Redundant Human Omentum Fat: A Leap Towards Regenerative Medicine

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Introduction

Mesenchymal stem cells possess a ground-breaking potential and appear to offer a wonderful opportunity, indeed a responsibility to understand important aspects of human biology involving tissue repair and regeneration [1, 2]. The ubiquitous existences of multipotent mesenchymal stem cells (MSCs) annex to be a regenerative tool rendering the replacement of worn-out cells. Researchers have averted their attention towards identification of various sources of adult mesenchymal stem cells from our own body tissues and fluids [3–11]. Despite the existence of several advantages and potentials of MSCs from several sources being investigated, bringing stem cells adaptable for regenerative medicine applications in adequate quantities at the right time is a challenge. This is with regard to the inevitable fact that the frequencies of mesenchymal stem cells and their proliferative capacities and differentiation potentials as well as phenotypical and immunomodulatory properties have been shown to vary among sources. Furthermore, cell-based therapies rely to a larger degree on the preparation of an effective dose of ex vivo expanded cells, capable of self-renewal and differentiation. The identification of physiologically relevant and ideal source of stem cells that might be more useful in clinical setting needs to be investigated to ascertain an assured quality in cellular therapy. Additionally, changing the perception, about the successful treatment of stem cells for various diseases, in the light of recent findings becomes mandatory to cure these diseases and further to broaden the potential applications of stem cells. Adult stem cell therapies are routinely used to treat diseases using umbilical cord blood stem cell transplants [12] and peripheral blood stem cell and bone marrow stem cell transplants [13–17] which are probably the most well-known therapy.

Although umbilical cord blood stem cells are a promising therapeutic determinant in regenerative medicine, their applicability is limited by the lesser frequency of MSC, HLA matching for allogenic transplantation as well as long-term storage difficulties in autologous transplantation [18]. The multitude of research on bone marrow and peripheral blood stem cell has proved them the most favourable candidate for autologous stem cell transplantation. The limitations of bone marrow and peripheral blood stem cells in terms of patient discomfort, reduction in yield and frequency of stem cells with age and body mass index, have forced the researchers to find alternate sources of stem cells [19–22]. In recent years, researches are heading towards identification of novel source of MSC from redundant tissue sources. The main factor that makes redundant tissue an attractive source of stem cell is its non-invasive nature and tissue abundance.

The major redundant tissue sources under research for stem cells are the umbilical cord tissue, cord blood, placenta, endometrial tissue, menstrual blood and subcutaneous adipose tissue. In view of the fact that most of the redundant tissue sources are pregnancy related, their applicability in

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autologous transplantation is limited to women as well as due to the aforesaid reasons to umbilical cord blood stem cells. In contradictory to the difficulties related to these sources, endometrial tissue and menstrual blood (maternity-related samples) have far wider applicability in autologous stem cell treatments. In comparison to all these above-discussed sources, yet another potent source recognised in the realm of adult stem cells similar to that of subcutaneous fat is the omentum fat that possesses far wider applicability as it is not even limited by the sex of the patient. Visceral or omentum (intra-abdominal) fat has attracted much interest than the subcutaneous fat as accumulation of excess of omentum fat is responsible for many metabolic abnormalities associated with obesity [23]. Besides, removal of omentum fat has a synergistic effect on their insulin responsiveness. This synergism arises from the higher rate of triglyceride turnover in omentum fat compared to subcutaneous depot, attributed to the decreased sensitivity towards the antilipolytic effects of insulin [24–26]. This indicates the significance of omentectomy in prevention of its deleterious effects. At the same time, although many accumulating evidences exist on the advantageous and applicability of mesenchymal stem cells derived from subcutaneous fat in therapeutics, the efficacy, feasibility and applicability of omentum fat-derived stem cells for clinical approaches remain unclear.

This chapter demonstrates an overview on the angelic and demonic side of the redundant human omentum fat. It reveals the imperativeness of omentectomy as a double-edged sword, whereby it plays an important role in reduction of pathophysiology associated with metabolic diseases as well as serves as an alternative therapeutic source for the treatment of wide range of diseases, as current research data had reported on the proliferative and multi-differentiation ability of omentum fat-derived MSC. This chapter will further confer consistency on certain unexplored aspects of the omentum fat. Overall, it is anticipated that this chapter will act as a reference for further exploration on these aspects and work towards the achievement of reduction in pathology associated with diseases as well as to create an environment where curative therapeutics can be successfully achieved using omentum fat-derived stem cell transplantation.

