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Adipose-Derived Stem Cells (ASC) Communicate with Residual Breast Cancer Cells

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Abstract

Purpose: Based on aesthetics and long-term stability, call-assisted autologous lipotransfer is a promising method for post-oncological breast reconstruction. Thereby, autologous fat grafts enriched with autologous adipose-derived stem cells are transferred to the breast. However, as adipose-derived stem cells (ASC) have the ability to secrete exosomes and growth factors, they could communicate with residual breast cancer cells.

Methods: We performed a systematic review of the published literature to evaluate whether adipose-derived stem cells- based treatments for breast cancer are associated with tumor growth of rest breast cancer cells and therefore that it could exist an oncological risk. An electronic database search was performed.

Results: As described, all current studies can prove that the gene expression is influenced by the direct cell contact between adipose-derived stem cells and breast cancer cells.

Conclusion: These observations suggest that information is substituted via exosomes which can migrate intercellularly and transfer genetic material between both cell types.

Keywords: Adipose-derived stem cells; Exosomes; Autologous lipotransfer; Breast cancer; Adipose-derived stem cells; Exosomes

Introduction

With approximately 225,000 annual incidences, cancer is the most common cause of death of women in Germany. Based on the demographic development it is expected that cases of cancer will rise about 20% between 2015 and 2030 [1]. The most frequent form of cancer in women is by far breast cancer [1]. On the basis of current rates of incidence, one in eight women will be diagnosed with breast cancer in the course of her life and in 2015 the number of breast cancer fatalities in European woman amounted to 90.800 [1,2]. Nowadays, after a tumorigenic removal, the breast is reconstructed by cell-assisted lipotransfer in which adipose tissue is enriched with adipose-derived stem cells before the transplantation [3]. Adipose-derived stem cells offer an advantageous stem cell population as they are abundant in human fat tissue, they are easy to extract and they provide supporting properties for the fat graft. Even though the clinical evidence concerning safety and efficiency are not clear, the clinical application of this stem cell therapy is on the increase [3]. In the last few years, adipose-derived stem cells were associated with the recurrence of cancerous breast tumors i**n** *in vitro* studies so that adipose-derived stem cells could be discussed as the cause of certain tumors in current studies [4-6]. In this context, the influence of adipose-derived stem cells on the gene expression of breast cancer cells with direct cell contact was investigated [4]. Thereby it was shown that the expression level of transcriptional genes for typical malignant markers is significant higher in the direct co-culture than in the single culture [4]. This suggests that adipose-derived stem cells could have the potential to promote the tumor growth of breast cancer cells and therefore that it could pose an oncological risk [4].

Cell-assisted autologous lipotransfer

The cell-assisted autologous lipotransfer (CAL) is a combined transplantation of fat tissue which is removed from another part of the body and adipose-derived stem cells (ASC) [4]. As this regenerative therapy promises a stable, functional and naturally emerging tissue, the cell-assisted autologous lipotransfer is being used more and more frequently for the reconstruction of the breast after an ablative operation for breast cancer treatment [5-7]. With the cell-assisted lipotransfer, one part of the removed fat tissue is fermented and centrifuged to gain the stromal vascular fraction containing the adipose-derived stem cells [4]. This fraction is mixed together with the other part of the untreated fat tissue, a process in which ASC-poor fat is converted to ASC-rich fat which is then injected to re-sculpt the breast (Abb.1) [7].

It is assumed that the adding of adipose-derived stem cells to complete fat grafts promotes the formation of new blood vessels and that it improves the survival rate of fat grafts [8]. Several studies indicate that adipose-derived stem cells enhance the angiogenesis, prohibit the apoptosis and support the differentiation of the adipocytes by secretion of growth factors, cytokines and chemokines [6,9,10]. The understanding that the enrichment of grafts with adipose-derived stem cells improves the clinical efficiency has led to the innovative use of ASC in post-oncological breast reconstruction. Thereby frequent complications that occur in the conventional fat transplantation, like necrosis, are avoided [10].

