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Abstract

Breast cancer diagnoses may necessitate a bilateral or unilateral mastectomy; this involves the removal of breast tissue and affected surrounding area. Breast reconstruction to restore pre-surgical appearance has become commonplace as the rate of breast cancer incidence has increased. Shortcomings and frequent complications with these treatments have resulted in the proposition that established treatment methods be supplemented with adipose-derived stem cells (ADSCs) collected from the patient. ADSCs may be isolated from adult adipose tissue and are widely applicable in stem cell therapeutics due to their unique characteristics such as pluripotency and widely observed paracrine effects. Although concerns have been voiced over safety and efficacy due to ADSCs' purported role in oncological processes when employing in vitro or non-human models, a vast majority of experiments have suggested that this is a promising treatment method and may help moderate postoperative complications. Further studies are necessary to review clinical benefits and establish standard results and practices.

Introduction

Cancer is a common biological disease caused by the unregulated proliferation of cells which eventually results in body tissue destruction and patient health degradation. Clinically, cancer is defined by the body part in which cell abnormalities originate; breast cancer is among the most common forms. A secondary analysis of globally documented cancer occurrences found that as of 2020, breast cancer surpassed lung cancer as the most prevalently diagnosed form of cancer worldwide (Cao et al. 2021). It is also cited as one of the five leading diagnoses in cancer-related death.

The American Joint Committee on Cancer has produced eight editions of the TNM Staging System, a standardized staging system that determines cancer prognosis using tumor size (T), spread to lymph nodes (N), and the presence or lack of metastasis (M) (Koh and Kim 2019). As identified by Maughan et al. 2010, the stages of cancer are as follows: Stage 0 refers to the presence of abnormal tissue growth contained within a portion of the breast and no observed invasion of abnormality to surrounding tissue. Stages I and II are considered early-stage invasive breast cancer. Stage I is designated by either the presence of a primary tumor less than or equal to two cm in size without axillary nodal involvement or axillary micometastases, clusters of tumor cells between 0.2 mm and two mm in size, with or without a primary tumor less than or equal to two cm in size. Stage II is designated by larger tumors or increased lymph node involvement in comparison to Stage I. Stage III is known as locally advanced breast cancer, as the primary tumor has exceeded five cm in size, has become inoperable without distant metastases, or abnormalities have spread to the chest wall or underlying skin. At Stage IV, the cancer has become metastatic and spread beyond local regions, such as to the bones, liver, or lungs.

For stages I to III of breast cancer, a partial removal of only the affected breast tissue (lumpectomy) or mastectomy combined with chemotherapeutic drugs is the common form of treatment. A mastectomy consists of the surgical removal of affected breast tissue, including the nipple and tissues covering the chest musculature (Bianchini et al. 2016). The complete removal of this organ may cause patients to feel mutilated, less attractive, and depreciated; post-mastectomy patients with low physical self-esteem display significant linear correlations to low amounts of hope and depreciation in mental wellbeing (Heidari and Ghodusi 2015). As a result, some patients may elect to undergo reconstructive surgeries of the chest to restore a semblance of preoperative appearance. Individuals that pursue reconstructive surgery display a lower incidence of symptoms related to depression or anxiety (Bredicean et al. 2020). Hence, the outcomes of these surgeries play a pivotal role in not only the confidence, but also the general well-being of the patient.

Various techniques are employed for breast reconstruction involving synthetic implants, patient-derived lipotransfer, or both. Although these methods are standard, postoperative success has been riddled with sequelae since their conception. Silicone and saline prosthetics are the modern forms of breast implants. Silicone models used today are typically derived from silicone gel, but more than 200 separate models have been proposed since their introduction to the United States in 1962 (Powell et al. 2021). Evolved manufacturing provided later versions with more natural breast contour, and new implant anchoring designs have improved stability, yet there are still frequent complications observed such as contracture of the implantation pocket (narrowing of implant pocket due to build-up of scar tissue), infection, and high incidences of rupture as the implants age (Powell et al. 2021). Hedén et al. (2006) observed that in a total of 106 women with at least one Inamed-brand silicone breast implant postoperative rupture incidences occurred after 10.9 years. Increasing public concern over the incidence of implant-related risks led the Food and Drug Administration to temporarily restrict the usage of these prosthetics, only approving updated models for reintroduction to the market as of 2012 and 2013 (Kaoutzanis et al. 2019). Original saline implants were first used in France in 1965 and were initially favored because a smaller incision was necessary for insertion in comparison to silicone models. Early designs were extremely prone to rupture; however, this issue became relatively resolved when the implant model was reworked. Despite this, the new design proved to be similarly problematic as palpation of these prosthetics offered a comparable feel to that of water rather than viscous breast tissue and yielded an unnatural inflexibility if overfilled. They are now primarily used in patients with thick tissue as they are prone to provide a more synthetic feel without proper tissue padding. Currently, patients and surgeons alike still experience a variety of postoperative difficulties when using either type of synthetic implant, including capsular contracture of the implant pocket, hematoma (accumulation of blood), seroma (accumulation of plasma or lymphatic fluid), infection, postoperative separation of incision, implant migration, rupture, and patient dissatisfaction with results (Siggelkow et al. 2004).

