A REVIEW OF THE ADIPOSE-DERIVED STEM CELL, REGARDING NERVE REGENERATION

VLAD BLOANCĂ[1], ZORIN CRĂINICEANU[2], TIBERIU BRATU[3], MONICA MARILENA ȚÂNȚU[4]

[1,2,3]"Victor Babeș" University of Medicine and Pharmacy, Timișoara, [4]University of Pitești

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Abstract: *Introduction: The knowledge in the field of nerve regeneration is incomplete, there is a constant input of information regarding better techniques, materials and more important, the use of regenerative medicine. The adipose-derived stem cell is a new tool in this field with promising results and clearly stated advantages, like ease of harvest and availability. In this study, we aim to gather the latest research and perform a review on the matter. Materials and methods: Pubmed and Medline were used as databases, the search words were: adipose-derived stem cells and nerve regeneration, forty two publications were found and after revision, sixteen were used. Results and conclusions: We noted a clear potential from the adipose-derived stem cell to enhance the nerve regeneration process, the majority of the articles used laboratory settings, few of them describe a clinical setting. We analyzed the different possibilities of isolation, but also their effects and applicability.*

INTRODUCTION

The stem cell is the non-differentiated cell that can multiply and differentiate in all cell lines. There are two types of stem cells: the embryonic ones (derived from the internal mass of the blastocyst) and the adult ones, corresponding to postnatal life; the first have the ability to differentiate in all cell lines, meaning they are pluripotent, while the adult ones can only differentiate along the cell line from which they come from, depending on the embryonic origin (ectoderm, endoderm, mesoderm), meaning they are multipotent.(1) The process through which a stem cell can differentiate by changing the origin line is called transdifferentiation (originated in the mesoderm, but differentiation done in endoderm-derived cells). Adult stem cells were described by McCullock and Till (2), in Ontario, in 1963, as self-renewing cells in the bone marrow of mice.(3) Later, these cells, which were subsequently identified and called hematopoietic stem cells, were used in the therapy of severe bone marrow transplantation syndrome.(4) In 1968, mesenchymal stem cells were introduced by Friedenstein.(5) Reynolds and Weiss announce the identification of a neural stem cell population in the striatal layer of mice in 1992.(6) In other words, the only stem cells with clinical potential were those found in the haematogenous bone marrow, having limited applicability, low cell count, and morbidity at harvest or in the umbilical cord, having the related ethical aspects. Almost 10 years will pass before Zuk and his collaborators describe a population of cells with regenerative potential isolated from the processed lipoaspirate tissue, in other words, from the residual tissue after liposuction.(7)

The adipose-derived stem cell

The study of the adipose-derived stem cell continues with the reference article published by Zuk et al. in 2002 in Molecular Biology of the Cell.(8) But the conversion of adipose tissue into other tissues has been observed before, for example the bone calcifications that appear pathologically in lupus and Paget's disease.(9) Adipose tissue is macroscopically composed of lobules, which consist of 90% mature adipocytes and other cells forming the stromal vascular fraction: preadipocytes, fibroblasts, endothelial cells, vascular smooth muscle cells, monocytes, macrophages, lymphocytes and adipose-derived stem cells. From a histological point of view, there are two types of adipose tissue, namely white and brown. White adipocytes are spherical, having a diameter between 30 and 70 micrometers. Depending on the amount of stored lipids, the nucleus is pushed to the periphery. The brown adipocytes are polygonal, having a central core and a diameter between 20 and 40 micrometers. There is also a clear distinction in vascularisation, the brown ones being more vascularised and containing more mitochondria, with both of these aspects explaining the brown colour. Structural differences also translate into functional differences: both store the lipids as a form of energy reserve, the white ones use it as a response to metabolic activity, while the brown ones use it in the production of heat - thermogenesis. In the human species, brown adipose tissue is found only in newborns and children, disappearing at maturity. The embryonic origin of adipose tissue is found in the mesoderm, thus explaining the possibility of a population of mesenchymal stem cells, similar to the one in the bone-marrow. According to this principle, differentiation can be made on the same line, i.e. it can be differentiated in adipocytes, chondrocytes, osteocytes or myocytes, elements shown in the article mentioned above.(10) Subsequently, a series of studies appeared that also demonstrated the capacity for transdifferentiation; 2002 Safford and 2003 Ashjian demonstrate the emergence of ectodermal lines with neuronal-like differentiation (11,12), and the list continues with neuronal differentiation (13), oligodendrocytes(14) and Schwann cells.(15,16) In terms of endodermal transdifferentiation, studies have not ceased to appear, and among the first ones have demonstrated hepatocyte formation.(17,18) Thus, the ability of the adipocyte-derived stem cell to be pluripotent, not multipotent, just as the one derived from bone marrow, has been demonstrated.