However, the angiogenesis supporting role of the engrafted fat tissue has, at the same time, distressing consequences in oncology. The problem is that in the use of ASC-enriched fat grafts, the same elements which promote the stability of the fat graft by angiogenesis and growth factor production could also support the survival of remaining tumor cells [6,8]. In this context, it cannot be safely ruled out that after a breast amputation, the breast cancer cells are still in the mammary parenchyma so that an injection of metabolic active fat tissue would

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Exosomes		Microvesicles	Apoptotic vesicles
Size	50 – 100 nm	100 – 1.000 nm	50 – 500 nm
Secretion	Exocytosis	Constriction	Vesication by apoptosis
Isolation	Ultra-centrifugation at 100.000 x g	10.000 x g	1.200 x g
Lipid composition	Cholesterol and sphingomyelin	Phosphatidylserine	Not determined
Detection	Western Blot, FACS	FACS	FACS
Protein markers	Tetraspanins (CD9, CD63, CD81)	Integrins, selectins	Histones
Intracellular origin	Internal compartments (endosomes)	Plasma membrane	Not determined

Table 1: Physicochemical properties of different extracellular vesicles (modified on Theory [20]).

possibly stimulate the dormant cancer cells [11]. According to this, the risk of tumor recurrence is raised as unfortunately the factors that accompany tissue regeneration and revascularization are also critical to cancer growth and metastasis [5].

Interaction between adipose-derived stem cells and breast cancer cells

Adipose-derived stem cells can influence the tumor biology because they migrate selectively to tumors and as they interact with tumor cells via direct contact and paracrine mechanisms [12]. Furthermore adipose-derived stem cells have the ability to mold the micro-environment of the tumor through which the behavior of the tumor cell is influenced *in vitro* and *in vivo* [13]. Adipose-derived stem cells are derived from mesenchymal stromal cells (MSC) which offer extensive immunosuppressive properties that facilitate the reconfiguration and reparation of the tissue [14]. For this reason, it is suspected that adipose-derived stem cells can detect tumors as a site of inflammation and therefore migrate selectively to locations with active tumorigenesis [11]. This appears to be the case as the tumor cells secrete chemokines which attract the ASC and promote their migratory activity [15].

Based on this observation several preclinical studies view MSC as suitable candidates to deliver chemotherapeutical drugs *in vivo* directly to the breast tumor [16]. On the one hand, adipose-derived stem cells are considered to be suitable means of transport for antitumor substances, while on the other hand different studies prove that ASC play a decisive role in the tumor pathogenesis and tumor progression, in particular in the case of breast cancer as they can communicate intercellularly with breast cancer cells [13].

Research from Kuhbier et al. suggests a stimulation of breast cancer cells which is predicated on direct cell-cell contact with ASC [4]. Karnoub et al. injected immunocompromised mice with human ASC together with MDA-MB-231 breast cancer cells and showed that ASC accelerate the tumor growth and decrease the apoptosis of breast cancer cells [16]. Similar observations were made by Mandel et al. [17]. A subcutaneous injection of a direct co-culture of ASC with breast cancer cells (MDA-MB-231) injected into a mouse exhibited a tumor ten times larger and an increased capacity of metastasis than an injection of a MDA-MB-231 isolate [17]. In this context, adipose-derived stem cells could communicate intercellularly with breast cancer cells by building gap junctions and substitute components with a low molecular weight among each other [10]. The presence of gap junctions correlates with a tightened invasive phenotype of both cell types [17].

In respect to the post-oncological autologous fat transplantation, Zhao et al. expect that multipotent adipose-derived stem cells could change the microenvironment in the breast directly and favor the transition from a pre-malignant tumor to a malignant tumor [15]. Dormant breast cancer cells can have the status of the cell cycle arrest which can be transformed in an active metastasis by paracrine and autocrine factors [15]. Since adipose-derived stem cells secrete the growth factor VEGF, which is involved in the initial tumor growth, ASC could stimulate dormant tumor cells with their proangiogenic activity and therefore trigger a complete tumor development [15].

In summary, this means that ASC and breast cancer cells interact with each other in a complex dynamic manner and therefore influence the tumor behavior dramatically in a way that an increased risk in the post-oncological breast reconstruction by cell-assisted autologous lipotransfer could exist [4,10]. Previous findings indicate that the proximity and direct cell-cell interactions between ASC and breast cancer cells are a requirement to transmit signals for the induced cell growth [15]. However, it is possible that different mechanisms and signaling pathways apart from those that are described so far are involved in the stimulation and proliferation of tumor cells [15]. For example, it is supposed that the impact of adipose-derived stem cells on breast cancer cells is not only mediated by soluble factors, but also exosomes could play a role, as they can also transfer genetic material [18,19].