Lipotransfer, also commonly referred to as fat grafting or fat transfer, is another method used to reestablish breast volume. Fat grafts are taken from the patient and redistributed to the breast to supplement the implant and provide natural volume restoration. In general, modern liposuction involves the transplantation of undesired subcutaneous deposits to newly identified locations (Van Milligen et al. 2006). Autologous collection decreases the risk of tissue transfer rejection and allows for more optimal volume enhancement. Common donor sites are the abdomen, hip, and thigh. Predicating liposuction's conception in the 1970s, the use of sharp carving instruments for subcutaneous sculpting of excess hereditary adipose-tissue deposits or significant incisions for simultaneous resection of fat and skin were standard practice (Coleman 1999, Venkataram 2008). However, both methods provided varied, less

than desirable results; unnatural deformities caused by reaccumulated fat around the incision, frequent hematomas and seromas, and further complications yielded low patient satisfaction. As a result, Italian surgeons Arpad and Giorgio Fischer designed a hollow, blunt cannula attached to a suction source for crisscrossed adipose collection from multiple sites; this was the prototype for the modern liposuction instrument (Fischer and Fischer 1976). "Wet liposuction", where a solution of saline and hyaluronidase is injected pre-procedure, became the popular method of collection due to the vasoconstriction offered by this approach (Illouz 1983). Current practices have taken this methodology and expanded upon its approach to develop a procedure termed "cell-assisted lipotransfer", or CAL.

Adipose-derived stem cell assisted lipotransfer (ADS-CAL) involves conjunctive use of adipose-derived stem cells and autologous fat transplants as a solution for typical lipotransfer's unpredictable outcomes and frequency of graft necrosis (Yoshimura et al. 2008). Stem cells are self-renewing cells found in most multicellular organisms that are uniquely capable of producing terminally differentiated cells of various germlines while maintaining their undifferentiated state (Zakrzewski et al. 2019; Hima Bindu and Srilatha 2011). Cell differentiation is the highly regulated process in which non-specialized cells develop unique characteristics, such as cell shape or extracellular signal responsiveness, to become mature cells of unique function. The broad category of stem cells may be further classified by several increasingly specified characteristics, such as the number of different cell lineages they can produce (potency) and specific cell-surface antigens (clusters of differentiation or CDs) (Zakrzewski et al. 2019). Adipose-derived stem cells are tissue specific stem cells present in adult adipose tissue that are capable of meso-, ecto-, and endodermal cell differentiation (Bunnell et al. 2008). They are ideal for use in regenerative medicine due to the ease with which they can be harvested and transplanted, large population size, and reproducible differentiation patterns (Bunnell et al. 2008; Naderi et al. 2017).

As a direct result of ADSC attributes, ADS-CAL procedures may provide the recipient with enhancements in graft retention by inducing angiogenesis and ideal wound repair factors, leading to an improvement in patient-desired aesthetics. Others have proposed that this treatment could pose a threat to patient safety due to their poorly understood, but suggested, role in tumorigenesis or metastasis. This is of relevance to those undergoing reconstructive breast surgeries as they are typically women with a history of cancer. Promotion of favorable tumor conditions may put them at high risk of metastasis or redevelopment during their remission. The primary aim of this review is to characterize adipose-derived stem cells in consideration of their efficacy and patient safety to discern whether ADS-CAL should be considered a highly regarded method for breast reconstruction.

Adipose-Derived Stem Cells: Systematic Definition, Nomenclature, and Historical Observations

Stem cells may be categorized by the degree to which they are able to differentiate, developmental stage presence, tissue location, and expressed cell-surface receptors (CDs). All these characters lend themselves to capabilities that foster observed post stem cell treatment effects.

Potency

Potency refers to the degree of mature cell type differentiation a stem cell is capable of (Hima Bindu and Srilatha 2011). Unipotent cells are the most limited, only capable of producing a singular cell type, but they still exhibit self-regenerative mechanisms; they are highly regarded for therapeutic applications due to their narrow maturation trajectory (Argentati et al. 2018). Oligopotent classes can differentiate into a limited number of mature cell types (Hima Bindu and Srilatha 2011); a common example are myeloid stem cells which are capable of white blood cell, but not red blood cell, differentiation (Zakrzewski et al. 2019). Multipotent stem cells are those that can differentiate to a greater degree, but only to cells of closely related family groups. For example, human hematopoietic stem cells may differentiate into several blood cell types (Argentati et al. 2018). Pluripotent stem cells are those that can differentiate into cells of the three germ layers to produce any mature cells of the adult organism, only restricted by their inability to differentiate into embryological structures like the placenta. They are largely represented by embryonic stem cells derived from embryos during development. Totipotent cells may differentiate into all cell types, including extraembryonic structures, and are only observed during the first 4 days of development following spermatic fertilization of the ova. The large population sizes of pluripotent and totipotent cells arise from their asymmetric method of self-replication; pluri-/toti- potent cell division produces two daughter cells, one that retains the parental stem cell phenotype and one that exhibits mature cell characteristics (Argentati et al. 2018).

