

STEM CELLS AND
BIOTECHNOLOGY
CENTER

EVIDENCE OF THE
MEDICAL BENEFITS
OF **STEM CELLS**



Regencord



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INTRODUCTION

“The regenerative medicine revolution is upon us. Like iron and steel to the industrial revolution, like the microchip to the tech revolution, stem cells will be the driving force of this next revolution.”

Cade Hildreth, founder of BioInformant, a stem cell industry research firm. Cited by: Tony Robbins, Peter Diamandis and Robert Hariri. Life Force; Simon and Schuster, 2022.

“Stem cells seem to hold major promise for contemporary medicine, one which could almost be more significant than a discovery of DNA”.

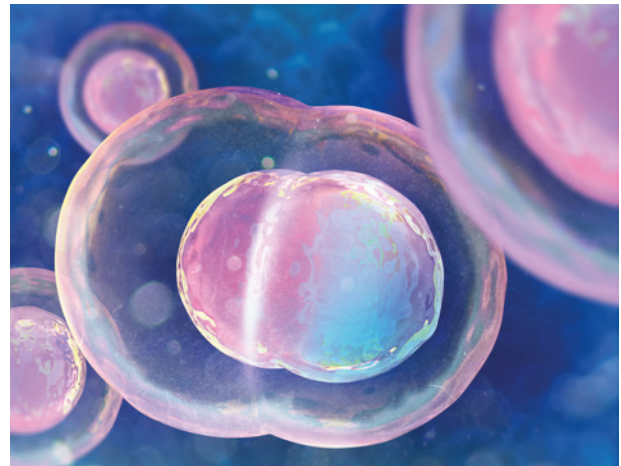
Kurpisz M. New Technologies Based on Stem Cell-Therapies in Regenerative Medicine and Reproductive Biology. Cells. 2022;12(1):95.

“Regenerative medicine is the new frontier of medicine”

Lampiasi N. Mesenchymal Stem Cells: What We Have Learned and How to Manage Them. Biology (Basel). 2024;14(1):1.

Stem cells are present in all tissues of the body, where they remain in a quiescent and undifferentiated state within specific locations known as “stem cell niches.” Despite their dormant state, they retain full capacity to generate progeny in response to the body’s needs. They exhibit distinctive properties that endow them with remarkable therapeutic potential. First, they can proliferate indefinitely while maintaining their stem cell status (symmetric cell division). Second, under appropriate stimuli, they can differentiate into various specialized cells, such as those of the brain, heart, liver, and others (asymmetric cell division). Third, they are capable of targeted migration throughout the body in response to biochemical signals emitted by damaged or

diseased tissues. Thus, they remain with us throughout life, although they progressively lose vitality as we age or develop disease.



The main breakthrough in the development of “regenerative medicine” was the ability to isolate stem cells from an individual, culture and expand them *in vitro*, and then transfer them either back to the original donor (autologous transplantation) or to another person (allogeneic transplantation), thereby harnessing their therapeutic potential. Thus, it enabled the large-scale production and availability of stem cells in quantities sufficient for various applications in which their usefulness has been demonstrated.

Autologous stem cells are being used less frequently for therapeutic purposes, not only because a patient’s underlying disease may impair their own cells, but also because stem cells age alongside the individual. It has been shown that as stem cells grow older, they may acquire anti-regenerative properties (for instance, promoting cell death). On the other hand, among exogenous sources of stem cells, those derived from the wall of the umbilical cord stand out as an excellent source of “universal donor” cells. These cells do not trigger immune rejection, exhibit high

proliferative capacity, possess broad differentiation potential, retain their biological properties over time, and can be obtained in large quantities from non-invasive sources, without the ethical and legal concerns associated with other sources. Finally, these cells can be cryopreserved and stored under laboratory conditions for extended periods without compromising their identity (surface marker and epigenetic profile), their proliferation and differentiation capacity, or their therapeutic potential.

HOW DO STEM CELLS WORK?

These cells exert their therapeutic effects through four primary mechanisms:

1. Stem cells can differentiate into the specific cell types of the affected organ, thereby replacing injured or dead native cells.
2. Through direct cell-to-cell interaction, stem cells transfer intracellular organelles to local cells that are undergoing aging and cell death. Such is the case of mitochondrial transfer, organelles with vital roles in energy production, regeneration, and cellular aging, through which native diseased cells are revitalized and biological balance is restored.
3. Stem cells also engage in direct cell-to-cell communication by transferring transcription factors that carry epigenetic instructions, prompting surrounding cells to modify their harmful behavior, for example, inducing pro-inflammatory white blood cells to shift toward an anti-inflammatory phenotype.
4. Once they reach the affected organ, stem cells can release hundreds of biologically active molecules that help counteract damage (such as inflammation, oxidative stress, fibrosis, or cell death).

Finally, as science and technology advance continuously, it is relevant to mention the stem cell-derived extracellular vesicles (EVs), which are loaded with biologically active molecules and,

according to current scientific evidence, have practically all the therapeutic virtues of these cells, but with important advantages, such as their small size that allows them to easily reach the injured area and to escape destruction by the immune system; not inducing an immune response in the patient, have no tumorigenic activity (tumor formation), as they are not living organisms that self-replicate and, finally, be stable particles easily modifiable and storable for long periods. For these reasons, many authors consider EV-based therapy to represent the “second generation” of regenerative medicine.

The wide safety margin and promising potential of stem cells and EVs suggest that we are on the verge of a new therapeutic paradigm. However, it must be acknowledged that, in many cases, clinical evidence remains limited, and several challenges must be overcome before stem cells can be incorporated into official treatment protocols. It is also important to clarify that this publication does not aim to provide an exhaustive review of the available evidence on the clinical uses of stem cells. Instead, it briefly highlights those clinical conditions for which there is an acceptable level of evidence regarding the safety and efficacy of stem cells/EVs, supported by high-quality scientific literature.

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OSTEOARTICULAR DISEASE AND PAIN

Osteoarticular disorders, including osteoarthritis, spinal degenerative conditions and, tendon injuries, are among the most extensively studied in regenerative medicine. This field is now recognized as a safe and cost-effective approach with the potential to repair damage and promote tissue regeneration (1).

OSTEOARTHRITIS

Articular cartilage has a low concentration of stem cells and poor vascularization, which explains its limited self-repair potential. Stem cells repair articular cartilage and restore joint function through several mechanisms: a) differentiating into new chondrocytes (the normal cartilage cells); b) regulating inflammation in the joint microenvironment; and c) alleviating pain (2,3).

Conventional osteoarthritis treatment, which includes physical therapy, analgesics, and anti-inflammatory agents, provides only modest clinical benefits and carries a high incidence of adverse events from medications or surgical intervention. On the contrary, dozens of clinical studies and meta-analyses involving thousands of patients have demonstrated that intra-articular stem cell therapy leads to significant cartilage regeneration and improvement in clinical parameters (pain and functional limitation), imaging findings, arthroscopic outcomes, and quality of life (4-19). An increasing number of experts suggest that stem cells (or their exosomes) may exert a preventive effect on the progression of osteoarthritis and advise against considering surgery as the sole treatment option for elderly patients with severe osteoarthritis (20-22). This may be the most cost-effective treatment compared to options such as glucocorticoids or hyaluronic acid, particularly for



joints where stem cells can be applied locally (23-26). It is important to mention that the combination of stem cells with hyaluronic acid or platelet-rich plasma has an analgesic effect and achieves superior outcomes on the WOMAC scale compared to either treatment alone (27).

MUSCULOSKELETAL INJURIES

It has been demonstrated that stem cells and growth factors enhance the recovery of a wide range of musculoskeletal injuries, with fewer adverse effects compared to traditional approaches based on analgesics, anti-inflammatory drugs, physical therapy, and, when conservative management is insufficient, surgery. Frequently, when non-surgical treatment is unsatisfactory, glucocorticoid infiltration at the injury site is used. However, its effectiveness is temporary, and these drugs carry the risk of

gradually altering tissue metabolism, leading to weakening and an increased probability of injury progression. Regarding regenerative medicine, most published clinical studies indicate that the intralesional application of stem cells, with or without growth factors, improves pain, functional performance, and structural defects of the injured tissue. Among the musculoskeletal injuries that respond positively to regenerative therapy are plantar fasciitis, tendinopathies, musculotendinous tears, ligament injuries and ruptures, rotator cuff tears, arthritis, and avascular necrosis of the femoral head (28-33).

DEGENERATION OF THE INTERVERTEBRAL DISC

The intervertebral disc prevents direct contact between vertebrae and absorbs compressive forces on the spine. Intervertebral disc degeneration is associated with the loss of vitality in its stem cells, leading to disc deformation and instability. This process can result in localized pain or even severe, disabling nerve injury. Treatment options for disc degeneration include palliative approaches such as pain medication and physical therapy. In many cases, surgery is required, though it may lead to biomechanical complications and accelerated degeneration of adjacent segments. The intradiscal application of stem cells is a safe, minimally invasive procedure with long-lasting benefits. It does not require surgery or hospitalization and compares favorably to surgical interventions such as spinal fusion or disc replacement, offering similar outcomes at significantly lower costs (34-38).

