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Stem Cell Therapies for Neurodegenerative Diseases: Emerging Frontiers in Regenerative Medicine

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ABSTRACT

Neurodegenerative diseases (NDDs) like Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis present a major global health challenge due to their progressive nature and the lack of effective cures. These conditions involve a harmful cascade of events, including unfolded proteins, oxidative stress, inflammation, and disrupted nerve cell connections, ultimately leading to neuron death and cognitive decline. Current treatments mainly focus on managing symptoms and addressing the underlying causes. Stem cell therapy offers a promising new approach by potentially replacing damaged cells, neuroprotection, immunomodulation, and anti-inflammatory mechanisms. Research is actively exploring various stem cell types, such as embryonic (ESCs), induced pluripotent (iPSCs), mesenchymal (MSCs), and neural stem cells (NSCs), for their ability to generate healthy neurons, control inflammation, and support neuron survival. Induced pluripotent stem cells (iPSCs), created from somatic cells, offer the advantage of avoiding immune rejection and enabling personalized treatments. MSCs show potential in promoting healing through cell signaling, releasing neurotrophic factors, and strengthening the blood-brain barrier. However, challenges remain in ensuring the long-term survival and integration of transplanted cells, as well as managing the risks of tumor formation and ethical concerns. Ongoing research, including clinical trials, indicates that stem cells hold therapeutic potential for NDDs. The future of regenerative medicine aims to combine these technologies to develop personalized and truly effective treatments for these devastating diseases and to create efficient and tailored therapies for neurodegenerative disorders.

1. Introduction

Neurological disorders, alongside other significant global health issues, have increasingly captured worldwide attention because they contribute more and more to the overall burden of disease. A key feature of NDDs is the buildup of misfolded or altered proteins, which disrupts the health of nerve cells and leads to brain damage [1].

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In these NDDs, oxidative stress (OS) occurs when there's an imbalance between the production of harmful reactive oxygen molecules and the body's natural ability to neutralize or repair the damage they cause. This imbalance contributes to neuroinflammation, which is essentially an inflammatory response within the brain or spinal cord. Furthermore, synaptic cell adhesion molecules (CAMs) play a vital role in how connections between nerve cells (synapses) are formed, and many genes linked to the risk of developing NDDs are involved in this process [2].

Alzheimer's disease (AD) is characterized by a decline in thinking abilities, memory loss, and impaired reasoning [3]. Studies examining postmortem the brains of individuals after they passed away from AD show that oxidative damage, triggered by a protein called amyloid beta (Aβ or A-beta), the early stages of AD are linked with abnormal growth of mitochondria [4]. Similarly, PD, also known as paralysis agitans, is a common neurological disorder that typically develops between the ages of 55 and 65 years. In Parkinson's disease PD, the loss of nerve cells is concentrated in specific areas of the brain region called the ventrolateral and caudal regions (SNpc), while normal ageing tends to affect a different part of this region [5]. In addition, MS is an autoimmune disease of the central nervous system where the body's defence system mistakenly damages the protective myelin sheath of nerve fibers and the cells that produce it (oligodendrocytes). Moreover, several genes can slightly increase the risk of developing MS, in addition to some recognized environmental factors [6].

Likewise, Huntington disease is a devastating neurodegenerative condition (ND) that severely impacts individuals with cognitive, behavioral, motor, and metabolic problems. The development of a polyglutamine stretch within the huntingtin protein (HTT) is the major cause of HD [7]. Despite ongoing research and advancements in treatment strategies, current therapies for neurological illnesses generally conerge on managing symptoms and retard the disease's progression rather than directly underlying disease mechanisms [8]. Given these limitations, stem cell-based therapies could offer a valuable approach by working through various mechanisms, including 1) cell-replacement treatment [9]. For example, transplanting stem cells has been shown to lead to increased levels of acetylcholine, a brain chemical important for enhancing cognition and memory [10].

2. Stem Cell Therapy for Neurodegenerative Disorders:

Stem cells are remarkably unspecialized cells with the unique ability to transform into several types of cells within the body and to replenish themselves [11]. Excitingly, these stem cells can be grown and multiplied, which means cell proliferation in the lab for extended periods while still retaining their potential to develop into neurons [12]. However, it's crucial to clearly define what is needed for stem cell-based treatments to be clinically competitive and what level of risk is acceptable for patients. Several cell types are commonly involved in neurodegenerative diseases, and stem cell-based therapies may offer benefits through a variety of approaches [13] (Fig. 1).