It should be noted that while adipose-derived stem cell potency is often designated multipotent due to their mesenchymal origins, they have displayed maturation into non-familial cell groups such as myogenic differentiation when treated with promyogenic conditions (Mizuno et al. 2002; Dominici et al. 2006). As they have shown their ability to differentiate into non-familial germlines, the pluripotent label supplied by Zuk et al. (2002) is corroborated (Savoia et al. 2017; Simonacci et al. 2019; Ong et al. 2021). Their unique degree of potency may be responsible for the notable postoperative effects discussed later in this review.

Developmental Stage

Stem cells are further categorized by their presence during certain stages of development. Totipotent cells are only observed after blastocyst formation during early embryonic development. While these cells are desirable for their unrestricted differentiation potential, they are only present and collectable for short periods of time; their safety due to the lack of restriction and morality of collection requirements prevents any in vivo applications (Zakrzewski et al. 2019; Hima Bindu and Srilatha 2011). Fetal stem cells (FSCs) are pluripotent cells residing in fetal organs that may be collected from fetal blood, tissue, or bone marrow. As with the previous stem cell group, their usage is complicated and riddled with moral dilemmas. In 2001, President Bush fully prohibited federal National Institute of Health funding for research involving derivatization or use of any FSCs (Lo and Parham 2009). Research for their medical application is minimal as a result. Adult mesenchymal stem cells (Adult MSCs), or tissue stem cells, persist within the niche of developed organs and tissues of adult organisms (Argentati et al. 2018). Adult MSCs were first reported following the observation of cells with the capacity for osteogenic differentiation (Friedenstein et al. 1968, 1974). Due to advancements in collection methods, Zuk and co-authors were able to positively identify the presence of adipose-derived stem cells by collecting human-adipose tissue via liposuction, and subsequently isolating what was described as a population of "fibroblast-like cells" (Zuk et al. 2001). Initially labeled as processed lipoaspirate (PLA) cells, their behavior suggested they were a newly discovered population of pluripotent, multi-germline potentiated cells, closely related to MSCs. This was later confirmed after extensive biochemical and molecular characterization identified similarities between the following: CD surface antigens, induced product differentiations, and lineage-specific metabolic activities (Zuk et al. 2002). However, further testing began to distinguish PLA cells from MSCs by their unique capacity for chondrogenic and myogenic differentiation, expression of group-specific CD antigens (CD49d+, CD106-), possible variations in genomic expression, and ability to be characterized independently of sera screening (Zuk et al. 2001). Adipose-derived stem cells of adult adipose tissue origin may be largely collected without major ethical or political controversies as the adult donors are able to provide informed consent.

Tissue-Sites

Tissue-sites, where cells are collected, lend themselves to the nomenclature of stem cells but do not give rise to the cells themselves. The tissue location of stem cells also contributes to their medical relevance. Mesenchymal stem cell (MSC) is the hypernym for all adult stem cells that arise from mesenchymal tissues with adipogenic, osteogenic, or chondrogenic differentiation capabilities (Argentati et al. 2018). Adult MSCs can be found in almost all postnatal organs and tissues, most notably bone marrow and white adipose tissue (Ong et

al. 2021). Adipose-derived stem cells are considered MSCs specifically derived from adipose tissue (Dominici et al. 2006), but are notably populous in subcutaneous fat deposits. As a result, there is an additional benefit for usage when considering the anatomical region ADSCs are derived from. Non-ADSC MSCs are most often procured from bone marrow (BM) through the introduction of a biopsy needle to the collection site; standard methods yield aspirated samples from consecutive heterosite needle insertions (Sivasubramaniyan et al. 2018). Procurement of BM is a highly invasive and painful procedure that necessitates a substantial application of anesthesia (Berebichez-Fridman and Montero-Olvera 2018). In contrast, the lateral location of adipose tissue allows for relatively painless harvesting with minimal invasiveness, increased safety, and avoidance of donor morbidity (Coleman 2001, Nordburg and Loboa 2015).

Surface Antigens

To standardize characterization and provide a uniform nomenclature for cross-referencing, The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy put forth a minimal set of criteria for human MSCs that has been adopted by those in relevant fields of study. Cells designated as MSCs must (1) adhere to plastic in standard culture conditions, (2) be CD44+, CD105+, CD73+ and CD90+, (3) be CD45-, CD34-, CD14- or CD11b-, CD79α- or CD19- and HLA-DR-, all of which are positive indicators for hematopoietic stem cells, and (4) show osteogenic, chondrogenic, and adipogenic differentiation in vitro (Dominici et al. 2006). Specificity beyond this is limited by inadequate knowledge of stem cell "heterogeneity", a term used to describe the differences in morphology and phenotypes of cells regarding factors such as cell-specific antigens, the predilection for certain mature cell types, and genetic expressions (Mabuchi et al. 2021). Currently, CD90+, CD44+, CD29+, CD105+, CD13+, CD34+, CD73+, CD166+, CD10+, CD49c+, CD59+, and CD31 are all frequently characterized in ADSC results. The presence of CD31, more commonly known as PECAM-1, is particularly of note for therapeutic usage of ADSCs due to its modulating effects on endothelial junction activity in inflammatory or thrombotic conditions (Lertkiatmongkol et al. 2016). Additionally, the unique expression of cell-surface antigens allow ADSCs to induce a variety of other ideal paracrine effects on surrounding cells due in part to their secreted paracrine factors (Sikora et al. 2021, Argentati et al. 2018). The "paracrine effect" is a mechanism by which donor cells signal surrounding cells to repair diseased tissue without the signaling donor cells directly contributing to the new tissue. However, the positive presence of other antigens such as CD90 and CD44 provide support for arguments against widespread usage as these are two identified cancer stem cell (CSC) markers (Ong et al. 2021; Su et al. 2011).