Omentum Fat: Angels or Demons?

White adipose tissue (WAT) present in the *omentum majus*, lying intra-abdominally between the abdominal muscles and the visceral organs, is called as omentum fat. It is also known as intra-abdominal fat, as it is located inside the abdominal cavity, packed in between organs (the stomach, liver, intestines, kidneys, etc.). It is considered to be a shock absorptive fat layer protecting the visceral organs from external impacts. Visceral or omentum (intra-abdominal) fat has attracted much interest than the subcutaneous fat as accumulation of excess of omentum fat results in production of very less fat-regulating adiponectin, leading to many of the metabolic abnormalities associated with obesity [23]. Consequently, it has become a key measurement for the definition of the metabolic syndrome [27]. These disorders include abdominal obesity, high blood pressure, high cholesterol and other risk factors associated with cardiovascular risk and type 2 diabetes risks in obesity [28, 29]. On the other hand, similar to the existence of subcutaneous fat-derived stem cells, there are evidences that omentum fat does possess putative stem cell population [30, 31]. Data reported that identification of putative stem cell population in omentum adipose tissue could represent a very useful tool to investigate, at the cellular level, the molecular mechanism and process involved in the onset of obesity and related metabolic dysfunctions. In addition, stromal cells isolated from human omentum fat were identified to retain the stem cell characteristics such as proliferative and multilineage differentiation potential inclusive of its angiogenic and regenerative potential [30–35]. Thus, just as either sides of the coin, omentum fat can be considered both as angels and demons of the body. Increasing the angelic activity and decreasing its demonic activity are of utmost importance for cure of various disorders and its regenerative therapeutics.

Omentectomy: A Double-Edged Sword

Humans have enormous quantity of omentum fat as that of subcutaneous fat, and it has been demonstrated from accumulating evidences that the omentum fat can be harvested for the isolation of stem cells, thereby providing omentum fat as a reservoir of stem cells. On the other hand, omentum adipose tissue is more closely associated with an adverse metabolic risk profile rather than subcutaneous fat. This is further supported by both animal and human studies [30, 31] demonstrating that subcutaneous adipose tissue liposuction influences BMI and overall weight, whereas only reduction of visceral fat can also substantially ameliorate metabolic parameters [36]. Thus, existing evidence supports the reduction of omentum fat tissue (omentectomy) to be beneficial in both ways and hence serving dual purpose, substantiating its imperativeness in pathophysiology as well as further stem cell-oriented clinical applications.

Pathophysiological Rationale for Omentectomy

The redundancy of excess omentum fat is reinforced by the pathophysiological complications associated with increased

omentum fat accumulation. Most of the epidemiological studies have correlated the relation between severe obesity and mortality due to increased rates of diabetes and cardiovascular and cerebrovascular diseases [37–42]. Adipose tissue is an endocrine organ which secretes peptide and protein hormones (adipokines) that regulate storage and release of energy [43]. The major adipokines of fat metabolism are adiponectin, leptin, visfatin, retinol-binding protein-4 and adipsin. Any dysregulation in the production or release of these adipokines results in metabolic disturbances leading to metabolic disorders. Adiponectin and adiponectin receptors are the major determinants which play a significant role in the aetiology of obesity-related chronic diseases [44]. High molecular weight (HMW) adiponectin is an important factor that controls the activity of the adiponectin receptors AdipoR1 and AdipoR2. AdipoR1 activates AMP kinase pathway resulting in adipogenesis and inhibition of lipolysis, whereas AdipoR2 activates peroxisome proliferator-activated receptor alpha (PPARα) pathway in liver leading to increased insulin sensitivity and decreased inflammation leading to their antidiabetic effects.

In view of the above-discussed positivity regarding adiponectin, several researches showed a reduction of adiponectin levels in patients with visceral/omentum obesity which is considered to be the reason for insulin resistance leading to type 2 diabetes and cardiovascular and coronary artery diseases [45–48]. Since adiponectin being an antidiabetic factor, its reduced production and release in obese subjects lead to chronic diabetes [49].

