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Apoptotic Effects of Adipose-Derived Stem Cell Secretome in Breast Cancer Stem Cells: A Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Adipose-derived stem cells (ASC) are cells from the core of fat tissue that secrete various cytokines, growth factors, proteins and extracellular vesicles that can be used in regenerative therapy, especially in the case of cancer. This ASC produces a secretome which is an exosome derived from ASC. In many studies it has been proven that the secretome has proangiogenic, neurotrophic and epithelialization activities and has the potential to be used for cardiovascular, respiratory, neurodegenerative, inflammatory and autoimmune diseases, as a wound healing treatment and as an immunomodulator in anticancer therapy through induction of apoptosis. Due to the limited use of stem cells in cell-based therapies, secretomes from ACS-derived exosomes may be a safer alternative treatment in the future with higher levels of effectiveness and lower side effects. Therefore in this review, we focus on the current knowledge about the ASC secretome that can induce breast cancer cell apoptosis.

Keywords: Adipose-derived stem cells; secretome; apoptosis; breast cancer therapy; breast cancer stem cells.

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1. INTRODUCTION

Mesenchymal stem cells are stromal cells that have the ability to differentiation and self-renew. Mesenchymal stem cells can be isolated from various tissues, such as bone marrow, endometrial polyps, umbilical cord, menstrual blood, adipose tissue, etc. This is because the easy of retrieval and quantity obtained make these sources the most practical for experimental and clinical applications. Mesenchymal stem cells are stromal may be the best choice for experimental or clinical applications in the future. The multipotent ability of Mesenchymal stem cells makes it an alternative therapy options for the development of cancer treatments [1,2].

Mesenchymal stem cells are a type of Adipose Derived Stem Cell that can be used in breast reconstruction. Adipose Derived Stem Cells have paracrine and autocrine factors that can increase the recruitment of endogenous precursors, it can be considered as a cancer therapy. Adipose-Derived Stem Cells secrete many important proteins, including growth factors and cytokines [1], as well as extracellular vesicles and RNA [3,4,5] to support cell regeneration, proliferation, differentiation, and migration [6]. Many studies have optimized the conditions for ASC stem cell-based therapy by manipulating the route of administration, cell dose and time [1,7] to reach the site of inflammation, but currently the results are not satisfactory [8,9]. In other research, ASC was demonstrated at 1×10^6 human ASC administered intravenously to have anti-pain effects in a mouse model with neuropathic pain". [10]. Therefore, new strategies for ASCs-based treatment are needed, and secretome ASCs may be a promising therapy as a cell-free, cell-based therapeutic agent that is safe and easy to store for long-term use [11,12].

This review provides information on the current knowledge about the secretome of adipose-derived stem cells, with a special focus on their exosomes using all available sources such as PubMed and Google Scholar databases, as well as Clinical Trials. This review summarizes information from *In vitro*, in vivo, and clinical trials on the apoptotic effects of adipose-derived stem cell secretomes in the context of use in breast cancer therapy. The literature study was based on keywords such as adipose-derived stem cells, secretome, apoptosis, breast cancer therapy, breast cancer stem cells and combinations of these keywords [13].

2. ADIPOSE-DERIVED STEM CELLS CHARACTERISTICS

Adipose-derived stem cells are mesenchymal stem cells that can be harvested via direct excision surgery, liposuction. Separation of ADSCs is performed from lipoaspiration material in which cells of the stromal vascular fraction can be found; from this fraction, different cell types can be isolated after washing then enzymatic digestion and centrifugation of the sample" [14]. The types of cells found in SVF include preadipocytes, fibroblasts, adult mesenchymal stem cells, macrophages, monocytes, lymphocytes and pericytes which are associated with the angiogenesis process [14].