Cell-Assisted Lipotransfer: An Adaptation of the Body's Natural Repair System

There has been a notable increase in the usage of ADSCs as test subjects in stem cell research for therapeutic application. Collected samples yield a high number of cells per tissue volume, proliferation rates are more pronounced than other MSCs, and ADSC products or surface receptors have been shown to induce regulatory effects on paracrine activity, inflammation, angiogenesis, apoptosis, and immune response (Sikora et al. 2021; Naderi et al. 2017; Merrick et al. 2019; Iyyanki et al. 2015; Tsekouras et al. 2017b; Cheng et al. 2021; Ong et al. 2021). Stem cells occur naturally within the body and have inherent roles within the body's mechanisms. ADSCs serve as an ideal repair source for breast tissue, as their adipose-tissue location predisposes their differentiation to preadipocytes and produces favorable aesthetic enhancement (Ong et al. 2021). As liposuction already involves the procurement of these adipose tissues, methods for aspirate enrichment with ADSCs have been developed through a natural progression. Coleman first reported what was eventually adapted as standard practice for adipose-tissue harvesting via liposuction: (1) The patient is administered a localized anesthetic, or general anesthetic upon request, to induce vasoconstriction and the harvesting site is sterilized, (2) a stab incision is made by a blunt, two-hole syringe attached to a cannula with a large entry portal, (3) collection of fat deposits proceeds, (4) collection syringe is centrifuged and 3 layers result, (5) the top layer of oil byproduct is poured off and the bottom aqueous layer of lidocaine, erythrocytes, and blood plasma is drained, (6) a 17 gauge syringe is attached to a Coleman Infiltration Cannula (Coleman 2001). Subsequent placement of adipose tissue into the breast occurs by numerous small passes using gentle pressure to deposit isolated fat in extremely small quantities of ideally only 0.2-0.5 mL within any one pass.

The procedure for cell-assisted lipotransfer (CAL) requires an additional step following the collection of aspirated samples using modified Fischer cannulas. The stromal vascular fraction (SVF) of aspirate adipose tissue is isolated during centrifugation and used to enrich progenitor cells in the graft before placement occurs (Yoshimura et al. 2010). In the initial trial of CAL, noticeable augmentation was observed, and postoperative atrophy of the fat grafts was minimal (Yoshimura et al. 2008). Follow-up measurements of postoperative results after 12 months found that the surviving transplant volume was 155 +/- 50 mL on average in the right breast and 143 +/- 80 mL in the left after an initial CAL of 264 mL (Yoshimura et al. 2010). Following this trial, the usage of ADS-CAL was highly recommended for further evaluation.

Evidenced Merits for Liposculpture with ADSC Assistance

Though implants and fat grafts are considered a relatively effective way to aesthetically augment breasts, they have a plethora of undesirable secondary effects that may arise. Loss of implant integrity and minimal retention of grafts can confound surgical outcomes, necessitating remedial surgeries or the removal of the implant altogether (Siggelkow et al. 2004). In a study of implant-related complications, 53 women, some of whom underwent cosmetic implantation and others who required implants for reconstructive purposes, were observed for post-operative sequela; 28 patients had a total of 35 complications, 21 patients had one, five patients had two, and two patients had three (Siggelkow et al. 2004). Siggelkow et al. 2004 additionally found there were also notably higher occurrences of complications in patients undergoing surgery for reconstructive purposes ($P < 0.02$). Graft retention following placement displays undesirable and common hindrances as well: they may quickly degrade due to ischemic cell damage, be encapsulated after incorrect implantation, or become calcified if transplant volume is sizable (Savoia et. al 2017). The introduction of ADSCs to lipoaspirate has shown an ability to minimize many of these issues.

Aesthetics

As breast reconstruction is an elective cosmetic surgery, one of the necessary outcomes is improvement in the chest's aesthetic. ADSCs have been shown to aid in a more ideal implant outcome by supporting correction of breast defects and overall asymmetries. In one clinical trial involving two female patients that had received reconstructive surgery, ADSC-rich autologous fat transplants were administered, and, in both cases, patients exhibited significant contour improvement with no further complications (Tsekouras et al. 2017a). Another clinical trial performed by Ito et al. (2017) treated 10 females with ADSC-enhanced fat grafts to observe the long-term aesthetic benefits of ADS-CAL. After 7.8 ± 1.5 years, six of the nine available patients reported "more than or equal to average" satisfaction with the appearance of their postoperative breasts, and five of nine reported "more than or equal to average" overall satisfaction. A metanalysis on studies comparing the aesthetic outcomes of ADS-CAL versus standard lipotransfer found that of the 17 weighted preclinical trials, 15 of them favored CAL for improvement of weight and volume; six of the seven clinical trials favored CAL (Toyserkani et al. 2016). Reconstructive surgeries partially seek to replace the lost tissue volume, so evidenced improvements in volume retention post-treatment suggest ADS-CAL is effective in achieving aesthetic improvements.