Leah Di Mascio and his co-workers identified that adiponectin is an essential factor for the proliferation and function of haematopoietic stem cells even in their niche [50], which may be a potential reason for the reduction in bone marrow volume in obese patients. Adiponectin has also proved its potential to induce adipocyte [51] and osteocyte differentiation [52]. The adipogenic effect of adiponectin causes the proliferation and differentiation of preadipocytes into adipocytes leading to its accumulation and obesity. There are also research outcomes suggesting the deleterious effect of omentum fat accumulation on androgen activity in female subjects. The androgen inactivation effect of omentum fat accumulation is considered to be due to the higher expression of 3α-hydroxysteroid dehydrogenase (3α-HSD) [53].

The preadipocytes of the omentum are also reported to mature into macrophages, which contribute to local immune and inflammatory responses. The formation of local immune factors such as dendritic cells in visceral fat leads to inflammatory conditions associated with Crohn's disease [54]. Further research confirms the role of visceral adiposity in the development of cardiovascular and cerebrovascular diseases. The reduced adiponectin levels associated with increased visceral adiposity cause development of inflammations and atherogenesis by the migration and maturation of monocytes and macrophages leading to their transformation into foam cells on vascular wall [55, 56]. Thus, omentectomy is emerging as a major treatment for chronic diabetes, whereby reduction in omentum fat leads to increase in production of adiponectin. In addition, omentectomy acts as a doorway towards diminutive pathophysiological deleterious effects, and it further moves a step forwards in annihilating several aforesaid debilitating disorders that occur due to accumulation of omentum fat.

Omentectomy: Promising Days in Regenerative Epoch

Harvesting of the redundant omentum fat obtained through omentectomy not only serves the aforesaid purpose but also harbours a highly heterogeneous population of cellular components that support its applicability in cellular transplantation for regenerative medicine. These heterogeneous cellular components of human omentum fat constitute the stromal vascular fraction (SVF) characterised by the abundance of preadipocytes, microvascular endothelial cells, mastocytes, fibroblasts, monocytes/macrophages, progenitor cells of bone marrow origin, leukocytes and granulocytes. The macrophage richness of omentum fat is comparatively higher than all other major adipose tissues. In fact omentum adipose tissue distribution and their cellular dynamics are determined by the proliferative and differentiation capacity of the preadipocytes. Despite the fact that SVF is a heterogeneous cell population, subsequent expansion of the SVF (preadipocyte culture) in vitro selects for a homogenous mesenchymal stem cell population that holds a greater potency for its cellular transplantation. The proliferative capacity of this adipose tissue was explored to be persistent with ageing compared to the subcutaneous adipocytes which lose its proliferative capacity with ageing [57].

These distinctive aforesaid properties of omentum fat highlight on the imperativeness of omentectomy for harvesting of stromal vascular fraction as well as homogenous mesenchymal stem cells that showcase omentum fat as a promising base for regenerative epoch. Thus, emphasising on the potential benefits of omentectomy as a double-edged sword creates a mass of attention in the midst of scientific community to research on yet another potent redundant source of stem cells, the omentum fat for its use in tissue repair and regeneration. Current research focusing on characterisation and culturing of omentum fat-derived MSC has proved its proliferative and multi-differentiation ability, guaranteeing its potential as a regenerative therapeutic source [30–33, 35]. However, there have been scanty citations with human omentum fat-derived stem cells, as the research is in its incipient stage. Hence, the efficacy and fea-

sibility of its application for clinical approaches remain unclear. This chapter had further paid attention to certain existing uncertainty by focusing towards the attributes of omentum fat-derived stem cells in view of its morphoproliferative capacity, biomarker expression and multitude differentiation potency.