SPINAL AND LOWER BACK PAIN

Aparte del disco, todas las demás estructuras que hacen parte de la anatomía de la columna (músculos, articulaciones intervertebrales, raíces nerviosas, articulaciones sacroilíacas, etc) son capaces de provocar dolor en la región comprometida o irradiado a la extremidad inferior. En estos casos el beneficio de la infiltración local de células madre/exosomas ya ha sido

demostrado en ensayos clínicos controlados, con una relación riesgo/beneficio superior a otras alternativas convencionales (39-43).

PAIN

Clinical evidence is steadily accumulating, demonstrating the benefits of stem cells/exosomes in the treatment of neuropathic pain, including pain secondary to complete spinal cord injury or diabetic neuropathy. This suggests that stem cell therapy may represent a novel approach to treating a condition that significantly impairs patients' quality of life and for which conventional medicine offers limited treatment options (44). It has been demonstrated that, at injury sites, stem cells inhibit the production of pain-inducing substances while simultaneously releasing analgesic compounds, thereby correcting the imbalance between pain mediators and analgesic factors. This mechanism establishes stem cell therapy as a novel strategy for managing pain associated with a wide range of diseases (45-57). It is useful to note that some evidence suggests stem cells enhance the analgesic effect of opioids in cases of intractable cancer-related pain (58).

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CARDIOVASCULAR DISEASES

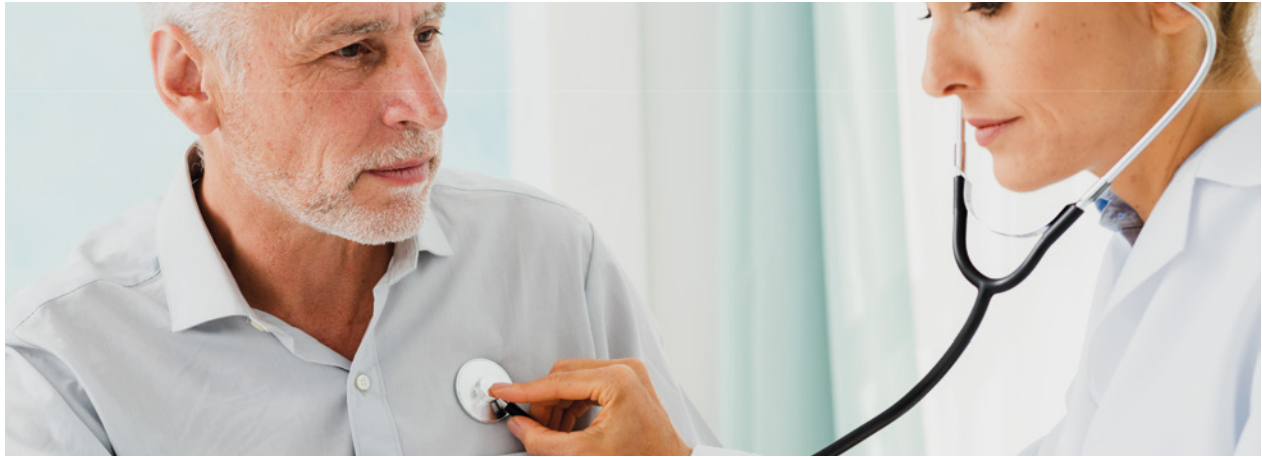


A causal relationship between inflammatory cytokines and cardiovascular diseases, including stable and unstable angina, myocardial infarction, and heart failure, has already been demonstrated (1). The regenerative and paracrine actions (anti-inflammatory and immunomodulatory) of stem cells/exosomes, reflected in inflammation and fibrosis control, preservation of cardiac muscle contractility, and stimulation of new blood vessel formation, have driven research into the role of regenerative medicine, particularly in ischemic heart disease (angina, myocardial infarction) and cardiomyopathy (heart failure). These conditions remain among the leading causes of morbidity and mortality worldwide, despite significant advances in technology, surgery, and cardiovascular pharmacology (2). However, It is important to clarify, that certain gaps remain to be addressed before establishing specific protocols, such as dosage, cell type, timing of application, and route of administration.

Additionally, long-term parameters, such as survival rates, do not always yield consistent results. These discrepancies are often attributed to factors like the source of the applied cells, donor age, laboratory practices, and administration routes, among others. (3,4). Current research explores strategies to enhance the cardiac regenerative potential of stem cells/exosomes. These approaches include controlled-release methods, molecular or genetic modifications, and the use of biomaterials, all aimed at maximizing the beneficial effects of regenerative medicine (5,6).

REFRACTORY ANGINA

Referred to as refractory, this condition is characterized by persistent angina despite several months of standard treatment. Patients are often ineligible for revascularization due to the presence of diffuse coronary lesions or severe comorbidities. Stem cell therapy is emerging as a valuable approach for managing these patients, as supported by clinical trials (7). When comparing patients receiving standard treatment plus stem cells with those undergoing only optimal conventional management, studies report improvements in angina indicators and attack frequency, increased exercise tolerance, and a reduction in all-cause mortality, without a rise in adverse reactions among those treated with stem cells. Angina or ischemia with non-obstructive coronary artery disease (ANOCA/INOCA) are conditions with poorly understood pathophysiological mechanisms, though they are associated with microcirculatory dysfunction and spasms. In addition to conventional pharmacological treatment for angina, stem cell therapy represents a novel and promising therapeutic approach for these cases (8,9).



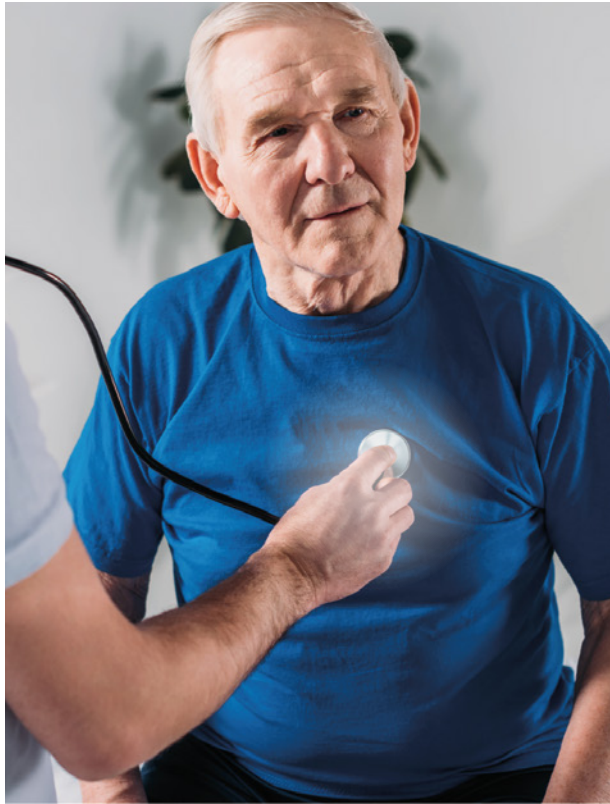
MYOCARDIAL INFARCTION (MI)

Cell death secondary to myocardial infarction (MI) triggers a strong inflammatory response aimed at repairing the cardiac muscle. However, this process also initiates ventricular remodeling, the duration and intensity of which determine the prognosis of the infarction. In other words, ventricular remodeling begins as an adaptive response but, when prolonged, leads to adverse consequences such as ventricular wall thinning and dilation, ultimately resulting in myocardial dysfunction. In this context, pharmacological therapy and established reperfusion strategies (thrombolysis, angioplasty, or surgical revascularization) offer only limited benefits (10). According to available evidence, the anti-inflammatory and immunomodulatory activity, on the one hand, and the regenerative activity, on the other, explain how stem cells/exosomes restore the balance between inflammation and repair, regulate cardiac remodeling, and improve infarction prognosis (11-15). Meta-analyses including randomized controlled clinical trials with thousands of patients who experienced a myocardial infarction (MI) and received timely surgery and/or conventional pharmacological treatment indicate that the addition of stem cells/exosomes is associated with significant clinical improvement and enhanced cardiac function parameters (ejection fraction, infarct size, hospital readmission rates, survival, and risk of major adverse events such as cardiovascular death, reinfarction, and stroke); patients with microvascular obstruction who

suffer ST-elevation MI appear to represent a subgroup that benefits most from intracoronary stem cell application. The achievement of this level of evidence explains why an increasing number of experts consider regenerative therapy with stem cells/exosomes as a viable option to be included in myocardial infarction treatment protocols. Notably, in the treatment of heart failure and myocardial infarction, umbilical cord-derived stem cells have demonstrated more favorable outcomes compared to bone marrow-derived cells, with two doses proving more effective than a single dose (16-26).

CARDIOMYOPATHY (ISCHEMIC AND NONISCHEMIC)

As previously mentioned, ischemic injury and the subsequent death of cardiac muscle cells lead to cardiac fibrosis, in which damaged tissue is replaced by fibrotic scarring. While this scarring plays a crucial role in preventing ventricular wall rupture in the infarcted area, over time, it progressively extends to non-infarcted regions, ultimately worsening cardiac function. Despite optimal medical and surgical management, many patients with heart disease remain susceptible to a gradual process of myocardial damage, which can progressively impair the heart's ability to contract and relax. In other words, current treatment protocols may not fully prevent the decline in myocardial viability over time, potentially contributing to cardiomyopathy. Under these circumstances, it is unsurprising that the medical community has sought to explore the potential



benefits of stem cells/exosomes, given their anti-inflammatory, anti-fibrotic, angiogenic, and immunomodulatory properties (27). Since 2018, multiple meta-analyses have been published, encompassing dozens of studies involving thousands of patients with heart failure, systematically evaluating the effects of stem cell-based therapy. The findings can be summarized as follows: compared to conventionally treated controls, patients who received stem cell therapy showed significant improvements in nearly all clinical and paraclinical indicators of cardiac function, regardless of the underlying cause of heart failure. These improvements included heart failure severity classification, walking distance, quality of life, and overall mortality. Notably, no significant differences in the incidence of serious adverse events were observed between the treatment and control groups (28-34).