Regulation of Inflammatory Factors Promotes Implant Retention

Capsular contraction wherein scar tissue tightens around an implant is a high incidence complication that leads to implant displacement (Sood et al. 2017). This is suspected of arising from implant site fibrosis induced by complex inflammatory responses. Several methods, such as massaging the tissue postoperatively, have been postulated to have preventative benefits, but the efficacy of these techniques is unsubstantiated. In contrast, secreted factors from ADSCs perform a documented regulatory role in the inflammatory and immune response that may reduce the likelihood of capsular complications. Sikora et al. (2021) performed an in vitro experiment on human limbal epithelial stem cells treated with a derived ADSC-conditioned medium to observe effects on the genetic expression of pro- and anti- inflammatory factors relative to cytokine secretion. Levels of cell viability, cytotoxicity, apoptosis, and cellular proliferation were recorded in induced inflammatory and standard conditions; results suggested that ADSC paracrine activity played a role in the regulation of factor expressions associated with autoimmune function in response to outstanding infection. ADSCs secrete IL-6, an interleukin directly responsible for the regulation of cell viability, cytotoxicity, apoptosis, and cellular proliferation levels which contribute to epithelial cell maintenance during wound healing.

Similarly, ADSC effects on levels of cytokines promoting inflammation and bone morphogenic proteins induced by inflammation were observed during an in vivo experiment where ADSCs were applied to murine specimens with surgically induced osteoarthritis (Cheng et al. 2021). ADSCs displayed regulatory effects on pro-inflammatory factors by reducing IL1-β (pro-inflammatory cytokine) expression and lowering apoptotic rates. They additionally upregulated the expression of crucial structural components in the cartilage. To observe these effects in a breast implant setting, a separate in vivo study was conducted on rabbits to see if adipose-derived stem cells affected the outcomes of implant reconstruction after engraftment to the acellular dermal matrix (Jin et al. 2017). Silicone implants were inserted into 16 rabbits randomly assigned to control or experimental treatments, and histological analysis was collected at the one and three-month marks. Data comparison showed that there was an increase in gene expression related to angiogenesis and inflammation, suggesting that ADSCs aid with the early incorporation of donor tissue. With the regulation of postoperative inflammation, the likelihood of fibrosis and thereby contracture of the capsule would be reduced, resulting in a decreased frequency of implant migration. Furthermore, ADSCs have been shown to lessen the amount of time required for complete wound healing due to their ability to differentiate into new epithelial cells and promote the formation of granulated tissue (Gawronska-Kozak et al. 2018), which would reduce probability of infection at the incision and diminish recovery time for patients following implant placement.

Regulation of Angiogenesis and Degree of Potency Increases Graft Retention

Following adipose-tissue transplantation, three zones become distinct: (1) the superficial surviving zone where old adipocytes and stem cells remain, (2) the regenerating zone in which only ADSCs survive, and (3) the necrotic zone where both adipocytes and ADSCs die due to the ischemic conditions (Caldeira et al. 2018). After 12-weeks post-operative in human patients, the measurable adipogenesis within the graft reaches completion, but the regenerating zone continues to stabilize with the assistance of resident ADSCs (Kato et al. 2014). Non-enriched fat grafts without supplemented populations of ADSCs in human recipients have displayed 45.1% retention during four-month postoperative evaluations, while those with supplementation have displayed retention of 80.2% of graft volume on average (Kølle et al. 2020). In a preclinical trial using porcine models, a 41% enhanced retention rate was observed in all enriched grafts with no noted difference in morphology when compared to non-enriched controls (Rasmussen et al. 2019). These observations may be a result of ADSCs' ability to promote angiogenesis, thereby increasing fat graft retention by reducing ischemic adipocyte apoptosis. ADSCs' ability to regenerate endothelial cells can counteract ischemic complications by increasing the perfusion of blood and promoting proper vascular reformation, thus minimizing the size of the necrotic zone. One study utilized the acellular dermal matrix (ADM) of mice combined with human ADSCs in an in vivo murine model to investigate regenerative capabilities on full-thickness cutaneous wounds (Huang et al. 2012). Subjects treated with ADM ADSCs had improved granulation (tissue growth as part of the healing process), an increased rate of re-epithelialization, and a greater blood vessel density.

