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Stem cell and extracellular vesicle therapy in Huntington's disease

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Huntington's disease (HD) manifests as a debilitating neurodegenerative disorder characterized by a genetic mutation in the huntingtin (HTT) gene, leading to motor deficits, cognitive impairments, and psychiatric symptoms. HD's major influence on patients' daily living warrants the development of new, safe, and effective treatment strategies beyond symptomatic management and disease modification. We systematically explore the preclinical studies and clinical trials focusing on the application of cell-based therapy and extracellular vesicle therapy in HD. The review aims to map the current landscape of cell and extracellular vesicles (EVs) therapy research, pinpointing the successes in ameliorating disease phenotypes and mechanisms, assessing safety and efficacy, and identifying the challenges and limitations encountered. Moreover, we highlight significant gaps in knowledge and propose areas for future research, emphasizing the need for more targeted studies to fully understand the mechanisms of action in the hope of more effective treatments for HD.

Keywords: Huntington's disease, Cell therapy, Stem cell therapy, Regenerative medicine, Extracellular vesicles, Exosome

Highlights

This paper presents recent advances in cell- and cell-free regenerative medicine approaches for Huntington's disease (HD), which is a debilitating neurodegenerative disorder with life-threatening motor, cognitive, and psychiatric symptoms. Here, we discuss the therapeutic potential of stem cells and their secreted extracellular vesicles. We review the scientific evidence that both stem cells and extracellular vesicles capture a novel approach relevant to conditioning medicine, in that their treatment intervention in HD may not only retard disease progression but also modify the disease pathology by specifically combating the genetic mutation in the huntingtin gene. Hence, we advance the concept that stem cell and extracellular vesicle therapy is a new, safe, and effective conditioning medicine strategy for symptomatic management and disease-modification of HD.

Introduction

Huntington's disease (HD) is a progressive neurodegenerative disorder manifesting as a triad of motor, cognitive, and psychiatric symptoms. It impacts populations worldwide, with a prevalence rate of 4 cases per 100,000 individuals. Typically, HD emerges in adulthood, with most diagnoses occurring between the ages of 35 and 44 (Medina et al., 2022). This condition follows an autosomal dominant inheritance pattern stemming from a mutation in exon 1 of the huntingtin (HTT) gene (Bates et al., 2015). The mutation is characterized by an expanded CAG trinucleotide repeat in the HTT gene on chromosome 4, leading to the accumulation of an abnormal form of the huntingtin protein, known as mutant huntingtin (mHTT). The number of CAG repeats is inversely proportional to the age at onset and directly correlates with the disease's severity (Walker, 2007). Accumulation of mHTT in neurons precipitates cellular dysfunction and apoptosis, predominantly affecting the striatum and cortex. The disease's pathogenesis is marked by disruptions in protein folding and degradation, mitochondrial dysfunction, excitotoxicity, and altered gene expression (Li and Li, 2004). The symptomatic spectrum of HD includes involuntary "chorea" motor actions, learning and memory impairments, and psychiatric alterations (Ross and Tabrizi, 2011). Despite extensive research, treatments remain symptomatic, with no current therapy able to alter the disease's progression, highlighting the need for novel therapeutic

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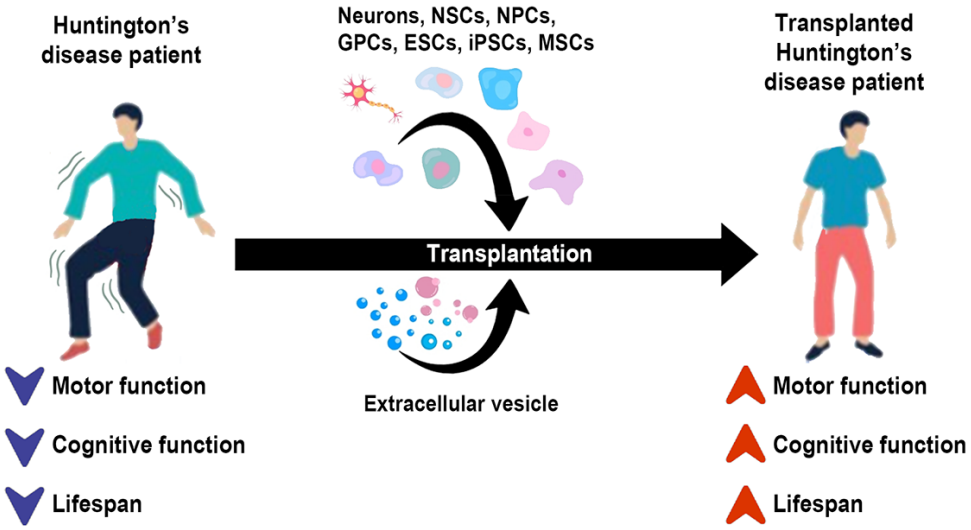

Figure 1. HD is a neurodegenerative disorder characterized by motor and cognitive dysfunctions and a shortened lifespan. Novel therapies, including cell and extracellular vesicle therapy, can improve HD phenotypes and clinical symptoms, opening a new conditioning medicine opportunity for HD treatment.

strategies (Frank, 2014).