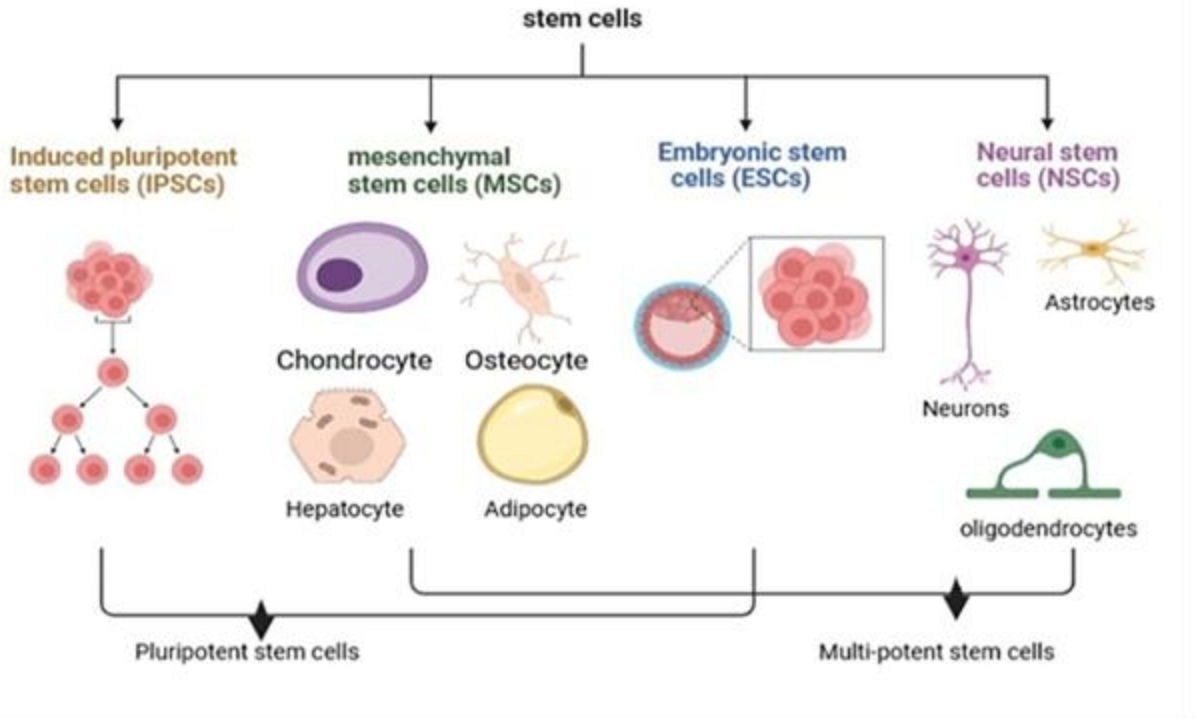

Fig. 1. Stem cells types and their differentiated cellular types.

2.1. ESCs:

The company Geron is currently exploring the use of oligodendrocyte precursor cells, which modified type of embryonic stem cells, to treat injuries to the thoracic spinal cord [14]. For therapeutic purposes, neural progenitor cells or cells resembling (NSCs) are developed from both ESCs and iPSCs [15]. These true "stem cells," originating from the inner cell mass of a blastocyst and possessing the ability to both self-renew and develop into any cell type (pluripotent), can be directed to become neural progenitor cells (NPCs) [16].

2.2. iPSCs:

These cells hold great promise for autologous (self-to-self) cell therapy because they don't typically trigger immune rejection. Due to their ESC-like pluripotency, iPSCs can be coaxed into producing a wide range of specialized cells, including neurons [17]. Interestingly, brain cells derived from iPSCs of individuals with age-related neurodegenerative disorders might not show obvious differences in appearance, development, and survival compared to brain cells from healthy individuals. Therefore, it may be necessary to employ specific tests to challenge these cells to identify and understand the characteristics of the complication [18].

2.3. MSCs:

These cells are attractive for therapy because they have low immunogenicity (less likely to cause an immune response) and can be easily obtained from various sources within the brain, they have a role in controlling the inflammation, reducing cell death (apoptosis), and promoting the growth of the brain's neurons [19]. Human MSCs (hMSCs) have been studied in the context of several neurodegenerative diseases and acute brain traumas, and they are safe for administration into the central nervous system via intravenous injection or directly into the spinal fluid (intravenous and intrathecal transplantation) [20].

2.4. NSCs:

Both neural stem cells and extracellular vasculature release (NSC-EVs) play crucial roles in biological processes related to neurodegenerative diseases [21]. Following the transplantation of human NSCs (hNSCs), there is a two-way communication of information between the transplanted cells and the host's own cells through these EVs, which encourages the activation of programs aimed at regeneration [22].

2.5. Therapeutic methods for the treatment of neurodegenerative diseases:

Cell Replacement: Research has demonstrated the exciting possibility of generating dopamine (DA) neurons from human embryonic stem cells. By optimizing the conditions, scientists have achieved a significantly improved yield, with mesencephalic progenitor cells now producing neurons containing 24% dopamine, a substantial leap forward [23]. This opens a promising avenue for PD by potentially restoring a crucial component of the damaged brain circuitry. The idea is to permanently replace the lost native dopamine neurons in a specific brain region (putamen) with these lab-grown DA neurons [24].

Immunomodulation: MSCs possess remarkable immunomodulatory abilities, meaning they can interact with and influence the immune system. This makes them potential therapeutic agents for diseases like ALS, PD, AD, and multiple sclerosis (MS). MSCs can migrate to areas of injury and interact with immune cells, although the precise mechanisms at play can differ depending on the specific disease [25]. For instance, in AD, MSCs might help regulate the behavior of astrocytes, which play a role in the development of neuroinflammation, suggesting a potential benefit in AD treatment [26,27]. Importantly, the positive effects of MSCs on neurorestoration and recovery are largely due to their ability to release various beneficial substances (paracrine effects). They secrete numerous neurotrophic (nerve-nourishing) and angiogenic (blood vessel-forming) factors that encourage the growth and specialization of neurons [28].

Neuroinflammation: In multicellular organisms, inflammation serves as an active defense mechanism against various threats. Within the brain, the activation of specialized immune cells called microglia, which have a central role in controlling neuroinflammation, acts as a critical switch between neuroprotective and neurotoxic effects [29]. In conditions like AD, there are significant interactions between different defense cells in the brain, including astrocytes, microglia, and immune cells that enter from the bloodstream. These interactions can influence the course of neuroinflammation and neurodegeneration [30]. It seems that inflammation initially starts as a localized and defensive mechanism of site-specific and time-specific, aiming to clear out irreparably damaged neurons and support the survival of cells that still have the potential to recover [31].