Similarly, ADSCs have shown efficient production of cell sheets by increasing paracrine secretions in the extracellular matrix with or without collagen sheets, meaning their reconstructive properties are not dependent on assistance of additional tissue engineering (Mazini et al. 2020). Their degree of potency also allows them to mature into keratinocytes, fibroblasts, and endothelial cells, the last being of note for graft retention due to their role in refractory wound repair (Li and Guo 2018). Damage to cellular junctions yields hyperpermeable endothelial barriers that lack vascular homeostasis, which in turn cause tissue impairment and reduced angiogenesis (Park-Windhol and D'Amore 2016). ADSCs are CD31+, an antigen now commonly referred to as "platelet/endothelial cell adhesion molecule-1" (PECAM-1) and can therefore directly regulate vascular permeability and integrity, and molecular trafficking (Lerkiatmongkol et al. 2017). ADSCs play an important role in modulating the inflammatory, immune, and angiogenesis responses, particularly when the body is under stress by inducing signal cascades. Thus, incorporation of ADSCs into transplant tissue show markedly improved results by ensuring the graft receives proper oxygenation via promotion of angiogenesis and by encouraging ideal environments for wound repair.

Treatment for Lymphedema

Breast-cancer-related lymphedema (BCRL) is another common sequela of reconstructive surgery that lacks a reliable method of treatment. In a pilot study conducted on 20 human patients, the efficacy of ADSCs was observed as a postoperative treatment method to fluid build-up in the brachium (Maldonado et al. 2011). Twenty women exhibiting postoperative lymphedema were randomly assigned to either the control group, those given the typical decongestive treatment method (a compression sleeve), or the experimental group, those injected with ADSC in the affected arm. Results were reported by patients after treatments were allowed to proceed over a 12-week period. The study concluded that while both treatments provided improvement of lymphedema volume, the experimental group treated with ADSCs continued to show an overall reduction in the fluid build-up after treatment, while the control group experienced a recurrence of the complication after the sleeve was removed.

A separate study attempted to assess whether these results were applicable long-term. A group of ten post-operative patients elected to undergo ADSC injections for treatment of their BCRL, and follow-ups were conducted at the 1, 3, 6, 12, and 48 month marks (Jørgensen et al. 2021). While there was no overall fluid reduction, patients reported the following: all expressed increased mobility in the extremity's function, six of the ten patients had reduced conservative treatments, and five of ten felt as though there was some reduction of the lymphedema. It should be noted that this more recent study was not constructed as a blind, randomized control study, so further tests are necessary to accurately evaluate its clinical applicability. Although the two studies do not corroborate a reduction in volume, both show that patients feel an overall improvement in their condition. Quality of life is important to consider when assessing the efficacy of treatment, and ADSCs have been shown to improve lymphedema symptoms, again displaying the benefits of ADS-CAL.

Safety Concerns and Evidence to the Contrary: ADSCs and Cancer

Upon review of the frequency with which efficacy of the procedure is reported, ADS-CAL is shown to largely provide beneficial effects during clinical application. Purported harms have been reported by studies conducted in vitro or in non-human models, suggesting that these results require further testing before they can be used to negate therapeutic observations. No issues regarding tissue site collection were noted in any studies referencing potential issues with adipose derived stem cell applications, and none reported instances where ADSCs differentiated into CSCs, as this is not a predisposition they have displayed in any setting,

clinical or otherwise. Most oncologic issues arise from extra membranous markers and secreted paracrine factors, though results directly contrary to some of these effects have been reported as well. However, a holistic consideration of ADS-CAL should still be taken as patient safety is of the utmost importance for any clinical procedure, therefore, in vitro model results must be considered.

Cancer Cell Immunomarkers

ADSCs express the cell surface protein CD44 (Dominici et al. 2006). Positive expression of CD44 is linked with cells observed to express biological CSC characteristics due to comparable proliferation rates, differentiation inclinations, and related radiosensitivity and chemosensitivity levels (Su et al. 2011). Adhesion properties of CD44 mediate activation, aggregation, and migration of cells which may then undergo splicing events, resulting in variants (vCD44) with larger exons that encourage further vCD44 proliferation (Senbanjo and Chellaiah 2017). This variant interacts with ligands to produce CD44-ICD, which induces metastatic gene transcription in the nucleus.

Despite CD44 being linked to cancer, this potential involvement cannot be simplistically resolved. In a study conducted with ADSCs to investigate potential oncological risk and patient-specific responses to ADSCs, breast tissue samples were collected from five healthy female patients that had received breast reduction surgery, and one female patient with Stage III breast cancer (Kengelbach-Weigand et al. 2019). Previously known cell lines for normal mammary epithelial cells, ADSCs, and Stage III breast cancer cells were cultured in ADSC-conditioned medium alongside patient-derived samples. Normal mammary cell (NORMA1-5 MEC) migration and invasion was found to increase upon introduction to cultures treated with ADSC-conditioned mediums. The ADSC-conditioned medium was also shown to increase normal cell gene expression and proliferation to varying degrees reliant upon donor characteristics when comparing between patient-derived samples and the known cell lines. However, this study also showed ADSCs to have a similar effect on cancerous mammary cells (IFDUC1-5 MEC) which directly illustrates the outstanding lack of mechanistic understanding concerning ADSC signal transduction. Several studies have alluded that this deficit in knowledge disallows conclusions regarding expressed ADSC immunomarkers and their role in oncologic promotion (Ong et al. 2021; González-Cruz et al. 2012; Brielle et al. 2021). ADSCs have not been observed as tumerogenic in in vivo settings since they cannot prompt the oncologic transition of normal mammary cells, but may amplify pre-existing tumor activity through HGF/c-MET pathway activity (Eterno et al. 2014). Therefore, screening with c-MET can be used to predict the probability of tumorigenesis following ADS-CAL graft placement, which would assist in monitoring patient risk.