Heart failure with preserved ejection fraction (HFpEF) warrants special consideration, as its pathophysiology has been attributed to three primary mechanisms: a) microvascular damage resulting from comorbid conditions, b) low-grade

cardiac inflammation in response to chronic mechanical stress, and c) dysfunction driven by intrinsic pro-inflammatory activity within the heart, potentially influenced by hereditary factors. Emerging evidence suggests that stem cell therapy plays a role in modulating cardiac remodeling and improving microcirculation in HFpEF, positioning it as a promising therapeutic option (35).

ATHEROSCLEROSIS AND PERIPHERAL ARTERIAL DISEASE

Atherosclerosis is a chronic inflammatory vascular disease that constitutes the pathological basis of peripheral, cerebrovascular, and cardiovascular disease (36). Atherosclerosis has both inflammatory and immune components, driven by cells and inflammatory markers that can be measured and used to assess the risk of atheromatous plaque progression (37). Due to their anti-inflammatory, immunomodulatory, and angiogenic properties (promoting the formation of new blood vessels), stem cells/exosomes play a key role in controlling atheroma formation and stabilizing established plaques, thereby reducing the risk of inflammation, rupture, and thrombus formation (38,39). For these reasons, regenerative therapy based on stem cells/exosomes represents an innovative approach to the treatment of atherosclerosis (40-44).

Moreover, in individuals with atherosclerotic ischemia of the lower limbs, stem cells have been reported to stimulate neovascularization and the development of collateral circulation, thereby improving blood supply to tissues. This effect has been associated with a reduction in amputation rates, even in patients with critical limb ischemia who are not candidates for revascularizations (45).

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PULMONARY DISEASES



The lungs possess an extraordinary capacity for self-repair but are exposed to numerous harmful environmental and endogenous factors. These factors contribute to the development of obstructive, restrictive, and inflammatory diseases, both acute and chronic, ranging from pneumonia and acute respiratory distress syndrome (ARDS) to asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and pulmonary fibrosis. With the rising global prevalence of these diseases, their high morbidity and mortality, and the limited treatment options for some, regenerative

medicine, based on stem cells/exosomes, has gained significant attention. By fulfilling a dual role in mitigating inflammation-related damage and promoting lung regeneration. Clinical research is rapidly expanding, with growing evidence of its safety and efficacy reshaping the medical landscape (1-4). However, it is important to note that in the advanced stages of these diseases, the benefits of regenerative medicine remain limited. Furthermore, consensus has yet to be reached on factors such as the optimal cell source, dosage, administration routes, and treatment frequency, among others.

Viral pneumonia is the leading cause of **acute respiratory distress syndrome** (ARDS). Stem cells/exosomes from diverse sources have demonstrated benefits in controlling the inflammatory cascade triggered in ARDS (including COVID-19 and H1N1 influenza) by reducing the expression of pro-inflammatory cytokines responsible for lung tissue damage (5-9). A recent systematic review and meta-analysis on the role of stem cells in ARDS, involving hundreds of patients from randomized controlled trials, reported the following findings: improved clinical and pulmonary function, reduced inflammation markers and mortality, no increase in adverse events, and no statistically significant differences in ICU stay duration or ventilator-free days (10).

Pulmonary fibrosis is a chronic, progressive disease characterized by lung tissue remodeling, fibrous tissue accumulation, scar formation, and consequent loss of lung elasticity (11). Stem cells/exosomes, administered through inhalation or intravenous infusion, have shown anti-fibrotic activity in the lungs. Recent studies suggest that this therapy mitigates both idiopathic pulmonary

fibrosis (of unknown cause) and fibrosis secondary to ARDS, such as post-COVID-19 pulmonary fibrosis, a recognized complication of long COVID (12-19).

In **asthma**, the dynamic balance between Th1 and Th2 lymphocytes is disrupted, leading to inflammation, hyperreactivity, and airway remodeling (20). Although proven, effective, and safe treatment protocols exist, a small group of patients does not achieve therapeutic goals with current options (21). Stem cells/exosomes help restore the balance between these lymphocyte populations and have demonstrated benefits in asthma by controlling inflammation and airway remodeling. The potential benefits of nebulized airway delivery are worth highlighting. An interesting *in vitro* finding revealed that exposing blood from asthma patients to stem cell-derived exosomes induced immunomodulatory effects, evidenced by the inhibition of pro-inflammatory cytokines and the expansion of anti-inflammatory lymphocytes (22-25).

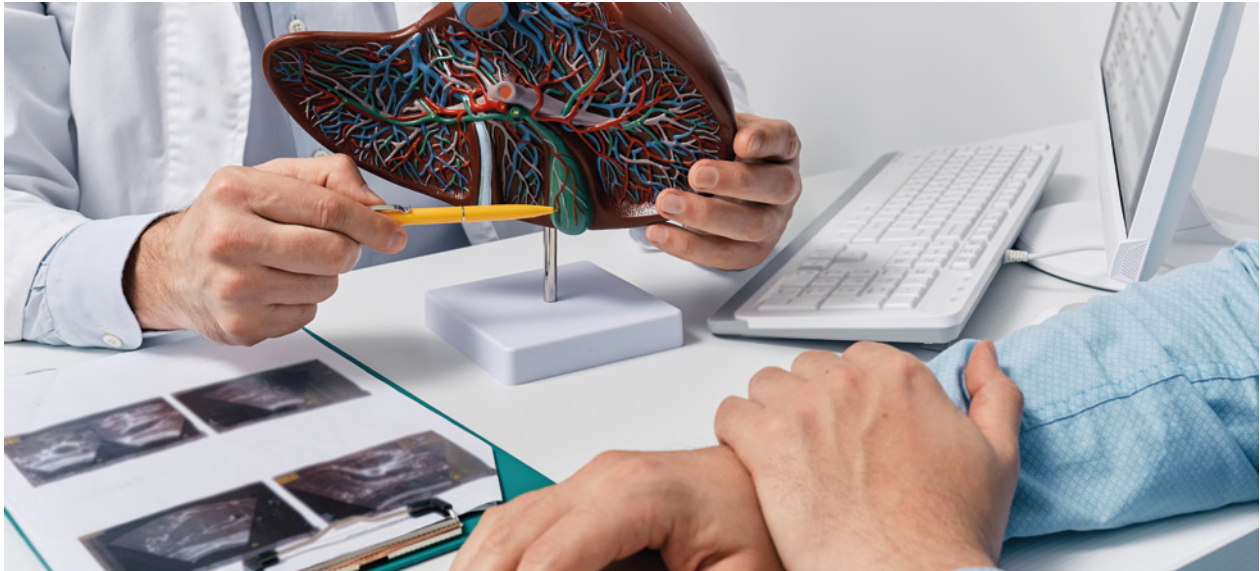
Stem cells and exosomes have also demonstrated a favorable safety and efficacy profile in **COPD** (26,27). A randomized controlled clinical trial in patients with stage II to IV COPD, which was highlighted in an editorial by JAMA (28), found that airway-administered stem cells improved lung function. Six months post-treatment, patients who received stem cells showed enhanced pulmonary function and increased six-minute walk distance, whereas the control group experienced a decline. Adverse events were minimal. Notably, the editorial emphasized that, until now, lung damage caused by COPD was considered irreversible.

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LIVER DISEASES



Although the liver possesses a remarkable regenerative capacity, viral infections, drugs, toxins, metabolic disorders, and genetic or immune diseases can still cause acute liver failure or lead to chronic inflammation and cirrhosis, even with appropriate medical and surgical treatment (1) For some patients, liver transplantation is not a viable option due to donor shortages, immunosuppression-related complications, surgical complexity, and high costs.

Metabolic-associated fatty liver disease is the most common chronic liver condition and can progress to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. While treatments have been approved for these conditions, their effectiveness remains limited, which is unsurprising given the intricate metabolic, inflammatory, and immune pathways driving disease progression (2) It is now widely accepted that an abnormal immune response plays a critical role in the onset and progression of nearly all liver diseases. A striking example is the decline in lymphocytes and the loss of T-cell function, which are strong predictors of imminent acute liver

failure in patients with cirrhosis. As a result, hepatology research is increasingly focused on strategies to restore immune homeostasis. Beyond their regenerative properties, stem cells/exosomes exhibit potent immunomodulatory, anti-inflammatory, antioxidant, and anti-fibrotic activity. As a result, regenerative medicine has emerged as a promising therapeutic option for several liver diseases, including metabolic-associated fatty liver disease, non-alcoholic and alcoholic liver disease, viral and autoimmune hepatitis, acute-on-chronic liver failure, and cirrhosis (3-14).

