagreement with findings from the paper cited above. Similar superior results were found with ADSCs from the gluteal fat tissue [51]. Within the abdominal subcutaneous tissue, it seems that superficial fat (above Scarpa's fascia) could have higher yield and adipogenic capacity, as well as increased multipotency and stemness [52][53]. Other possible sources of ADSCs have also been explored. Omental, percicardial, mediastinal, synovial, and other specific localizations of fat tissue have been studied in a limited number of studies, and their characteristics seem favorable for treatment purposes of inflammatory, regenerative, or ischemic issues of nearly located organs [23][54][55]. Although ADSCs from different sites express the same surface markers, they are proven to be genetically different and express different capacities. For example, epicardial and omental ADSCs were found to have a higher osteogenic and adipogenic potential than pericardial ADSCs, but only the epicardial ADSCs exhibit a high cardyomyogenic potential [55][56]. However subcutaneous ADSCs have higher proliferation and adipogenic capacity than visceral ADSCs [56][57][58].

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