3. iPSCs in NDDs Research

3.1. An overview of iPSCs:

iPSCs share key traits with ESCs, meaning they can essentially renew themselves indefinitely and have the remarkable ability to transform into any of the diverse types of cells that make up our bodies [32]. What's interesting is that scientists can create iPSCs artificially by reprogramming mature somatic cells using either genetic or chemical methods. The first successful genetic approach, back in 2006, involved introducing four specific proteins – OCT4, SOX2, KLF4, and c-MYC (often called Yamanaka Factors) – into adult cells, effectively turning them back into a versatile pluripotent state [33].

Later, in 2013, a different strategy emerged. Researchers discovered that a combination of seven small chemical compounds, including VPA (Valproic Acid), CHIR99021, and Forskolin, could also coax adult cells into becoming pluripotent stem cells, offering an alternative to using those transcription factors [34]. These chemically generated cells were then named "Chemically induced pluripotent stem cells" (CiPSCs). iPSCs are proving to be incredibly helpful for understanding neurodegenerative diseases (NDDs). Scientists can generate them in specific

forms to investigate: (1) (AD) by guiding them to become neurons [35], (2) (PD) by turning them into dopamine-producing neurons, (3) (HD) by reprogramming them into the medium spiny neurons affected by the disease [36], (4) (ALS) by developing them into motor neurons [37], and (5) (MS) by differentiating them into oligodendrocytes [38].

3.2. Generation Methods of iPSC:

3.2.1. Genetically Inducing Method:

The researchers engineered mice to have a built-in marker that could be selected using drugs like neomycin or puromycin. This marker would activate when adult skin cells were successfully converted into cells resembling embryonic stem cells. The ability to resist these antibiotics was linked to the activity of important genes like Pou5f1 or Nanog, which are telltale signs of pluripotency [39]. Cells that didn't switch on these resistance genes simply didn't survive. Later, the scientists took skin cells (fibroblasts) from these specially designed mice and introduced the genes for those four key Yamanaka factors – Oct-4, Sox2, Klf-4, and c-Myc – using a technique called retroviral transfection [40].

As a result, they observed rare clusters of cells that looked just like embryonic stem cells. These were then carefully grown and expanded into stable lines of genetically induced pluripotent stem (GiPS) cells [41].

What's truly remarkable is that when these iPS cells were injected into the very early embryos (blastocysts) of normal mice, they could develop into all the forms of cells of the mouse, even cells that produce sperm and eggs (germ line cells). When these "chimeric" mice (containing cells from both the normal embryo and the iPS cells) were bred with regular mice, they could produce offspring that carried the genetic material originating from the iPS cells, or the development might proceed up to the embryonic stage [42] (Fig. 2).

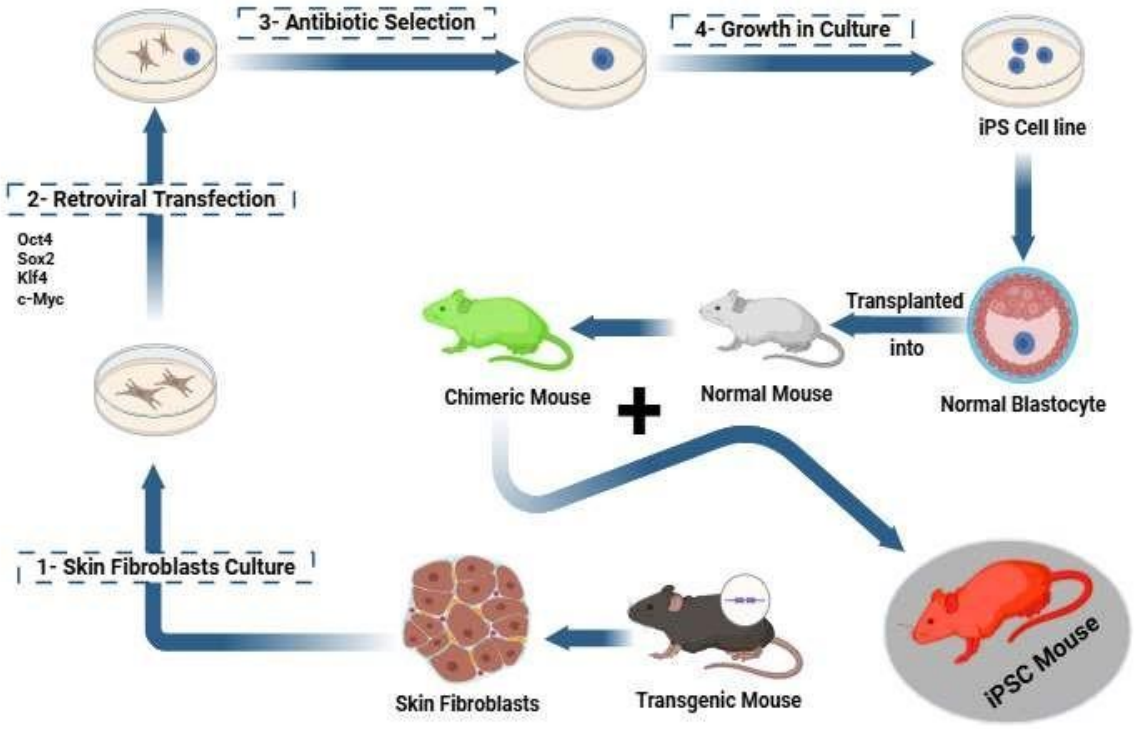

Fig. 2. Strategies for Generating Gene-Targeted Mice via Embryonic Stem Cell and Chimera Techniques.