Adipose-derived stem cells are a heterogeneous population and no unique surface markers have yet been described. However, ADSCs express characteristic markers of mesenchymal stem cells established by ISCT and the International Federation for Adipose Therapy and Science (IFATS) and described by CD73 (+), CD90 (+), CD105 (+), and CD36 (+) but also CD31 (−), CD45 (−), CD11b (−), CD106 (−). Increased CD36 expression and lack of CD106 expression distinguish ASCs from BM-MSCs [1]. In addition, ASCs express integrin β-1 (CD29) which plays a role in the process of angiogenesis as well as CD44 hyaluronate and osteopontin receptors, which play a role in the development of the extracellular matrix and pathological processes such as neoplasia [1]. There are no consistent data regarding whether ASCs isolated from the stromal vascular fraction can express CD34 and CD106 or not [1]. It is recognized that cultured Mesenchymal stem cells do not express CD34, in contrast to freshly isolated cells. Several studies have shown that CD34 is present at the start of culture in freshly isolated ASCs but after the first and subsequent passages CD34 disappears [6] or remains at low expression levels [1,14].

3. ADIPOSE-DERIVED STEM CELLS SECRETOME

Adipose-derived stem cells produce various molecules that act as cell signals, such as growth factors [15,16], cytokines [1,17], morphogens, chemokines [1], and extracellular vesicles [18,19,20], which improves various cellular mechanisms. It has also been shown, in vivo, that ASCs are better at secreting bioactive factors such as monocyte chemotactic protein 1 (MCP-1), neural hepatocyte growth factor (HGF),

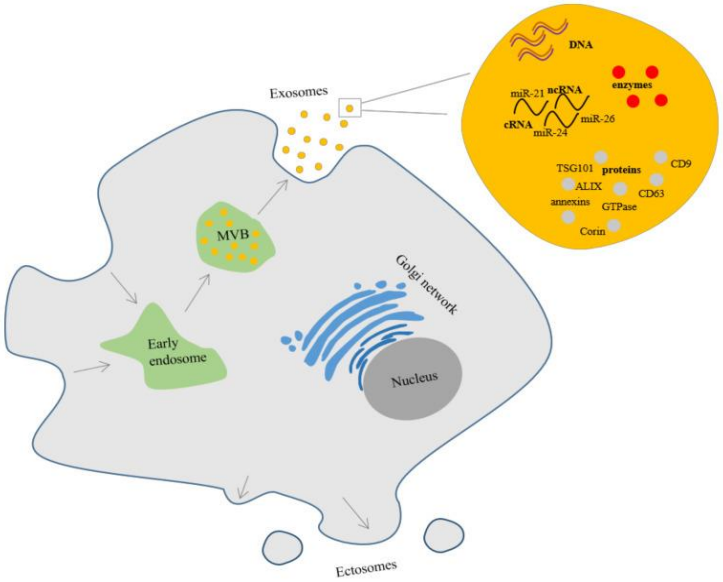

Fig. 1. Exosomes secretion in Adipose-derived stem cells

growth factor (NGF), granulocyte colony-stimulating factor (CSF), stimulator granulocyte colony-macrophage factor (GM-CSF), interleukin 1 receptor antagonist (IL-1RA), interleukin (IL)-6 and IL-8 versus bone marrow mesenchymal stem cells [1]. This bioactive factor plays a role in better migration, differentiation, proliferation and autocrine activity compared to bone marrow mesenchymal stem cells [1].

Adipose-derived stem cells (ASCs) secrete various cytokines, growth factors, proteins, and extracellular vesicles with which they can be used in regenerative medicine, especially in the case of cancer. This has great potential, and can be developed as a new treatment strategy using the secretome of ASCs of global interest as a future medicine. The secretome has importan role in non-coding RNAs such as miR-21, miR-24, and miR-26 carried through exosomes secreted by adequate cells. The entire secretome, including ASC-derived exosomes [13] (Fig. 1) in many studies has been shown to have proangiogenic, neurotrophic, epithelializing activities, immunomodulatory and has the potential to be used for cardiovascular, respiratory, neurodegenerative, inflammatory and autoimmune diseases and as a wound healing treatment [1].

4. ROLE OF PATHOLOGY IN BREAST CANCER STEM CELLS

The origin of breast cancer stem cells has remained controversial in the field of research for many years. It remains unclear whether BCSCs originate from multipotent mammary stem cells (MaSC) which are a progenitor population resulting from dedifferentiation of non-stem cells, or arise from a combination of both. The currently accepted opinion is that breast cancer stem cells arise from MaSC and progenitor cells. Lineage tracing studies indicate the presence of basal progenitor cells and unipotent luminal cells in the developing mammary gland that support fully differentiated luminal and basal cell lineages, respectively, for long periods of time [21]. “It is thought that the accumulation of mutations in these progenitor cells can give rise to breast cancer stem cells because evidence suggests similar CD44+/CD24−/low phenotypic features are present in multipotent mammary stem cell populations and breast cancer stem cells” [21].