Another clinically significant factor is the association between non-alcoholic fatty liver disease and insulin resistance, obesity, diabetes, dyslipidemia, hypertension, and cardiovascular disease. Complementing existing pharmacological and lifestyle interventions for this complex metabolic and cardiovascular dysfunction, stem cell- and exosome-based therapy is emerging as a highly cost-effective and safe treatment option (15,16).

Extensive preclinical evidence demonstrates the ability of stem cells to differentiate into liver cells, highlighting their anti-inflammatory, antifibrotic, and immunoregulatory properties, as well as their therapeutic effects on acute liver failure in different animal models (17). The effectiveness and safety of stem cells/exosomes have been confirmed in multiple clinical trials and large meta-analyses involving thousands of patients. These studies consistently demonstrate benefits in the treatment of fatty liver disease, cirrhosis at various stages, and acute liver failure, with biochemical, histological, functional, and clinical improvements. The main reported benefits can be summarized as follows (18-22): a) clinical improvement of symptoms such as edema, fatigue, anorexia, and abdominal distension; b) enhanced biochemical parameters, including increased serum albumin levels (reflecting improved protein synthesis), better coagulation function, total bilirubin reduction, and improved enzyme activity related to carbohydrate and lipid metabolism; c) reduction in MELD scores, which assess disease severity; d) increased survival rates. e) decreased incidence of liver cancer, although this effect varies across studies; f) no severe adverse events were reported in any of the included studies.



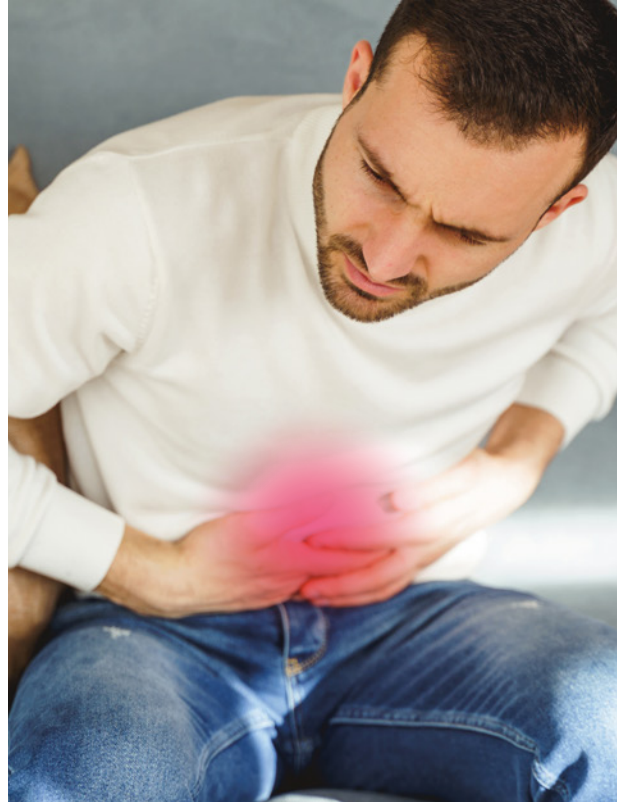
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INFLAMMATORY BOWEL DISEASE (IBD)

This includes **ulcerative colitis** (UC) and **Crohn's disease** (CD). Both conditions share an autoimmune disorder in which different immune cells and mediators attack the digestive tract, leading to chronic inflammation, gut microbiota alterations, and intestinal tissue damage. Consequently, treatment focuses on immune system normalization and inflammation control (1,2). However, despite the growing availability of anti-inflammatory and immunosuppressive drugs, up to 30% of patients with IBD fail to respond to existing treatment protocols, and up to half of those who initially benefit eventually lose their response over time (3). In this context, stem cells/exosomes have been investigated for their capacity to promote tissue regeneration, exert paracrine effects (by releasing molecules that mitigate damage and support gut microbiota balance), regulate immune responses, and reduce inflammation (4,5).



The benefits of stem cell and exosome therapy for IBD have been confirmed in numerous clinical trials and meta-analyses involving thousands of patients, with the strongest evidence in CD, including severe, refractory cases with fistula formation (ano/rectal/vaginal). Reported clinical and paraclinical outcomes include extended remission duration, histological and radiological improvements with signs of tissue regeneration, reduced hospitalizations and surgeries, and a safety profile comparable to conventional therapy (6-21).

Key Considerations: a) the best outcomes were observed in patients with a disease duration of under five years, with complete remission associated with disease evolution under three years (22); b) while evidence on potential interactions between stem cells and conventional drugs remains inconclusive, studies suggest that combining stem cells with glucocorticoids or azathioprine (and possibly other medications) enhances therapeutic benefits in IBD (23-25); c) in an animal model of ulcerative colitis, exosomes achieved better outcomes than infliximab (26).

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DIABETES MELLITUS



Type 1 diabetes mellitus (T1DM) arises from a complex interaction between pancreatic β -cells (responsible for insulin production) and the immune system, ultimately leading to their autoimmune destruction (1). On the other hand, energy imbalance associated with overweight and obesity triggers a metabolic disorder characterized by hyperglycemia, inflammation, β -cell dysfunction, and insulin resistance, eventually progressing to the metabolic syndrome known as **type 2 diabetes mellitus** (T2DM) (2).

The differentiation potential of stem cells, their anti-inflammatory and immunoregulatory properties, angiogenic capacity, and positive

impact on carbohydrate and lipid metabolism (3-5), have drawn significant interest from researchers and clinicians, triggering a surge in preclinical and clinical studies. These investigations aim to evaluate the safety and efficacy of stem cells and their extracellular vesicles in treating T1DM and T2DM, while also defining their mechanisms of action, optimal sources, dosages, administration routes, and dosing intervals. As a result, a substantial body of scientific evidence now supports stem cell/exosome therapy as a safe and cost-effective treatment option for diabetes mellitus.

Numerous individual studies, systematic reviews, and meta-analyses of randomized controlled clinical trials, involving hundreds of patients, confirm the safety and efficacy of stem cells/exosomes in treating both T1DM and T2DM. These therapies have demonstrated clinical and quality-of-life improvements, including better glycemic control, reduced glycated hemoglobin levels, decreased daily insulin requirements, and increased C-peptide levels. Additionally, they contribute to lowering the risk of chronic complications such as nephropathy, retinopathy, neuropathy, peripheral ischemia, and diabetic foot, among others (6-31). Furthermore, the generation of β -cells from engineered and enhanced stem cells is emerging as a promising curative approach for T1DM (32-34). Notably, baseline C-peptide concentrations serve as predictors of clinical outcomes in disease-modifying therapies like regenerative medicine (35,36).

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RENAL FAILURE



Apart from renal transplantation, no available treatment for chronic renal failure can reverse disease progression; current management strategies focus solely on slowing its progression and controlling comorbidities such as hypertension, electrolyte imbalances, and anemia. Under these circumstances, the development of new therapeutic strategies aimed at restoring renal function is imperative (1,2).

The key pathological phenomenon in renal failure is inflammation and remodeling, a process in which normal structures are replaced by fibrotic tissue and blood vessel destruction, ultimately leading to the loss of renal function. Stem cells represent a promising therapeutic option for renal disease due to their regenerative properties and paracrine mechanisms, which regulate the immune response, prevent renal cell death, mitigate oxidative stress, and promote the formation of new blood vessels (3-6).

The nephroprotective effects of stem cells, by promoting regeneration and improving renal function, have been recognized in both **acute kidney injury** (AKI) and **chronic kidney failure** (CKD) of unknown origin or secondary to conditions such as diabetes, lupus, and nephrotic syndrome. In these cases, the benefits appear to be greater when stem cell therapy is combined with established treatments (1,2,5,7-15).

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GRAFT-VERSUS-HOST DISEASE

Hematopoietic stem cell transplantation, derived from bone marrow, peripheral blood, or cord blood, is indicated for the treatment of leukemia, lymphomas, certain anemias, and immune disorders. The increased prevalence of these diseases in elderly individuals is primarily attributed to aging and the dysfunction of their hematopoietic stem cells (1).



However, post-transplant mortality rates remain high, mainly due to disease recurrence, infections, and graft-versus-host disease (GVHD), a consequence of a complex immune response, that can manifest in both acute and chronic forms. Although immunosuppressive drugs can help reduce its incidence, it remains high, for instance, the acute form affects between 40% and 80% of transplant patients, highlighting the urgent need for novel therapeutic approaches.

Given their potent anti-inflammatory and immunomodulatory properties, mesenchymal stem cell transplantation (e.g., from Wharton's jelly) has been investigated as a potential treatment for GVHD. While further evidence from controlled clinical trials is needed and

management protocols require standardization (2), numerous studies have reported the beneficial effects of stem cells in both the prophylaxis and treatment of acute and chronic GVHD in pediatric and adult patients. Whether used alone or in combination with other immunosuppressants, stem cell therapy has been associated with improved survival. Importantly, its benefits also extend to patients with steroid-resistant GVHD (3-11).