Exosomes

In multicellular organisms, especially the secretion of proteins and the subsequent binding to receptors of neighboring cells are involved in the intercellular communication [20]. Another way of communicating between cells is the release of exosomes which do not require direct cell contact and can function across long distances [21]. Exosomes are small membrane vesicles with endosomal ancestry that are secreted from most cell types into the extracellular space and are involved in a plurality of biological tasks [22,23]. In the extracellular space, one must differentiate between three groups of extracellular membrane vesicles [24]; the exosomes, the microvesicles and the apoptotic bodies [24]. The main characteristics and differences are listed in (Table 1).

The identification of vesicles as exosomes is based on morphological and biochemical properties [25]. Exosomes are spherical structures that are bordered by a lipid bilayer with transmembrane proteins and that enclose hydrophilic components of the cytosol of their donor cell [20]. With a diameter of 50 to 100 nm exosomes distinguish particularly in their size from different small membrane vesicles [20].

Secreted exosomes can stay in the extracellular space close to their donor cell, or they can reach spots far away via bodily fluids like the lymph system [26,27]. Compared to a single soluble factor which is secreted by cells, exosomes can carry a range of functional molecules that contain special proteins, lipids and microRNAs [28]. Immunocytochemical analyses indicate that intracellular exosomal proteins are a cell-type specific compilation of protein families from the plasma membrane and from the cytosol of the donor cell [22,25]. Proteins of other intracellular components like the nucleus, Golgi apparatus or endoplasmic reticulum are just slightly contained [22,25]. However, as a result of their endosomal origin, exosomes from different

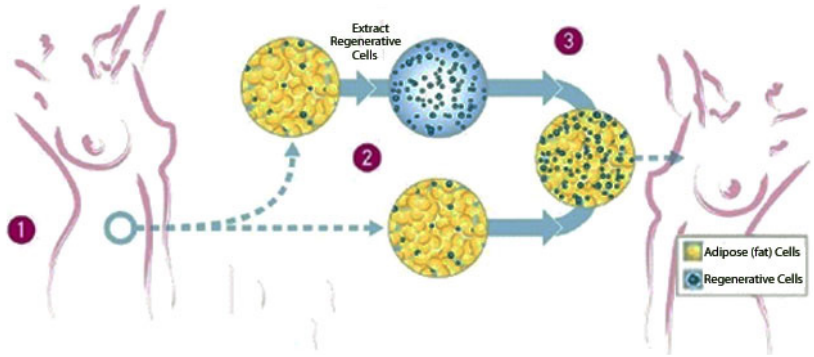

Figure 1: Process of the cell-assisted lipo-transfer (CAL): Liposuction, processing and injection of fat grafts that are enriched with adipose-derived stem cells; 1) 200-500 ml of body's own fat tissue is removed, 2) the fat tissue is enriched with ASC, 3) reconstruction of the breast with cell-enriched fat graft, yellow = Adipose (fat) cells, blue: regenerative adipose-derived stem cells [9].