Exposure of the cellular environment to chemotherapy and radiotherapy causes genetic and epigenetic changes in non-stem cells, resulting in the de novo generation of breast cancer stem cells” [21]. Changes in the tumor microenvironment may also contribute to the process of dedifferentiation of non-stem cells to a breast cancer stem cells phenotype and recent studies have shown that MYC-driven epigenetic reprogramming results in dedifferentiation of mammary epithelial cells resulting in a breast cancer stem cells-like phenotype [22]. In summary, it appears that “stemness” in breast cancer is a phenotype that can arise through the mechanism of tissue stem cell mutation or through the acquisition of a stem-like phenotype

by transformed cells, and is induced by EMT, chemotherapy, or targeted therapy. Recent studies have shown that in triple-negative breast cancer, resistance to mTOR, and/or PI3K inhibitors arises through the emergence of Notch-dependent breast cancer stem cells [23].

In breast cancer, the name “luminal” of the luminal-A/B subtype and the name “basal-like” of the basal-like subtype originate from the similarity of transcriptomes between breast tumors and normal mammary luminal or basal tumors associated with the epithelium. However, the origins of luminal and basal breast cancer cells are actually very different from their naming conventions. Oncogenic events in various types of breast cells lead to various types of breast tumors (Fig. 2).

PIK3CA (α-catalytic subunit of PI3K) mutations in breast cancer occur in around 30%, including luminal and basal tumors. However, a study reported that mutant PIK3CA in mammary luminal progenitors produced heterogeneous tumors with luminal and basal differentiation” [24]. Expression of mutant PI3KCA in luminal cells induces luminal or basal-like breast tumors is characterized by CK8, whereas its expression in basal cells giving rise to luminal tumors is characterized by CK5 [25]. BRCA1 basal-like breast cancer may originate from basal stem cells. Interestingly, however, BRCA1 deletion in breast luminal epithelial cells targeted by Blg, can produce basal-like breast tumors, which phenocopy BRCA1-associated breast cancers in humans, whereas BRCA1 deficiency in basal cells targeted by CK14, can only cause BRCA1-associated breast cancers in human cancer [26] results in malignant adenomyoepithelioma which is a rare form of BRCA1-associated breast cancer in humans. Furthermore, luminal CK8+ cells carrying the Etv6-NTRK3 fusion oncogene can induce heterogeneous tumors with expression of luminal and basal markers [27]. Recent evidence suggests that luminal progenitors may be the origin of luminal-like and basal-like breast cancer cells in humans, whereas genetic mutations occurring upon transformation of luminal progenitors may be different and be a determining factor in luminal-like or basal-like breast cancer tumor phenotypes [28]. Genetic sequencing results have described different mutation profiles between luminal-like tumors and basal-like tumors. PIK3CA, FOXA1 and GATA3 mutations in luminal-like tumors show distinct mutations, whereas basal-like tumors show high levels of mutations in p53 and BRCA1 [29-31]. Somatic loss of BRCA1 and p53 indeed results in the development of basal-like breast cancer [31].