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AUTOIMMUNE AND ALLERGIC DISEASES

After the immunomodulatory and anti-inflammatory activity of stem cells was demonstrated in *in vitro* and preclinical studies, researchers began exploring their role in various autoimmune diseases in humans, all of which are characterized by the loss of immune tolerance to self-tissues. The immunomodulatory mechanisms of stem cells and exosomes include: a) inducing the differentiation of pro-inflammatory T lymphocytes into regulatory T lymphocytes; b) inhibiting the proliferation of B lymphocytes and the production of immunoglobulins; c) promoting the conversion of pro-inflammatory macrophages into anti-inflammatory macrophages; d) inhibiting neutrophil recruitment; e) preventing the maturation of pro-inflammatory dendritic cells (1-4).

In certain autoimmune diseases, the current evidence regarding the safety and efficacy of stem cell/exosome-based therapies is considered sufficiently robust for experts from various scientific societies to issue consensus recommendations, such as the following: "Cell therapy may be considered as a therapeutic option in patients with severe autoimmune diseases being active or progressing despite the use of standard (guideline-based and/or regulatory approved) therapy" ... "Depending on the half-life and efficacy of the cellular product, repeated application might be necessary, as already shown for stem cells" (5).

RHEUMATOID ARTHRITIS (RA)

30-40% of patients with rheumatoid arthritis (RA) do not respond adequately to or cannot tolerate conventional treatments; in such cases, stem cells/exosomes have emerged as a promising therapeutic option. Increasing evidence supports the benefits of stem cell/exosome-based

therapies in patients with poor responses to standard treatment, including reductions in inflammation markers and clinical improvements (6-19). It has even been shown that stem cells have an enhanced effect when combined with conventional drugs like gamma-interferon (20).

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

This is one of the autoimmune diseases with the strongest evidence supporting the benefits and safety of stem cells/exosomes, both in animal models and humans (21-27). The results from clinical trials on the safety and efficacy of stem cell/exosome therapies are promising, with several positive outcomes reported, including a) improvement in clinical manifestations and damage to renal, pulmonary, hepatic, and bone tissues; b) enhancement of immune parameters, such as the conversion of pro-inflammatory lymphocytes into anti-inflammatory ones, and a reduction in autoantibody levels (including antinuclear antibodies and anti-DNA antibodies) (28); c) increased survival rates; and d) a broad safety margin. It is important to highlight that stem cell/exosome-based therapy is currently the most viable option for patients with lupus refractory to conventional treatment, including glucocorticoids (18,29-31).

SYSTEMIC SCLEROSIS (SS)

It is an autoimmune disease characterized by vascular damage, immune system dysfunction, and fibrosis of the skin and multiple organs. Treatment options are highly limited, and the medications that may be useful have a narrow safety margin. Cell therapy emerges as not only a safe option but also one capable of correcting many of the inflammatory, fibrotic, and

immune-related disorders inherent to this disease. Clinical studies and reviews have confirmed the safety and significant benefits of stem cell/exosome therapy, with some cases demonstrating superior efficacy compared to traditional immunosuppressive agents, and no increase in the incidence of adverse events, when applied to patients with systemic sclerosis (32-42).

SJÖGREN'S SYNDROME (SS)

In this disease, the immune system initially targets the patient's own salivary and lacrimal glands, resulting in dry mouth and eyes. In more severe forms, however, it can lead to chronic inflammation and dysfunction in other organs, including the lungs, kidneys, liver, and brain (43). The imbalance among different T lymphocyte populations plays a key role in the progression of the disease, and currently, no effective treatment is available (44,45).

Although clinical evidence on the risk/benefit of regenerative medicine remains limited, recent studies have demonstrated that stem cells/exosomes are effective in treating Sjögren's syndrome by modulating the immune response and promoting tissue repair (46-50). It is worth noting that stem cells/exosomes have also demonstrated benefits in other forms of xerostomia (dry mouth), such as that secondary to radiation therapy (51).

PSORIASIS

A significant number of patients with psoriasis do not respond adequately to current therapies. As an autoimmune disease, psoriasis involves the patient's stem cells in the excessive and sustained production of inflammatory substances. Given the anti-inflammatory and immunomodulatory properties of stem cells/exosomes, a positive response to stem cell therapy was anticipated. The therapeutic effect and safety of stem cells/exosomes in the treatment of psoriasis are no longer debated. Instead, expert consensus focuses on refining aspects such as the source of

the cells and exosomes, dosage, administration routes (injection or topical), and other related factors. (18,52-58).



ATOPIC DERMATITIS

Stem cells/exosomes have emerged as a promising strategy for treating allergic diseases (such as asthma, rhinitis, dermatitis, conjunctivitis, and anaphylaxis) due to their immunoregulatory and anti-inflammatory properties (59). This therapeutic potential has been demonstrated through preclinical and clinical studies. However, atopic dermatitis is the allergic disease with the strongest evidence supporting the benefit and safety of stem cell/exosome treatment (60-64).

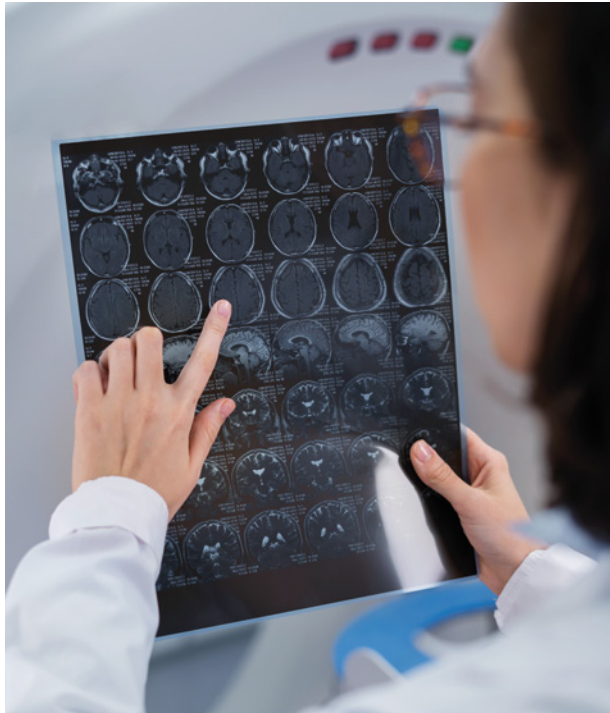
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NEURODEGENERATIVE DISEASES



Several neurodegenerative diseases, including multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease, are considered incurable. Current medical treatments are primarily palliative; for instance, disease-modifying therapies can help control the progression of intermittent forms of multiple sclerosis, but none can repair existing damage. In recent years, there has been significant interest in determining the role of stem cell/exosome based therapies in various neurodegenerative diseases. *In vitro* studies and diverse animal models have confirmed several properties of different types of stem cells, including the restoration of blood-brain barrier (BBB) integrity, the formation of new myelin, the transfer of mitochondria to vulnerable neurons, the prolongation of neuronal viability, the reduction of oxidative stress, immunomodulation, and the formation of new blood vessels, all of which contribute to neuroprotection. However, for some of these diseases, further evidence is still

needed regarding safety and efficacy, optimal cell types, appropriate dosing, and administration routes, among others (1–8).

MULTIPLE SCLEROSIS (MS)

It is caused by the destruction of myelin, which disrupts neuronal electrical activity and leads to a progressive loss of brain function. Regenerative medicine-based treatment has achieved a level of evidence that has led scientific organizations to recommend it for severe forms of the disease. Health authorities have also approved it in some countries. Current research is focused on refining critical aspects, including identifying the most responsive disease subtypes (particularly relapsing-remitting forms) optimizing administration routes, determining optimal dosing and intervals, and assessing interactions with conventional therapies (9–16). Compared to standard immunotherapy, stem cell/exosome treatments have been associated with disease stabilization, delayed progression, improved Expanded Disability Status Scale (EDSS) scores, reduced brain lesion volume, enhanced cognitive function, and increased life expectancy. Additionally, these benefits are accompanied by a reduction in biomarkers of disease activity in blood and cerebrospinal fluid (17–29). Moreover, when hematopoietic stem cell therapy was compared to disease-modifying treatments including "high-efficacy" drugs such as natalizumab, stem cell therapy has proven to be more effective and less expensive in patients with the aggressive relapsing-remitting form of the disease (30,31).

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Elit is a disease with genetic and non-genetic determinants, characterized by the destruction of motor neurons in the brain and spinal cord, neurovascular damage, and muscle degeneration, leading to paralysis, respiratory failure, and premature death (32). Stem cell/exosome therapy has been consolidated as a safe procedure and a promising strategy that protects motor neurons, slows the loss of motor function, reduces symptom severity, and improves survival rates (33–39).

PARKINSON'S DISEASE (PD)

More than 10 million people worldwide are believed to be affected by PD, a condition characterized by the progressive degeneration of neurons in specific areas of the brain. At the molecular level, PD is associated with the formation of abnormal aggregates of the α -synuclein and the disruption of the BBB (which regulates the entry and exit of molecules in the brain and maintains the normal functioning of the central nervous system). This disruption leads to inflammation and neuronal damage. Stem cells/exosomes help restore BBB integrity and prevent α -synuclein aggregation, resulting in reduced inflammation and neuronal toxicity (40,41).