Acquired Drug Resistance

Particularly aggressive forms of breast cancer, such as triple-negative breast cancer, necessitate chemotherapeutic drugs for systemic treatment (Bianchini et al. 2016). As patients undergo chemotherapy, initial success can slowly diminish and many tumors can become unresponsive to original treatment methods, developing resistances that result in metastasis or death (O'Reilly et al. 2015). ADSCs have the potential to contribute to chemoresistance by increasing the expression of ABCG2, also known as breast cancer resistance protein, on surrounding cells in an in vitro model , which results in the efflux of doxorubicin (Yeh et al. 2017). Additionally, the ADSC medium also increased cell viability and reduced doxorubicin's ability to induce apoptosis as a result of the ABCG2 upregulation.

In contrast, ADSCs have also been shown to inhibit ovarian cancer growth in chemoresistant cells by shuttling paclitaxel (PTX) into the cells following PTX priming (Borghese et al. 2020). PTX-treated ADSC cell medium was even found to be more active than non-treated PTX, able to counteract resistance in all drug-resistant cell lines with notable efficacy. Since ADSCs can also be used to counteract displayed chemoresistance in cells, this should not be labeled as an inherent safety risk and instead be considered for therapeutic contextualization.

Supposed Promotion of Ideal Metastatic Environment

The greatest concern is that ADSCs might induce the recurrence of cancer in postmastectomy patients due to their proximity to the mammary gland upon deposition and propounded ability to increase the rate of metastasis in in vitro models. To discern if adipose-derived stem cells gave effect within tumor environments, ADSCs were isolated from human adipose tissue and transplanted alongside tumor cells in an in vitro model; results indicated that cohabitation with H460 or U87MG murine cells promoted tumor growth in test subjects (Yu et al. 2008). Results of another study found that after the administration of ADSCs from the abdominal tissue of two of the three human female subjects, multiple mouse organs administered with these xenografts exhibited breast cancer cell migration and metastasis (Rowan et al. 2014). The ADSCs of the third female subject yielded an expression of MMP-9, an enzyme common to cancer pathology as it is known to aid in metastasis and cell invasion. Other studies have also further speculated about the effect that ADSCs have on cancer growth due to their unknown, but considerable, effect on tumor behavior (Freese et al. 2015). Gebremeskel et al. (2019) observed that in a murine model, mice treated with an ADSC medium had increased proliferation of cancer cells ($p = 0.03$), migration ($p < 0.01$), tumor growth ($p < 0.05$), and other transcription factors related to metastasis.

However, a long-term study on ten female recipients of ADSCs-enriched adipose grafts over a period of 7.8 ± 1.5 years found no recurrence or metastatic disease (Ito et al.

2017). When treated with medium containing ADSC secretomes, mammary epithelial cells upregulated the proliferation of normal ADSCs collected from urologic neoplasms, exhibited non-tumorigenic differentiation upon introduction to xeno-free growth conditions, and no genomic abnormalities were observed within their molecular karyotype (García-Contreras et al. 2014). They were still able to produce exosomes with unaltered miRNA, which are proposed contributors to the traditional paracrine benefits displayed by healthy preadipocytes from xeno-free samples. This suggests that, so long as ADSCs are expanded in xeno-free culture conditions before therapeutic administration, they should not pose a threat to patient welfare regardless of their health. Previous studies that asserted ADSC encouragement of tumorigenesis employed co-injection with tumor cells (Yu et al. 2008), unaltered expansion conditions predicating collection (Rowan et al. 2014), or untreated ADSC medium applied to pre-existing tumorigenic-favorable environments (Gebremeskel et al. 2019). Despite this, careful consideration for ADSC usage on patients of oncologic concern is still advised and further studies should be conducted for further confirmation as patient safety should be the crux of stem cell research.

Final Considerations: Applicability and Limitations

Oncological concerns are not unjustified but may be due to inadequate stem cell standardization or lack of established methodology. Additionally, studies that support concerns over ADSCs' role in cancer solely employ in vitro models. Stem cell populations are heterogeneic, which confounds current identification methods; functional criteria and nomenclature do not take into account ADSC-specification, cells from common donor sites are not adequately categorized, variation of patient attributes (such as body mass index, age, sex) can result in variations in preadipocyte maturation, in vitro models may not accurately represent in vivo interactions, and non-standardized experimental instruments further complicate comparison of reported data (Ong et al. 2021). To resolve this issue and truly establish ADSCs as a safe method of treatment, a labeling system that no longer uses CD positive or negative designations to identify could be implemented instead. González-Cruz et al. (2012) found that mechanical properties of ADSCs could be related to lineage differentiation potential and used for subpopulation groupings which were corroborated with high statistical significance. More recent studies have found that single-cell RNA sequencing, performed during multiple stages of differentiation, allowed for notably complex understandings of the biomechanical roles of stem cells in vivo (Brielle et al. 2021). Since ADSCs have shown beneficial effects long-term with metastatic concerns being solely reported within in vitro models, further studies on their oncologic roles should be conducted with techniques that more accurately consider ADSC behavior in an in vivo setting. Additionally, the results of