Morphoproliferative Possessions

Isolation and morphological characterisation of a multipotent stromal cell population from visceral/omentum tissue have been reported to share the same morphological and electrophysiological properties of stem cells isolated from subcutaneous adipose tissue from the recent findings [30–33]. They report that omentum fat showed similar and homogenous fibroblast-like (Fig. 12.1) and similar ultrastructural organisation as detected by transmission electron microscope. In contrary, omentum fat-derived stem cells were found to differ morphologically than that of subcutaneous adipose tissue in some reports. Literature provided evidence for the omentum fat-derived MSCs being large and having more spread appearance, whereas subcutaneous MSCs have comparatively smaller size and varying morphology such as spindle-shaped neuron-like appearance [58]. Additionally, it was reported that omentum MSCs appeared to contain more fat droplets and were seldom granulated. This phenomenon was not observed in subcutaneous MSCs. It was also identified that omentum fat possesses more of blood-derived cell population than subcutaneous fat, whereas subcutaneous fat alone was identified to possess more of adipose tissue-derived cell population [30, 31]. Moreover, the comparison of replicative capacity of omentum preadipocytes to that of subcutaneous preadipocytes revealed that the proliferation capacity in subcutaneous preadipocytes was found to be superior to those of omentum cells since subcutaneous cells proliferate faster under in vitro conditions [33, 59]. On the other hand, the proliferative capacities of omentum adipose tissue were explored to be persistent with ageing compared to the subcutaneous adipocytes which lose its proliferative capacity with ageing [57].

Despite the existence of these uncertainties, omentum fat-derived mesenchymal stem cells had never lost the battle and provided evidence for it to withstand the unique characteristics of mesenchymal stem cells when competing with subcutaneous fat-derived stem cells in certain aspects. Omentum fat-derived MSC had evinced to retain its unique characteristics until extensive long-term culturing of greater than P10 as reported in literature [58]. It was confirmed by the presence of stable immunophenotypic characteristic of hMSC and the absence of any genetic transformations by stable karyotyping. However, it has been reported that omentum fat-derived stem cell exhibits the presence of CD34 and CD45 at later passages, exhibiting the presence of cells of other lineages than MSCs. A high demand on omentum fat-derived MSC applicability for clinical advances relies on the ease of their isolation, extensive capacity for in vitro expansion, their functional plasticity and retention of MSC characteristics in long-term culture condition without undergoing epigenetic changes. Although omentum fat has emerged themselves as a novel redundant source of stem cells substantiated with limited body of evidence, extensive expansion of MSC derived from omentum fat with exclusive retention of unique characteristics had not been reported yet.

In lieu of this, our group demonstrated and initiated the optimisation of culture condition for omentum fat-derived