Current treatment approaches primarily focus on symptom management through medications or neurosurgery, but they do not address the prevention of neuronal damage. Therefore, there is a critical need to develop neuroprotective strategies that offer the potential to replace lost neurons. Studies on the safety and efficacy of stem cell/exosome therapy in animal models have yielded conclusive results, making regenerative medicine a central focus of attention within the medical community. Currently, clinical evidence from trials and meta-analyses can be summarized as follows: i) safety studies in humans are unequivocal, showing that stem cells are a therapeutic tool with a very low incidence of undesirable effects and are not associated with

serious adverse events; ii) evidence from efficacy studies continues to strengthen, with stem cells emerging as a promising therapy linked to improvements in patients' clinical condition and imaging findings; iii) stem cells regenerate damaged areas of the brain and provide neurotrophic support; iv) they also improve neuropsychological scores in patients (42–49). It is worth noting that, based on various experimental findings, induced pluripotent stem cells (iPSCs) demonstrate exceptional therapeutic potential in Parkinson's disease and may rapidly emerge as the leading option for regenerative treatment (50,51).

ALZHEIMER'S DISEASE (AD)

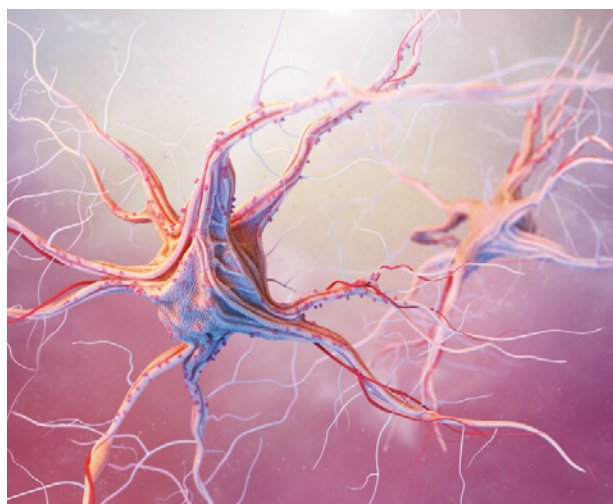
It is a highly prevalent disease and a leading cause of mortality in the elderly, characterized by cognitive decline, memory loss, disorientation, language impairments, and a reduced ability to solve problems. The accumulation of intraneuronal tau protein deposits and the formation of extraneuronal β -amyloid ($A\beta$) plaques are key molecular events that ultimately lead to neuroinflammation and neuronal degeneration.

Due to the complexity of this disease, the therapeutic approach to AD is inherently multimodal, integrating pharmacological and non-pharmacological components. However, the outcomes of these recommended interventions remain discouraging, as they can, at best, manage certain symptoms but do not cure the disease, repair the damage, or stop its progression. In this context, stem cells/exosomes have emerged as a promising alternative, as they have demonstrated the ability to regulate numerous biochemical signals involved in the brain damage caused by AD (52–57).

In vitro and preclinical studies have confirmed the neuroprotective and neuroregenerative effects of stem cells/exosomes in animal models of AD, including the following outcomes: a) reduction of cognitive deficits, accompanied by increased levels

of neurotrophic factors; b) memory improvement; c) promotion of neurogenesis and synaptic plasticity, the site of communication between neurons; d) inhibition of A β plaque deposition and enhancement of its degradation (58-60).

Although evidence in humans remains limited, the safety and efficacy results obtained so far have secured stem cells/exosomes a prominent place in the treatment of AD. This topic is under scrutiny by the scientific community, with numerous clinical trials either published or currently underway. Several authorities consider the clinical outcomes so promising that they are steadily advancing in the identification of biomarkers to predict and/or monitor the response to this regenerative therapy (61-68).



EPILEPSY

It is an electrical disorder of the brain, characterized by recurrent convulsive seizures that progressively damage neurons. Approximately 70% of patients respond favorably to existing anti-epileptic agents, while up to 30% remain refractory to pharmacological therapy, which is associated with significant adverse effects. In these circumstances, the pursuit of new therapeutic options remains a top priority in neuroscience research.

As the anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective effects of stem cells have been increasingly confirmed,

evidence of their safety and efficacy has also been strengthened in preclinical and clinical studies, including drug-resistant forms of epilepsy. Stem cells have been associated with a reduction in the frequency, intensity, and duration of seizures, as well as the management of certain neuropsychiatric disorders that often result from this condition (69-72).

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PERINATAL NEUROLOGICAL DISORDERS



HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

It is a neurological complication of preterm birth, associated with high mortality and long-term complications, resulting in substantial personal, familial, medical, and socioeconomic burdens. The damage results from conditions that disrupt blood circulation and oxygenation of nervous tissue, leading to energy depletion and cell death in the affected area. When HIE is not fatal, the majority of patients develop neurological deficits, including hearing and vision loss, developmental delay, cerebral palsy, and epilepsy. Hypothermia is the primary current therapy, which must be initiated within the first hours after birth. While not without risks, its role is neuroprotective rather than neurorestorative (1). This devastating scenario underscores the urgent need for developing new strategies to manage HIE.

It is widely recognized that stem cells within the central nervous system can detect the microenvironment at the site of injury and secrete paracrine factors that promote repair. These factors regulate processes such as inflammation, oxidative stress, cell death, and fibrosis. For instance, various microRNAs (miRNAs) from stem

cells and their derived exosomes modulate neuroinflammation, prevent cell death, promote neuronal repair, and enhance myelination. The most notable clinical outcomes include neuropsychological and motor improvement, a reduction in the severity and frequency of seizures, and a decreased need for anti-epileptic medications. Additionally, the combination of stem cell therapy with hypothermia appears to enhance therapeutic outcomes (2-9).



CEREBRAL PALSY AND GLOBAL DEVELOPMENT DELAY

Due to their neuroprotective and neuroregenerative potential, stem cell/exosome transplantation has emerged as an effective therapeutic alternative for improving various aspects of brain injury in children, including intellectual disability, global developmental delay, and cerebral palsy, when combined with conventional rehabilitation programs. Different clinical studies, including case series, controlled



clinical trials, and meta-analyses, conducted on hundreds of patients aged 6 months to 15 years have confirmed the safety and efficacy of various types of stem cells. Although there is still no consensus protocol regarding the optimal cell source, dosage, route of administration, timing, and frequency of applications, most studies have reported positive responses in cognitive function, language, self-care, motor function, neck control, seated balance, postural tone, seizure frequency, social adaptability, and quality of life. Subgroup analyses indicate that umbilical cord-derived cells and intrathecal administration yield better outcomes. Additionally, younger children and those with less severe disabilities tend to respond more favorably. Adverse events have been minimal and temporary (10-18).

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AUTISM SPECTRUM DISORDERS (AUTISM)

Autism spectrum disorders (ASD) are a group of clinical conditions characterized by impairments in communication, cognition, perception, motor skills, executive function, and emotional regulation. Although the pathophysiology remains unclear, evidence suggests immune system dysfunction and neuroinflammation originating in prenatal life. This process, known as “maternal immune activation” is triggered by inflammation during pregnancy and induces inflammatory signals that disrupt neurodevelopment and cause structural abnormalities in the fetal brain. Elevated levels of inflammatory markers from pro-inflammatory cells have been found in the blood of individuals with autism compared to normal controls (1-3).



Current treatment options are scarce and primarily focused on symptom management, highlighting the need to explore new therapeutic strategies. Based on growing evidence that autism is a neuroimmune disorder, new possibilities arise for treatment with agents that modulate

neuroinflammation. In this context, the anti-inflammatory and immunomodulatory properties of stem cells/exosomes emerge as a promising therapeutic option for enhancing brain function in patients with autism (4,5). An increasing number of individual studies and meta-analyses have investigated the effects of these cells in patients with ASD, reporting benefits in biochemical markers of neuroinflammation and in severity scales of ASD symptoms (including language, social communication, repetitive behavior, and hyperactivity) in patients aged 2 to 15 years. Notably, no serious adverse effects related to the intervention have been reported in any of the clinical studies published to date (6-10).

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Currently, there is no effective treatment for conditions involving the death of neurons and glial cells, as the regenerative capacity of nervous tissue is very limited. Consequently, a major focus of the scientific and clinical communities is on minimizing damage, promoting the reconstruction of nervous tissue, and restoring its structure and function following injury (1). Stroke is the most common neurological disorder in adults, and its incidence has risen primarily due to population aging and the growing prevalence of cardiovascular disease. In addition, current interventions to manage acute stroke have helped reduce mortality. However, many patients are left with residual cognitive, sensory, and/or motor impairments. Therefore, interventions aimed at preventing stroke, treating its acute phase, or addressing its sequelae are being actively explored. Stem cell/exosome based regenerative therapy represents a novel approach to reducing stroke-related disability.

Although the therapeutic mechanism of action of stem cells/exosomes in **ischemic stroke** is not yet fully understood, it is known to involve: a) the release of factors that increase neuronal survival

(neurotrophic) and the formation of new blood vessels (angiogenic); b) inhibition of inflammation and the immune response triggered by ischemia; c) regeneration of myelin (the insulating layer surrounding neurons, essential for efficient inter-neuronal communication); d) restoration of the blood-brain barrier (which prevents potentially harmful substances from entering the brain), whose disruption following stroke further impairs neurological function; stem cells/exosomes have been shown to help restore the integrity of this barrier during the acute phase of stroke (2-6).