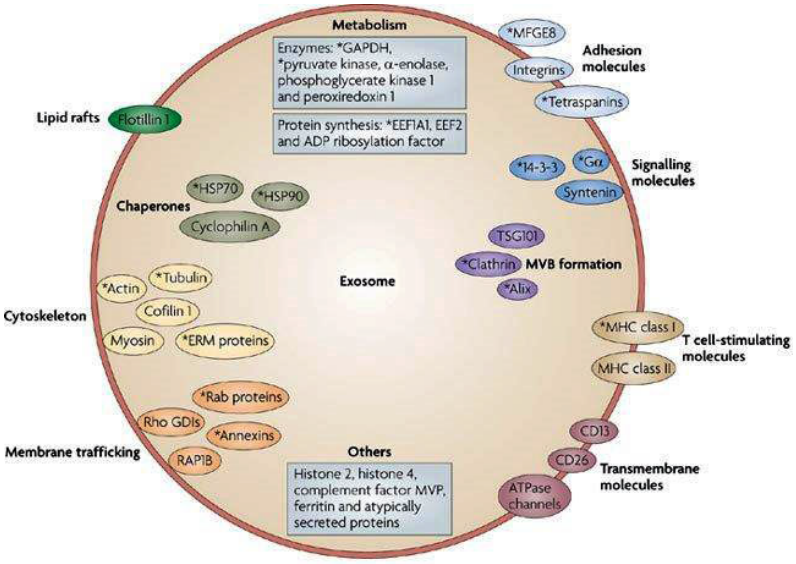

Figure 2: Schematic representation of the protein composition of a canonical exosome. The data is based on 15 proteomic analyses of exosomes extracted from cultured cells and from biological fluids. (EEF: Eukaryotic Translation Elongation Factor; ERM: Ezrin, Radixin and Moesin; GAPDH: Glyceral-Dehyde 3-Phosphate Dehydrogenase-Activating Protein; HSP: Heat Shock Protein; MFGE8: Milk Fat Globule EGF Factor 8 Protein; MVB: Multivesicular Body; MVP: Major Vault Protein; RAP1B, RAS Related Protein 1B; Rho GDI: Dissociation Inhibitor; Tetraspanins: E.G. CD9, CD63, CD81; TSG101: Tumour Susceptibility 101 [20]).

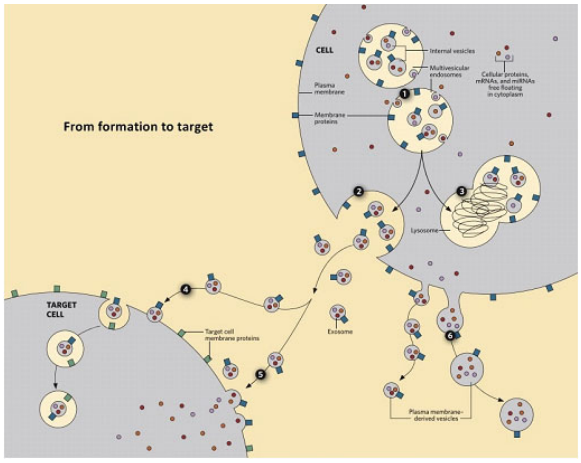

Figure 3: Schematic representation from the formation of the exosomes to the release of the components in the recipient cell. For the description of the numbering see text [22].

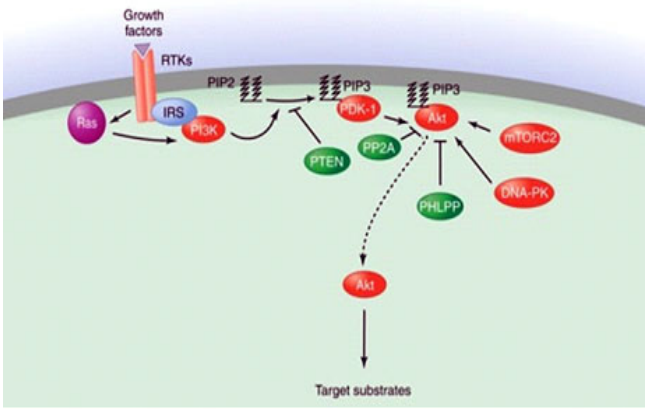

Figure 4: Activation of PKB/Akt via the PI3K signaling pathway. PKB: Protein kinase B, PI3K: Phosphoinositid-3-Kinase [33].

cell types contain the same proteins that are involved in membrane transport, in the fusion and in biogenesis as well as adhesion molecules like tetraspanins (CD9, CD81, CD63) which represent typical exosomal surface markers [25] (Abb. 2).

Exosomes contain not only proteins but also functional messenger RNA and microRNA [29,30]. The RNA content is protected by the stable membrane of the exosomes that consists, for the most part, of sphingomyelin and cholesterol, so that it is possible to transfer RNA messages across long distances from one cell to another [21,29]. The discovery that there are new proteins in the recipient cell after a transfer of exosomes, indicates that transferred exosomal mRNA can still be translated after entering another cell [30].

The process, from the formation of the exosomes in the donor cell to the release of the components in the recipient cell, is represented in Figures 1-3. In the first step of exosome formation, multivesicular endosomes (MVE) constrict the proteins mRNAs and miRNAs from the cytoplasm to form small internal vesicles (Figure 3), (1). These internal vesicles are secreted as exosomes when the multivesicular endosomes fuse with the cell membrane (2). Alternatively, multivesicular endosomes can also fuse with lysosomes which results in the degradation of the contained proteins (3) [22,26]. After reaching the recipient cell, exosomes have various ways in which they can enter: either by complete uptake of the exosomes from the recipient cell by endocytosis (4) or by fusion of the exosomes with the recipient cell's membrane and subsequent release of their contents directly into the cytosol of the cell (5). As already described, cells also secrete other membrane vesicles such as microvesicles and apoptotic vesicles which are directly bound by the donor cell's plasma membrane (6) [22].

