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A Review of the Therapeutic Potentials of Stem Cells, Fibroblast Growth Factors and T-cells in Regenerative Medicine

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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

The human body is a complex structure with the innate ability to protect, defend, repair, and heal after damage or disease. For decades, medicine has faced problems that need the evolution of standard treatments and finding a way to accelerate the regenerative capabilities of the body, which possibly would not just treat but also cure certain diseases that previously had no cure. The question researchers have pondered on is whether or not it was possible as humans to use the body's innate healing power to our advantage and clinically accelerate or modify it to upgrade the treatment of certain diseases. The answer they found was in Regenerative Medicine (RM).

Historically the term regenerative medicine was found for the first time in a paper published in 1992 by Leland Kaiser. He made a list of approaches that would impact the future of hospitals. However, it is widely believed to have been coined during a 1999 conference on Lake Como by William Haseltine in an attempt to describe a novel field of medicine that combined knowledge from subjects like cell transplant, biochemistry, nanotechnology, prosthetics biomechanics, tissue engineering, and stem cell biology.

Regenerative Medicine is a relatively new field of clinical applications and research that is focused on the development of therapies like tissue engineering and stem cell technologies to repair,

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regenerate or replace defective, aged, injured, diseased, or permanently damaged organs, tissues or cells in order to restore them to their normal function.
It is important to note that RM has rapidly become one of the top treatment options for acute and chronic injuries, congenital diseases, and a wide range of acute and chronic diseases. It is more than just a field of medicine involving basic replacement therapies or traditional transplantation; it applies approaches like gene therapy, reprogramming of cell types, stem cell transplantation, and the use of soluble molecules, tissue engineering, and lots more.
The review article focuses on the therapeutic effects of fibroblast growth factors (FGFs), adipose-derived stem cells (ADSCs), and regulatory T cells (Tregs), and the possible role they play in tissue regeneration. They are apparently useful in the treatment of myriads of diseases expectedly having no cure.

Keywords: Regenerative medicine; stem cells; T-cells (Tregs); adipocytes; fibroblast growth factors.

1. INTRODUCTION

Humans experience different events that could injure our bodies, from simple cuts to systemic diseases. It is crucial that we possess ways to heal damaged tissues. Tissue damage is simply an injury to a body tissue that causes an impairment of the function of the injured tissue [1,2].

There are two types of healing that can be done depending on the type of tissue damage: first-intention healing and second-intention healing. First intention healing is done in a short amount of time and does not involve much inflammation or granulation tissue. This type of healing is done by wounds with relatively small connective or epithelial tissue damage like minor cuts, superficial stab wounds, or well-apposed surgical incisions.

Second intention healing, on the other hand, takes longer to heal, and has a more intense inflammatory response, abundant fibrin and necrotic debris deposition, wound contraction, and granulation tissue. This type of healing occurs in wounds with margins not well apposed, such as ulcers, infarctions, burns, and large excisional skin wounds.

In nature, only a few animals, after tissue damage, can completely regrow parts of their bodies (an example is an earthworm that regrows its head after bisection). Humans, compared to these animals, are sadly lacking in this ability. The human body heals after tissue damage mostly by repair rather than regeneration [3].

Healing after tissue damage can occur in two processes: Regeneration or Replacement/repair. Regeneration refers to healing that restores the continuity of the tissue at its original anatomical site through synthesizing its kind of cell. Repair refers to healing in which some specialized cells lay down connective tissue (granulation tissue that later becomes a scar) to heal severely damaged or non-regenerative tissues [4,5].

Tissue repair has been noted to be more of an adaptation to loss, meaning that it restores some of the original architecture (epithelial layers) and function of the damaged tissue. However, it could also lead to various abnormalities in the structure (scarring) of the organ that can cause it to function less than it did prior to the injury [4].

Regeneration restores the normal structure and function of the organ while repair does not. Some types of tissue injury (like minor cuts) can be healed in a way that does not cause permanent damage. Self-healing of the body consists of both replacement and regeneration, with replacement being the more commonly chosen form of healing [5].

The ultimate aim of regenerative medicine is to return the patient to full health as before tissue damage, or in cases where the normal functions were initially absent, like in congenital abnormalities, to give normal function to those tissues. Therefore, even as much as repair is invaluable and very important as a process of healing the body, the consequences of repair can be unpleasant and undesirable (internal/external scarring) [3,4].

Replacement or regeneration in wound healing depends on the type of tissue injury and the extent of the damage. Some tissues are more inclined to cellular proliferation (regeneration) than others. In this regard, there are three types of tissues: continuously dividing tissues, quiescent tissues, and non-dividing tissues (Fig. 1) [3,6].

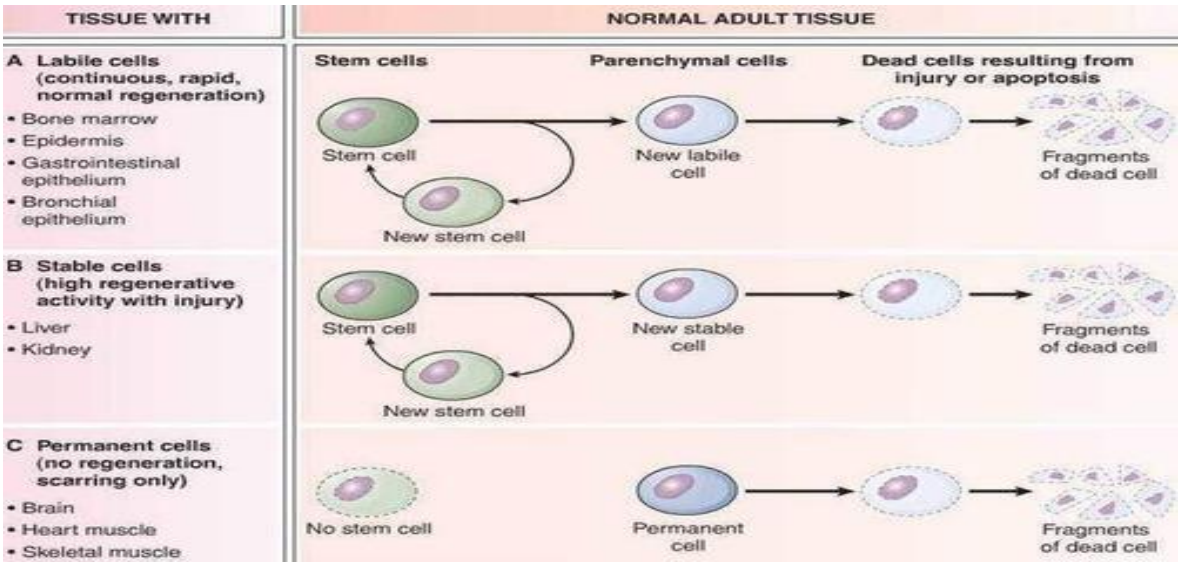

Fig. 1. Showing the three types of tissues, their regenerative potentials, where they are found, and how they divide [7]

The Continually dividing tissues (also known as labile tissues) are cells that possess enormous proliferative and self-renewing abilities. These cells proliferate (continuously divide) to replace sloughed-off or dead cells. Some examples are stem cells (adult or embryonic), epithelia of the skin (stem cells in the basal layer), salivary gland tissue, basement membrane cells, hematopoietic tissues (CD 34+ cells), and epithelia of the small and large bowel (mucosal crypt cells). These cells asymmetrically replicate, giving rise to numerous types of cells; each stem cell gives rise to two daughter cells, one matures and differentiates while the other cell remains undifferentiated and is capable of starting another self-renewing cycle [7].

The next class is the stable cells, also known as quiescent tissues. These tissues are composed of cells that normally exist in a non-dividing state but could enter the cell cycle in response to cell injury stimuli. Quiescent tissues may heal without scarring/ by regeneration if the damage is limited and the injured tissue still has the scaffolding surrounding its cells intact (an example of this is the regeneration of the liver after partial resection by compensatory hyperplasia). Tissues in this category of cells are renal tubular cells, parenchymal cells of the pancreas, endothelial cells, hepatocytes, lymphocytes, and mesenchymal cells (smooth muscle cells and fibroblasts).

The last class is called permanent cells (non-dividing tissue). These cells cannot proliferate because they have permanently left the cell cycle. Examples of non-dividing tissues are the skeletal and cardiac muscles. Tissue repair in these tissues always leaves a scar [3].

True regeneration in which the tissue is restored to its original state is relatively infrequent in humans and is, as of now, a process relegated to certain animal species, mythologies, and sci-fi films. Earlier mentioned were two conditions that must be met for any tissue to undergo true regeneration, re-iterating them after explaining the different types of cells and adding a third; those conditions are:

a. The capability of the damaged cells to proliferate.
b. The intactness of the underlying stromal framework.
c. The duration of the injury and inflammatory response.

To expatiate on condition B, if a continuously dividing tissue undergoes damage and only the cells of its parenchyma are damaged, it can undergo regeneration. In contrast, if it is a non-dividing tissue that undergoes damage or if the damage is so severe that it damages the underlying stromal framework as well as the parenchyma cells (which is what happens most times), even though that tissue is a continuously dividing tissue, regeneration would not be possible. In situations where regeneration is not possible, repair of the tissue occurs by depositing fibrous tissue in the defect. This is more of an

expanded definition of patching, not restoration [3].

There are so many therapies in the field of regenerative medicine, but the ones highlighted and reviewed in this article would be mainly fibroblast growth factors (FGFs), adipose-derived stem cells (ADSCs), and regulatory T cells (Tregs).

2. FIBROBLASTS GROWTH FACTORS (FGFs)

The proper functioning of a system within a multicellular organism relies greatly on proper communication within and between each cell. Proteins (paracrine/ endocrine) play a key role in proper communication between cells. Hence, it is safe to note that cell communication is restricted when a cell is injured. The healing of damaged tissues by either repair or regeneration is coordinated by diverse cytokines, differentiation, and growth factors. One of those growth factors is the fibroblast growth factors (FGFs), which are one of the important regulators in the regeneration and repair of damaged tissues [8,9].

FGFs regulate most aspects of organogenesis, physiology, and development of the organism from birth to regular maintenance of its tissues. They also potentiate other factors involved in regeneration to be expressed. They are involved in initiating/assisting different types of cells in their survival, adhesion, differentiation, proliferation (they can also negatively affect a cell's proliferation), migration, and metabolic activities. FGFs deliver information by synthesizing and secreting signalling molecules (through the RAS/MAP kinase, PI3 kinase/AKTz, or PLCγ pathway) into the extracellular space that would cause fibroblast growth factor receptors (FGFRs) to be activated [8,9].

Paracrine-acting FGFs are involved mostly in the repair of damaged tissues. Lately, the functions of endocrine-acting FGFs are being identified as relevant. An example is the Fgf15 (an endocrine-acting FGF produced by epithelial cells of the intestines, although not found in humans), which has been noted by researchers Uriarte and Padrissa-Altes to be involved in stimulating the repair of an injured liver [8].

2.1 Subtypes and Family

In 1974, FGF activity was discovered by Rudland, Seifert, and Gospodarowicz in partially purified extracts from bovine pituitary. In 1989, Burgess and Macaig isolated the acidic FGF (FGF1) and basic FGF (FGF2) from the brain and pituitary gland and noted them as fibroblast growth factors. FGFs are present in all multicellular animals.

The communication system of FGFs comprises a family of signal transducing cell surface receptors, fibroblast growth factor receptors (FGFRs), co-receptors, a family of ligands, and the FGFs. The Human FGF has 23 members identified to belong to its family, and it has also been grouped into seven subfamilies through phylogenetic analysis and six subfamilies through gene location analysis. Additionally, it has four homologous FGF factors (FGF members that do not bind to FGFR: FGF11, FGF12, FGF13, and FGF14) and 8 FGFR ligands.

The members of the FGF family are: FGF1, FGF2, FGF3 (INT2), FGF4, FGF5, FGF6, FGF7 (KGF), FGF8 (AIGF), FGF9, FGF10, FGF11, FGF12, FGF13, FGF14, FGF16, FGF17, FGF18, FGF19, FGF20, FGF21, FGF22, and FGF23.The play important roles in cellular proliferation, migration, differentiation and angiogenesis (Table 1) [9,10].

2.2 Molecular Signal Pathways

The binding of an activated FGFR to an FGF ligand enables the kinase activation loop to phosphorylate tyrosine residues at the cytosolic part of the FGFR, which would then become sites of attachment for numerous signalling proteins that would go on to potentiate different specific functions in the cell [10]. The most highlighted pathways are the PLCγ pathway, RAS/MAP kinase pathway, and PI3 kinase/AKT pathway [9,10].

2.3 Clinical Applications of FGFs

FGFs can be used therapeutically for many diseases/wounds (acute and chronic) and have been found to have different degrees of success in treating those diseases. The repair of damaged tissues using FGFs has been researched for decades; however, it has not been widely used clinically until recently. Major clinical findings on the therapeutic effects of FGFs have shown its effectiveness in treating conditions like pressure ulcers, chronic wounds, vascular ulcers, burns, scleroderma, oral ulcers, aging (wrinkles), diabetic ulcers, and recessive dystrophic epidermolysis bullosa [9].