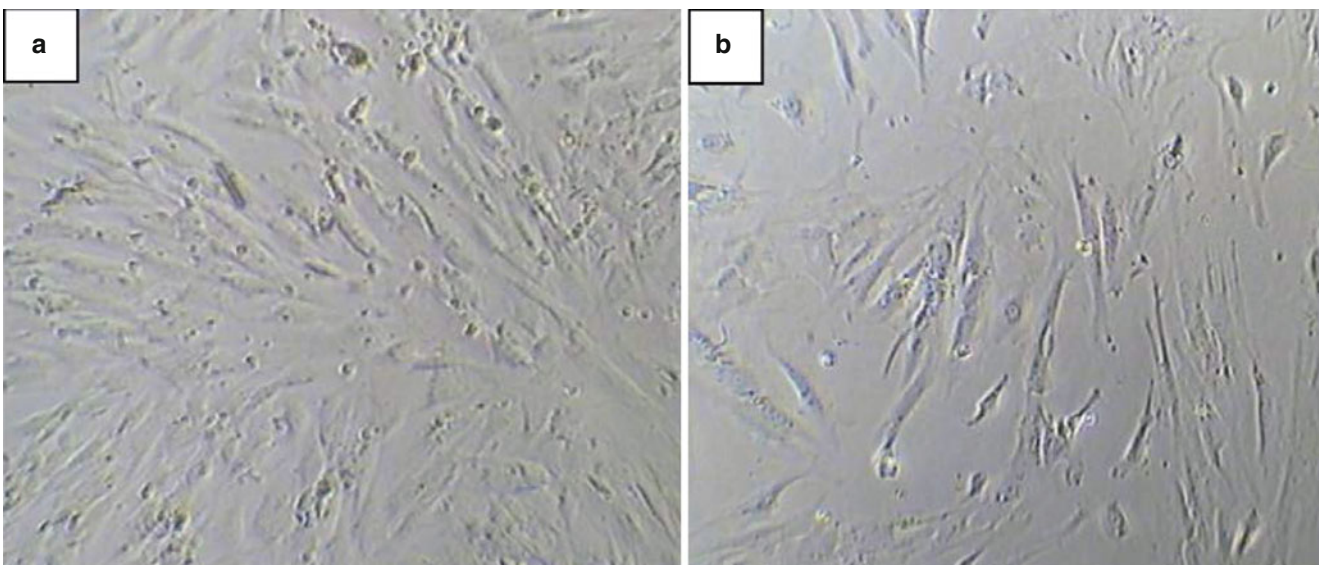

Fig. 12.1 Morphological appearance of mesenchymal stem cells derived from omentum fat

MSC by extensive culturing of these cells in different media. The study was carried out in view of its various attributes such as proliferation, phenotypic characterisation and differentiation potential, thereby exploring its imperativeness as a deserving candidature of stem cells. The study substantiated the results by all means by retaining its characteristic features under extensive culturing and hence identified as an alternative and additional redundant source of stem cells, thereby serving as an additional supportive data for enhancing its application in regenerative medicine [60].

Biomarker Expression Profile

While an extensive body of research exists pertaining to phenotypic characterisation of stem cells from bone marrow and subcutaneous adipose tissue, the phenotypic characterisation of omentum fat-derived stem cell is at its infancy. Though there is paucity on characterisation of omentum fat-derived stem cell until today, existing little evidence on immunophenotypic characterisation of omentum fat at early passage reveals the similarities on the expression of cell surface markers of omentum fat in comparison to the subcutaneous fat and bone marrow [1, 61–64]. Omentum fat was identified to express wide range of markers. The heterogeneous stromal vascular fraction isolated from omentum fat was found to express the cell surface markers specific for haematopoietic stem cells, mesenchymal stem cells, cell adhesion molecules, endothelial cells and other non-stem cell population as well (Table 12.1 and Fig. 12.2).

Although omentum fat has evinced themselves as a potent source of stem cells in certain attributes, there is no unique biomarker that can reliably be identified specific to omentum fat-derived stem cells. Identification of these unique markers potentially serves several purposes both in terms of identification of the cellular and molecular mechanism of the diseased status and specific markers of MSC, by which taking a step forwards from bench to bedside. From the expression profile of the markers identified so far in current studies, it was presumed that, under culture condition, the omentum fat expresses remarkable expressions of the MSC markers (CD90, CD105 and CD73) as reported by ISCT [65] and also expresses various cell adhesion molecules such as CD29, CD44, CD31, CD106, CD54, CD49d and CD166 favouring the migratory and regenerative potentialities of omentum fat-derived MSC. In addition, the cell surface markers such as CD34, CD31, CD45, CD133 and HLA-II were found to be decreasing/negative in its expression [30, 32, 33, 35, 58] (Table 12.1). Apart from the expression of the routine cell surface markers, omentum fat also possesses the expression similar to the expression of embryonic stem cell marker such as Oct 4, Sox 2, Nanog and so on. This explains not only its multipotent nature but also pluripotent property of omentum fat, thereby enhancing its applicability (Table 12.1).

Table 12.1 Cell surface marker expression profile of freshly isolated SVF versus cultured MSC derived from omentum fat

Markers	SVF	OF-MSC
CD45	+	–
CD31	+	–
CD34	+	+
CD105	+	+
CD14	+	–
CD44	+	+
CD29	+	+
HLA-I	+	+
HLA-II	+	–
CD106	+	–
CD146	ND	–
CD90	+	+
CD13	ND	+
CD133	+	–
CD73	+	+
CD49d	–	+
CD166	–	+
CD54	+	+
ABCG2	–	+
ALDH	+	+
CD117	+	+
LIF	ND	+
Keratin 18	ND	+
SOX2	ND	+
Nanog	ND	+
Oct-4	ND	+
SSEA-1	ND	+
SDF-1α	ND	+
CXCR4	ND	+
WT-1	ND	+
VEGF	ND	+