The safety and functional improvement of stem cell/exosome therapy has already been confirmed in animal models of ischemic stroke (7). Evidence in humans has been accumulating rapidly, to the point that the risk-benefit profile of regenerative medicine approaches for the treatment of various forms of ischemic stroke leaves little doubt. Stem cell transplantation in acute, subacute, and chronic ischemic stroke is considered safe and has been associated with neurological improvement, as measured by significant clinical outcomes including severe disability, recurrent stroke, and



mortality. This therapeutic potential also extends to cerebral small vessel disease, a condition with unclear pathogenesis that is linked to cognitive impairment and dementia. A favorable safety and efficacy profile has been reported for stem cell therapy administered through various routes and at different doses during the acute, subacute, and chronic phases of ischemic stroke. Regarding the routes of administration, intravenous therapy appears to be the safest option during the acute and subacute phases, while the intrathecal route is preferred in the chronic phase. Intracarotid infusion has also been utilized in the acute phase (8,9). The current evidence includes randomized controlled trials, systematic reviews, and large meta-analyses (10–18).

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CENTRAL NERVOUS SYSTEM INJURIES

Due to the limited regenerative capacity of the central nervous system (CNS), one of the most prominent features of stem cell/exosome based regenerative medicine is its potential to replace lost neurons and reconstruct neuronal circuits. In addition, these therapies exert paracrine and immunomodulatory effects in a variety of neurological disorders, including CNS injuries (1,2).

early administration of exosomes (within 90 minutes post-injury) can prevent neuroinflammation, preserve neurogenesis, and avoid the loss of inter-neuronal connections. These effects are accompanied by an increase in the concentration of brain-derived neurotrophic factor (BDNF), the principal neurotrophic factor in the brain (4).



TRAUMATIC BRAIN INJURY

It is the brain damage caused by an external force, leading to physical and cognitive dysfunction. Traditional therapeutic approaches have produced limited results, and only recently have stem cells/exosomes emerged as a promising treatment option (3).

The precise biological mechanism by which stem cells/exosomes reduce neurological deficits and cognitive sequelae following traumatic brain injury is not yet fully understood. However, studies in animal models of brain trauma have shown that

Clinical studies to date have shown that stem cell/exosome therapy, administered through intrathecal, intravenous, or intranasal routes, is more effective than conventional treatments: Patients exhibit improvements in cognitive function, muscle spasticity, muscle strength, and fine motor skills, along with radiological findings and biological markers (5,6).

SPINAL CORD INJURY

It can be a devastating condition, leading to sensory, motor, and autonomic dysfunction below the level of the injury. Immediately after the trauma, a cascade of events, known as “secondary injury” is triggered, involving hemorrhage, ischemia-reperfusion injury, oxidative stress, neuroinflammation, and degeneration of nervous tissue. Conventional treatment modalities have very limited effectiveness (7).

In spinal cord injury, stem cells and their exosomes promote angiogenesis and axonal growth, modulate inflammation and immune responses, exert analgesic effects, regulate cell death, and preserve the integrity of the blood–brain barrier (7–12). For these reasons, regenerative therapy has become a therapeutic option with increasing scientific support. Indeed, the literature confirms its safety and efficacy through a range of studies, from small clinical trials to large-scale



meta-analyses involving hundreds of patients. As a result, the use of stem cells in brain and spinal cord injuries has already been authorized by health regulatory agencies in several countries (13).

The reported benefits of stem cells/exosomes include functional improvement and enhanced quality of life during the acute, subacute, and chronic phases of spinal cord injury (14–19). Moreover, the safety of the procedure has been demonstrated across multiple routes of administration, at various spinal levels, and over a broad range of dosing regimens. In this regard, a particularly noteworthy statement from the authors of a recent review and meta-analysis on the topic reads: “We concluded that the frequency of life-threatening adverse events following cell therapy clinical trials in chronic spinal cord injury patients is very scarce and can be ignored” (20–23).

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INFERTILITY



FEMALE INFERTILITY

Female infertility, defined as the inability to achieve pregnancy despite regular sexual intercourse for at least 12 months, has multiple underlying causes, and treatment options vary depending on the specific type of infertility. Premature ovarian failure (POF, defined as amenorrhea before the age of 40, accompanied by endocrine disturbances and menopausal symptoms), endometrial disorders (such as intrauterine adhesions and thin endometrium), and polycystic ovary syndrome (characterized by elevated masculine hormones, ovulation abnormalities, and insulin resistance) are among the most common causes of female infertility. Stem cell/exosome therapies have increasingly been established as innovative treatment options for these conditions (1–3).

Although the exact mechanism of action in POF remains unclear, *in vitro* and animal studies have demonstrated that various types of stem cells promote follicular growth, maturation, and viability of cultured follicles (4). In women, stem cells improve ovarian function, with greater benefits observed in patients with amenorrhea lasting less than one year. According to some authors, current evidence has demonstrated that cellular therapy is the most effective approach for treating POF compared to other therapeutic options, as it improves pregnancy rates and results in the birth of healthy babies (5–14).

Recurrent implantation failure is defined as the inability to achieve pregnancy after three or more embryo transfer attempts (15). Two common causes of this condition are a local predominance of pro-inflammatory factors due to immune system imbalance, and the accumulation of fibrotic tissue in the endometrium, leading to partial or complete obstruction of the uterine cavity (16,17). Additionally, biochemical and cellular studies have shown that endometrial stem cells from women with endometrial atrophy and intrauterine adhesions are prone to differentiate into pro-fibrotic cell types. In these cases, stem cell/exosome therapy helps regulate local inflammation, improves endometrial thickness and integrity, and increases implantation rates and the likelihood of pregnancy (2,15,18–22).

In women with polycystic ovary syndrome, intra-ovarian injection of stem cells has been associated with reduced androgen levels, restoration of insulin sensitivity, and decreased inflammatory markers (2,23,24).



ERECTILE DYSFUNCTION

Erectile dysfunction is caused by endothelial dysfunction and impaired neural conductivity, often associated with neuropathy and microangiopathy secondary to nervous system trauma, atherosclerosis, diabetes, and other age-related conditions. While the evidence supporting the benefits of regenerative medicine for this clinical condition remains limited, several reports have confirmed the effectiveness and rapid response to intracavernosal administration of stem cells/exosomes. Moreover, their therapeutic effect appears to be enhanced when combined with established treatments such as phosphodiesterase type 5 inhibitors (e.g., sildenafil) or low-intensity extracorporeal shock wave therapy (LI-ESWT). There is also some evidence that stem cells may promote nerve and vascular regeneration, beyond merely alleviating symptoms (25–32).

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AGING AND FRAILITY



The remarkable advances in biology and medicine have succeeded in extending life expectancy, leading to a demographic transition marked by an increasing elderly population across all countries. However, the prevalence of age-related diseases has also increased, reflecting a progressive decline in the body's ability to maintain biological balance with advancing age and resulting in a greater incidence of chronic, debilitating, and painful conditions (1). Accordingly, there is a growing need to elucidate the mechanisms underlying aging and to develop novel therapeutic strategies aimed, at the very least, at making the process more manageable. For this reason, the World Health Organization is committed to promoting measures that ensure what it refers to as “healthy aging,” which it defines as “the process of developing and maintaining the functional ability that enables well-being in older age.” Functional ability is about “having the capabilities that enable all people to be and do what they have reason to value” (<https://www.who.int/news-room/questions-and-answers/item/healthy-ageing-and-functional-ability>).

Although chronological age correlates with several clinical conditions, it does not always accurately reflect an individual's functional capacity, overall well-being, or risk of mortality. In contrast, biological age provides better information about an individual's health status and indicates how rapidly or slowly they are aging. Technological advances have facilitated the identification of aging biomarkers, and the “biological clocks” are algorithms built from these markers, allowing for the estimation of an individual's biological age (2). More than a dozen aging biomarkers have been identified, including genomic instability, telomere shortening, epigenetic alterations, mitochondrial dysfunction, chronic inflammation with excessive production of free radicals, stem cell senescence, and microbiota imbalances, among others. These biomarkers are intricately interconnected, and many of them represent potential targets for anti-aging therapy (1,3-5).

The *frailty syndrome* in older adults is characterized by reduced muscle mass, tone, and strength; slowed mobility and decreased physical activity; weight loss; fatigability; a decline in physiological functions; and elevated levels of molecular markers of inflammation. It constitutes a major predisposing factor for falls, disability, and hospitalization among the elderly. Although timely healthcare interventions such as exercise, proper nutrition, social engagement, and pharmacological treatments can improve quality of life and reduce healthcare costs, no specific treatment currently exists for managing frailty in older adults. Given that stem cells and exosomes possess biological properties that may help control or even reverse many of the signs and symptoms of frailty, regenerative medicine has generated significant interest as a therapeutic option, especially considering that, as stem cells become senescent, they begin to secrete degenerative factors that negatively affect young stem cells and progressively lose their therapeutic potential.



The regenerative capacity of stem cells/exosomes, as well as their ability to modulate chronic inflammation, reduce biochemical markers of senescence, restore mitochondrial function (the cellular energy centers), and regulate

immunosenescence (the aging of the immune system) and the loss of muscle tone and mass (sarcopenia), has been well documented in the scientific literature. Moreover, they have shown benefits in other clinical conditions frequently associated with frailty, such as chronic lung disease, cardiovascular disease, diabetes, osteoarthritis, and osteoporosis, among others (2,6-20).