Table 1. Showing the functions of various FGFs and their target cells [10]

Function	Subtypes	Target cell
Cell proliferation	FGF1, FGF2	Preadipocytes, endothelial cells, epithelial cells, fibroblasts, neural stem cells.
	FGF4	Trophoblastic stem cells.
	FGF7, FGF10	Epithelial cells.
	FGF18	Osteoblasts, chondrocytes, osteoclast.
Cell migration	FGF2	Astrocyte, myogenic cell
	FGF4	Myogenic cells
	FGF7	Epithelial cell, Keratinocytes
	FGF8	Neural crest cells
Cell differentiation	FGF1,FGF2	Neuroepithelial
	FGF7	Keratinocytes
	FGF20	Monkey stem cell
Angiogenesis	FGF1,FGF2	Endothelial cell

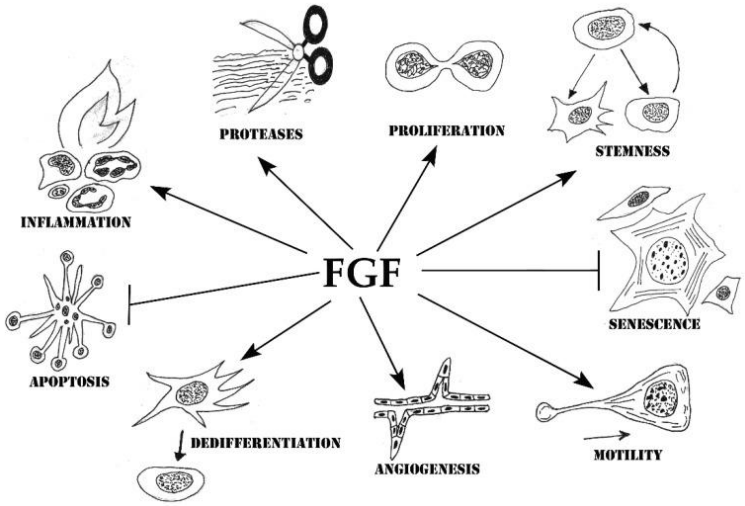

Fig. 2. Schematic showing functions of FGF
Source: Cellular Mechanisms of FGF-Stimulated Tissue Repair - PubMed (nih.gov)

2.3.1 Therapeutic effects of FGFs on the skin

FGFs can stimulate fibroblasts to proliferate and promote angiogenesis, suggesting that they could be used to heal skin wounds and facilitate re-epithelization. Macrophages present at sites of damaged endothelial cells and release FGF1 and FGF2 (speeds up the healing process and promotes scar-free healing) to help with angiogenesis of the wound. In contrast, FGF 7 and FGF10 are released by the dermis around the site of damage and granulation tissue fibroblasts. They act on local keratinocytes to aid their stimulation, proliferation, and migration [8,10].

2.3.1.1 Burns

The use of FGF2 in treating chronic wounds and burns was researched in 2005 by researchers Liu, Tan, and Jang. In their study, they divided patients into three separate groups: a chronic wound group (represented were: pressure ulcers, wounds that even after four weeks of routine treatment could not be healed, diabetic ulcers, residual granulation wounds, and sinuses) of 65 people, a burn wound group (represented were: deep partial thickness burns and superficial partial thickness burns) of 62 people and a donor site wound group of 36 people. Participants in the three wound groups were treated with the standard treatment for burns and FGF2. Randomization (self-controlled) was applied to the donor site wound group and the burn wound group, comparing the same participants before and after the treatment. Participants in the control group were treated with the standard treatment and saline in equal amounts for each participant in the control group. The results

showed that FGF2 greatly reduced the wound healing time for participants in the three wound groups compared to those in the control group [9].

A study was done in 2006 by a researcher named Guo. Randomization (self-controlled) was also applied in this study, including a control group and a treatment group (80 cases of deep partial thickness burn, some of them having a few superficial partial thickness wounds). In the treatment group, a gauze pad impregnated with FGF2 solution was applied to the debrided wound, which was then covered with another gauze pad containing 1% (w/w) silver sulfadiazine. In the control group, the same treatment method was given as those in the treatment group, but instead, the FGF2 was substituted with normal. The results showed that FGF2 greatly reduced the wound healing time for participants in the deep partial thickness burn wounds group in comparison to the control group (9.51 ± 1.86 days *vs.* 12.43 ± 2.03 days, $p < 0.05$ for superficial partial thickness wounds and 18.36 ± 4.87 days *vs.* 22.35 ± 5.60 days, $p < 0.01$ for deep partial thickness wounds) [9].

2.3.1.2 Orthopaedic trauma wounds

It has been observed that infection of skin grafts, grafted flaps, fresh skin defect wounds, and tissue necrosis may occur after an orthopaedic trauma surgery. Physicians have started applying FGF2 to both debrided and fresh necrotic skin wounds to reduce the time required to heal these wounds and severely limit the need for re-grafting of the skin.

In 2005, researchers Yao, Zha, and Zang investigated using an FGF2 biological protein sponge for traumatic skin ulcers. They used a sterile FGF2 biological protein sponge and applied it to 20 patients with traumatic skin ulcers. The primary outcome of their research was that within three weeks of applying the FGF2 biological protein sponge, the wound healing time in the control group was 55% and 95% in the treatment group. It was shown as part of the findings that peri-wound inflammation, skin re-grafting, and wound secretions were significantly reduced in the treatment group compared to the control group. It is important to highlight that neither of the groups experienced any obvious adverse effects. So it is safe to say that the data collected by these researchers support the motion that FGF2 biological protein sponges could reduce the healing time and effectively enhance healing in patients with traumatic skin wounds [9].

2.3.1.3 Pressure ulcers

For a long time, there have been difficulties associated with the clinical care of patients with pressure ulcers. Pressure ulcers are extremely painful, could prolong a patient's illness's duration, and even progress to be fatal if sepsis from a secondary infection occurs. Treatment for pressure ulcers usually includes dressings, creams, ultraviolet heat lamps, solutions, ointments, ultrasonography, surgery, and innovative mattresses.

In 1992, a researcher named Robson studied the treatment of pressure ulcers using FGF2. It was a blinded, randomized (placebo-controlled) trial with 50 patients with pressure ulcers (different sizes from 10 to 200 cm^3). It was observed that the number of patients treated with FGF2 had a huge increase in their capillary and fibroblast numbers, and also, their ulcers were 70% reduced in size (60/100 *vs.* 29/100, $p = 0.047$) as compared to the patients treated with placebo [9].

2.3.1.4 Diabetic foot ulcers

Diabetic foot ulcer (which can potentially lead to a diabetic-related disability) is a serious complication of diabetes and can cause the feet of the patient to develop ulcers, injuries, infections, or gangrene.

In 2009, known diabetic patients were involved in a study that did a dose-ranging, double-blind, randomized (placebo-controlled) trial to clinically test the use of FGF2 for the treatment of diabetic foot ulcers. Diabetic foot ulcer patients were randomly put into a 0.001% (w/v) FGF2 treatment group (n = 49), a placebo group (n = 51), and a 0.01% (w/v) FGF2 treatment group (n = 50). The result of the study proved that FGF2 significantly increases the healing rate of diabetic foot ulcers. Showing that there was a 75% and more reduction in the area of the ulcer in 57.5% (27/47), 72.3% (34/47), and 82.2% (37/45) in the placebo, 0.001% (w/v) FGF2 and 0.01% (w/v) FGF2 groups, with significant differences between the 0.01% (w/v) FGF2 treatment and placebo groups ($p = 0.025$). Cure rates were 46.8%, 57.4%, and 66.7% in the placebo, 0.001% (w/v) FGF and 0.01% (w/v) FGF2 groups [9]. These studies imply that FGFs could be an effective treatment option for various skin defects

in cases where conventional treatment choices fail.

2.3.2 Therapeutic effects of FGFs on oral ulcers and dental tissues

A relatively common and recurrent disease of the oral mucosa is the oral ulcer (which mainly involves the formation of non-specific ulcers caused by the dissolution, rupture, and shedding of the mucosal epithelium of the mouth) [9].

In 2013, a study was carried out investigating the use of FGF2 paste and topical application of an insoluble silicate (diosmectite; DS) to treat recurrent aphthous stomatitis (non-infectious, benign mouth ulcers). One hundred twenty-nine individuals with recurrent aphthous stomatitis participated in this study and were split into four groups according to the different groups of pastes. Paste 1 had FGF2 and DS, Paste 2 had DS alone, Paste 3 had FGF2 alone, and Paste 4 had placebo. In comparison to the other pastes, Paste 1 significantly reduced the score for ulcer pain ($p < 0.05$ for days 3, 4, 5, and 6) and the size of the patient's ulcer ($p < 0.05$ for days 2, 4, and 6). It is also important to note that the researchers observed no obvious adverse reaction in participants [9].

A study was conducted in which researchers surgically made 2-wall, 3-wall, and furcation class II alveolar bone defects on beagle dogs and topically applied FGF2 to the artificial bony defects. After eight weeks following topical application of FGF2, the following findings were noted:

- There is no root resorptions, ankylosis, or down growth of the epithelium observed.
- Compared to the control group, the results in the treatment group had significant increases in the amounts of new bone and periodontal tissue formation with new cementum deposits in all places where FGF2 was applied.
- FGF2 stimulation caused an upregulation of periodontal laminin mRNA levels (involved in angiogenesis), but there was a downregulation in type I collagen levels.

This study showed that FGF2 could be used for periodontal tissue regeneration by highlighting that proliferation in periodontal tissue cells increased, and there was an inhibition of alkaline phosphatase (ALP) activities and the formation of mineralized nodules following FGF2 application [11].

Another study on periodontal tissues was a double-blind, multicentre randomized (placebo-controlled) trial. In this study, researchers followed the guidelines of good clinical practice and highlighted that for the regeneration of periodontal tissues, FGF2 was ultimately efficacious and safe. They had a treatment group and a placebo group, and results showed that at 36 weeks, the bone fill percentage in the FGF2 group was higher compared to the placebo group, and no adverse effects were noted [9].

These studies imply that FGFs could be an effective treatment option for oral ulcers and diseases involving dental tissues in cases where conventional treatment choices fail.

2.3.3 Therapeutic effects of FGFs on autosomal recessive dystrophic epidermolysis bullosa recessive (RDEB)

This is an inherited mucous membrane and skin-erosive/blistering disorder caused by a loss of function *COL7A1* gene mutation (a mutation in this gene causes a decrease in collagen type VII and the dermal-epidermal junction to be defective, thereby destroying the attachment between the dermis and the epidermis).

Dermal fibroblasts and basal keratinocytes secrete and synthesize Type-VII collagen, with the main secretors of anchoring fibril protein being keratinocytes. Currently, RDEB has no clinically effective treatments available [12].

The focus of studies is to develop new and effective RDEB treatments mainly on cell-based, gene, and protein therapies. However, it has also been observed that these studies, which use cultured keratinocytes, tend to have an increased risk for skin infections and ultimately lead to increased patient mortality. Following the outcomes of studies done on cultured keratinocytes, researchers have made it a point of focus to highlight that fibroblasts could be a better option to target in these therapies. Observe, for instance; the results got from two separate studies, where immunodeficient mouse skin (in study 1) and human RDEB skin (in study 2) were injected with human RDEB fibroblasts with corrected *COL7A1*-gene that were overexpressing type-VII collagen. The control group was injected with normal human fibroblast (without any gene correction).

The results of both studies showed the effectiveness of the fibroblasts (normal and gene-corrected) in sustaining the deposition of human type-VII collagen at the DEJ and the formation of the anchoring fibril protein in both groups (treatment group and control group). However, findings in the treatment group were more significant. Nevertheless, it is quite intriguing that the control group, injected with normal fibroblasts, had a notable restoration of skin phenotype, as findings showed that the new type-VII collagen at the DEJ was sustained for several months [9]. These studies imply that FGFs could be an effective treatment option for RDEB in cases where conventional treatment choices fail.

2.3.4 Therapeutic effects of FGFs on systemic sclerosis

Systemic sclerosis (SSc), also known as scleroderma, is a group of rheumatic autoimmune diseases that causes pathologic remodeling of connective tissues, vasculopathy, scarring, and diffuse fibrosis of the skin and internal organs. Scleroderma is classified based on the extent and pattern of skin involvement. In limited cutaneous scleroderma, fibrosis is predominant on the face, arm, and hands. However, the progression of diffuse cutaneous SSc (dcSSc) is rapid and affects both the extremities and trunk of an individual with the disease. SSc occurs when there is excessive deposition of extracellular matrix protein (collagen type 1) and fibroblast production, disrupting the affected tissue's structure.

Activation of fibroblasts is one of the most important steps that lead to the development and progression of fibrosis. Much like the process of healing by repair, fibrosis develops because of the activation of fibroblasts, their proliferation, migration, and deposition of matrix proteins (collagen and fibronectin) into trauma sites. After repair, the myofibroblasts and fibroblasts activated during the repair process are cleared through a mechanism that's still unknown, but in diseases like scleroderma, the activated myofibroblasts and fibroblasts remain. Initiating the enhanced secretion of growth factors like connective tissue growth factor (CTGF; CCN2) and FGFs, which create an ECM-rich pro-fibrotic environment [13]. In the treatment of SSc, therapies are focused more on alleviation rather than limiting its progression or curing it entirely.

In a study done using single-cell RNA sequencing to reveal each cell's unique identity, researchers collected skin samples from 95 volunteer patients with SSc (study group) and 48 healthy (control group). The researcher in the study group identified a specific subset of fibroblasts that had a sharp drop in its concentration in the early stages of SSc and a continuous reduction in concentration over the course of the progression of the disease. The subset of fibroblasts they identified was named Scleroderma-Associated Fibroblasts, also known as scaffolds (ScAFs).

The researcher in the control group still had their ScAFs present, and it was observed that these ScAFs accounted for nearly 30% of all fibroblasts. With these findings, researchers could conclude that a possible therapy that could significantly reduce/limit the progression of SSc could be developed with a sufficient and appropriate understanding of ScAF- related signalling pathways [14]. These studies imply that FGFs could be an effective treatment option for SSc in cases where conventional treatment choices fail.

2.3.5 Therapeutic effects of FGFs on nerves

Compared to nerves of the peripheral system (PNS), neurons in the central nervous system (CNS) do not possess many regenerative abilities (because glial cells are quick to develop gliotic [scar-like] tissue), and this becomes one of the main issues related to healing/cure when patients develop CNS injuries [8].