This review comprehensively assesses the efficacy and safety of cell therapy and extracellular vesicle (EV) therapy in HD across preclinical studies and clinical trials (Figure 1). We seek to pinpoint research gaps that warrant further investigation, guiding future scientific research in this field.

Pathogenesis of HD

Mutant Huntingtin Protein

The pathogenesis of HD is characterized by protein misfolding due to a polyglutamine expansion, leading to oligomer formation (DiFiglia et al., 1997; Cooper et al., 1998; Hoffner et al., 2005; Tabrizi et al., 2020). These oligomers serve as precursors for protofibrils and intracellular inclusions. Contrary to previous assumptions that mHTT inclusions were the main contributors to pathology, recent studies suggest that these inclusions may not be directly responsible for cell death (Ross, 1997; Saudou et al., 1998; Arrasate et al., 2004; Hoffner et al., 2005; Slow et al., 2005), and might even be protective (Arrasate et al., 2004; Nucifora et al., 2012). The current hypothesis is that mHTT toxicity could be largely due to N-terminal fragments containing the toxic exon 1 of the HTT gene produced by proteolytic cleavage of mHTT or CAG length-dependent aberrant splicing, with the toxicity of oligomers potentially reduced by their assembly into larger inclusions (Nagai et al., 2007; Takahashi et al., 2008; Lajoie and Snapp, 2010; Miller et al., 2011; Nucifora et al., 2012; Pieri et al., 2012; Sahl et al., 2012; Leitman et al., 2013). In animal models of HD, polyglutamine-containing N-terminal fragments of mHTT accumulate in the brain more rapidly than the full-length mHTT (Wang et al., 2008; Castiglioni et al., 2012; The Hd iPsc Consortium, 2012).

Furthermore, evidence suggests that mHTT can be transferred between cells through tunneling nanotubes and extracellular vesicles, indicating a potential mechanism for its propagation within the brain. In vitro models of HD have demonstrated that cells can absorb polyglutamine peptides from both the culture media and co-cultured cells (Yang et al., 2002; Herrera et al., 2011; Costanzo et al., 2013; Monsellier et al., 2016). A study in Drosophila showed that mHTT is released from synaptic terminals and subsequently endocytosed by adjacent neurons (Babcock and Ganetzky, 2015). However, evidence of intercellular spreading in humans is currently limited to post-mortem analyses, with inclusion bodies found in the extracellular matrix of striatal transplanted grafts, suggesting the release of mHTT by neurons (Cicchetti et al., 2014).

Ubiquitin-Proteasome System

Perturbation of the ubiquitin-proteasome system, which affects cellular protein degradation (Lin et al., 2013; Cortes and La Spada, 2014), is also found in HD. Evidence showed that mHTT interferes with this system by depleting important proteins such as vasolin-containing protein (also known as p97), ubiquitin fusion degradation protein, nuclear protein localization protein, ubiquitin-specific protease 14, and activating transcription 5, leading to failure in the endoplasmic reticulum stress response (D'Egidio et al., 2023). Moreover, the accumulation of toxic proteins due to the altered ubiquitin-proteasome system strengthens the toxicity inside affected cells, eventually stressing organelles such as mitochondria, thereby elevating oxidative stress. In this view, the induction of autophagy, a process facilitating the clearance of damaged or unnecessary cellular components, has demonstrated promise in reducing HD phenotypes and enhancing the clearance of mHTT in animal models (Ravikumar et al., 2004).

Mitochondria Function

Mitochondrial function is compromised in HD. Analysis of post-mortem brain specimens reveals a reduction in ATP production in HD human (Browne and Beal, 2004) and mouse model brains (Mochel et al., 2012) compared to normal brains. Alterations in mitochondrial structure, quantity, and enzymatic activity have been documented (Goebel et al., 1978; Gu et al., 1996; Browne et al., 1997; Kim et al., 2010; Johri et al., 2013). Brain imaging studies frequently demonstrate downregulated glucose metabolism and upregulated lactate concentration in HD patients, suggesting diminished mitochondrial metabolic function (Jenkins et al., 1993; Antonini et al., 1996; Feigin et al., 2001; Reynolds et al., 2005). Research in HD animal models has identified disruptions in mitochondrial mobility, both anterograde and retrograde, which blocks mitochondrial distribution (Trushina et al., 2004; Orr et al., 2008; Shirendeb et al., 2011; Shirendeb et al., 2012). Moreover, the expression of