3.2.2. Chemical Induction Approach:

To start, adipose tissue was taken from the subcutaneous fat of the patient's abdomen. These adipose samples were then processed in the lab to specifically isolate adipose-derived mesenchymal stromal cells (ADSCs) [43]. This cultivation took place in an environment carefully controlled at 37°C with a 5% CO2 atmosphere [44]. ADSCs are coaxed into a reprogrammed state, they were treated with a cocktail of chemical factors, including Valproic Acid (VPA), BIX01294, and Forskolin. The process of separating these cells was made easier by using an enzyme called Accutase [45]. Afterwards, the cells were nurtured in mTeSR1 medium, which helps in selecting the cells with the desired characteristics [43]. The grown cells then underwent thorough checks to ensure they didn't have any abnormalities, karyotypical or morphological [44]. To keep an eye on whether the cells were alive, which is known as cell viability and health, chemical indicators like trypan blue were employed [46]. To confirm that the selected and expanded cells truly possessed stem cell properties, specific markers like Stage-Specific Embryonic

Antigen-4 (SSEA-4) were used [47]. If everything looked satisfactory based on these evaluations, the lab-grown, chemically induced pluripotent stem cells (CiPSCs) were then "autologously transplanted" meaning they were given back to the same patient from whom the initial fat tissue was obtained [43]. In general, CiPSCs are known to be more genetically stable compared to GiPSCs [48] (Fig. 3).

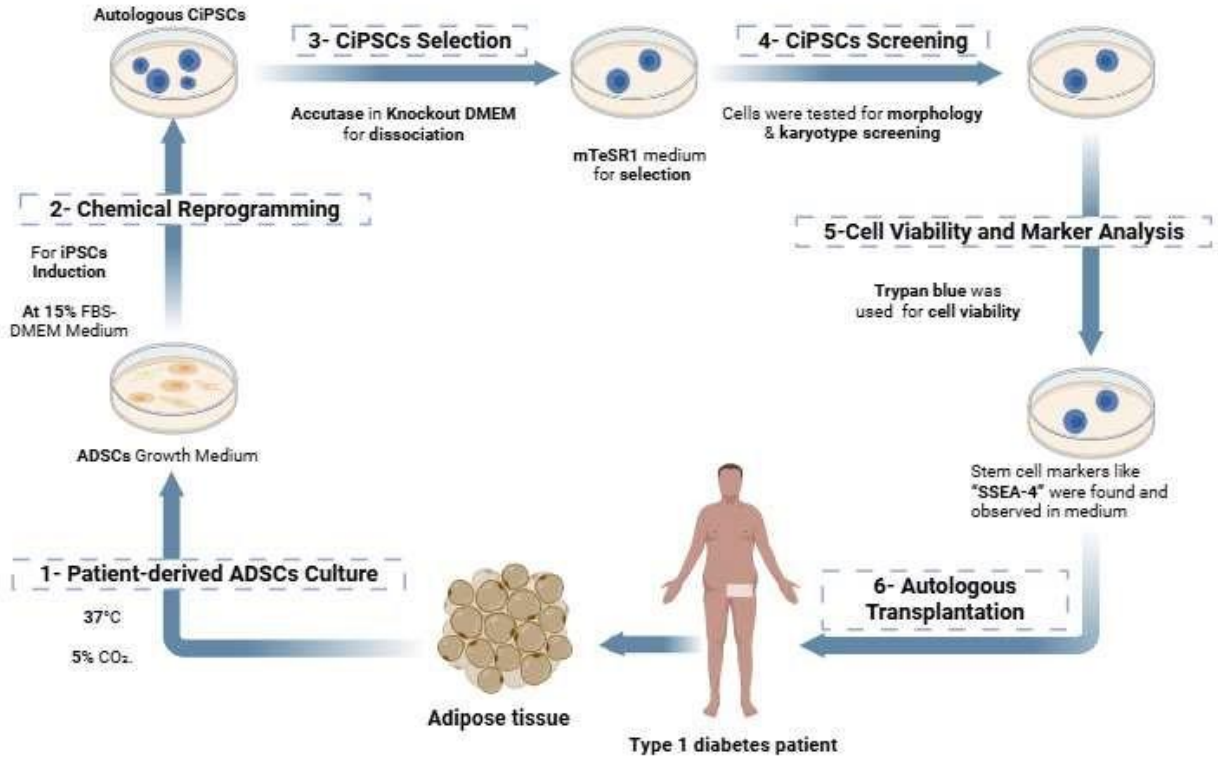

Fig. 3. Restoring Insulin Function in Type 1 Diabetes Through Autologous iPSC-Derived Islet Transplantation.