ADSCs can be variable and do not work with the same amount of efficacy among harvesting techniques. Techniques applied during the preparatory phase of the procedure can have profound effects as well. Iyyanki et al. (2015) conducted adipose tissue harvesting in human patients by four methods, mechanical liposuction, direct fat excision and deposit, and Coleman's technique with or without centrifugation, and found that there was significant variation in the level of SVF and ADSCs obtained. Of the techniques employed, direct excision yielded the largest number of ADSCs ($P = 0.007$), while Coleman's technique yielded more SVF cells ($P < 0.005$), but not an observable amount of ADSCs. Another study sought to quantify differences between solely mechanic (MC) (involving the primary use of centrifugation) versus mechanic plus enzymatic (ME) (requiring an additional treatment with a collagenase digestion solution) isolation techniques (Raposio et al. 2017). ME was observed to isolate a greater number of ADSCs from the human donor tissue.

Donor sites also have significant implications for ADSC harvesting, with some suggesting that outer thighs are more ideal harvesting locations due to significantly higher viable stem cell count following isolation ($p<0.05$) (Tsekouras et al. 2017b). Others report that the abdomen should be more highly regarded for yield (Iyyanki et al. 2015). In contrast to all of this, Oedayrajsingh-Varma et al. (2006) purported that harvesting procedures and donor sites affected the characteristics of ADSCs but did not affect the isolation number of viable cells; their data suggested that changes in yield were merely due to a decreased ability to proliferate depending on collection method. Further studies must be conducted to positively identify the quintessential site for collection, harvesting method, and isolation technique, though this may be confounded by patient-composition variations. A proposed study could be one designed for comparison of ADSC yield of outer thigh or abdomen donor sites by mechanical liposuction, direct excision, or Coleman's technique with or without centrifugation. Additionally, tissue obtained from these two sites could be isolated by either ME or MC means. This may assist in determining ideal procedural methods for the synthesis of an industry paradigm, eventually allowing for the standardization of reported data and better comparability of observed results.

A task force formed by the American Society of Plastic Surgeons evaluated autologous fat grafts and found that, upon review of documented case studies, they were confirmed as a safe and effective procedure in clinical settings up to 12 months following use on human recipients (Gutowski et al. 2009). Villani et al. (2010) later verified these findings by employing fat grafts for scar remodeling in 250 patients and observing only beneficial aesthetic outcomes, normal histological data, and patient reported satisfaction.

However, the most recent and compelling evidence for the viability of ADS-CAL comes from the meta-analysis of Li and Chen (2021), which found that the CAL results showed statistically significant improvements in fat graft retention rates compared to control groups (Standard mean difference = 1.79). Additionally, no abnormal or significant complications

were reported within ADS-CAL treatment groups. As with the previous meta-analysis, these results prompted Dominic et al. (2021) to write a letter to the editor of the Aesthetic Plastic Surgery journal that emphasized the conclusions of Li and Chen's (2021) review and implied the necessity of further meta-analyses to rectify controversies found in literature. The efficacy of ADS-CAL was undisputed. Yoshimura (2020) submitted that within the years following his initial implementation of ADSC-assisted lipotransfer, its usage has provided patient grafts with extensive rejuvenation, regeneration, and therapeutic resolve.

There is even the potential for ADS-CAL to replace previous methods altogether, an ideal progression for patient satisfaction since autologous deposits provide natural breast pliancy upon palpation. Within the study conducted by Kølle et al (2020), additional results found that there was an average enlargement of 2.6 times that original volume, and no further surgeries were necessary to achieve the desired effect. This level of graft retention suggests that with increased uniformity and development of methods, ADS-CAL may be able to render synthetic implants obsolete. So, while more studies should be conducted and techniques should be standardized, ADS-CAL can be considered an effective and tentatively safe treatment method for breast reconstruction purposes based upon reported treatment outcomes.

Summation of Considered Efficacy and Safety

With the assistance of ADSCs, it has been shown that angiogenesis is promoted, inflammation is moderated, and wound healing is idealized through influence on the endothelial barrier. Increased proliferation and vascularization yield a higher degree of graft retention, frequency of fibrosis may be reduced to negate capsular contracture, and other secondary effects such as lymphedema may be minimized as well. All these effects provide ameliorated aesthetic outcomes which lead to improved patient satisfaction and a predicted boost in mental wellbeing. However, their antigens and secreted paracrine factors have still been shown to induce various carcinogenic effects in experimental in-vitro or non-human models.

As such, it is concluded that ADS-CAL has impressive efficacy for improved aesthetic outcomes of breast reconstructive surgeries and can regulate undesirable secondary effects but should be implemented with reasonable caution until oncologic results are better understood. Ideal harvesting techniques, donor sites, and other methodological factors are still under review, but must be standardized to provide equitable data for comparison.

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