Table 1. Neuron and Other Non-stem Cell

Study Design	Cell sources	HD models	Route of administration	Outcomes	Therapeutic Effects	Articles
In vivo	hMSNs	QA-lesioned rat	Unilateral intrastriatal implantation	MSN-like neurons ↑Behavioral function	Neuron replacement	(Delli Carri et al., 2013)
	Human GABAergic neuron	QA-lesioned rat	Unilateral intrastriatal implantation	GABAergic neurons ↑Motor and cognitive function	Neuron replacement	(McLeod et al., 2013)
		QA-lesioned mouse	Intrastriatal implantation	GABAergic neurons ↑Motor function	Neuron replacement	(Ma et al., 2012)
	Mouse GABAergic neurons	QA-lesioned mouse	Bilateral intrastriatal implantation	MSN-like neurons ↑Ki67 expression	Neuron replacement	(Shin et al., 2012)
	Encapsulated neonatal pig porcine choroid plexus cells	QA-lesioned rat	Unilateral intrastriatal implantation (prior to QA injection)	↑Motor function ↓Weight loss ↓Lesion volume Culture duration does not affect efficacy	Growth factors and nutrient production	(Emerich and Thanos, 2006)
		QA-lesioned cynomolgus monkey	Intrastriatal implantation (prior to QA injection)	↓Striatal neuron loss	Growth factors and nutrient production	(Emerich et al., 2006)
	hCNTF-secreting BHK fibroblast	QA-lesioned rat	Unilateral intraventricular implantation (prior to QA injection)	↑Behavioral function ↓Striatal neuron loss	hCNTF → neurotrophic effect, modified NMDA excitation, antioxidants	(Dwaine et al., 1996)

peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a key regulator of mitochondrial biogenesis, is significantly reduced in HD models (Cui et al., 2006; Johri et al., 2013). However, impairments of mitochondrial fission and fusion have also been observed (Jurcau and Jurcau, 2023). Moreover, evidence suggests that mHTT disrupts the mitochondrial outer membrane, inducing calcium release that leads to cell death, and compromises the inner membrane, obstructing protein transport (Panov et al., 2002; Choo et al., 2004; Yano et al., 2014; Yablonska et al., 2019).

Somatic Instability

In addition to the toxicity of the mHTT protein, the RNA associated with HD is also implicated in cellular toxicity. Studies in animal models of HD demonstrate neurodegeneration even in the absence of CAG repeat translation (Martí, 2016). Various animal models featuring knock-in CAG repeats have highlighted the toxicity of RNA foci (Li et al., 2008; Hsu et al., 2011; Wang et al., 2011). Research involving individuals with HD has shown a correlation between CAG repeats and disease onset and severity, supporting the idea that CAG repeat instability contributes to disease pathogenesis (Swami et al., 2009; Lee et al., 2019). A predictive model indicates that motor symptoms manifest when the CAG repeat count surpasses 115 units and a significant number of cells become vulnerable (Squitieri et al., 2006; Kaplan et al., 2007). The extent of somatic instability varies across tissues, with the pattern of tissue sensitivity aligning with HD neuropathology (Telenius et al., 1993; Aronin et al., 1995; La Spada, 1997; Shelbourne et al., 2007). Repeat-associated non-ATG (RAN) translation has been observed in the brains of HD patients in a CAG repeat-dependent fashion (Bañez-Coronel et al., 2015; Gao et al., 2017). However, the impact of monopeptide aggregates resulting from this unconventional translation process remains to be fully elucidated.

Stem Therapy in HD

Neurons and Other Non-Stem Cells

Neurons primarily harvested from embryonic stem cells (ESCs) and neural precursor cells (NPCs) are anticipated to replace degenerated striatal neurons in HD transplantation. Delli Carri et al. (2013) successfully induced differentiation of human ESCs into medium spiny neurons (MSNs), known to be the most susceptible type of neurons in HD, and upon transplantation into the striatum of quinolinic acid (QA)-lesioned rats, the grafted neurons persisted and committed along the DARPP-32 positive neuronal lineage, integrating with the host brain, altogether dampening the apomorphine-mediated rotational behavior. Furthermore, McLeod et al. (2013) demonstrated that γ-aminobutyric acid (GABA)-ergic cells differentiated from human NPCs (hNPCs) could significantly improve motor and memory deficits following transplantation. Additionally, the transplantation of the choroid plexus has shown to confer benefits: pig porcine choroid plexus encapsulated in alginate microcapsules and grafted into the striatum of QA-lesioned rats, reduced weight loss and motor impairment, as well as neural loss and striatal atrophy when transplanted prior to QA injection (Emerich and Thanos, 2006; Emerich et al., 2006).