4. Getting to Know Mesenchymal Stem Cells:

4.1. A Closer Look at MSCs:

MSCs are one of the adult stem cells that aren't hematopoietic and have the remarkable ability to develop into various cell types, so it is called multipotent, originating from the mesoderm layer during development [26]. These versatile cells can be found in several places in the body, such as bone marrow, the umbilical cord, the placenta, adipose tissue, and even the pulp of our teeth. When scientists look at their surface, they find specific markers like CD90+, CD105+, and CD73 +, but they don't see others like CD14, CD11b, CD34, CD19, CD79a, and HLA-DR [49]. These MSCs are responsible for creating the diverse connective tissues that hold our bodies together and can even give rise to other cell types, like myocytes and functioning neurons [50]. Because of their impressive ability to renew themselves and maintain their potential to become different cell types [51], MSCs hold significant promise for medical treatments, especially as a potential source for transplanting cells in NDDs. Their low profile in terms of triggering an immune response (immunogenicity) and their ability to control the immune system (immunomodulatory) make them suitable for both transplanting a patient's cells (autologous) and using cells from a donor (allogeneic). On top of that, they can help anti-apoptotic, paracrine (communicate with nearby cells through secreted factors), and differentiate into multiple cell lineages [52].

4.2. MSCs mechanism:

The precise ways in which MSCs offer therapeutic benefits in neurological diseases are still being actively explored, but it seems that several processes are likely involved [53].

Firstly, MSCs often exert their positive effects by paracrine signals to other cells through secreted factors. They can produce neurotrophic growth factors, which are like neurotrophic growth factors, including glial cell-derived neurotrophic factor (GDNF), vascular endothelial growth factor, insulin-like growth factor 1, and brain-derived neurotrophic factor (BDNF). These factors not only help in stopping neuronal degeneration and death but also encourage the growth of new nerve cells (neurogenesis) by endogenous neural stem cells and neural progenitor cells [26,53].

MSCs also release a variety of regulatory molecules, such as growth factors, cytokines, chemokines, and various enzymes, which have a strong influence on immune responses, angiogenesis, and the process of

programmed cell death (apoptosis) [54]. They have a unique knack for migrating to areas of inflammation and acting as inflammatory cells. MSCs display CXCR4, which is a receptor that recognizes SDF1α (CXCL12) – a chemical signal that attracts them to sites of inflammation [55,56]. They play a role in changing the behavior of microglia, shifting them from a pro-inflammatory state (M1) to an anti-inflammatory state (M2). This results in a decrease in the levels of harmful cytokines associated with M1 microglia and an increase in the levels of protective cytokines associated with M2 microglia [26,57].

Secondly, MSCs can control the immune system through five main ways of suppressing immune responses: they reduce the activity of helper and cytotoxic T cells, upregulate the number of regulatory T cells, and suppress the activity of B cells, dendritic cells, and natural killer cells [55].

Finally, (MSCs) might help stabilize the blood-brain barrier (BBB), which is a highly selective membrane made of specialized endothelial cells tightly connected, by interacting with other cells like pericytes, astrocytes, and neurons. MSCs also create tiny vesicles called exosomes (MSC-exos) that contain biologically active compounds. These exosomes can cross the blood-brain barrier, enter brain cells by fusing with their membranes, and then influence their normal functions [55].

4.3. Clinical trials:

Lately, there's been a lot of research exploring if using MSCs (that's a type of stem cell) can help with different brain and nerve problems. However, some early findings suggest that MSCs could be a safe and effective way to treat these neurological conditions [58].

4.3.1. Alzheimer’s disease:

It looks like MSC-based stem cell therapy has a lot of promises for treating AD [59]. Mane previous investigations performed early-stage research using MSCs to manage AD. They've mostly used rodents in these studies [58]. When they put MSCs BY intracerebral transplantation directly into the brains of these animal models of AD, it helped reduce the buildup of harmful proteins (Aβ) by boosting the body's natural cleaning process and slowing DOWN the endogenous mechanism of Aβ clearance and lowering the activity of secretases that cleave the amyloid precursor protein (APP) [60]. Since 2011, studies using bone marrow MSCs in these animal models have shown encouraging results, enough so that researchers felt it was okay to start testing this in people with AD. Right now, there are several ongoing clinical trials using MSCs in non-invasive ways for AD [59]. Even though many of these trials have happened or are happening to check if MSC treatment is safe and works for AD, we haven't seen much of the data published yet [61]. The very first clinical trial looked at using HUC-MSCs to see what effect they had on Alzheimer's.

In the first phase of human trials (in 2015), doctors used Human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSC) to treat 9 people who had mild to moderate AD. They carefully stereotactically injected these cells into specific areas of the brain (the hippocampus and anterior hippocampal area). After following these patients for 2 years, they found that giving the stem cells was safe and doable, and there weren't any significant side effects [59].

4.3.2. Parkinson’s disease:

Early results from past human studies using MSCs to treat Parkinson's disease have been promising. Back in 2010, a study in India by Venkataramana and colleagues [62] gave autologous bone marrow MSCs to seven people with Parkinson's. The dose was 106 cells per kilogram of body weight, and they were carefully injected into one side of the brain. Out of these seven patients, three showed better mobility, according to standard Parkinson's rating scales, over a follow-up period of 10 to 36 months. Things like facial expressions, movement, and freezing episodes also seemed to get better for them. Plus, two patients were able to take much lower doses of their regular Parkinson's medication (L-DOPA). A previous study showed that the procedure was safe, as none of the patients got worse during the study. Also, brain scans didn't show any unusual changes [49,63]. This research also indicates that delivering the patient's MSCs through the nose or a combination of nose and vein is safe and might protect and restore brain function [64].

More recently, in early 2022, Shigematsu and team [65] treated 3 Parkinson's patients with either five or six repeated infusions of their fat-derived MSCs, given about a month apart. During the six months they watched the patients after the last treatment, no bad side effects were seen, and all three patients showed improvements in their movements [65].