Exosomes can influence the physiology of the recipient cell in a different manner [20]. The biological effects of exosomes therefore depend on the donor cell, on the composition of the exosomes and on the microenvironment in which the recipient cells reside [28]. The main functions of exosomes are the induction of the intracellular signaling effect and the transmission of gene products whereby the immune response can be modified and the recipient cells acquire new qualities [26,20]. Further key roles of exosomes are the antigen presentation and immunostimulatory and inhibitory activities which is why exosomes can be involved in physiological as well as pathological processes [24]. The fact that exosomes serve as natural vectors for the transmission of genetic material between cells makes them interesting candidates as vectors in gene therapy [21]. However, exosomes also play an essential role in oncology as well [22]. Previous studies hypothesize that exosomes can inhibit the activation of macrophages and the secretion of cytokines whereby the immune response is alleviated and tumor cells can easily spread [22]. Secreted exosomes, especially those from tumor cells, could be pivotal intermediators in the tumor microenvironment, as they express components which are responsible for the facilitation of the angiogenesis, for the stromal rearrangement and for the activation of signaling pathways by transferring growth factors and genetic material [23].

Discussion

Recent studies have been demonstrated that MSCs exosomes have therapeutic effects in tissue repair in liver, skin and heart [31-36]. A number of studies have examined the role of MSC- derived exosomes in cancer development, metastasis, drug resistance and progression of cancer [37-40]. They could promote tumor growth *in vivo* by activating the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway [41] and breast cancer cells migration through the activation of the Wnt signaling pathway [42]. Lastly, molecular analysis of exosomal mRNA indicates that some exosomes carry a specific selection of mRNAs which are associated with, amongst other things, signaling pathways such as the PI3K/Akt signaling pathway [26]. The PI3K/Akt signaling pathway plays a crucial role in the regulation of gene expression, which is involved in the proliferation, migration and metastasis of tumor cells [31]. The protein kinase B (PKB), also known as Akt, is a serine/threonine-specific protein kinase which is encoded by the genes *Akt1, Akt2* and *Akt3* [32]. The main functions of Akt are the inhibition of the apoptosis and the promotion of the proliferation so that an over-expression or a non-regulated activation of this protein kinase can result in cancer [32]. The PI3K/Akt signaling pathway is highly conserved and its activation is strictly controlled via a multilevel process (Figure 4) [33]. But the exact mechanisms of the effects of stem cell-derived exosomes on cancer have been largely unexplored and untested.

Summing up, exosomes are pivotal intermediators in cell-cell communication not only during physiological but also in pathological processes [43]. Due to the fact that exosomes are secreted by numerous cell types including immune cells, neural and stem cells they are involved in many physiological processes like antigen presentation, transfer of RNA or tissue repair [43]. However, exosomes have also been associated with the progression of disease conditions including neurodegenerative disease, cardiovascular disease and cancer [43]. Exosomes play an important role in the cross talk between cancer stem cells and their microenvironment wherefore they are necessary for the maintenance of a stem cell niche [44]. It also has been shown that stem cell-derived exosomes may potentially transmit stem cell phenotypes to recipient cells whereat they mediate interactions among stromal elements, promote genetic instability in recipient cells and induce malignant transformation [45,46]. At last exosomes have the ability to mediate tissue repair and regenerative outcomes in injury and disease that recapitulate observed bioactivity of stem cell populations [47]. Even if the application of exosomes in treating cancer is challenging, there are potential clinical applications of exosomes as biomarkers and potential therapeutic tools [43]. The detection of exosomes in serum of tumor patients and the identification of mRNAs in exosomes from isolated carcinoma cells emphasizes the potential utility of exosomes and their contents as biomarkers cancer and other pathological conditions [48].

Conclusion

The understanding of the intercellular communication between adipose-derived stem cells and breast cancer cells is thus far limited to the direct cell contact and paracrine mechanisms such as the secretion of growth factors, cytokines and chemokines. As described, all current studies can prove that the gene expression is influenced by the direct cell contact between adipose-derived stem cells and breast cancer cells. These observations suggest that information is substituted via exosomes which can migrate intercellularly and transfer genetic material between both cell types. The involvement of exosomes in the signaling effect of the tumor microenvironment would constitute a previously disregarded mechanism and would also represent new perspectives in the cancer therapy.

Author Contributions

TR and VB wrote the manuscript with substantial contributions from PMV. All authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

Not applicable.

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