Neural Stem Cells (NSCs)

NSCs have garnered significant interest for transplantation due to their dual role in neuron replacement and neurotrophic factor secretion (Tuazon et al., 2019). The pioneering study by Deckel et al. (1983) demonstrated the potential of this approach. Indeed, rat fetal striatal tissues transplanted into the bilateral striatum of kainic acid (KA1)-injected rats showed notably fewer behavioral abnormalities and well-differentiated grafts with reduced striatal atrophy. Subsequent research predominantly focused on fetal striatal tissue, especially the subventricular zone (SVZ), whole ganglionic eminence (WGE), medial ganglionic eminence (MGE), and lateral ganglionic eminence (LGE), consistently demonstrating the amelioration of HD symptoms and robust neural differentiation. NSCs derived from ESCs and induced pluripotent stem cells (iPSCs) have shown a similar impact across various mouse models of HD (Al-Gharaibeh et al., 2017; Holley et al., 2023). However, some studies have reported no significant effects from NSC transplantation, highlighting the need for further investigation into optimal regimens (Hurelbrink et al., 2003; Jiang et al., 2011; El-Akabawy et al., 2012). Various experiments have aimed to enhance the therapeutic effects of NSCs, including multitract implantation, optimization of transplantation timing,

Table 2. Neural Stem Cells (NSCs)

Study Design	Cell sources	HD models	Route of administration	Outcomes	Therapeutic effects	Articles
In vivo	rNSCs, rBM-MSCs	QA-lesioned rat	Intrastriatal implantation	Stem cell factor (SCF) *in situ* induces graft migration and proliferation	SCF facilitates graft transplantation	(Bantubungi et al., 2008)
	hNSCs	QA-lesioned rat	Bilateral intrastriatal implantation	MSNs and GABAergic neurons with BDNF expression ↑Behavior function ↑Endogenous neurogenesis/angiogenesis ↓Glial scar, ↓Inflammation (↑M2 microglia)	Neural replacement, BDNF secretion, Endogenous neurogenesis, anti-inflammation	(Yoon et al., 2020b)
		QA-lesioned rat	Single-dose intravenous administration	IV NSCs migrate to lesions ↑Behavioral function ↓Striatal atrophy	Neural replacement, NGF secretion	(Lee et al., 2005)
		QA-lesioned rat	Unilateral intrastriatal implantation	Immature neurons ↑Motor function ↑Striatal volume	Neurotrophic factor more than neural replacement	(McBride et al., 2004)
		R6/2 and Q140-knock-in mouse	Bilateral intrastriatal implantation	Neurons and astrocytes ↑Motor, cognitive, behavioral function ↑BDNF expression ↓mHTT accumulation	Neuronal replacement, BDNF secretion, mHTT clearance/formation inhibition	(Reidling et al., 2018)
		zQ175 mouse	Bilateral intrastriatal	MSNs and interneurons ↑Behavioral function ↑BDNF levels ↓mHTT accumulation	Neural replacement, BDNF secretion, mHTT aggregation inhibition	(Holley et al., 2023)
		R6/2 mouse	Bilateral intrastriatal	↔Clinical symptoms Poor neuronal differentiation/survival		(El-Akabawy et al., 2012)
		3-NP induced rat	Unilateral intrastriatal implantation (prior to 3-NP)	↑Motor function ↓Striatal neuron damage (Transplantation after 3-NP is ineffective)	BDNF secretion	(Ryu et al., 2004)
	rNSCs	3-NP induced rat	Bilateral intrastriatal implantation	↑Learning ability ↑Motor coordination ↓Striatal neuronal loss	Neuronal replacement	(Roberts et al., 2006)
	mNSCs	QA-lesioned mouse, R6/2 mouse	Unilateral intrastriatal implantation; at 2, 7, and 14 days after QA lesioning; either neurospheres or suspension	↑Graft survival rate in early transplantation of neurospheres Delayed gliosis ↔BDNF level		(Johann et al., 2007)
		YAC128 mouse	Bilateral intrastriatal implantation	MSN differentiation ↑Motor function ↑BDNF and BDNF receptors (TrkB) levels	Neuronal replacement, BDNF neurotrophic effect	(Al-Gharaibeh et al., 2017)
	Human fetal WGE, LGE, MGE tissues	QA-lesioned rat	Intrastriatal implantation	Graft from LGE and MGE of young fetus (E14) yield more functional recovery than older fetus	Neuronal replacement	(Watts et al., 1999)
	Rat fetal WGE tissue	QA-lesioned rat	Unilateral intrastriatal implantation	Environmental enrichment → ↑motor function, ↑BDNF, ↑neural spines and cell volume	Neuronal replacement and BNDF neurotrophic effect	(Döbrössy and Dunnett, 2006)
		QA-lesioned rat	Unilateral intrastriatal implantation, either multitract or single tract	Multitract implantation → ↑MSNs differentiation (host factors/inflammation) No functional difference	Neuronal replacement	(Jiang et al., 2011a)
		QA-lesioned rat	Unilateral intrastriatal implantation	Microtransplantation → ↑MSNs, ↑Motor function, ↓GFAP expression	Neuronal replacement	(Zhu et al., 2013)
	Rat and human fetal WGE tissues	QA-lesioned rat	Unilateral intrastriatal implantation	rWGE yields more MSNs but less motor recovery than hWGE	Neuronal replacement	(Lelos et al., 2016)
	Human fetal WGE cells	QA-lesioned rat	Unilateral intrastriatal implantation	Xenografts migrate, differentiate into neurons and astrocytes	Neuronal replacement	(Hurelbrink et al., 2002)
	Rat fetal LGE cells	QA-lesioned rat	Unilateral striatal implantation	Graft volume is not linearly correlated with MSNs ratio, survival, and graft size (optimal limit)	Neuronal replacement	(Watts et al., 2000)