The future of using stem cells to treat Parkinson's looks hopeful, with ongoing research and studies trying to figure out if this new approach can help cure this serious brain disease [66].

4.3.3. Amyotrophic lateral sclerosis:

Because of positive results in animal models of ALS, several clinical trials have looked at whether injecting MSCs is safe and the effects of therapy for people with ALS [67]. These preclinical studies in animals showed that giving MSCs through spinal fluid intrathecal, intraspinal, intravenous, or combined intraspinal and intravenous, is safe. It seemed to slow down motor impairment, reduce inflammation, and encourage the release of specific helpful substances like cytokines that promote cell survival, allowing the symptomatic transgenic animals to live longer [68]. A more recent and larger study in 2020 by Barczewska and colleagues [69] used intrathecal cord MSCs in a controlled study. All the patients received 3 injections of MSCs derived from Wharton's jelly (a part of the umbilical cord) into their spinal fluid every two months, with a dose of 30×10^6 cells each time. The researchers used a standard ALS rating scale (ALSFRS-R scale) to check the patients. They reported that the average survival time doubled for all patients, and in some, the disease seemed to progression more slowly. The researchers are optimistic about these results and suggest it would be

interesting to see if combining MSC therapy with regular ALS medications could be even more effective in the future [69].

5. Neural Stem Cells (NSCs)

5.1. What are NSCs and How Do They Form?

These undifferentiated cells have the amazing ability to transform into any of the main cell types in our nervous system: neurons, oligodendrocytes, and astroglia. Importantly, these NSCs can also make more copies of themselves, a process called self-renewal [70]. Exciting new developments in creating adaptable and expandable multipotent induced neural stem cells are on the horizon. These hold incredible promise for future medical treatments and are set to revolutionize how we study neural stem cells [70].

Currently, NSCs can be obtained in three key ways: Directly isolating them from specific regions of the central nervous system (CNS), like the subventricular zone or subgranular zone. Guiding (PSCs), including (ESCs) and (iPSCs), to develop into NSCs. Directly reprogramming (somatic cells) to become NSCs [71].

A significant advancement is that these directly reprogrammed NSCs don't go through a multifunctional phase, making them a safer and quicker resource. This is a major step forward for cell transplantation therapies, offering a strong potential source of NSCs for treating diseases of the nervous system [72].

Back in 2007, Takahashi and Yamanaka [33] discovered a method to dedifferentiate mouse body somatic cells back into cells resembling ESCs. Soon after, it was shown that we could do the same with human body cells, creating iPSCs [73]. There are now many established methods for generating NSCs from ESCs and iPSCs in vitro. These methods generally involve creating specific environments and adding various molecules that guide the stem cells' development. As we learn more about neurogenesis, these methods have become more detailed and often combine different approaches. We can guide PSCs to become neural cells in flat, two-dimensional cultures (monolayer) or in three-dimensional structures called embryoid bodies [73].

5.2. Direct Programming of Somatic Stem Cells

Our research, along with others, has recently shown that we can convert mouse and human skin cells (fibroblasts) into neural stem or precursor cells using somatic cell reprogramming technology [74].

Furthermore, we can directly reprogram other body cells into neurons by overexpressing certain transcription factors (TFs), microRNAs (miRNAs), or using tiny molecules [73]. So far, there were established two main approaches for directly transdifferentiating somatic cells into neural cells: The first approach focuses on directly converting somatic cells into mature induced neurons (iNs). However, this method often results in a limited number of functional cells. The second approach aims to create neural precursors, which is induced neural progenitor cells (iNPCs), which can still proliferative. This is more promising for applications that require a large number of cells in vitro [75].

6. Challenges and Limitations of Stem Cell Models in NDD

6.1. overview on challenges:

Neurodegenerative diseases (NDDs affect over 50 million people globally and pose a major health crisis [76]. Human pluripotent stem cells (hPSCs), which include both induced pluripotent stem cells and embryonic stem cells, offer incredible potential for understanding diseases that unfold during development, like these neurodegenerative disorders [76]. However, these promising models still face several significant challenges that they need to overcome. A key difficulty, especially for rare NDDs, is that we often don't fully grasp how these diseases naturally progress or the intricate mechanisms driving them [77].

6.2. Obstacles with Induced Pluripotent Stem Cells (iPSCs):

Despite the exciting possibilities iPSCs bring, we need to tackle several hurdles to truly harness them for therapies and effectively translate research findings [77]. For instance, if we transplant iPSC-derived cells, they'll encounter the same inflammatory environment that originally destroyed the patient's specialized cells, making effective cell replacement a tough therapeutic nut to crack [78]. Cell therapy itself is a complex undertaking, presenting considerable logistical, safety, and quality control issues, especially when it comes to iPSC-based treatments [79]. Moreover, neurons derived from iPSCs tend to be in an early, embryonic-like stage. This means they might lack or have altered the epigenetic marks that reflect the ageing process or the progression of a disease. On a brighter note, our research and that of others shows that we can transform the phenotypic of a single somatic cell type directly into another – a process called transdifferentiation. This allows us to create neurons or glial cells directly from somatic cells, bypassing the need for an intermediary stem cell stage [80].