Refs. [30, 32, 33, 35, 58]
SVF stromal vascular fraction, *MSC* mesenchymal stem cells, *OF* omentum fat

The marker positivity explained involves its expression pattern in early passage condition. However, retention of its marker positivity for longer culture period substantiates the identification of unique marker specific to MSC derived from omentum fat. Thus, results obtained from our study emphasise the fact that all media articulate almost similar expressions of all the markers except slight variations. Two attributes clearly became evident regarding the withholding capacity of the cell surface marker expression until extensive culturing. Firstly, as omentum fat does not lose its phenotypic characteristics in prolonged culture condition and maintain the similar phenotypic expression throughout, it deserves to be an efficient alternative source of curative therapeutics. Secondly, it is evident that five media inclusive of

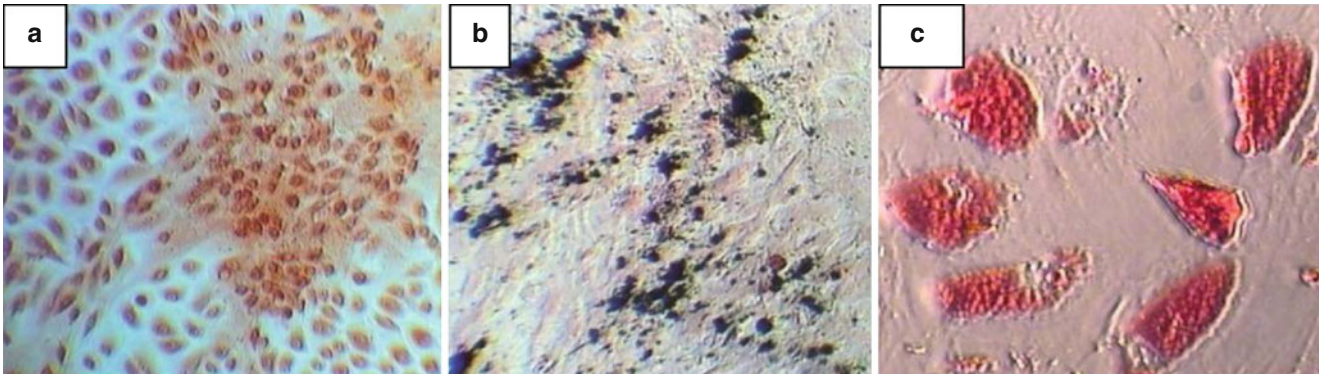

Fig. 12.2 Confirmation of osteogenesis and adipogenesis: (**a**) alizarin red staining and (**b**) von Kossa staining of osteoblast calcium deposits; (**c**) oil red O staining of lipid vacuoles in adipocytes

lower and higher glucose concentrations do not affect the phenotypic expression profile of these cells in longer passages [unpublished data]. Hence, it can be concluded that omentum fat can be regarded as an efficient alternative source of curative therapeutics with regard to the cell surface antigenic expression profile. However, other attributes such as its multitude differentiation ability are mandatory to confirm the potency of omentum fat-derived stem cells.

Multitude Differentiation

Adipose-derived stem cells have been proved to be capable of multilineage differentiation [66, 67]. As stem cells from adipose tissue have their origin in the mesoderm, it is no longer surprising that these cells can undergo different mesenchymal lineage conversions. Accordingly, omentum fat-derived stem cells have a higher capacity to differentiate into both osteogenic and adipogenic lineages. It was noted that, however, omentum fat differentiation into adipocytes is inferior to that of subcutaneous fat [33, 68]. When maintained in appropriate inductive medium, omentum fat-derived stem cell cultures displayed in vitro multipotency and were proved differentiation towards specific lineages. Omentum fat-derived stem cells were able to differentiate into mesodermal lineages of adipogenic, osteogenic and chondrogenic lineages. The differentiation ability of omentum fat-derived stem cells was first identified in rat in the year 2003 by SS Tholpady and his co-workers [31]. They reported that the visceral fat of rats contains MSCs with multilineage differentiation ability like subcutaneous fat despite the well-documented difference in the metabolic and biochemical properties among anatomically distinct depots of fat.