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Table 2. Neural Stem Cells (NSCs) (Continued)

	Mouse fetal LGE cells	YAC128 mouse	Bilateral intrastriatal implantation	Grafts are well vascularized	Neuronal replacement	(Cisbani et al., 2014)
	Human fetal striatal cells	QA-lesioned rat	Unilateral intrastriatal implantation	Graft hibernation does not affect graft survival and striatal differentiation	Neuronal replacement	(Hurelbrink et al., 2003)
	Rat, mouse, and human fetal striatal cells	QA-lesioned rat	Unilateral intrastriatal implantation	Xenograft's migration range depend on donor adult brain size	Neuronal replacement	(Hurelbrink and Barker, 2005)
	Rat fetal striatal cells	KA-lesioned rat	Bilateral intrastriatal implantation	↑Motor function	Neuronal replacement	(Deckel et al., 1983)
		IA-lesioned baboon	Unilateral intrastriatal implantation	Immunological rejection → reappearance of abnormal movements ↓Chorea symptom (only striatal graft)	Neuronal replacement, neurotrophic factors	(Hantraye et al., 1992)
	GDNF-expressing NSCs	QA-lesioned mouse	Bilateral/unilateral intrastriatal implantation	↑Motor function ↓Striatal neuron degeneration Grafts grow more in the lesion than normal brain	Neuronal replacement, GDNF secretion	(Pineda et al., 2007)
	hNGF-secreting NSCs	QA-lesioned rat	Unilateral intrastriatal implantation	↑Cholinergic fibers from basal forebrain ↓Lesion size ↓Striatal neuron loss	NGF secretion	(Kordower et al., 1997)
Clinical trials	Human fetal LGE tissue		Bilateral intrastriatal implantation	↑Cognitive functions	Neurotrophic factors and neurotransmitter replenishment	(Philpott et al., 1997)
			Bilateral intrastriatal implantation	Grafts survived with striatal phenotype, integrated with hosts no mHTT aggregation	Neuronal replacement	(Freeman et al., 2000)
			Bilateral intrastriatal implantation	↑Motor function ↑Cognitive function	Neuronal replacement	(Kopyov et al., 1998)
			Bilateral intrastriatal implantation	Poor integration No change in clinical symptoms	Neuronal replacement, neurotrophic factors	(Keene et al., 2007)
			Bilateral intrastriatal implantation	↑Striatal D2 receptor binding ↑Clinical function (varied)	Neuronal replacement	(Reuter et al., 2008)
	Human fetal WGE tissue		Bilateral intrastriatal implantation	↑Anti-HLA Ab ↓HD symptoms ↓Disease progression		(Krebs et al., 2011)
			Bilateral intrastriatal implantation	↑Motor/cognitive function (temporary and varied) ↑Metabolic activity ↑Anti-HLA Ab Same disease progression	Neuronal replacement	(Bachoud-Lévi et al., 2000a; Bachoud-Lévi et al., 2000b; Bachoud-Lévi et al., 2006; Bachoud-Lévi et al., 2020)
			Bilateral intrastriatal implantation	No change in motor function and disease progression	Neuronal replacement	(Barker et al., 2013)
			Bilateral intrastriatal implantation	↑immature mitotic ↑neuroepithelial cells	Neuronal replacement	(Capetian et al., 2009)
			Bilateral intrastriatal implantation	Stable overgrowth mass ↑Brain metabolism ↑Motor/cognitive function (temporary) ↓Cognitive decline rate ↑Anti-HLA Ab	Neuronal replacement, neurotrophic factors	(Gallina et al., 2010; Gallina et al., 2014; Gallina et al., 2008)
			Bilateral intrastriatal implantation	↑Cortical metabolism ↓Clinical symptoms	Neuronal replacement	(Gaura et al., 2004)
			Bilateral intrastriatal implantation	↑Anti-HLA Ab	Neuronal replacement	(Porfirio et al., 2015)
	Human fetal lateral ventricular eminence tissue		Bilateral intrastriatal implantation	↑Host atrophic astrocytes ↓Graft large blood vessels ↓Graft astrocytes and gap junctions Subdural hemorrhage		(Cisbani et al., 2013)
			Bilateral intrastriatal implantation	No significant change in motor function Subdural hemorrhage	Neuronal replacement, possible neurotrophic support	(Hauser et al., 2002)
	Human fetal striatal cells		Unilateral intrastriatal implantation	No change in disease progression	Neuronal replacement	(Rosser et al., 2002)