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SKIN DISORDERS AND ALOPECIA

AESTHETIC MEDICINE



SKIN LESIONS

The benefits of stem cells/exosomes, and growth factors have been extensively studied and confirmed not only in aesthetic medicine but also across a wide range of skin diseases and lesions caused by chronic inflammation, infections, trauma, burns, surgeries, aesthetic procedures, neuropathies, and vascular insufficiency, with varying outcomes (1-4).

Several reviews and meta-analyses of clinical trials investigating the effects of stem cells/exosomes in the treatment of ulcers and chronic skin wounds confirm that regenerative therapy is a safe procedure associated with significant improvement in conditions such as venous ulcers, diabetic foot ulcers, and ulcers secondary to severe ischemic disease, leading to a reduction in amputation rates. The intralesional application of stem cells/exosomes for the treatment of scars is

a simple, safe, and effective approach, not only in clinical but also in histological terms. The prophylactic intradermal application of stem cells in surgical wounds helps prevent the formation of postoperative hypertrophic scars while preserving the normal structure and function of the skin. For these reasons, many experts consider stem cell/exosome based regenerative therapy a novel and effective treatment alternative, particularly when combined with appropriate medical and surgical interventions (5-9).

ALOPECIA

Thanks to the regenerative properties of stem cells and their ability to release factors that stimulate hair growth, hair regeneration has become a key focus of regenerative medicine. Several studies have reported beneficial outcomes with minimal adverse effects, positioning stem cell therapy as one of the most promising and potentially effective treatments for various forms of alopecia (10-15).

AESTHETIC MEDICINE

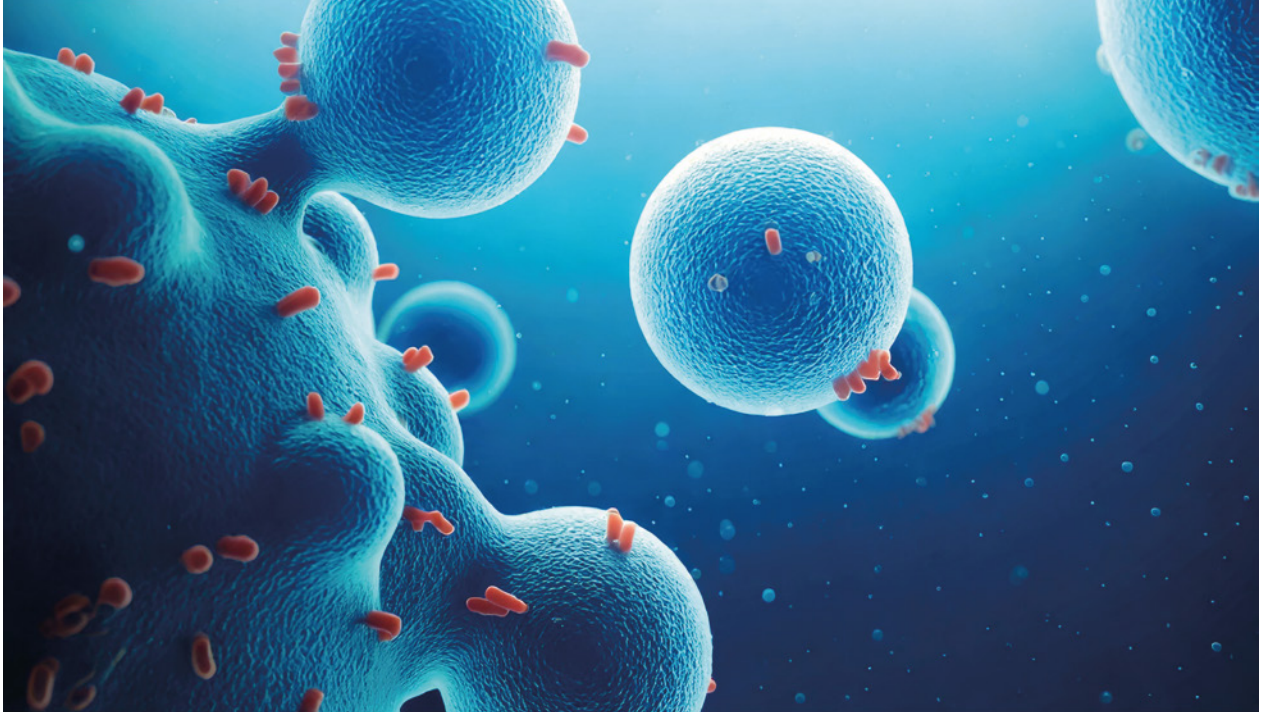
The skin is a tissue with a high capacity for renewal, but it is continuously exposed to adverse environmental conditions, such as ultraviolet radiation, which causes structural damage and loss of vitality. As a result, skin aging is inevitable, although it can be slowed down. Regenerative medicine has emerged as a novel strategy for facial rejuvenation, the filling of furrows and expression lines, and the treatment of scars, acne, vitiligo lesions, and other skin conditions (10,14-25).

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EXTRACELLULAR VESICLES (EVs)



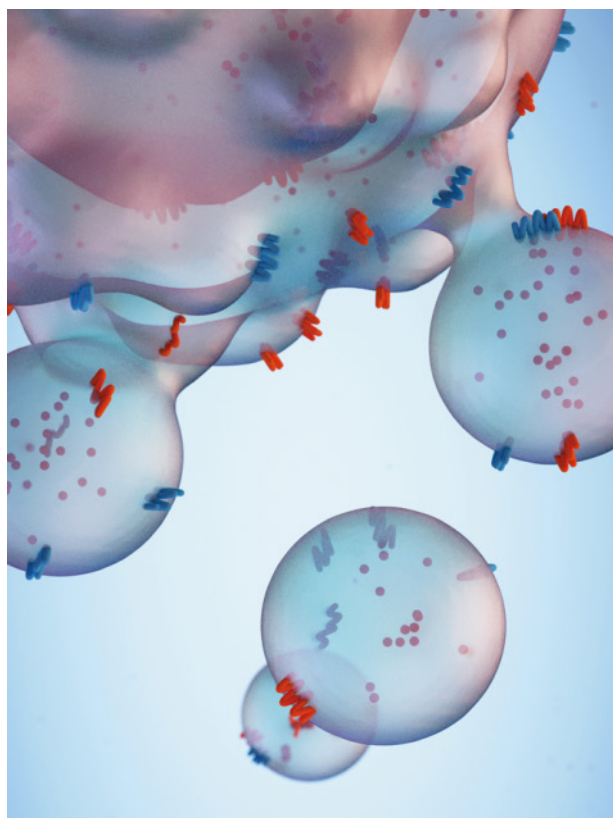
All cells have the ability to secrete biologically active molecules into their surrounding environment, contributing to tissue repair and maintaining their vitality or that of other organs (paracrine activity). One mechanism by which cells optimize this function is through the release of hundreds of active molecules, packaged in membrane-bound vesicles that resemble the cell membrane. Proteins, lipids, nucleic acids, and other biologically active factors are transported within these vesicles, which can be transferred to recipient cells to modify their functional state. These vesicles play a pivotal role in the paracrine activity of cells and cell-to-cell communication (1).

These vesicles are classified based on their size and the cellular compartment from which they originate. *Exosomes* are vesicles ranging from 30 to 120 nm in diameter; *microvesicles* (or *ectosomes*) range from 50 nm to 1 μm , while *apoptotic bodies* measure between 50 nm and 2 μm . In addition to their size, they also differ in the

composition of their biologically active molecules. It should be noted, however, that current techniques for isolating the different types of vesicles are not yet sufficiently refined, making the classification into these three categories imprecise. Therefore, the use of the more general term “extracellular vesicles” (EVs) has been proposed. Nevertheless, the term “exosomes” remains more commonly used in the literature (1,2).

Although EVs are released by all cell types, in this section we focus exclusively on those derived from stem cells, as they exhibit biological properties similar to the cells from which they originate. In other words, they retain the ability to replicate nearly all the therapeutic activities demonstrated by stem cells, suggesting that they may be used for the same therapeutic indications as their cells of origin (3).

Additionally, EVs possess several advantages over the cells from which they are derived. Due to their small size and the physicochemical properties of their membranes, EVs can cross all types of biological barriers, distribute easily throughout the body, and penetrate deeply into tissues. Their small size and lack of immunogenicity also allow them to evade destruction by the patient's immune system. Unlike living cells, EVs are non-replicating and do not carry the risk of tumor formation, thereby avoiding many of the ethical and legal concerns associated with the use of live cells. Furthermore, they can be easily modified, are stable, and can be stored for extended periods (4,5).



Beyond their therapeutic attributes, the medical potential of EVs extends further: they can be used to transport and deliver drugs to tissues that would otherwise be inaccessible to the target organ, or conversely, to prevent distribution to organs where they could cause harm. As drug delivery systems, EVs are less immunogenic and more biocompatible than the synthetic particles conventionally used by the pharmaceutical industry for systemic drug transport (6). Finally,

since all cells are capable of producing EVs, they have potential as biomarkers for the early diagnosis of various diseases, including cancer and neurodegenerative disorders (7,8).

Although the use of EVs as therapeutic tools is highly promising, this strategy still faces several challenges and limitations, including the availability of an adequate stem cell source; difficulties in identification, isolation, and purification; storage conditions that preserve biological activity; the determination of optimal doses and administration routes; and confirmation of long-term safety and efficacy.

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