6.3. Challenges Facing Mesenchymal Stem Cells (MSCs):

For MSCs to potentially restore brain function in NDDs, they need to undergo Neurogenic differentiation, replace damaged cells, and secrete neurotrophic factors. Unluckily, transplanted MSCs often die off within just a few days due to natural ageing, the harsh disease environment, and/or lack of nutrients after being directly placed at the injury site or injected into the bloodstream. Consequently, the ongoing difficulty in obtaining fully mature and well-differentiated neurons limits how helpful it might be to turn MSCs into neurons for treating NDDs [81]. Getting MSCs to efficiently travel to skeletal muscle or other target tissues for optimal migration, integration, and survival has also been a major hurdle for using them in ALS [81]. Interestingly, Suzuki and colleagues have largely addressed this by finding ways to boost the survival of these transplanted cells. The most exciting part of Suzuki's work showed that neurotrophic factors, like GDNF, can effectively prevent the death of motor neurons and improve

survival in a rapidly progressing animal model of ALS, sparking significant interest in these factors as a potential treatment for the disease [82].

6.4. Limitations of Neural Stem Cells (NSCs):

While NSCs hold promise for neurological problems, their widespread use is still quite limited, and we need more robust evidence to support their effectiveness [72]. One key limitation of transplanted NSCs is their short survival in situ within the body (both in terms of the number of cells that survive and how long they last). This might explain why we haven't seen strong therapeutic effects and, frankly, hinders the translation of promising preclinical findings into real-world clinical trials. One potential way to tackle this issue is to make the environment more supportive using tissue engineering techniques [83].

7. Future Directions in Stem Cell Research for NDDs

The conventional strategy of therapy based on cells ran into many obstacles connected to the vast volume of data processing [84]. Defined as “a system’s ability to accurately interpret external data, to learn from such data, and to use those learnings to reach certain objectives and tasks through flexible adaptation [85] (Fig. 4).