Table 2. Neural Stem Cells (NSCs) (Continued)

		Bilateral intrastriatal implantation	↑Striatal/cortical metabolism ↑Motor function ↓Cognitive decline rate	Neuronal replacement	(Paganini et al., 2014)
		Bilateral intrastriatal implantation	Graft survived long-term and connected with cortical neurons ↓mHTT aggregated in graft extracellular matrix	Neuronal replacement, neurotrophic factors	(Cicchetti et al., 2009; Cicchetti et al., 2014)
		Bilateral intrastriatal implantation	↑Stable graft size		(Mascalchi et al., 2014)
		Bilateral intrastriatal implantation	↑Inflammation mHTT aggregrated in grafts	Neuronal replacement	(Maxan et al., 2018)
	Human fetal neurons	Bilateral intrastriatal implantation	Grafts differentiated into neuron	Neuronal replacement	(Ross et al., 1999)
		Bilateral intrastriatal implantation	Alloimmunization (encephalitis and graft dysfunction)		(Krystkowiak et al., 2007)
	Human fetal striatal cells, co-grafted with autologous sural nerve	Bilateral intrastriatal implantation	Overgrowing masses and ependymal cysts ↓Clinical symptoms	Neuronal replacement, neurotrophic factors	(Keene et al., 2009)

exploration of NSC sources, and graft storage impact (Watts et al., 1999; Hurelbrink et al., 2003; Hurelbrink and Barker, 2005; Johann et al., 2007; Kelly et al., 2007; Lelos et al., 2016). Pineda et al. (2007) and Kordower et al. (1997) engineered NSCs to overexpress glial cell line-derived neurotrophic factor (GDNF) and human nerve growth factor (NGF), achieving rescue of striatal degeneration and improvement in motor functions (Kordower et al., 1997; Pineda et al., 2007).

Clinical trials of stem cell therapy in HD have primarily involved fetal striatal tissue transplantation, with neurons derived from the WGE and SVZ harvested from elective abortions. The first pilot study of cellular transplantation in HD patients occurred in 1995 (Madrazo et al., 1995), with subsequent trials conducted in locations including Cuba, Czechoslovakia, the United Kingdom, Florida, California, and France. These trials generally reported improved cognitive and motor functions, brain metabolic activity, and disease progression rates. Post-mortem analysis also indicated robust graft survival, striatal neuron differentiation, and host-brain integration (Freeman et al., 2000). Nevertheless, some studies have shown that the benefits of neural stem cell therapy can be temporary (Bachoud-Lévi et al., 2006; Gallina et al., 2014) or even yield no significant improvement (Hauser et al., 2002; Keene et al., 2007; Barker et al., 2013; Bachoud-Lévi et al., 2020), underscoring the importance of long-term follow-up and alternative regimens that allow for continuous treatment. Despite the therapeutic effects of stem cell transplantation, several studies have reported complications, including the development of anti-human leukocyte antibodies antibodies leading to encephalitis and graft dysfunction, as well as concerns about the tumorigenesis potential of stem cells, with some patients developing overgrowing masses causing clinical deterioration (Krystkowiak et al., 2007; Gallina et al., 2008; Keene et al., 2009; Gallina et al., 2010; Krebs et al., 2011; Gallina et al., 2014; Porfirio et al., 2015; Bachoud-Lévi et al., 2020). Cisbani et al. (2013) reported that fetal striatal tissue transplantation decreased blood vessels, astrocytes, and gap junctions in grafts, raising concerns about impaired blood-brain barrier integrity resulting from stem cell therapy. Despite a well-established protocol for intrastriatal implantation, some patients have experienced procedural complications, such as subdural hemorrhage and infection, highlighting the need for careful consideration of these risks (Bachoud-Lévi, 2017; Cisbani et al., 2013).