Researchers have noted that astrocytes stimulate the production of soluble form FGF2 and matrix-bound FGF2 in the blood-brain barrier. These FGF2 cells have both autocrine and paracrine effects that potentiate the stellation and proliferation of astrocytes and hence have neuroprotective capabilities [15].

In addition, a study done in 2006 (Grothe et al.) and reviewed in 2002 by Werner and Alzheimer showed that after traumatic, ischemic, and metabolic nerve injuries of the hippocampus, FGF2 was important for the potentiation of neurogenesis and also functioned as a regulator for the repair and protection of neurons.

A regenerative study was carried out on the peripheral nerves of mice (in vivo and in vitro). The study involved implanting FGF2 (in a polymer tube) through a 15mm gap in the sciatic nerve of the mice [16]. The trial's outcome was that they could regenerate the nerve cables

bridging nerve stumps (in vivo), and the release of FGF2 with biological activity was sustained [10].

Researchers also checked the therapeutic effects of FGF2 on facial nerve injuries, cerebrospinal fluid leaks, and age-related atrophy of the vocal cord.

- In the trial on facial nerve injuries, FGF2 embedded in an anionic gelatine medium was implanted into the intra-temporal facial nerve of patients in the treatment group. The trial outcome six weeks after showed significant improvements in facial movements, histological plus electrophysiological appearance, and general functions of the facial nerve in the treatment group [10,17].
- In 2005, a case of a patient with a surgical history of relapsing Rathke cleft cyst who presented with intractable cerebral spinal fluid rhinorrhoea was reported (Kubo et al.). Physicians used an endonasal endoscopic approach to repair the patient's sellar floor using mucosal flaps. The fistula was occluded through the application of FGF2, which helped potentiate granulation. Repeated application of FGF2 endoscopically to the mucosal flaps was done, and this enabled the flaps to turn into granulation-like tissue and attain the desired result of complete coverage of the mucosa [9].
- A case of a patient with glottal insufficiency (age-related atrophied vocal cords) was reported in 2008 (Hirano et al.). This patient was treated by injecting FGF2 into the vocal folds. The results after a week showed the disappearance of the glottis gap and significant improvement in the vocal fold [9].

3. ADIPOCYTES

Regeneration of tissues using adipose tissue is an emerging branch in regenerative medicine. The reason why adipose tissue, more specifically adipose-derived stem cells (ASCs), is used in tissue regeneration is that these cells release growth factors that decrease inflammation regulate the immune system, and perform a range of important cellular functions that eventually aid complete healing of damaged tissues (leaving behind no scars whatsoever).

The therapeutic uses of adipose tissues have been noted for the treatment of diseases like psoriasis, pulmonary fibrosis, acute respiratory distress syndrome (ARDS), systemic lupus erythematosus (SLE), asthma, osteoarthritis, chronic obstructive pulmonary disease (COPD), non-small lung cancer, degenerative vertebral disk disease, ischemic heart disease, atopic dermatitis, neurodegenerative disorders (such as amyotrophic lateral sclerosis, Huntington, Alzheimer and Parkinson's) and diabetes [18,19].

There are four types of Adipose tissue (distinguished by the color of the adipose tissue): Brown adipose tissue (BAT), white adipose tissue (WAT), pink adipose tissue, and beige adipose tissue. White adipose tissue (made up of monocular adipocytes and lipid storage cells) has many endocrine receptors (like glucocorticoids, insulin, norepinephrine, and sex hormones), and they function as one of the main regulators of homeostasis and metabolic physiology [20,21]. The development of WAT (differentiated through the transcriptional cascade from undifferentiated preadipocytes) in humans starts around the mid-gestation period. Nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ) is a protein that promotes gene expression, regulates members of the CCAAT/enhancer-binding protein family, and regulates the process of WAT differentiation and the metabolism of glucose and storage of fatty acid. PPARγ is a highly required protein for the maintenance of adipocytes and the process of angiogenesis [21].

Usually, there are two major locations in the human body where WAT can be found. These areas are the intra-abdominal and subcutaneous (directly below the skin) areas of the body. The WATs found in the subcutaneous area mostly consist of single adipocytes. It is also important to note that the percentage of healthy WAT in humans depends on various factors. However, the approximate gender values range from about 14-35% for adult women and 6-25% for adult men [21].

White adipose tissue helps thermoregulation, regulates endocrine communication, and is critically important for insulin sensitivity and energy storage. It was initially thought that the mechanism of action for WAT energy storage was breaking down fat into fatty acids (a fuel source for muscles) because of the activation of the dephosphorylation cascade by insulin receptors of WAT cells after receiving signals from insulin released from the pancreas, which then causes the inactivation of hormone-sensitive fats cells .It has been proven that the

previously noted mechanism of action is wrong because glucagon acts solely on the liver; hence, the evidence supporting the claim that glucagon affects WAT lipolysis is unfounded. Instead, the mechanism of WAT energy storage is thought to be mediated by noradrenaline, adrenocorticotropic hormone, and adrenaline [21, 22]. White adipose tissues are also what make up most of the adipose-derived stem cells.

Brown adipose tissue has many functions in humans, such as improving bone density, insulin sensitivity, and adaptive thermogenesis through the expression of UCP1 in specific tissues .UCP1 is stimulated by β-adrenergic receptor activation and functions in the mitochondria, and uncouples the respiratory chain of oxidative phosphorylation and glucose homeostasis [23]. The development of BAT cells starts from the paraxial mesoderm (middle layer of the trilaminar disc). Note that the paraxial mesoderm is also the layer that gives rise to muscle cells (myocytes). Hence it is not confounding that both BAT cells and myocytes can activate the myogenic factor 5 (Myf5) promoter involved in the development of many tissues.

A study was done using the PRDM16 transcription factor as a culture medium on BAT and myocytes. BAT cells cultured without PRDM16 transcription factor converted to myocytes, and myocytes cultured with PRDM16 converted to BAT cells [24].

Previously, BAT in humans was thought to exist only during infancy around organs (trachea, pancreas, and kidney) and in suprarenal, interscapular, para-aortic, supraclavicular, and pericardial areas. Evidence from imaging studies done in 2007 revealed that a few metabolically active BAT were present in adults in suprarenal, para-aortic, and paravertebral (thoracic and supraclavicular) regions. A huge prevalence of BAT in adults is an anomaly and exists as a tumor called hibernoma. the percentage of BAT that can be detected in adult humans depends on various factors. However, it has been noted that women generally have more BAT cells than men [24,22].

In 2014, Pink adipocytes were discovered in the subcutaneous WAT of pregnant female mice (17-18 days gestation). These adipocytes persisted through the periods of lactation and a few weeks post-lactation. Pink adipocytes are derived from WAT milk-secreting alveoli cells (they have epithelial-like features that help them form milk) that look slightly pink. Pink adipocytes have structures similar to the architecture of epithelial cells because they possess abundant organelles (mitochondria, peroxisomes, and rough endoplasmic reticulum), cytoplasmic projections, and compartmentalized lipid droplets. No study has been done to indicate if pink adipocytes exist in humans, but it is for a fact that they exist trans-differentially in rodents [25].

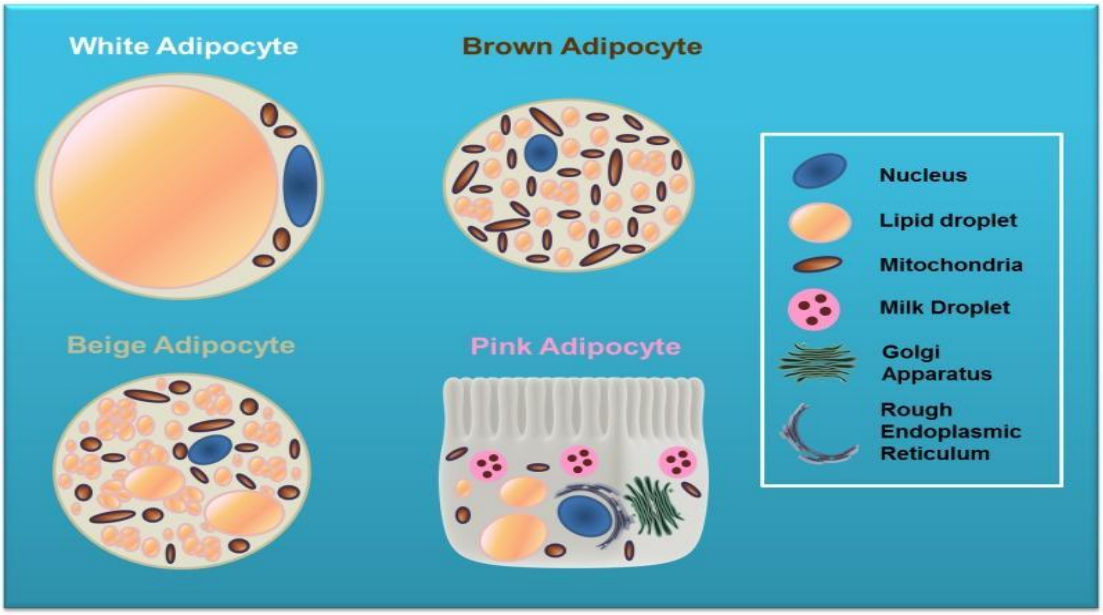

Fig. 3. Showing the different types of adipocytes and their properties [22]

Beige adipocytes can form by trans-differentiating WAT cells or can develop from specific subsets of preadipocytes (found within WAT cells below the skin). They have characters of both BAT and WAT cells [26-28]. They generally have significantly increased lipid droplet proportion and size variation compared to WAT cells, giving it its slightly brown color [29].

4. STEM CELLS

Stem cells are considered the body's raw materials, and are basically the foundation of every specialized tissue and organ in a eukaryotic organism [30,31]. Researchers have found out that stem cells can make copies of themselves (self-renewal), generate new cell types, and differentiate into specialized cells with specific functions (osteoclasts, myocytes, neurons, blood cells, etc.). The abilities of stem cells have not been found in any other cell in the body [30,31]. Stem cell research is a high-yield research topic in modern biology, and these studies hope and help to understand more about stem cells and how they can be medically beneficial now and in the future [19]. Stem cell types are classified according to the body's formation or origin. The types of stem cells are perinatal stem cells, embryonic stem cells (ESC), somatic/adult stem cells (ASC), and induced pluripotent stem cells (iPSC) [30,31].

4.1 Perinatal Stem Cells (PSC)

These were discovered recently by researchers, and are found in the blood of the umbilical cord and the amniotic fluid (the fluid surrounding a fetus) after carrying out amniocentesis on pregnant women in a study [31]. Little research has been done on these types of stem cells, so little is known.

4.2 Embryonic Stem Cells (ESCs)

In 1998, researchers carried out a stem cell study on human embryos from consenting donors who went through in vitro fertilization and no longer needed the embryos for reproductive purposes. This led to the discovery of a group of stem cells that were later named 'embryonic stem cells, found in the inner cell mass of the blastocysts (which is formed 3-5 days after fertilization) [30,31]. The results after growing these stem cells under specific laboratory conditions (mixing with growth factors), similar to the normal development of an embryo, meaning that they found these cells to be able to divide and form different types of cells. The summary is that embryonic stem cells are pluripotent, leading to future expectations for their therapeutic uses (cure and hopefully the regrowth of organs). Although research on ESC is limited because of ethical guidelines created in 2009 by the National Institutes of Health (guidelines detailing the acceptable procurement of embryos for research purposes), there are available ESC therapies for certain diseases like muscular dystrophy, loss of vision, diabetes, diseases of the heart, hearing loss and spinal cord injuries [31,32, 33].

4.3 Adult Stem Cells (ASCs)

Adult stem cells, also known as tissue-specific or somatic stem cells, are undifferentiated stem cells found in specific tissues in the body. In 1948 scientists extracted the first ASCs and used them to produce blood. Though ASCs are undifferentiated cells, they are generally found in specialized tissues (like the brain, bone marrow, skin, muscles, adipose tissues, gut, and muscles), and not only do they function to generate cell types of their resident tissues during repair but they can generate other types of tissues as well (trans-differentiation). ASCs, compared to ESCs, are generally present in small numbers and are limited in their self-renewal and differentiation abilities, thus reducing the scope for their therapeutic use [31, 32].

In about half a century, scientists have used ADCs (peripheral blood and bone marrow transplants) in treating diseases like lymphoma and leukemia. It was also noted in a study done on animals with heart failure that their heart function was improved after the injection of ADC heart cells, and survival time increased [33]. The types of ASCs are stromal/mesenchymal stem cells (MSC), epithelial stem cells, blood stem cells (hematopoietic stem cells), skin stem cells, and neural stem cells [31,32].

4.4 Induced Pluripotent Stem Cells (iPSCs)

The history of iPSCs started in 2006 when various conditions that could aid the genetic reprogramming of ASCs to assume an ESC-like state (mimicking the properties of an ESC) started.

In 2007, induced pluripotent stem cells were discovered, and these are laboratory-created pluripotent stem cells made from the process of introducing embryonic genes into a tissue-specific cell and causing it to become 'stem cell-like.' [33].

Apart from the cost and general difficulties associated with using ESCs, while using donor ESCs to treat a patient, the patient would need to be on lifelong immunosuppression or have issues with histocompatibility. Since iPSCs are basically laboratory-engineered ESC-like cells, the use of iPSCs is more conducive to treating diseases. However, there is only a limited understanding of iPSC, and further research is still ongoing [30,34].

4.5 Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells are types of ASCs, and it is a canopy term that refers to stem cells from the surrounding connective tissue of tissues/organs (stroma). MSCs can be grown from cord blood and adipose cells, but they were first found in the bone marrow and had immunological and stem cell properties. MSCs differ based on how they were isolated, where they came from, or how they are grown [30].

MSCs can differentiate into cells like muscle cells, osteocytes, connective tissue, and adipocytes; this differentiation depends on where these cells are located. It has been theorized that MSCs come from preadipocytes (the precursor cell of adipocytes); this has led scientists to believe that it gives MSC the ability (based on stimuli) to differentiate into brown or white adipose cells.