This observation has greatly extended the scope of applicability, given the ease with which this tissue can be harvested and processed, its availability and low morbidity.

[1]Corresponding author: Vlad Bloancă, Str. Eftimie Murgu, Nr. 2, Timișoara, România, E-mail:vlad.bloanca@gmail.com; Tel: +40722 741702
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There is also a major difference in the amount obtained after harvesting. If approximately one mesenchymal stem cell is obtained from the bone marrow from 25.000 to 100.000, 2% of the lipoaspirated adipose tissue cellularity consists of adipose-derived stem cells.(19) Thus, the existence of such a cell population with multipotent properties has been demonstrated. It remained to establish effective methods of isolation, ways of influencing certain cell lines and, last but not least, clinical applicability in solving certain pathologies (table no. 1).

Table no. 1. Differentiation possibilities of adipose-derived stem cell and necessary factors (adapted from Vindigni V. et al., Adipose Derived Stem Cells: Current State of the Art and Prospective Role in Regenerative Medicine and Tissue Engineering).(48)

Differentiation	Stimulating factor
Adipogenic	Insulin, isobutylmethylxanthine, dexamethasone, rosiglitazone, indomethacin
Osteogenic	Dexamethasone, beta-glycerophosphate, vitamin D3, morphogenetic bone protein (BMP-2)
Chondrogenic	Insulin Growth Factor (IGF), BMP, Growth Factor and Beta Transformation (TGF-beta)
Miogenic, cardiomiogenic	Dexamethasone, hydrocortisone, IL-3, IL-6
Vascular, endothelial	Specific, hypoxic environment
Neurogenic	Valproic acid, Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), Nerve Growth Factor (NGF), Neural Derived Neurotrophic Factor (NDNF)
Tendinous	FGF, platelet-derived growth factor (PDGF), EGF, TGF-Beta, IGF-1, BMP.

Isolation

Isolation and extraction were performed initially under laboratory conditions; this involves repeated washing with phosphate buffer solution in order to separate erythrocytes and incubation with type I collagenase 0.075% (20) 37°C for one hour, the infranatant is separated, followed by centrifugation at 1.200 rpm for 10 minutes, re-suspended in ammonium chloride, then again centrifugation and repeated scrubbing to form the stromal vascular fraction and, in the end, culture on fetal bovine serum. The whole process takes about 2 hours. Another variant, more cost-effective, is the enzymatic digestion with trypsin.(21) But these processes are often lengthy and costly. In addition, the use of animal collagen for isolation and subsequently for clinical application may be accompanied by the appearance of undesirable effects such as: skin ulcers, nerve, tendon or ligament injuries, but also allergic reactions. No studies have been developed to evaluate the presence of the remaining collagenase. A series of initial effects were observed in surgical use, thus the liposuction graft was used to augment certain atrophic areas as, implicitly also in scars, and the result, in addition to the mechanical filling of the area, was also an observed improvement in the appearance of scars. Reference studies in this regard were undertaken by Coleman, who used the tumescent technique for harvesting and centrifugation at 3.000 rpm for 3 minutes.(22) Then, followed Raposio's study (23) that compared the classical method, based on collagenase, with a simpler, more mechanical variant. Here is how he proceeded: the fat was obtained through classical liposuction using a blunt cannula attached to the 10 ml Luer-Lock syringe; the lipoaspirate tissue was further subjected to laminar flow (to avoid contamination) to a vibration of 6.000 for 6 minutes, followed by centrifugation at 1.600 rpm for 6 minutes. The infranatant was collected, and, through flow cytometry, the presence of adipose tissue-specific antigens (AdSC) was examined: CD34APC, CD45APC-CY7, CD73PE, CD31FITC and CD90APC. The results were evaluated qualitatively and quantitatively, and the presence of AdSC in a considerable amount was established; namely, in 80 ml of fat, 5x105 cells were detected, approximately 5% of the total cells, the remaining 95% being blood-derived cells and endothelial cells. There have been differences and multiple studies regarding centrifugation speed. A study done by Kurita et al. in 2008 compares the effects of different centrifugation rates on adipose tissue transfer and derived stem cell viability; non-centrifuged and centrifuged concoctions are used at 400, 700, 1.200, 3.000 and 4.200 g for 3 minutes. Both the centrifuged concoction composition and the reaction of the athymic mice post-1 ml injection of the solution were observed. The conclusions were: the centrifugation process is beneficial for separating and concentrating adipose-derived stem cells, but the rate should be limited to 1.200 g (3.000 rpm) for optimal results.(24)