Later, multilineage differentiation potency of human omentum fat-derived stem cells as compared to human subcutaneous fat became evident [33, 68]. Additionally, the property of lipolysis of both differentiated adipocytes derived from omentum fat and subcutaneous fat was evaluated. Besides adipogenic differentiation, osteogenic differentiation of human omentum fat-derived stem cells was also identified. The presence of mineralised calcium nodules was confirmed in vitro using different staining methods such as alizarin red and von Kossa. It was also verified using the presence of genes for the osteoblast. It was identified that the omentum fat-derived stem cells were inferior in osteogenic differentiation when compared to subcutaneous fat. It is apparent that there are scanty citations of differentiation potential of omentum fat, thus creating an uncertainty in the efficacy of the differentiation potential of omentum fat.

Transdifferentiation

It was not surprising that the mesenchymal stem cell being mesodermal in origin differentiated into mesodermal lineages. To possess the attributes of mesenchymal stem cells, it is noteworthy that the omentum fat-derived MSC should undergo transdifferentiation. The ability of its transdifferentiation capacity will provide evidence for its plasticity and regenerative potency of omentum fat-derived stem cells. Although the existence of MSC is demonstrated with its multilineage mesodermal differentiation, not much is studied with respect to its transdifferentiation ability. Tholpady and his co-workers had reported that the rat omentum fat-derived stem cells could differentiate not only into the mesodermal lineages of osteocyte, adipocyte and chondrocyte but also undergo neuronal differentiation [31]. This phenomenon of differentiation of omentum fat-derived stem cells into neuronal lineage was also studied by Paul Kingham [69]. However, until recently, transdifferentiation of omentum fat-derived stem cells to other lineages was not demonstrated yet. It is of paramount importance that omentum fat-derived MSC possesses the ability to transdifferentiate in multitude of lineages before it has been considered efficient in regenerative medicine. However, regenerative potency of the omentum

fat-derived mesenchymal stem cells has also been elucidated by Rahim and his co-workers [34]. It was described that the freshly isolated whole cell population of omentum fat can regenerate sciatic nerves when injected into a mice model. They concluded that it may consider clinically as a translatable route towards new methods to enhance peripheral nerve repair without the limitations of BMSCs in clinical application. This reveals the fact that omentum fat can be considered further for study in the emerging field of regenerative medicine and surgery.

As omentum fat is associated with the metabolic disorders such as diabetes, it is noteworthy that besides being a potent source of MSC, removal of omentum fat from diabetic patients for the treatment of diabetes has a synergistic effect on their insulin responsiveness. This synergism arises from the higher rate of triglyceride turnover in OF compared to SF depot, attributed to the decreased sensitivity towards the antilipolytic effects of insulin [30, 31]. Hence, the wonder-working potential of the transdifferentiation of omentum fat-derived MSC into pancreatic islet-like clusters might bring a new era in the field of diabetology. Our group identified that the preliminary data on transdifferentiation of omentum fat-derived stem cells into pancreatic islet-like cluster revealed a positive expression of certain specific genes and morphological islet-like cluster [60].

Concluding Remarks

Overall, the wealth of knowledge on the biological function of white adipose tissue, especially omentum fat, has evinced them as an endocrine organ that is strongly associated with metabolic complications of obesity leading to debilitating diseases such as diabetes and cardiovascular diseases. On the other hand, new insight on omentum fat emerged when studies reported the existence of stem cells and emphasised its pivotal role in tissue repair and regeneration, thereby paving way for the researchers to identify both the angelic and demonic side of omentum fat. This further created an environment for the researchers to explore the imperativeness of double-edged sword of omentectomy, whereby working towards annihilating several aforesaid debilitating disorders that occur due to accumulation of omentum fat, on one side, and achieving curative therapeutics using omentum fat-derived stem cell transplantation, on the other side.

Furthermore, the perception of the far wider potential of mesenchymal stem cells derived from omentum fat has led to considerable excitement and a leap towards potential therapeutic applications in regenerative medicine and tissue engineering. Nevertheless, the incipient stage of the research on omentum fat-derived stem cells and its potential application becomes a major stumbling block for its advancement in regenerative medicine. Hence, a lot needs to be explored, inclusive of its proliferative and multitude differentiation ability, to rationale omentum fat as a successful redundant source of stem cells.

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