4.6 Adipose-derived Stem Cells (ADSCs)

These are multipotent white adipose tissue MSCs, known for their easy adherence to plastic flasks and effective in-vitro expansion capabilities. These cells also possess anti-apoptotic, anti-fibrotic, immunomodulatory, and anti-oxidative abilities, as well as the ability to differentiate into a wide variety of cells (neurocytes, myocytes, hepatocytes, osteocytes, chondrocytes) from the ectoderm, mesoderm or endoderm, offering the potential to maintain, repair or enhance any tissue [35,36].

Compared to bone marrow MSCs, plastic surgeons and researchers prefer ADSCs because they are extremely abundant in the human body. The extraction procedure is minimally invasive and is more suitable for allogenic transplantation (less donor site morbidity) [37,38]. The therapeutic uses of ADSCs vary from aesthetic purposes to the treatment of pathologies. Preferred sources of ADSCs are subcutaneous adipose tissues of the arms, abdomen, and thighs [19].

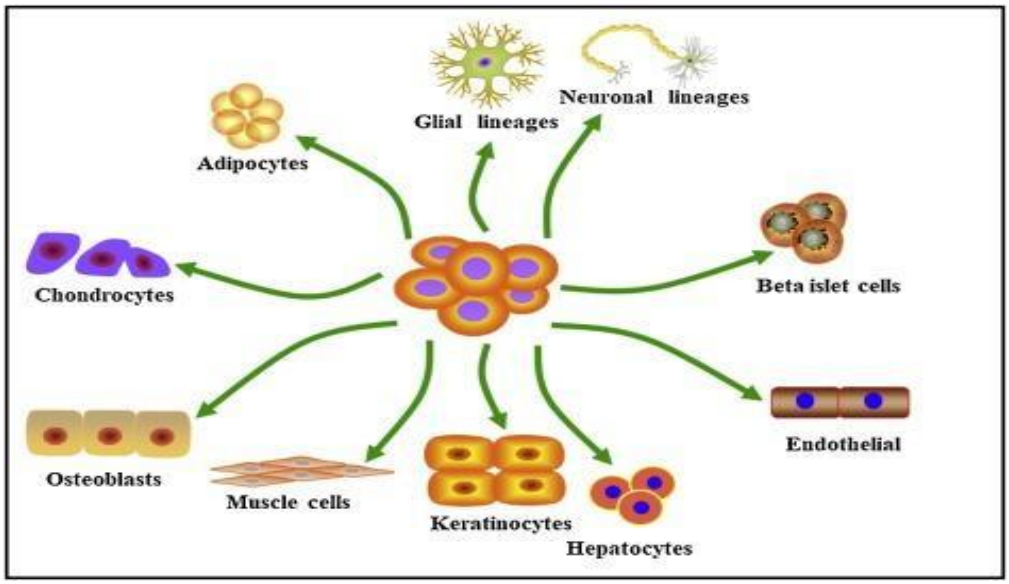

Fig. 4. Showing the differentiative potential of ADSCs

Adipose-derived stem cells: Sources, potency, and implications for regenerative therapies - Source: Science Direct

4.6.1 Identification of ADSCs

In 2006, the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT) stated three minimum criteria for ADSC identification, and these are:

(1) Adherence to plastic
(2) Expression of CD105, CD73, and CD90 but lack of expression of human leukocyte antigen-DR (HLA-DR), CD19, CD14, CD117, CD34, CD79a, CD11b, or CD45 on flow cytometry analysis
(3) They must be able to differentiate into preadipocytes, chondrocytes, and osteoblasts [39].

The immunophenotype of bone marrow MSC is >90% identical to the immunophenotype of ADSCs, with both types of stem cells expressing positive surface markers for CD73, CD44, CD105, and CD90 and negative for surface markers CD31 and CD45. The difference is that ADSCs also express CD49d and CD34, while bone marrow MSCs do not [35,38].

4.6.2 Immunomodulatory properties of ADSCs

ADSC's immunomodulatory abilities are still being researched. However, it is noted that due to their low expression and lack of major histocompatibility complex class I and II, their phenotype is hypoimmunogenic (less immune recognition) [40]. ADSCs are still noted to have a more powerful effect on the suppression of an immune response than MSCs from other tissue sources because they secrete cytokines in amounts greater than other MSCs can secrete.

In situations of allogeneic HLA mismatch, ADSCs, due to their low level of hypoimmunogenic phenotypes, are able to suppress the allo-proliferation of T cells and inhibit the proliferation and differentiation of B cells ADSCs may also potentiate the proliferation of a subset of CD5 + regulatory B cells (these cells secrete an anti-inflammatory cytokine called IL-10) that go on to inhibit inflammatory cytokine production by activated T cells proving the potential therapeutic use of ADSCs for the treatment of autoimmune diseases.

In a 2009 study (González et al.), an example of ADSCs immunologic effect was observed after injecting human ADSCs in mice with collagen-induced arthritis. The observed findings of the study were the production of IL-10 in joints and lymph nodes of the mice and the decrease in antigen-specific Th1/Th17 cell proliferation levels [40].

4.6.3 Immunomodulatory therapeutic effects of ADSCs in the treatment of immune thrombocytopenia (ITP)

Immune thrombocytopenia (ITP) is a multifactorial acquired autoimmune platelet characterized by abnormally decreased survival time and platelet count in the blood. Platelets are responsible for clotting the blood, but in ITP, macrophages in the spleen phagocytose and destroy antibody-coated platelets (PLTs), resulting in a loss of immune tolerance as well as excessive bleeding of the skin, viscera or mucosa, and persistent bruising of individuals with this condition [41,42].

ITP is more prevalent in women than men, and it is one of the top 3 chronic hemorrhagic disorders in women, with 11-24% resistant to standard treatment. The genetic factors for ITP include polymorphisms in FCγ receptors, MHCs, pro- and anti-inflammatory cytokines, pro- and anti-inflammatory receptors and/or transcription factors.

The environmental factors for ITP, as noted from cross-sectional studies of patients with ITP, include previous/current infections with Epstein-Barr virus (EBV), Human immunodeficiency virus (HIV), Cytomegalovirus (CMV), Helicobacter pylori, and Hepatitis C virus (Hep C). The immunologic factors of ITP include dysfunctional natural killer cells, dendritic cells and macrophages (innate immunity), and dysfunctional adaptive immune cells (both T & B cells), but most importantly, the subset Treg (CD4+CD25+Foxp3+ regulatory T) [41,42].

Several studies have been carried out on the treatment of ITP using ADSCs with relatively successful results. In 2011, a study was done by researchers Ling Mai, Baijun Fang, Yongping Song, and Ning Li on seven adult chronic refractory ITP patients and ten adult healthy volunteers (five males, five females from ages 23-47 years).Characteristics of the seven patients are:

i. Four males and three females from ages 21 to 45 years.

ii. Each has had ITP for 14-74 months and was previously treated with 4-8 of the standard treatment (cyclophosphamide, cyclosporine, splenectomy, azathioprine, prednisone, danazol, intravenous immune globulin, T cell-depleted autologous peripheral blood stem cell transplantation, and vincristine). They all had a history of one or more events of major hemorrhages. The seven chronic refractory ITP patients were intravenously administered at a dose of 2.0×10^6/kg with ADSC from haploidentical family donors. After the first week of treatment, the first response was recorded, and it showed that:
iii. Four out of the seven patients had a sustained response after a single course of ADSC without any further therapy during follow-up
iv. Three out of the seven patients had a relapse within six months after the first treatment with ADSC, but when ADSC was administered to them the second time, they responded better.

The results showed that all patients reached the overall response with these patients (in comparison to findings in patients with active ITP not in this study) having their serum levels of IL-10, IL-4, and transforming growth factor β1 (TGF-β1) significantly elevated. Serum levels of IL-2 and interferon-γ (IFN-γ) significantly reduced after ADSC administration. During follow-up, the cytokine profiles in patients maintaining sustained response remained stable compared with the post-treatment level. However, IFN-γ and IL-2 levels significantly increased, and those of TGF-β1, IL-4, and IL-10 were significantly reduced in relapsed patients. The findings of this study supported the motion that ADSC therapy can serve to treat severe chronic refractory ITP by causing a shift to normal in the cytokine balance of Th1/Th2 cells in these patients [43].

In another study done in 2009 (Fang et al.) [44] using ADSCs therapeutically for chronic ITP, complete hormone-independent platelet remission was achieved a few weeks after the injection of donor ADSCs but relapsed three months later. Another study done on models for murine transplantation models indicated that there was an increase in Th3 (TGF-β1), Th2 (IL-4 and IL-10), and platelet levels but a decrease in the levels of Th17 (IL-17) and Th1 (IL-2 and IFN-γ) in ITP mice that were treated with ADSCs [42,45]. These studies imply that ADSC could be an effective treatment option for ITP in cases where conventional treatment choices fail.

4.6.4 Immunomodulatory effects of ADSC in the treatment of pure red cell aplasia

In 1922, pure red cell aplasia (PRCA) was described by Paul Kaznelson as a rare type of aplastic anemia (normocytic normochromic anemia) that affects erythroid/red blood cell (RBC) precursors in the bone marrow and causes them not to produce RBCs (due to their absence) leading to severe reticulocytopenia. It is important to note that PRCA differs from other anemias because the only cells affected are RBCs the serum levels of other blood components are normal [46,47].

PRCA can be inherited/congenital, acquired, or transient, and it more commonly presents in males than females. The congenital form of PRCA is called Diamond-Blackfan anemia (diagnosis is usually made before one year of age). Children with this anemia have apparent physical abnormalities [48].

The acquired form of PRCA can either be primary acquired or secondary acquired. The primary acquired form is usually antibody (ABO) mediated as in, the PRCA gotten after ABO-incompatible hematopoietic stem cell transplant (AB-HSCT) believed to be caused when residual iso-hemagglutinins of the receiver inhibit donor erythroid progenitors. The secondary form of acquired PRCA is usually associated with autoimmune/vascular collagen disorders (like rheumatoid arthritis, chronic lymphocytic leukemia, systemic lupus erythematosus (SLE), or large granular lymphocyte leukemia), solid tumors (thymoma), drugs, common variable immunodeficiency (CVID) and viral infections, especially parvovirus B19 [49,47].

Transient PRCA is generally the most common type of PRCA. It is similar to the secondary form of acquired PRCA, with the only difference being that the course of the anemia is transient, meaning that the anemia goes away after the causal disease is treated. It is also less severe than other times, and sometimes patients may recover without knowing they had PRCA [50]. Generally, immunosuppression is the approach to treating PRCA, and it is known that ADSC also possesses immunomodulatory functions hence its use in treating this condition as indicated in the studies [47].

A study was done on two patients who developed PRCA after AB-HSCT. The patients were given intravenous infusions of ADSC at a dose of 1.5×10^6/kg of their weight as the treatment approach. The results showed that both patients experienced rapid recovery from PRCA without any side effects a few weeks after the infusions with ADSC [49].

Another retrospective study done between April 2004 and February 2006 successfully analyzed two patients (25- and 16-year-old females) that presented with refractory PRCA after undergoing AB-HSCT. A transplant of ADSC at a dose of 1.0×106/kg was given to both patients. The results showed no side effects and rapid PRCA recovery [51]. These studies imply that ADSC could be an effective treatment option for PRCA in cases where conventional treatment choices fail.

5. DISEASES THAT CAN BE TREATED WITH ADSCs

ADSCs are the most commonly opted treatment approach for treating many diseases of the respiratory system like Idiopathic pulmonary fibrosis (IPF), asthma, acute respiratory distress syndrome, non-small cell cancer, and chronic obstructive pulmonary disease (COPD) [52].

5.1 Therapeutic Uses of ADSCs in Idiopathic Pulmonary Fibrosis (IPF)

IPF is a type of fibroproliferative interstitial lung disease that is characterized by injuries that are chronic, progressive, irreversible, and fibrotic in nature. In IPF, there is a replacement of normal healthy lung tissues with damaged alveoli and destroyed extracellular cell matrixes. This leads to respiratory failure due to a reduction in lung compliance and disruption in the gas-exchange properties of the lung [53]. It is important to highlight that CT imaging of IPF presents similar to imaging of interstitial pneumonia (traction bronchiectasis with honeycomb and reticular opacities spread around basal and subpleural regions). However, interstitial pneumonia generally has more heterogeneous structural deformation and interstitial fibrosis than IPF .The prognosis and life expectancy of a patient with an untreated case of IPF is approximately 3–5 years. Available standard treatments do not effectively cure the disease but increase life expectancy [54].

ADSCs have shown successful results in therapy for patients with IPF. Its therapeutic mechanism is believed to be a result of its ability to produce interleukin (IL-1, IL-6, IL-8) receptor antagonists and hepatocyte growth factors (HGF) which serve as biochemical factors to limit the damaging effects of repeating intra-tracheal installations in bleomycin-induced lung fibrosis (BLM). It decreases the amount of thickened sputum, TGF-β levels, inflammatory cell infiltrations, alveolar epithelial type 1 cell (AEC) and Clara cell hyperplasia, alveolar enlargement, and apoptosis [53,55].

In Greece, a non-randomized, phase Ib, no placebo-controlled, clinical trial was conducted on 14 IPF patients (with mild to moderate disease intensity) by a group of researchers from the department of pneumology at Democritus medical university for 12 months. The patients were administered three endobronchial infusions of ADSC-stromal vascular fraction (SVF) at a dose of 0.5 million cells/kg of each patient's body weight. The study's result emphasized the safety and efficacy of using ADSC-SVF in treating IPF [56].