Differentiation, effects, applicability

After the discovery of the adipose-derived stem cell, reported by Zuk PA (25), studies referring to its differentiation and implicit clinical applicability began to appear. Most were performed under laboratory conditions (both in vitro and in vivo on laboratory animals) and under the influence of growth factors, and the clinical involvement was relatively modest by comparison. Depending on the differentiation line, there are several studies: for endodermal development, the studies conducted by Seo in 2005 (26) and Timper in 2006 (27) demonstrate the ability to form pancreatic tissue and hepatic tissue. And the list can continue with all cell lines, namely many types of tissues: adipose (28), bone (29,30), cartilaginous (31), striated muscle tissue (32), smooth muscle tissue (33), vascular (34), hematopoietic (35), epithelial tissue.(36) In parallel, research has also focused on applicability in various pathologies, via laboratory animal studies: intervertebral disc repair (37), spinal cord injuries (38), multiple sclerosis (39), stroke.(40) The transition to clinical trials was made in 2004 through the case study published by Lendeckel et al., where bone graft with addition of adipose stem cells was used to treat an extensive craniofacial bone defect.(41) Later, it was followed by a phase II clinical study on Crohn's disease (42) and organ transplant rejection.(43) Of course, the ethical aspect of these studies is shadowed by the risk of malignant transformation, by stem cell pluripotency and, in particular, by the use of growth factors; it is difficult to appreciate how these cells will differentiate and when they will stop.

The field of peripheral nerve regeneration has also been approached from the perspective of the adipose stem cell. Early research in the field used bone marrow stem cells, Woodbury et al. managing to obtain, through transdifferentiation, and under the influence of beta-mercaptoethanol, cells expressing neuron-specific enolase.(44) The Safford-led team uses a combination of butylated hydroxyanisole, potassium chloride, valproic acid, forskolin, hydrocortisone and insulin to obtain Schwann-like cells expressing the following markers: fibril glial acid protein (GFAP), microtubule associated protein 2 (MAP2) and Beta 2 tubulin.(45) When specific growth factors such as platelet-derived growth factor (PDGF) or fibroblast growth factor (bFGF) were added, changes in cell morphology and expression of specific markers for the Schwann cell, S100, GFAP , P75 and Beta 3 tubulin (46) were observed. Several experimental models based on a peripheral nervous defect have been established in order to demonstrate the ability of nerve regeneration; the defect was resolved by the use of nerve ducts (natural or synthetic) to which adipose stem cells have been added. The results were

contradictory, there being a possible interaction between the cells and the fabric of the duct. Another study, conducted by Lopatina et al., collects fat from the inguinal region of the rat, uses enzymatic digestion and induction towards nerve differentiation with retinoic acid; the model of injuries to which it applies is the crushing and ulterior application of matrigel containing culture cells; the study's final analysis is based on the usage of peroneal functional index, histology and PCR. The study determines the expression of genes encoding certain enzymes, cytoskeleton proteins, laminar adhesion molecules, myelin components (Krox20 gene), concluding that transplantation of adipose-derived stem cells stimulates nerve regeneration by two main means: angiogenesis (by VEGF, FGF), and brain-derived neurotrophic factor (BDNF) secretion.(47) This release of neurotrophic factors may act on the remaining Schwann cells (also activated by angiogenesis), causing a response supporting regeneration and nerve repair.

CONCLUSIONS

Adipose tissue has long been ignored by researchers, anatomists and physicians, but over the last two decades we can say that it has undergone a transition from being a simple form of energy storage to an important endocrine organ that plays a role in metabolism and immunity.(48) Naturally, the question that ensues is why does adipose tissue have such a vast and important supply of pluripotent stem cells, what is its actual role?

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