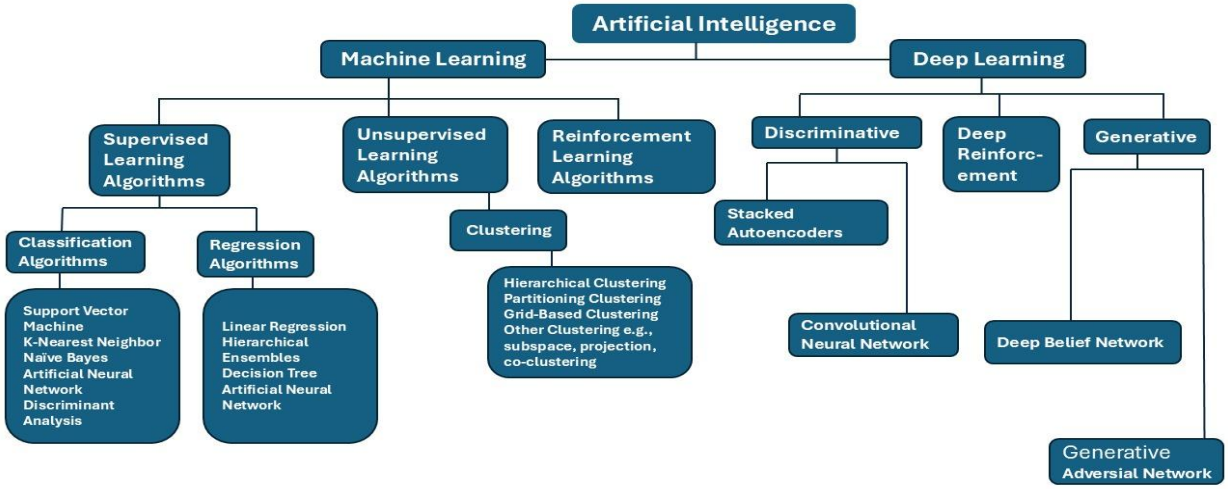

Fig. 4. Key Algorithms in Machine Learning and Deep Learning

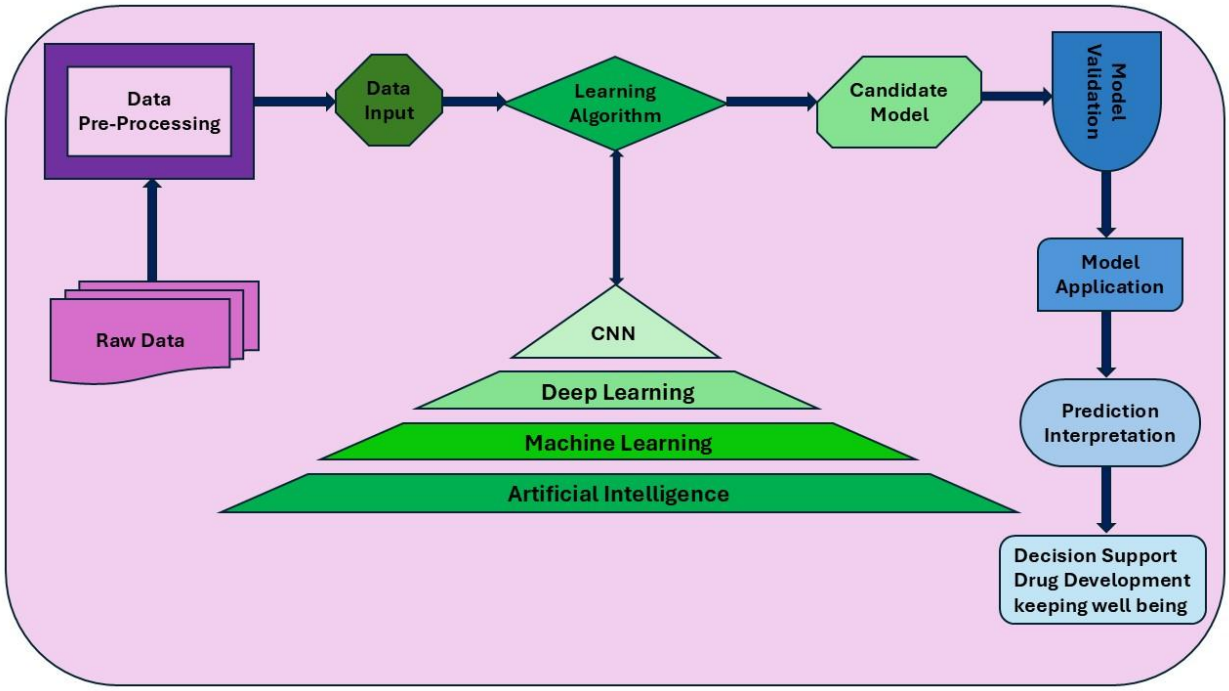

Fig. 5. Framework for Developing AI-Based Predictive Models

AI employs automated algorithms to clarify problems and aid in jobs like data mining and analyzing vast volumes of datasets, identifying patterns and forecasting outcomes that would not be achievable by human intelligence [85] (Fig. 5). Unconcerned with the definite technique, using computer algorithms is the general purpose of these technologies in medicine, which aid in revealing meaningful information from data and support clinical decision-making [86]. These models and methodologies can be employed in the research of stem cells, which could help in evaluating the safety and efficacy of stem cells more easily. Machine learning has major impacts on stem cells research and therapy, supporting the making a personalized clinical decision [87]. Machine learning-based predictive analytical methods are desirable to speed the identification of new stem cell markers for safety assessment and to forecast stem cell therapy efficacy to minimize the potential bad effects and to maximize the success of treatment [88].

The Allen Cell Explorer, published by the Allen Institute for Cell Science in Seattle, Washington, has a wide collection of more than 6,000 photographs of induced pluripotent stem cells (iPS), essential components of which glow thanks to fluorescent markers that identify certain genes [89]. Computer scientists studied many of the photos using deep learning tools and found correlations between the positions of cellular components. They also utilized that information to forecast where the structures would be when the computer was given just several indications, such as the position of the nucleus. The algorithm 'learned' by comparing its predictions to actual cells [89]. The typical process of image processing involves several key steps: acquiring the image, pre-processing it, segmenting the important parts, extracting relevant features, and finally, classifying the data. When it comes to microscopic images, this starts by capturing visuals of cells or tissue samples using a digital microscope camera or specialized imaging software [87].

ML either uses supervised learning, where the model is trained to use labelled data, which means that the input has been tagged with corresponding preferred output labels or uses unsupervised learning, where the model is trained to use unlabeled data but looks for recurring patterns from the input data [90]. Scientists believe artificial intelligence in many mediums, such as data mining (DM), ML- SVM, and DL - CNN, could help offer accurate measurements in tackling this complexity, which could be the key to perfecting the recipe for stem cell therapy [91]. To automatically assess and determine iPSC colony formation, a machine learning-based classification, segmentation, and statistical modelling system was created to guide colony selection [92].

Conclusion

Neurodegenerative diseases represent a growing global health crisis, marked by the progressive decline of neuronal structure and function, ultimately impairing cognition, mobility, and independence. While traditional therapeutic options have offered only symptomatic relief, recent advances in biomedical research are reshaping our understanding of disease mechanisms and presenting promising avenues for intervention. In particular, stem cell-based therapies, including the use of mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), emerging as innovative strategies capable of targeting the root causes of neuronal degeneration rather than merely alleviating symptoms.

These regenerative approaches demonstrate potential in restoring neural circuitry, modulating immune responses, and delivering neuroprotective factors directly to damaged brain regions. Furthermore, developments in artificial intelligence and bioengineering are enhancing the precision of stem cell manipulation and monitoring, paving the way for more personalized and effective treatments. However, despite their potential, these therapies are still met with substantial scientific, ethical, and logistical challenges. Issues such as cell source standardization, long-term safety, immune rejection, and regulatory approval remain to be addressed comprehensively.

Moreover, a multidisciplinary approach that integrates genomics, proteomics, and computational modelling will be essential to unravel the complex molecular pathways underlying neurodegeneration and to tailor interventions accordingly. Future research must focus not only on refining these therapeutic platforms but also on conducting robust clinical trials to validate their efficacy and safety in diverse patient populations.

In summary, while we are still in the early stages of translating these breakthroughs into routine clinical use, the progress made thus far inspires cautious optimism. Continued investment in interdisciplinary research, ethical oversight, and clinical innovation holds the key to transforming the management of neurodegenerative diseases and improving the quality of life for millions affected worldwide.

Declarations section

Ethical Approval and Consent to participate

Not applicable.

Human Ethics

Not applicable.

Consent for Publication

Not applicable.

Availability of supporting data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors have no competing interests to declare that are relevant to the content of this article.

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Author's Contributions

Conceptualization, A.A.K., K.M.A., M.M.. and M.H.A.G.; Data Collection, A.M.A., A.E., S.A.E., and M.M.E.; Writing–Original Draft Preparation, N.W.E., T.H., K.M.A., A.A.K., and M.H.A.G; Writing–Review & Editing, A. N., A.M.A, A.E., S.A.E., M.A.M., and M.H.A.G. prepared all figures. All authors reviewed the manuscript.

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