5.2 Therapeutic Uses of ADSCs in Non-small Cell Lung Cancer (NSCLCs)

Non-small cell lung cancer (NSCLC) has a 15% survival rate and is the most common cause of death among individuals working in industrial sectors. About 85% of the types of cancers affecting the lungs are NSCLCs: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The standard treatment methods for NSCLC involve radiotherapy, chemotherapy, and surgery (resection). No treatment improves prognosis or completely cures it [57]. ADSCs are a possible option for treating NSCLCs because of their innate qualities and the option to genetically modify them to target certain qualities that would improve prognosis and decrease malignancy in these tumours.

In a study done at the China medical university cancer hospital, 22 females and 46 males between the ages of 45-57 years old, all diagnosed with a type of NSCLC, had 5cm of tumor tissue (without prior chemotherapy) resected, stored in liquid nitrogen and later exposed to the ADSC exosome. The results showed that NSCLC colony formation and cell proliferation were inhibited, and there was a significant reduction in the levels of cyclin E1 and cyclin E2 (factors responsible for the entry of proliferating

cells into the S and G1 phases of the cell cycle) [58].

5.3 Therapeutic Use of ADSCs in Degenerated Intervertebral Discs (DID)

One of the most uncomfortable physical symptoms a person can have is back pain, affecting about 80% or more of the world's population at any given time. The degenerated intervertebral disc (DID) is one of the lead causes of lower back pain, spinal stenosis, disc herniation, and sciatica. The intervertebral disc (IVD) functions as a shock absorber that protects the spine from excessive compression, and it is composed of 3 parts- annulus fibrosus (AF), cartilaginous endplates, and nucleus pulposus (NP). AF is a tough circular fibrocartilaginous exterior tissue of the IVD that surrounds the NP and anchors the IVD to the vertebra. NP (a remnant of the notochord) is the soft inner gelatinous core of the IVD that is composed of a loose network of collagen fibers and water [59, 60].

The pathophysiology of DID is multifactorial, affecting mostly the NP, and starts with the breakdown of proteoglycan, cell loss/apoptosis, and consequently decreased water content which then leads to the fibrosis of the NP. Regenerative medicine with stem cell therapy is the most promising therapeutic approach to treating this disease. ADSCs have the functional ability to upregulate the expression of ACAN, COL2A1, and COL6A2 as well as inhibit the activities of caspase-3 and 9, which then leads to the synthesis of proteoglycan and ultimately the restoration of the degenerated NP [60,61].

A study was conducted on eight idiopathic scoliosis patients with DID (age 16-26) and eight healthy volunteers (age 24-39). ADSC collected from the healthy donor volunteers was injected into the DID patients. The study showed that a few weeks after the administration of ADSCs, apoptosis of the cells of the NP no longer occurred due to ADSC suppression of caspase 3 and 9. It was also noted that ADSCs had protective effects on the NP, protecting from the damaging effects of compressive load mediated factors [60].

Another study was carried out on male New Zealand white rabbits (n=20). The IVDs of the rabbits were artificially injured with a 19-gauge spinal needle, and after 15 weeks, with the help of magnetic resonance imaging, DID was observed. Nineteen weeks after the artificial DID, the researchers injected ADSCs into the disc space of half of the rabbits as a treatment group. They injected saline into the disc space of the other half as a control group using a 21-gauge spinal needle. NP proliferation was noted ten weeks after the injection of ADSC in the treatment group with little damaged cartilage ossification. It significantly increased extracellular matrix secretion as compared to the control group [61].

5.4 Therapeutic Uses of ADSCs in Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is seen in critically ill patients and is a life-threatening complication of severe systemic diseases. It is caused by the excessive build-up of fluids in the lungs, making them incapable of supplying the body with adequate amounts of oxygen. A few studies have been recorded on using ADSCs in treating ARDS, particularly in mice; more studies are still ongoing [62].

5.5 Therapeutic Uses of ADSCs in Atopic Dermatitis (AD)

Atopic dermatitis (AD), also called atopic eczema, is a common recurrent chronic inflammatory skin disease affecting approximately 10% of adults (male and female) and 20% of children (girl and boy). Symptoms usually comprise disruption of the epidermal barrier, xerosis, pruritic/eczematous skin lesions, immunoglobulin E (IgE) mediated sensitization to various allergens, and immune dysregulation [63,64].

It is believed that the pathophysiology of AD is because of the excessive activities of T helper cells 1,2,17, and 22 (Th-1, Th-2, Th-17, and Th-22). Standard treatment for AD includes the use of immunosuppressants, antihistamines, calcineurin inhibitors, corticosteroids, and leukotriene receptor antagonists. However, these drugs provide temporary relief and severe side effects, and a more sustainable and comfortable treatment option with little to no adverse effect has been proposed using ADSCs [63,64].

An investigative study was carried out to determine if an ADSC cultured media can be used to treat AD. The study was carried out on 25 eight-week-old hairless female AD-like mice.

ADSC cultured media was topically applied to the surface of their skin for five days, two times daily. The study showed an increased differentiation of keratinocytes, an enhanced mouse beta-defensin 3 (cathelin-related antimicrobial peptide) expression, and improved epidermal permeability [65].

5.6 Therapeutic Uses of ADSCs in Psoriasis

Psoriasis is a chronic autoimmune proliferative dermatological disease characterized by secondary skin inflammation, excessive proliferation of basal keratinocytes, and a thickened scaly epidermis. It is caused by hyperactivity/ mutations of genes encoding tumor necrosis factor-alpha (TNFAIP3; TNIP1), Th1/Th17 cytokine (IL-12B and IL-23R), IL-13, and Th2 cytokine/regulatory T-cell (interleukin-10/IL10). Standard (but not permanent cure) treatments for psoriasis include methotrexate, vitamin D3 cream, topical steroids, and ultraviolet light [66,67]. However, recent studies on ADSCs have led to the probability of a possible cure for psoriasis.

In a pilot study on seven patients aged 18-65 with mild to moderate psoriasis (one female, six males), ADSC was injected intravenously at a dose of 0.5×10^6 cells/kg of their body weight to them every four weeks for three months. The results of the study after one year showed a significant reduction in the symptoms associated with psoriasis. However, researchers also noted 16 adverse effects, although they believe they are unrelated to ADSC infusion. The most common adverse effects they noted were: Pharyngitis, transient fevers, and headaches [68].

5.7 Therapeutic Uses of ADSCs in Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is an autoimmune disease that occurs because of self-attacks by the immune system that leads to multiple system/organ damage. Below are a few studies that show the therapeutic use of ADSC in treating SLE.

An investigative study was carried out in which ADSCs were intravenously given to B6.MRL/lpr SLE mice had results showing that after the administration of ADSC, there was (a) serum decrease in IL-6, anti-ds DNA antibodies, and IL-6 expression and (b) renal downregulation of TAB 2, CD 86, IKK-α, and IL-17 expression and (c) renal upregulation of miR-23b, ROR-γt and Foxp3 expression [69].

In a study on ADSC lipo-injection of patients (n=6) with Parry-Romberg syndrome (Lupus profundus facial lipoatrophy), the results showed that all patients had an improved facial contour following injections with ADSCs [70].

5.8 Therapeutic Uses of ADSCs in Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus is a chronic inflammatory impairment resulting in the body's inability to use glucose as an energy source. T2DM has two characteristics; impaired secretion of insulin by the pancreas (Islet β cell) and resistance to insulin by the cells in the body. ADSCs can act on pancreatic β cells and improve their function, and they can also regulate the metabolism of glucose in the hepatic system, inhibit the body's resistance to insulin and treat diabetic ulcers [71].

In a study by Chandra et al., ADSC-differentiated pancreatic islet cells (IPC) were transplanted into diabetic murine Swiss albino mice. The results two weeks after ADSC-IPC transplantation showed normal levels of glucose [71,72].

Hu et al. studies on a high-fat diet/STZ-induced T2DM mouse model transplanted with ADSC found that ADSCs restored INSR and GLUT4 on cell membranes of the adipose, liver, and skeletal tissues and increased IRS-1 phosphorylation, which then helped in ameliorating insulin resistance and achieving normoglycemia in the mouse model [71,73].

There is a study focused on ADSC's therapeutic effects on diabetic ulcers where full thickness dorsal wounds of 6 × 5 cm in size were artificially made on two groups of streptozotocin-induced T2DM mice models. The first group were T2DM mice models not injected with ADSCs (diabetic control group), the second group were T2DM mice models injected with ADSCs (treatment group) then a third group consisting of normal mice models was added to serve as healthy control/donors of the ADSCs. The results at eight weeks post-injection showed that the treatment group increased tissue regeneration leading to an enhanced healing of their diabetic ulcers and neo-angiogenesis [74].

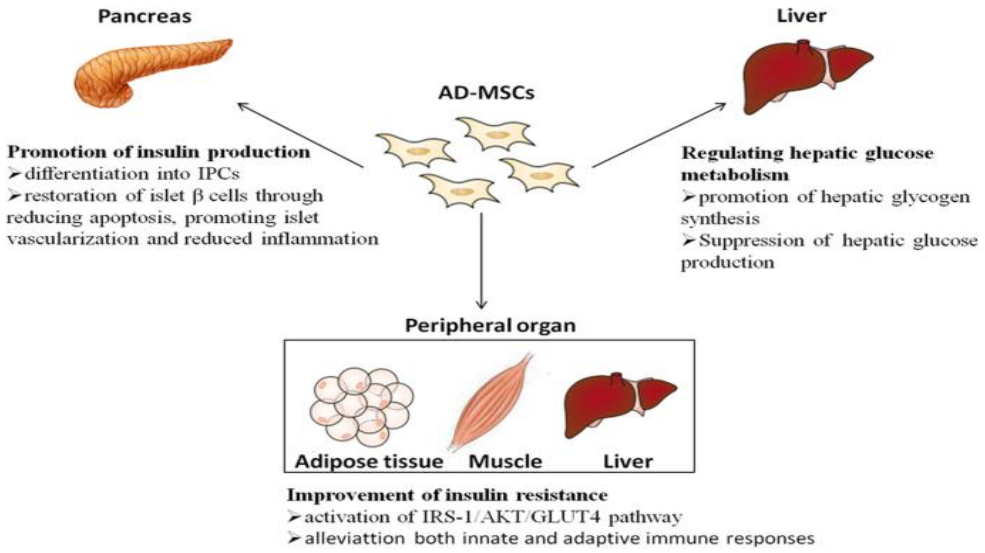

Fig. 5. Showing the therapeutic use of ADSCs relating to organs involved with the pathogenesis of T2DM and its functions for the potential treatment of the disease [71]

5.9 Therapeutic Effects of ADSC on Nervous System

Recent studies have reported the potential of ADSC in treating neural degenerative diseases like traumatic brain injury, Huntington's, amyotrophic lateral sclerosis (ALS), Alzheimer's, cavernous nerve injury, and Parkinson by neural differentiation, inhibiting apoptosis and reactive gliosis, promoting angiogenesis, immunomodulatory functions, expressing neutrophilic factors and/or enhancing neuronal integration [75].

5.9.1 Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig disease, is a progressive ND disease that causes apoptosis of the upper and lower motor neurons (UMN and LMN), leading to gradual weakening/loss of motor control, paralysis, and ultimately death (within 2-5 years after diagnosis). Most ALS cases are unknown, but about 5-10% of cases found seem to have been inherited. There are currently no effective treatment options for this disease, but studies propose the therapeutic effects of ADSCs for the treatment of ALS [76-78].

In 2013, a study on a 46-year-old male ALS patient was done, and he was given six intravenous infusions of autologous ADSC as the treatment method. The patient's symptoms prior to the start of the study were: coughing while eating or during conversations, lack of balance while walking down the stairs, dysarthria, weakness of muscles on the right side of his body, dysphagia, and fasciculations observed with his interossei dorsalis (left) and trapezius muscles. After the infusion with autologous ADSCs, the results showed that difficulty walking down the stairs was still present. However, the symptoms of dysarthria, fasciculations, coughing, right-sided muscle weakness and dysphagia were eliminated [76].

5.9.2 Parkinson's disease (PD)

Parkinson's disease (PD) is one of the top 5 most common ND disorders of the elderly. It is caused by apoptosis of dopaminergic neurons and/or dopaminergic conduction pathway disruptions in the ventral tegmental area and the basal ganglia of the substantia nigra [79,78]. Numerous successful studies have been conducted to test the therapeutic potential of ADSC on PD caused by 6-hydroxydopamine (6-OHDA). A few of them are highlighted below:

A study implanted ADSC into hemiparkinsonian rhesus monkeys (artificially induced using methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine). The study showed that a few weeks after the implantation of ADSCs, there was a reduction in symptoms and significant improvements in the behavior of these monkeys [78].

In another study model, human ADSCs were injected into the striatum of an artificially induced

6-OHDA mouse model. Pentraxin 3 (PTX3) was identified as the dopaminergic neuroprotective agent of ADSCs, preventing degeneration and apoptosis of dopaminergic neurons, which then led to the improved behavioral and motor performance of this mouse model [75].

5.9.3 Traumatic brain injury (TBI)

Traumatic brain injury (TBI) is an intracranial injury that happens when an individual sustains trauma to the external brain/skull, which causes impairment in the individual's cognitive and motor function. ADSC therapy has been speculated as a treatment option for patients with TBI, and it was further proven as the next therapeutic step when Tajiri et al. conducted a study. This study injected human ADSCs intravenously into rat models that had artificially induced TBIs. The study's results showed a significant decrease in hippocampal cell loss and cortical damage, as well as an improvement in the cognitive and motor functions of the rat [78].

5.9.4 Alzheimer's disease (AzD)

Alzheimer's disease (AzD) is one of the top 5 major ND diseases among older adults in the world. It is dementia caused by the brain's build-up of β amyloid proteins and neurofibrillary tangles (caused by tau proteins) [78].

In a study, human ADSC was intravenously injected through the blood-brain barrier (BBB) of AzD mouse model's brain. This model's memory, learning, and other previous pathologies were greatly improved [80].