Neural Progenitor Cells (NPCs)

NPCs correspond to brain progenitor cells responsible for generating glial and neuronal cells. Unlike NSCs, NPCs do not give rise to non-neural cells. Numerous in vivo studies have utilized NPCs derived from ESCs, iPSCs, or fetal brain tissue, demonstrating that NSC transplantation can improve clinical manifestations of HD, reduce neuroinflammation and mHTT accumulation, and enhance MSN differentiation (Aubry et al., 2008; Vazey et al., 2010; Nicoleau et al., 2013; Park et al., 2021; Park et al., 2022; Schellino et al., 2023). Various protocols have been employed to augment the therapeutic effects of NPCs, including priming with lithium chloride (LiCl) (Vazey and Connor, 2010), noggin priming (Vazey et al., 2010), combination therapy (Lee et al., 2006), graft forms (Johann et al., 2007; Kelly et al., 2007), and routes of administration (Lee et al., 2006). A study by Lee et al. (2006) compared intraventricular injection to intravenous administration of human NPCs in a QA-lesion rat model. They found that both methods effectively facilitated graft migration to the lesioned striatum, with the intravenous route resulting in higher graft density. However, concerns about tumorigenesis arose from detecting transplanted cells in other organs following systemic injection, underscoring the need for long-term observation. While some studies have explored NPCs as vehicles for gene therapy (Cho et al., 2019), such applications fall outside the scope of this review.

Glial Progenitor Cells (GPCs)

GPCs have received comparatively less attention than neural lineages in HD research. To date, only one study has focused on glial progenitor cells derived from hESCs. Following transplantation into HD chimera mice, the grafts rescued electrophysiological and behavioral phenotypes, maintained potassium homeostasis, decelerated disease progression, and improved survival rates (Benraiss et al., 2016). Since the pathology of HD might involve neuroinflammation, glia and GPCs-based therapy may be worth exploring to gain a complete understanding of HD pathogenesis and treatment.

iPSCs

Fibroblast-derived iPSCs represent a viable source for stem cell therapy in HD. Studies involving intrastriatal and intraventricular implantation of these iPSCs across various mouse models have reported enhancements in motor and cognitive functions, metabolic activity, levels of neurotrophic

Table 3. Neural Progenitor Cells (NPCs)

Study Design	Cell sources	HD model	Route of administration	Outcome	Therapeutic effects	Articles
In vivo	hNPCs	QA-lesioned mouse	Intrastriatal implantation	↑Behavioral function	Neuronal replacement	(Ma et al., 2012)
		QA-lesioned rat	Unilateral intrastriatal implantation	Neuron differentiation Overgrowing graft	Neuronal replacement	(Aubry et al., 2008)
		QA-lesioned rat	Unilateral intrastriatal implantation	Environmental enrichment → ↑MSNs differentiation, ↑integration	Neuronal replacement, BDNF effect	(Schellino et al., 2023)
		QA-lesioned rat	Unilateral intrastriatal implantation	↑Sensorimotor function ↓Neuroinflammation	Neuronal replacement, neurotrophic factors	(Besusso et al., 2020)
		QA-lesioned rat	Bilateral intrastriatal implantation	Noggin priming → ↑Neuronal differentiation Hyperplastic mass	Neuronal replacement	(Vazey et al., 2010)
		QA-lesioned rat	Unilateral intrastriatal implantation	Inhibition of Wnt-signaling → ↑telencephalic specification	Neuronal replacement	(Nicoleau et al., 2013)
		QA-lesioned rat	Unilateral intrastriatal implantation	↑Behavioral function	Neuronal replacement	(Song et al., 2007)
		R6/2 mouse	Bilateral intrastriatal implantation	↑Motor coordination ↑Survival rate ↓Disease progression	Neuronal replacement, neurotrophic factors	(Adil et al., 2018)
		YAC128 mouse	Bilateral intrastriatal implantation	↑Motor and cognitive functions ↑DARPP-32, synaptophysin, myelin basic protein ↑Astrocyte function ↓Reactive astrocyte differentiation ↓mHTT expression	Neuronal replacement, neurotrophic factors, gene therapy targeting an elongation factor	(Park et al., 2021; Park et al., 2022)
		QA-lesioned rat	Unilateral intrastriatal implantation	↑Trace memory	Neuronal replacement, neurotrophic factors	(Stavrovskaya et al., 2018)
		3-NP induced rat	Bilateral intrastriatal implantation	↑Locomotor activity ↑Behavioral function	Neuronal replacement, neurotrophic factors	(Stavrovskaya et al., 2017)
		QA-lesioned rat/hNPCs	Unilateral intrastriatal implantation	↑Behavioral function ↑Neural replacement ↑Endogenous neurogenesis ↑Neuronal connections ↓Inflammation	Neuronal replacement, immune modulation	(Yoon et al., 2020a)
		QA-lesioned rat	Unilateral intrastriatal implantation	↑Behavioral function ↓mHTT aggregate formation When add proteasome inhibitor (MG132) or examine at older age, HD pathology emerged	Neuronal replacement, neurotrophic factors	(Jeon et al., 2012)
		QA-lesioned rat	Intrastriatal implantation	↑Motor functions ↑Survival rates	Neuronal replacement	(Bosch et al., 2004)
		QA-lesioned rat	Unilateral intrastriatal implantation	Graft survived, differentiated to neurons with consistent morphology	Neuronal replacement	(Armstrong et al., 2000)
		QA-lesioned rat	Either unilateral intraventricular injection or intravenouse injection	(Intravenous injection) ↑Graft density around necrotizing cavities and vessels	Neuronal replacement	(Lee et al., 2006)
	rNPCs	QA-lesioned rat	Unilateral intrastriatal implantation	↑Motor function	Neuronal replacement, neurotrophic factors	(Vazey et al., 2006)
		QA-lesioned rat	Unilateral intrastriatal implantation	LiCl priming → ↑neuronal differentiation, ↑efferent projections, ↑sensorimotor function, ↓gliogenesis	Neuronal replacement, neurotrophic factors	(Vazey and Connor, 2010)
		QA-lesioned rat	Unilateral intrastriatal implantation	↑Brain metabolism No motor improvement	Improved glucose metabolism but no clear evidence of neuronal replacement	(Visnyei et al., 2006)
	mNPCs	R6/2 mouse	Unilateral intraventricular implantation	↑Lifespan ↑Motor function ↓Ubiquitin /polyQ aggregation ↓Striatal volume	Neuronal replacement, neurotrophic factors	(Yang and Yu, 2009)
		QA-lesioned mouse	Intrastriatal implantation	Grafts survived and did not form tumors	Neuronal replacement	(Dihné et al., 2006)
	hNPCs, mNPCs, human and mouse striatal tissue	QA-lesioned mouse	Unilateral intrastriatal implantation at 2, 7, and 14 days after QA lesioning, using either intact neurospheres or dissociated cell suspensions	Differentiation is independent of the immunogenic background but relied on cell source	Neuronal replacement	(Kelly et al., 2007)