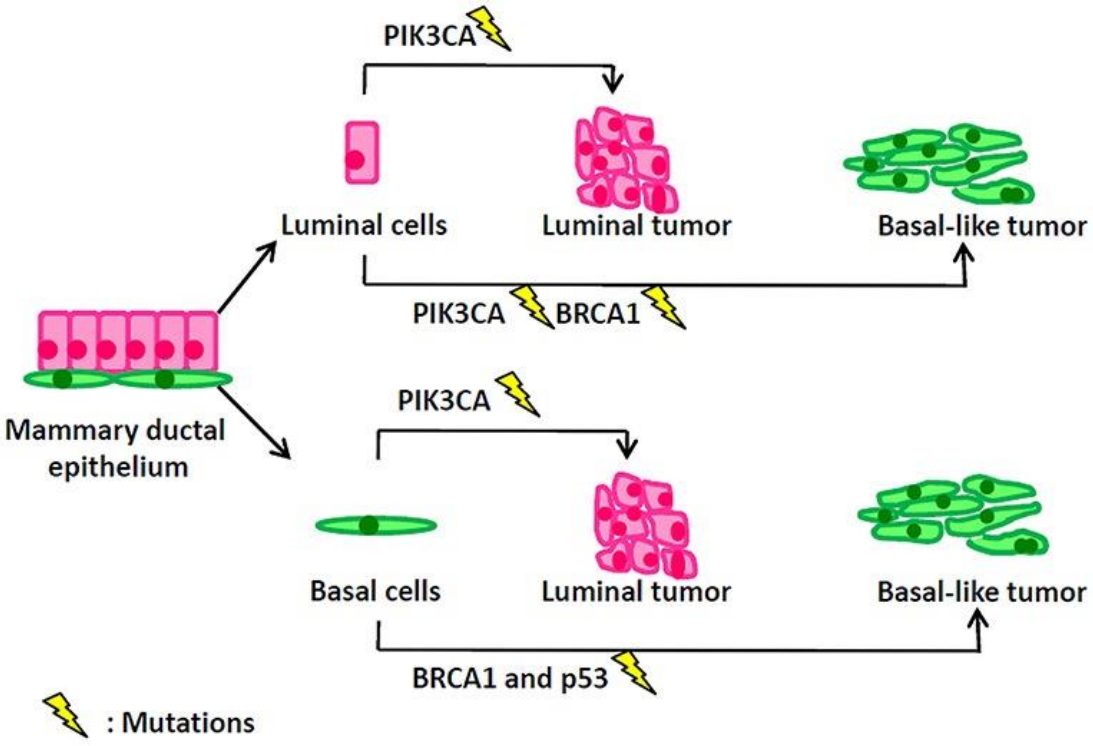

Fig. 2. Gene mutations in various types of breast cells cause different types of breast tumors

5. POTENTIAL APOPTOSIS OF ADIPOSE-DERIVED STEM CELLS SECRETOME IN BREAST CANCER STEM CELLS

In this study, there was a significant decrease in cell viability, and it still needs to be evaluated whether the cells are undergoing an apoptotic process. In another study, Adipose-derived stem cells Secretome Formulation had a dose-dependent apoptotic effect on cancer cells. The TNBC population showed an increase in the number of cancer stem cells with CD44+/CD24− markers, that cancer stem cells with CD44+/CD24− markers were reduced substantially despite the increased presence of a population of cancer stem cells with this phenotype in the chemically determined TNBC cell medium. Clearly, Secretome Formulation has a chilling effect on cancer stem cells. The MDR1+ (multidrug resistance protein 1) and PD-L1+ (programmed death ligand 1) phenotypes were substantially reduced after Secretome Formulation treatment at a dose of 70 mg/ml" [32].

To further assess whether SF is synergistic with the conventional chemo drug paclitaxel, it is still necessary to evaluate the viability of TNBC cells in chemically defined breast cancer cell media [32]. Can Secretome Formulation, especially on Adipose-Derived Stem Cells, be used as an apoptotic agent for other types of breast cancer? So further research needs to be carried out both *In vitro* and in vivo in the future.

6. CONCLUSION

Adipose-derived stem cell secretome has the potential to be an agent for the treatment of breast cancer with its apoptotic function. The properties of ASC are influenced by the specific contents of its secretome such as proteins, cytokines, growth factors, and exosomes with several types of RNA, characterized by bioactivity including antiapoptotic, angiogenic, neurogenic, vasculogenic, epithelial, and immunomodulatory activities. Application of bioactive factors without administration of whole cells is a safer and more effective alternative treatment. Currently, many *In vitro* and in vivo studies confirm the effectiveness of ASC secretome therapy. Mostly with ASC-derived exosomes. Several clinical trials are currently being evaluated for the safety and effectiveness of ASC-derived exosome therapy, but no results are yet available. Further in vivo and *In vitro* studies are needed to understand the specific role of ASC secretome in treating breast cancer through its apoptotic function that can be administered intravenously or locally in breast reconstruction.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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