Study of transplanted ADSCs into the hippocampus of transgenic APP/PS1 mice models with AzD was done. After the transplantation of ADSCs, it was observed that there was a reduction in oxidative stress levels, an increase in proliferation of $BrdU^+$ cells in the sub-granular zone, and enhanced activity in the subventricular zone of the dentate gyrus of the ADSC treated APP/PS1 mice model hippocampus [81].

A study performed with ADSC transplantation on transgenic APP/PS1 mice models with AzD. It was observed after the transplantation that the learning and spatial memory functions of these mice models were restored, and there was also a significant decrease in β amyloid deposition [57].

5.9.5 Cavernous nerve injury (CNI)

The cavernous nerves are postganglionic nerves of the parasympathetic nervous system that supply autonomic signals for clitoral and penile erection. Cavernous nerve injury (CNI) is an injury, damage, or atrophy of the cavernous nerve caused by trauma to the pelvis or a complication of pelvic surgeries. One of the huge complications of CNI is erectile dysfunction (ED). Presently researchers are looking into treatment modalities that can achieve cavernous nerve regeneration and finding neuroprotective/ neurotrophic agents for treating ED. Not only can ADSCs differentiate into neurons of the peripheral system (Schwann cells), but it has also been noted that they possess neurotrophic qualities useful for the regeneration of cavernous nerves.

A study by You et al. on an ED rat model with CNI found that after intra-cavernously injecting human ADSCs into the rat model, penile erection function was restored [78].

5.9.6 Huntington's disease (HD)

Huntington's disease (HD) is a rare, genetically transmitted (autosomal dominant caused by mutated CAG repeats), late-onset ND disorder, and symptoms mainly include changes in behavior, cognitive impairment, and loss of muscular coordination/involuntary muscle movements [78,82].

In a pre-clinical study model, ADSCs were transplanted into transgenic R6/2 mice models with HD, and the results showed that ADSC potentiated the secretion of multiple paracrine growth factors [83]. The effect of the protective factors is to prevent apoptotic phenomena and recover and improve the behavior of the mice models [78].

In another of similar study, 60-day-old transgenic R6/2 HD mice models had ADSCs transplanted into their striatal borders. The results showed that ADSC improved survival, limb clasping, and Rota-Rod performance and decreased Huntington aggregates' levels and striatal neurons' apoptosis [78]

6. REGULATORY T-CELLS (Tregs)

T cells are essential members of the adaptive immune system. Different members of the helper T cell family (Th) have unique cell surface

markers and specialized functions to make the adaptive immune response more robust and diversified.

Regenerative medicine is a very broad field of medicine. This section will highlight the roles of T cells, particularly CD 4^+ CD 25^+ regulatory T cells (Tregs), in treating various diseases.

6.1 What is a Regulatory T Cell (Treg)?

Regulatory T cells (Tregs) are cells that regulate the functions of T cells, particularly the Th-1 subset of CD 4^+ cells in the body. They secrete cytokines TGF-β and IL-10 which have inhibitory functions against Th-1 (activation of Th-1 leads to co-stimulation of other T cells).

Since the level of T cell activity in an individual depends on certain immune events or stimuli, the exact name for T cells used in regenerative medicine is Chimeric antigen receptor T cells (CAR-T cells) [84]. CAR-T cells are artificially engineered T cells that were genetically created to get specific subsets or receptors for treating certain diseases.

6.1.1 Therapeutic effects of T cells on alopecia areata disease (AAD)

Alopecia areata disease (AAD) is a multifactorial autoimmune inflammatory condition in which the hair follicles are attacked by the person's immune system causing hair loss in the individual. It can occur alone, along with other autoimmune diseases, or caused by stress. An impaired function of Tregs and an increased function of $CD8^+NKG2D^+$ T cells are said to be involved in the pathophysiology of AAD. Hence, some studies have been carried out to test the therapeutic benefits of CAR-Tregs in treating this disorder [85].

An open pilot prospective study was carried out on five patients with severe AAD resistant to standard treatments. Low dose IL-2 was given subcutaneously to these patients, and results showed an increase in Treg levels, and all patients successfully had different levels of regrowth of previously lost hair (Patient 1- 23% regrowth, patient 2- 40% regrowth, patient 3- 65% regrowth, patient 4- 92% regrowth and patient 5- 100% regrowth) [86].

6.1.2 Therapeutic effects of T cells on inflammatory bowel diseases (IBD)

Inflammatory bowel disease is a group term for ulcerative colitis and Crohn's disease (ChD), multifactorial chronic gastrointestinal inflammatory disorders. Standard IBD treatment options like immunosuppressants, amino-salicylate drugs, and corticosteroids do not provide a cure and have many side effects. However, many studies have been recorded using the Treg cytokine IL-10 to treat these diseases [87,88].

A double-blinded placebo-controlled 24-week study was reported by Fedorak et al. [88] in which 95 patients with active cases of moderate ChD were given subcutaneous 5 µg/kg doses of IL-10 and placebo in a randomized fashion. Results after 28 days showed moderate response to treatment and general improvement observed in the treatment group and no improvement in the placebo group [87,88].

6.1.3 Therapeutic effects of T cells on graft-versus-host diseases (GVHD)

Graft versus host disease (GVHD) is one of the complications of HSCT where the transplanted immune cells see the host body as foreign and attack. Studies have found that giving donor Tregs simultaneously as HSCT reduced the patient's risk of GVHD. It was also observed that giving low-dose IL-2 after HSCT reduced the risk of GVHD [89].

A clinical (human) study was done on 43 patients (10 with acute lymphoblastic leukemia and 33 with acute myeloid leukemia) to test the effects of giving donor Tregs at the same time as HSCT in preventing GVHD. In this study, no immunosuppressive therapy was given. The results showed that 15% of patients developed grade 2 GVHD. However, 95% of the patients achieved full donor engraftment with no GVHD, thereby supporting that to a relative degree infusing donor Tregs simultaneously as HSCT can prevent GVHD occurrence [90].

Another clinical (human) study was done with patients who already had GVHD. The patients were grouped into acute grade 4 GVHD and chronic GVHD, and the two groups were given CAR-Tregs. The results for chronic GVHD patients showed general improvement and significant alleviation of their symptoms, but those in the acute grade 4 GVHD group had little improvement [91].

6.1.4 Therapeutic effects of T cells in solid organ transplants

Therapies that could help patients who undergo transplant surgeries to gain more tolerance to the

allograft without requiring long-term immunosuppression are an ongoing research problem for researchers. However, it is believed with few studies to back it up that Tregs could be the therapeutic key they have searched for.

A study was done on mice with heart and skin allografts. Tregs were implanted into these mice models, showing that the Treg cells could promote tolerance by controlling the immune response between the mice's immune cells and allograft antigens [89]. There are studies on the therapeutic effects of T cells in solid organ transplants are still in progress.

6.1.5 Therapeutic effects of T cells on patients with type 1 diabetes mellitus (T1DM)

Type 1 diabetes mellitus (T1DM), sometimes referred to as juvenile diabetes, is the insulin-dependent type of diabetes in which the pancreas does not make as much insulin as the body needs for daily functioning because the person's immune cells destroy the β- islet cells of the pancreas (insulin-making cells). Researchers have noted that the pathophysiology of T1DM involves the impaired activity of Tregs, and this is the basis for all studies involving the therapeutic effects of Tregs in T1DM [89].

A randomized control trials of T cells was done on 10 children with T1DM was done. Polyclonal Tregs were given intravenously to children in the treatment group; those placed in the control group received saline. 2 months after the transfusions, it was observed that the children in the treatment group had increased C-peptide levels and needed lower insulin doses than those in the control group (even after six months) [89].

In an open-label trial (a phase study) in of 14 adult patients infused with *ex vivo* expanded Tregs in escalating doses, 7 of 14 patients had stable C peptide levels and insulin use for up to 2 years following infusion. However, the study was not powered to detect significant clinical improvement. There were no infusion reactions or therapy-related serious adverse events. Phenotypic analysis of the cell product after expansion and after infusion identified stable surface marker expression, demonstrating that the infused Tregs did not acquire a pathological phenotype. High-throughput TCR-β sequencing analysis indicated that expanded Tregs retained a high degree of diversity." [89].

6.1.6 Therapeutic effects of T cells on patients with pemphigus Vulgaris (PV)

Pemphigus Vulgaris (PV) is the most common form of pemphigus seen in clinical practice. It is a rare autoimmune disease caused by an IgG-mediated impairment of intraepithelial adhesion, which then leads to the development of erosions and painful blisters on the skin and mucous membranes of the genitals, throat, mouth, nose, eyes, and other parts of the body [92] Various studies have indicated the therapeutic effects of Tregs in this disease.

In a recent study, Tregs were infused into a PV HLA-DRB1^{+} transgenic mouse model. The results after the infusion showed that the infused Tregs successfully downregulated the expression of IgG desmoglein in three reactive Treg cells (these cells were identified in PV patients and carriers of PV HLA-class II allele) [93].

6.1.7 Therapeutic effects of T cells on patients with multiple sclerosis (MS)

Multiple sclerosis (MS) is a long-term multifocal demyelinating inflammatory disease of the brain and spinal cord [94] Current standard therapies for MS are not curative; rather, they help to promote comfort in the patient. Tregs though currently still being studied, have been highlighted to be useful for treating MS.

In a study by Niedbala et al., nitric oxide-induced Tregs were infused into 10-day-old C57BL/6 mice models with myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis. The results after the infusion showed a reduction in Th-17 levels and the severity of the disease. CNS infiltration by immune cells was also observed to be inhibited [94].

6.1.8 Therapeutic effects of T cells on patients with autoimmune hepatitis (AH)

Autoimmune hepatitis (AH) is a chronic autoimmune disease that happens when a person's immune system fight against the liver leading to inflammation and damage to the liver [95]. The standard treatment for AH is lifetime immunotherapy because the adverse effects of stopping the immunosuppressive therapies are worse than the side effects. Unfortunately, this is not comfortable for the patient, so strategies have been implemented to find more comfortable and permanent treatment options for AH [96].

In a recent clinical trial, low-dose IL-2 selective Tregs were implanted into AH murine mice models. After treatment with Tregs, there were increased systemic and intrahepatic levels of Tregs and a decrease in the levels of active T effector cells leading to a decrease in ALT levels and an improved liver architecture [97].

6.1.9 Therapeutic effects of T cells on patients with myasthenia gravis (MG)

Myasthenia gravis (MG) is a rare T-cell dependent, B-cell mediated progressive autoimmune long-term neuromuscular disease resulting from a person's immune cells attacking the acetylcholine receptors in the muscles of the individual, leading to weakness and fatigue in voluntary muscles Standard treatment options for MG like cholinesterase inhibitors, monoclonal antibodies, immunosuppressors, and corticosteroids can only function to alleviate symptoms but do not serve as a cure temporarily. Numerous studies have proposed Tregs to have therapeutic effects for the treatment of MG.

In a study, granulocyte-macrophage colony-stimulating factor (GM-CSF) induced Tregs were implanted into murine experimental mice with artificially induced MG. Results showed that GM-CSF-induced Tregs selectively inhibited the anti-acetylcholine immune response, alleviating MG symptoms in these mice [98].

In another this study, 1×10^6 ex-vivo generated Treg cells were administered intravenously to experimental autoimmune MG rats. Three weeks after the infusion, the levels of specific acetylcholine receptor antibodies were significantly reduced, and there was a noticeable modulation in the disease progression [99].

7. CONCLUSION

It is unquestionable the role of stem cells, growth factors and adipocytes and there derivates are essentially, and potentially therapeutic in the treatment of diseases we once thought are apparently incurable. Numerous studies have demonstrated the roles of these factors in the treatment of several diseases. The article highlighted few of the success stories in the use of stem cells, adipose tissues and T cells in the treatment of diseases affecting the skin, brain, heart and immune system [1,9].

FGFs are proven to be useful in the treatment of several skin diseases like burns and ulcers from diabetes mellitus and trauma. Likewise, it was shown be helpful in RDEB, SSc, and all sort of neuropathies. ADSc are essentially useful in treatment of numerous inflammatory conditions like lung, nervous and bone diseases, psoriasis, vertebrae disc disorder [9,10].

The stem cells are the largest the group and common ones are PSC, ESCs, ASCs, iPSCs, MSCs. They are useful in the treatment of endocrine disorders, autoimmune disorders, haematological disorders, dermatological diseases, neurodegenerative disorders among others [2,63].

Researches have shown that the era of cure of numerous diseases is fast approaching with the use of growth factors, stem cells and adipocytes or in combination with other form of therapy. It is a known fact that there exist numerous limitations in their use, as ethical issues, lack of political will and poor funding remain major obstacles, and hence limiting the usage [1,2,3]. The narrative article highlighted some of the known therapeutic potentials of these biological materials in reducing morbidity and mortality.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. May Griffith, Celeste Finnerty, and Cornelia Kasper .Skin Regeneration, Repair, and Reconstruction; 2015. Avilable:https://www.hindawi.com/journals/bmri/2015/892031/
2. N Sam MS. Tissue damage. Psychology Dictionary.org; 2013. Available:https://psychologydictionary.org/tissue-damage/
3. Krafts KP. Tissue repair: The hidden drama. Organogenesis. 2010 Oct-Dec; 6(4):225-33. DOI: 10.4161/org.6.4.12555. PMID: 21220961; PMCID: PMC3055648. Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3055648/
4. Engel AG, Shen XM, Selcen D, Sine SM. Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. The Lancet. Neurology. April 2015;14(4): 420–434.

5. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med. 2009; 15:1989–2003.
DOI: 10.1056/NEJMra0806188 [PubMed]]
6. Walter JB, Talbot IC, Gardner HA, et al. General pathology (7th Edition). Churchill Livingstone. NY, USA; 1996.
7. Mayo Clinic: Myathenia gravis; 2022.
Available:https://www.mayoclinic.org/diseases-conditions/myasthenia-gravis/symptoms-causes/syc-20352036
8. Antoine M, Wirz W, Tag CG, Gressner AM, Marvituna M, Wycislo M, Hellerbrand C, Kiefer P. Expression and function of fibroblast growth factor (FGF) 9 in hepatic stellate cells and its role in toxic liver injury. Biochem. Biophys. Res. Commun. 2007; 361:335-341.
Available:https://journals.biologists.com/dev/article/144/22/4047/48212/Fibroblast-growth-factors-key-players-in
9. Nunes QM, Li Y, Sun C, Kinnunen TK, Fernig DG. Fibroblast growth factors as tissue repair and regeneration therapeutics. Peer J. 2016;4:e1535
DOI:https://doi.org/10.7717/peerj.1535
Available:https://peerj.com/articles/1535/#fig-3
10. Hankemeier S, Keus M, Zeichen J, Jagodzinski M, Barkhausen T, Bosch U, Krettek C, Van Griensven M. Modulation of proliferation and differentiation of human bone marrow stromal cells by fibroblast growth factor 2: potential implications for tissue engineering of tendons and ligaments. Tissue Engineering. 2005;11(1–2):41–49.
11. Kazuhiro Watanabe, Syun Tahara, Hiroyuki Koyama, Mamu Shimizu, Mifumi Kawabe, Shingo Miyawaki. Visual and histological evaluation of the effects of trafermin in a dog oronasal fistula model, Journal of Veterinary Medical Science. 2022;84(1):64-68.
DOI:10.1292/jvms.21-0393
Available:https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1600-0765.1999.tb02277.x
12. Tracy Wong, Luke Gammon, Lu Liu, Jemima E. Mellerio, Patricia J.C. Dopping-Hepenstal, John Pacy, George Elia, Rosemary Jeffery, Irene M. Leigh, Harshad Navsaria, John A. McGrath. Potential of fibroblast cell therapy for recessive dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2008;128(9).
Available:https://www.sciencedirect.com/science/article/pii/S0022202X15340264
13. Gilbane AJ, Denton CP, Holmes AM. Scleroderma pathogenesis: a pivotal role for fibroblasts as effector cells. Arthritis Res Ther. 2013;15(3):215.
DOI: 10.1186/ar4230. PMID: 23796020; PMCID: PMC4060542.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4060542/
14. Rottlaender A, Villwock H, Addicks K, Kuerten S. Neuroprotective role of fibroblast growth factor-2 in experimental autoimmune encephalomyelitis. Immunology. 2011;133(3):370-378.
DOI:10.1111/j.1365-2567.2011.03450.x.
15. Takayama S, Murakami S, Shimabukuro Y, Kitamura M, Okada H. Periodontal regeneration by FGF-2 (bFGF) in primate models. Journal of Dental Research. 2001;80(12):2075–2079.
2-s2.0-0035544171.
16. Aebischer P, Salessiotis AN, Winn SR. Basic fibroblast growth factor released from synthetic guidance channels facilitate peripheral nerve regeneration across long nerve gaps. Journal of Neuroscience Research. 1989;23(3):282–289:2-s2.0-0024336588.
17. Kombucha H, Hato N, Teraoka M, Wakisaka H, Takahashi H, Gyo K, Tabata Y, Yamamoto M. Basic fibroblast growth factor combined with biodegradable hydrogel promotes healing of facial nerve after compression injury: an experimental study. Acta Oto-Laryngologica. 2010; 130(1):173–178
DOI:10.3109/00016480902896139
18. Adipose stem cells: biology and clinical applications for tissue repair and regeneration 2014. Lauren. Kokai, Kacey, Marra, J. PeterRubin
19. Casadei A, Epis R, Ferroni L, et al. Adipose tissue regeneration: a state of the art. J Biomed Biotechnol. 2012;2012: 462543.
DOI:10.1155/2012/462543
Available:https://www.hindawi.com/journals/bmri/2012/462543/
20. The role of adipocytes in tissue regeneration and stem cell niches (2016) Brett Shook,1 Guillermo Rivera Gonzalez,1 Sarah Ebmeier,1 Gabriella Grisotti,2 Rachel Zwick,1 and Valerie Horsley; 2016.
DOI:https://doi.org/10.1146/annurev-cellbio-111315-125426
Available:https://www.annualreviews.org/doi/full/10.1146/annurev-cellbio-111315-125426#_i2

21. White adipose tissue. In Wikipedia, The Free Encyclopedia.
Retrieved 01:50, September 13, 2022
Available:https://en.wikipedia.org/wiki/White_adipose_tissue
22. Richard AJ, White U, Elks CM, et al. Adipose tissue: Physiology to metabolic dysfunction [Updated 2020 Apr 4]
23. Adipose tissue. In Wikipedia, The Free Encyclopedia.
Retrieved 01:54, September 13, 2022.
Available:https://en.wikipedia.org/wiki/Adipose_tissue
24. Brown adipose tissue. In Wikipedia, The Free Encyclopedia.
Retrieved 01:17, September 13, 2022
Available:https://en.wikipedia.org/wiki/Brown_adipose_tissue
25. Cinti S. Pink adipocytes. Trends Endocrinol. Metab. 2018;1–16 [PubMed]
26. His-Hagen J, Melnyk A, Zingaretti MC, Ceresi E, Barbatelli G, Cinti S. Multilocular fat cells in WAT of CL-316243-treated rats derive directly from white adipocytes. Am. J. Physiol. Physiol. 2000;279(3):C670–C681 [PubMed]
27. Barbarella G, Murano I, Madsen L, Hao Q, Jimenez M, Kristiansen K, Giacobino JP, De Matteis R, Cinti S. The emergence of cold-induced brown adipocytes in mouse white fat depots is determined predominantly by white to brown adipocyte transdifferentiation. Am. J. Physiol. Metab. 2010;298(6):E1244–E1253 [PubMed]
28. Wu J, Boström P, Sparks LM, Ye L, Choi JH, Giang A-H, Khandekar M, Virtanen KA, Nuutila P, Schaart G, Huang K, Tu H, van Marken Lichtenbelt WD, Hoeks J, Enerbäck S, Schrauwen P, Spiegelman BM. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell. 2012;150(2):366–376.
29. Leask A, Abraham DJ. TGFβ signalling and the fibrotic response. FASEB J. 2004;15:816–827.
DOI: 10.1096/fj.03-1273rev [PubMed]
30. True stem cell therapy: The latest Technology; 2019.
Available:https://www.closerlookatstemcells.org/learn-about-stem-cells/types-of-stem-cells/
31. Mayo Clinic: Bone marrow transplant; July, 20, 2022.
Available:https://www.mayoclinic.org/tests-procedures/bone-marrow-transplant/in-depth/stem-cells/art-20048117
32. Mahla RS. (2016). "Stem cells application in regenerative medicine and disease threpeutics. International Journal of Cell Biology. 2016;7:1–24.
33. Assmus B, Schächinger V, Teupe C, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). Circulation. December 2002;106(24):3009–3017.
34. Stem cells: University of Nebraska medical Centre; 2020.
Available:https://www.unmc.edu/stemcells/educational-resources/importance.html
35. Fang B, Li N, Song Y, Lin Q, Zhao RC. Comparison of human post-embryonic, multipotent stem cells derived from various tissues. Biotechnol Lett. 2009;31(7):929-938.
DOI:10.1007/s10529-009-9968-6
36. Chen BL, Wang DA. 2016; *20*(30):4515-4523.
Available:https://www.ncbi.nlm.nih.gov/books/NBK549833/
37. Al-Ghadban S, Artiles M, Bunnell BA. In: Adipose stem cells in regenerative medicine: Looking forward. Front. Bioeng. Biotechnol. 2022;9:837464.
DOI: 10.3389/fbioe.2021.837464
Available:https://www.frontiersin.org/articles/10.3389/fbioe.2021.837464/full
38. Zizhen Si, Xue Wang, Changhui Sun, Yuchun Kang, Jiakun Xu, Xidi Wang, Yang Hui. Adipose-derived stem cells: Sources, potency, and implications for regenerative therapies; 2019.
Available:https://www.sciencedirect.com/science/article/pii/S0753332219307346
39. Kaewsuwan S, Song SY, Kim JH, Sung JH. Mimicking the functional niche of adipose-derived stem cells for regenerative medicine. Expert Opin. Biol. Ther. 2012;12:1575-1588.
40. Ceccarelli S, Pontecorvi P, Anastasiadou E, Napoli C, Marchese C. Immunomodulatory effect of adipose-derived stem cells: the cutting edge of clinical application. Front. Cell Dev. Biol. 2020; 8:236.
DOI: 10.3389/fcell.2020.00236
Available:https://www.frontiersin.org/articles/10.3389/fcell.2020.00236/full
41. Xiao, Jianhong, Zhang, Yangchun, Liu, Liqiong, Jin, Mengdi, Liu, Ning, Ye, Yuan, Li, Junjun, Liu, Zelin. Transplanting of adipose derived stem cells up-Regulate CD4+CD25+Foxp3+ T cells in a murine

model of passive chronic immune thrombocytopenia (2/22/2020).

42. He Y, Ji D, Lu W, Chen G. The mechanistic effects and clinical applications of various derived mesenchymal stem cells in immune thrombocytopenia. Acta Haematol; 2022.
Available:https://www.karger.com/Article/FullText/517989
43. Fang B, Mai L, Li N, Song Y. Favorable response of chronic refractory immune thrombocytopenic purpura to mesenchymal stem cells. Stem Cells Dev. 2012 Feb 10;21(3):497-502.
DOI: 10.1089/scd.2011.0231. Epub 2011 Aug 12. PMID: 21711157; PMCID: PMC3272240.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3272240/
44. Fang B, Song YP, Li N, Li J, Han Q, Zhao RC. Resolution of refractory chronic autoimmune thrombocytopenic purpura following mesenchymal stem cell transplantation: a case report. Transplant Proc. 2009;41(5):1827–30.
45. Xiao J, Zhang C, Zhang Y, Zhang X, Zhao J, Liang J, et al. Transplantation of adipose-derived mesenchymal stem cells into a murine model of passive chronic immune thrombocytopenia. Transfusion. 2012;52(12):2551–8.
46. Wikipedia contributors. Pure red cell aplasia. In Wikipedia, The Free Encyclopedia; 2021, September 2.
Retrieved 15:40, September 13, 2022
Available:https://en.wikipedia.org/wiki/Pure_red_cell_aplasia
47. Lipton J, Glader B, Means RT. Red cell aplasia: acquired and congenital disorders. In: Greer JP, Arber DA, Glader BE, List A, Means RT, Paraskevas F, Rodgers GM, eds. Wintrobe's Clinical Hematology. 13th ed. Philadelphia, PA: Lippincott Williams & Wilkins. 2013;975-89.
Available:https://ashpublications.org/blood/article/128/21/2504/35728/Pure-red-cell-aplasia
48. Young NS, Abkowitz JL, Luzzatto L. New Insights into the pathophysiology of acquired cytopenias. Hematology Am Soc Hematol Educ Program. 2000;18-38.
DOI:10.1182/asheducation-2000.1.18
49. Fang B, Song Y, Li N, et al. Mesenchymal stem cells for the treatment of refractory pure red cell aplasia after major ABO-incompatible hematopoietic stem cell transplantation. Ann Hematol. 2009;88: 261–266.
DOI:https://doi.org/10.1007/s00277-008-0599-0
Available:https://link.springer.com/article/10.1007/s00277-008-0599-0
50. Risitano AM, Maciejewski JP, Selleri C, Rotoli B. Function and malfunction of hematopoietic stem cells in primary bone marrow failure syndromes. Curr Stem Cell Res Ther. 2007;2(1):39-52.
DOI:10.2174/157488807779316982
51. Li YF, Li N, Song P, Yang, Zhang GL, Lin QD. Human adipose tissue-derived mesenchymal stem cells for treatment of refractory pure red cell aplasia after major ABO-incompatible hematopoietic stem cell transplantation; 2009 July.
DOI:10.3969/j.issn.1673-8225.2009.27.042
52. Abdul Halim NS, Fakiruddin KS, Ali SA, Yahaya BH. A comparative study of non-viral gene delivery techniques to human adipose-derived mesenchymal stem cell. Int J Mol Sci. 2014 Aug 26;15(9):15044-60.
DOI: 10.3390/ijms150915044. PMID: 25162825; PMCID: PMC4200830.
53. Maher TM, Wells AU, Laurent GJ. Idiopathic pulmonary fibrosis: multiple causes and multiple mechanisms? Eur Respir J. 2007;30:835-9.
Available:https://sci.amegroups.com/article/view/28199/html
54. Yang S, Liu P, Jiang Y, Wang Z, Dai H, Wang C. Therapeutic applications of mesenchymal stem cells in idiopathic pulmonary fibrosis. Front. Cell Dev. Biol. 2021;9:639657.
DOI: 10.3389/fcell.2021.639657
Available:https://www.frontiersin.org/articles/10.3389/fcell.2021.639657/full
55. Lee SH, Lee EJ, Lee SY, et al. The effect of adipose stem cell therapy on pulmonary fibrosis induced by repetitive intratracheal bleomycin in mice. Exp Lung Res. 2014;40:117-25 [Crossref] [PubMed]
56. Mangla A, Hamad H. Pure Red Cell Aplasia [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.
57. Bae JS, Carter JE, Jin HK. Adipose tissue-derived stem cells rescue Purkinje neurons and alleviate inflammatory responses in Niemann–Pick disease type C mice. Cell Tissue Res. 2010;340(2):357–369.
Available:https://journals.sagepub.com/doi/full/10.3727/096368913X672181

58. Liang Y, Zhang D, Li L, et al. Exosomal microRNA-144 from bone marrow-derived mesenchymal stem cells inhibits the progression of non-small cell lung cancer by targeting CCNE1 and CCNE2. Stem Cell Res Ther. 2020;11:87.
DOI:https://doi.org/10.1186/s13287-020-1580-7
Available:https://stemcellres.biomedcentral.com/articles/10.1186/s13287-020-1580-7
59. Wei- Wei Chen, Xia Zhang, Wen Juan Huang. Role of neuroinflammation in neurodegenerative diseases (Review). 2016;3391-3396. Published online on: 29 February 2016
Available:https://www.spandidos-publications.com/mmr/12/3/4664
60. Sun Z, Luo B, Liu ZH, Samartzis D, Liu Z, Gao B, Huang L, Luo ZJ. Adipose-derived stromal cells protect intervertebral disc cells in compression: implications for stem cell regenerative disc therapy. Int J Biol Sci. 2015 Jan 1;11(2):133-43.
DOI: 10.7150/ijbs.10598. PMID: 25561896; PMCID: PMC4279089.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4279089/
61. young-Joon Chun, Young Soo Kim, Byeong Kyu Kim, Eun Hyun Kim, Ji Hyang Kim, Byung-Rok Do, Se Jin Hwang, Ju Yeon Hwang, Yoon Kyoung Lee. Transplantation of human adipose-derived stem cells in a rabbit model of traumatic degeneration of lumbar discs. World Neurosurgery. 2012;78(3–4).
Available:https://www.sciencedirect.com/science/article/abs/pii/S1878875011016299
62. Han J, Liu Y, Liu H, Li Y. Genetically modified mesenchymal stem cell therapy for acute respiratory distress syndrome. Stem Cell Res Ther. 2019;10(1):386. Published 2019 Dec 16.
DOI:10.1186/s13287-019-1518-0
63. Vincent GJ Guillaume, Tim Ruhl, Anja M Boos, Justus P Beier, The Crosstalk Between Adipose-Derived Stem or Stromal Cells (ASC) and Cancer Cells and ASC-Mediated Effects on Cancer Formation and Progression—ASCs: Safety Hazard or Harmless Source of Tropism?, Stem Cells Translational Medicine. 2022;11(4):394-406.
DOI:10.1093/stcltm/szac002,
Available:https://onlinelibrary.wiley.com/doi/abs/10.1111/exd.13895
64. Guan J, Li Y, Lu F, et al. Adipose-derived stem cells ameliorate atopic dermatitis by suppressing the IL-17 expression of Th17 cells in an ovalbumin-induced mouse model. Stem Cell Res Ther. 2022;13:98.
DOI:https://doi.org/10.1186/s13287-022-02774-7
Available:https://stemcellres.biomedcentral.com/articles/10.1186/s13287-022-02774-7
65. Kern S, Eichler H, Stoeve J, Klüter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006;24:1294–1301.
Available:https://synapse.koreamed.org/articles/1045534
66. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm. 2005;(5):273–279.
Available:https://journals.sagepub.com/doi/full/10.3727/096368916X691998
67. Rajasekar Seetharaman, Anjum Mahmood, Prashant Kshatriya, Divyang Patel, Anand Srivastava. Mesenchymal stem cell conditioned media ameliorate psoriasis vulgaris: a case study. Case Reports in Dermatological Medicine. 2019;Article ID 8309103:5.
Available:https://www.hindawi.com/journals/cridm/2019/8309103/
68. Yao D, Ye S, He Z, Huang Y, Deng J, Wen Z, Chen X, Li H, Han Q, Deng H, Zhao RC, Lu C. Adipose-derived mesenchymal stem cells (AD-MSCs) in the treatment for psoriasis: results of a single-arm pilot trial. Ann Transl Med. 2021 Nov;9(22):1653.
DOI:10.21037/atm-21-5028. PMID: 34988162; PMCID: PMC8667096.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8667096/
69. He X, Zhang Y, Zhu A, et al. Suppression of interleukin 17 contributes to the immunomodulatory effects of adipose-derived stem cells in a murine model of systemic lupus erythematosus. Immunol Res. 2016;64:1157–1167.
DOI:https://doi.org/10.1007/s12026-016-8866-y
Available:https://link.springer.com/article/10.1007/s12026-016-8866-y
70. Qiuni Gao, Zuoliang Qi, Xiaolei Jin, Zhenyu Yang, Panxi Yu, Xihang Yuan, Yuling Hu, Xiaonan Yang, Biological characteristics of adipose derived stem cells from patients with progressive hemifacial atrophy: An in vivo study.

Journal of Cosmetic Dermatology; 2022.
DOI:10.1111/jocd.15162,
Available:https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1524-4725.2008.34256.x

71. Qi Y, Ma J, Li S, et al. Applicability of adipose-derived mesenchymal stem cells in treatment of patients with type 2 diabetes. Stem Cell Res Ther. 2019;10:274.
DOI:https://doi.org/10.1186/s13287-019-1362-2
Available:https://stemcellres.biomedcentral.com/articles/10.1186/s13287-019-1362-2
72. Chandra V, GS, Phadnis S, Nair PD, Bhonde RR. Generation of pancreatic hormone-expressing islet-like cell aggregates from murine adipose tissue-derived stem cells. Stem Cells. 2009; 27(8):1941–53.
73. Hu J, Fu Z, Chen Y, Tang N, Wang L, Wang F, et al. Effects of autologous adipose-derived stem cell infusion on type 2 diabetic rats. Endocr J. 2015;62(4):339–52.
74. Akino K, Mineda T, Akita S. Early cellular changes of human mesenchymal stem cells and their interaction with other cells. Wound Repair Regen. 2005;13(4):434–440.
Available:https://journals.sagepub.com/doi/full/10.3727/096368915X687921
75. Raghavendra Upadhya, Leelavathi N. Madhu, Shama Rao, Ashok K. Shetty, Proficiency of extracellular vesicles from hiPSC-derived neural stem cells in modulating proinflammatory human microglia: Role of pentraxin-3 and miRNA-21-5p. Frontiers in Molecular Neuroscience. 2022;15.
DOI:10.3389/fnmol.2022.845542
Available:https://faseb.onlinelibrary.wiley.com/doi/full/10.1096/fj.202100408RR
76. Chancellor AM, Slattery JM, Fraser H, Swingler RJ, Holloway SM, Warlow CP. The prognosis of adult-onset motor neuron disease: a prospective study based on the Scottish Motor Neuron Disease Register. J Neurol. 1993;240:339-346.
Available:https://www.europeanreview.org/wp/wp-content/uploads/4086-4090.pdf
77. Fontanilla C, Gu H, Liu Q, et al. Adipose-derived stem cell conditioned media extends survival time of a mouse model of amyotrophic lateral sclerosis. Sci Rep. 2015;5:16953.
Available:https://www.nature.com/articles/srep16953
78. Albersen M, Fandel TM, Lin G, Wang G, Banie L, Lin CS, Lue TF. Injections of adipose tissue-derived stem cells and stem cell lysate improve recovery of erectile function in a rat model of cavernous nerve injury. J. Sex. Med. 2010;7(10):3331–3340;.
Available:https://journals.sagepub.com/doi/full/10.3727/096368915X686940
79. Gonzalez C, Bonilla S, Flores AI, Cano E, Liste I. An update on human stem cell-based therapy in parkinson's disease. Current Stem Cell Research & Therapy; 2015.
80. Ager RR, Davis JL, Agazaryan A, et al. Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss. Hippocampus. 2015;25(7):813-826.
DOI:10.1002/hipo.22405
81. Yan Y, Ma T, Gong K, Ao Q, Zhang X, Gong Y. Adipose-derived mesenchymal stem cell transplantation promotes adult neurogenesis in the brains of Alzheimer's disease mice. Neural Regen Res. 2014 Apr 15;9(8):798-805.
DOI: 10.4103/1673-5374.131596. PMID: 25206892; PMCID: PMC4146257
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4146257/
82. Shyu WC, Chen CP, Lin SZ, Lee YJ, Li H. Efficient tracking of non-iron-labeled mesenchymal stem cells with serial MRI in chronic stroke rats. Stroke. 2007;38(2):367–374.
83. Lee W, Park ST, Oh JE, Shim HJ, Lim J, Chu J, Kim KM. Transplantation of patient-derived adipose stem cells in YAC128 Huntington's disease transgenic mice. PLoS Curr. 2: RRN1183; 2010.
84. Mackenzie W. Ferguson, Connor J. Kennedy, Thulani H. Palpagama, Henry J. Waldvogel, Richard LM. Faull, Andrea Kwakowsky. Current and possible future therapeutic options for Huntington's disease. Journal of Central Nervous System Disease; 2022.
DOI:10.1177/11795735221092517, 14, (117957352210925),
Available:https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.21788
85. Petukhova L, Duvic M, Hordinsky M, Norris D, Price V, Shimomura Y, Kim H, Singh P,

Lee A, Chen WV, Meyer KC, Paus R, Jahoda CA, Amos CI, Gregersen PK, Christiano AM. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature. 2010;466:113–117.
Available:https://www.science.org/doi/full/10.1126/sciadv.abd1866

86. Castela E, Le Duff F, Butori C, et al. Effects of low-dose recombinant interleukin 2 to promote t-regulatory cells in alopecia areata. JAMA Dermatol. 2014;150(7):748–751.
DOI:10.1001/jamadermatol.2014.504.
Available:https://jamanetwork.com/journals/jamadermatology/article-abstract/1876052

87. Li MC, He SH. IL-10 and its related cytokines for treatment of inflammatory bowel disease. World J Gastroenterol. 2004 Mar 1;10(5):620-5.
DOI: 10.3748/wjg.v10.i5.620. PMID: 14991925; PMCID: PMC4716896.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4716896/

88. Fedorak RN, Gangl A, Elson CO, Rutgeerts P, Schreiber S, Wild G, Hanauer SB, Kilian A, Chard M, LeBeau A, et al. Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group. Gastroenterology. 2000;119:1473–1482.

89. Clough JN, Omer OS, Tasker S, et alRegulatory T-cell therapy in Crohn's disease: challenges and advances. Gut. 2020;69:942-952.
Available:https://gut.bmj.com/content/69/5/942#ref-105

90. Kloosterman TC, Martens AC, van Bekkum DW, Hagenbeek A. Graft-versus-leukemia in rat MHC-mismatched bone marrow transplantation is merely an allogeneic effect. Bone Marrow Transplant. 1995;15(4):583-590.
Available:https://ashpublications.org/blood/article/124/4/638/33335/HLA-haploidentical-transplantation-with-regulatory

91. Piotr Trzonkowski, Maria Bieniaszewska, Jolanta Juścińska, Anita Dobyszuk, Adam Krzystyniak, Natalia Marek, Jolanta Myśliwska, Andrzej Hellmann. First-in-man clinical results of the treatment of patients with graft versus host disease with human ex vivo expanded CD4+CD25+CD127− T regulatory cells, Clinical Immunology; 2009.

92. Wu J, Ren B, Wang D, et al. Regulatory T cells in skeletal muscle repair and regeneration: recent insights. Cell Death Dis. 2022;13:680.
DOI:https://doi.org/10.1038/s41419-022-05142-8

93. Tapas Kumar Goswami, Mithilesh Singh, Manish Dhawan, Saikat Mitra, Talha Bin Emran, Ali A. Rabaan, Abbas Al Mutair, Zainab Al Alawi, Saad Alhumaid, Kuldeep Dhama, Regulatory T cells (Tregs) and their therapeutic potential against autoimmune disorders – Advances and challenges, Human Vaccines & Immunotherapeutics. 2022;18:1.
DOI:10.1080/21645515.2022.2035117
Available:https://onlinelibrary.wiley.com/doi/abs/10.1111/exd.12919

94. Sogkas G, Atschekzei F, Adriawan IR, et al. Cellular and molecular mechanisms breaking immune tolerance in inborn errors of immunity. Cell Mol Immunol. 2021;18:1122–1140.
DOI:https://doi.org/10.1038/s41423-020-00626-z

95. Tunio NA, Mansoor E, Sheriff MZ, Cooper GS, Sclair SN, Cohen SM. Epidemiology of Autoimmune Hepatitis (AIH) in the United States Between 2014 and 2019: A population-based national study. J Clin Gastroenterol. 2021;55(10):903-910.
DOI:10.1097/MCG.0000000000001449

96. Richard Taubert, Matthias Hardtke-Wolenski, Fatih Noyan, Artur Wilms, Anna K. Baumann, Jerome Schlue, Sven Olek, Christine S. Falk, Michael P. Manns, Elmar Jaeckel, Intrahepatic regulatory T cells in autoimmune hepatitis are associated with treatment response and depleted with current therapies. Journal of Hepatology; 2014.
DOI:https://doi.org/10.1016/j.jhep.2014.05.034
Available:https://www.sciencedirect.com/science/article/abs/pii/S016882781400381X

97. Laura Elisa Buitrago-Molina, Julia Pietrek, Fatih Noyan, Jerome Schlue, Michael P. Manns, Heiner Wedemeyer, Matthias Hardtke-Wolenski, Elmar Jaeckel, Treg-specific IL-2 therapy can reestablish intrahepatic immune regulation in autoimmune hepatitis. Journal of Autoimmunity; 2020.
DOI:https://doi.org/10.1016/j.jaut.2020.102591

Available:https://www.sciencedirect.com/science/article/pii/S0896841120302262

98. Jian Rong Sheng, Thiruppathi Muthusamy, Bellur S. Prabhakar, Matthew N. Meriggioli, GM-CSF-induced regulatory T cells selectively inhibit anti-acetylcholine receptor-specific immune responses in experimental myasthenia gravis. Journal of Neuroimmunology; 2011. DOI:https://doi.org/10.1016/j.jneuroim.2011.10.010 Available:https://www.sciencedirect.com/science/article/abs/pii/S0165572811002967

99. Revital Aricha, Debby Reuveni, Sara Fuchs, Miriam C. Souroujon, suppression of experimental autoimmune myasthenia gravis by autologous T regulatory cells. Journal of Autoimmunity; 2016. DOI:https://doi.org/10.1016/j.jaut.2015.09.005. Available:https://www.sciencedirect.com/science/article/abs/pii/S0896841115300445

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