Table 4. Glial Progenitor Cells (GPCs)

Study Design	Cell sources	HD model	Route of administration	Outcome	Therapeutic effects	Articles
In vivo	hGPCs	mHTT-transduced mouse	Intrastriatal implantation	↑Survival rate ↓Disease phenotype and progression	Glial replacement	(Benraiss et al., 2016)

Table 5. Induced Pluripotent Stem Cells (iPSCs)

Study Design	Cell sources	HD model	Route of administration	Outcome	Therapeutic effects	Articles
In vivo	hiPSCs	YAC128 mouse	Bilateral intrastriatal implantation	↑Motor coordination ↓mHTT aggregates	Neurotrophic factors	(Jeon et al., 2012; Jeon et al., 2014)
	riPSCs	3-NP induced rat	Bilateral intrastriatal implantation	↑Motor function ↓Striatal damage ↓Lateral ventricle enlargement	Neuronal replacement, neurotrophic factors	(Fink et al., 2014)
	miPSCs	QA-lesioned rat	Unilateral intraventricular implantation	↑Motor function ↑Metabolic activity ↑NTFs ↓Chemoattractant	Neuronal replacement, neurotrophic factors	(Mu et al., 2016)
		QA-lesioned rat	Unilateral intraventricular implantation	↑Learning and memory function ↑Striatal metabolism	Neuronal replacement, neurotrophic factors	(Mu et al., 2014)

Table 6. Embryonic Stem Cells (ESCs)

Study Design	Cell sources	HD model	Route of administration	Outcome	Therapeutic effects	Articles
In vivo	mESCs	QA-lesioned mouse	Unilateral intrastriatal implantation	GABAergic neurons ↑Behavioral function (temporary) ↓Cell proliferation	Neuronal replacement, neurotrophic factors	(Bernreuther et al., 2006)
	hESCs	Htt171-82Q-transfected mouse	Unilateral intrastriatal implantation	↑Behavior function	Neuronal replacement, neurotrophic factors	(Islam et al., 2021)

factors, as well as reductions in mHTT aggregation, inflammation, striatal atrophy, and ventriculomegaly (Jeon et al., 2012; Fink et al., 2014; Jeon et al., 2014; Mu et al., 2014; Mu et al., 2016).

Embryonic Stem Cells (ESCs)

Comparatively few studies have utilized ESCs for transplantation. To date, only two experiments have been conducted with ESCs. Bernreuther et al. (2006) performed the first study in 2006, intrastriatally implanting murine L-1 expressing ESCs into QA-lesioned mice. They found active graft migration, an increase in GABAergic neurons, and temporary behavioral rescue. Islam et al. (2021) conducted another study using human ESCs transplanted into an HTT knock-in mouse model and observing improved behavioral function.

Mesenchymal Stem Cells (MSCs)

MSCs, widely researched for their therapeutic potential, are derived from various tissues such as the adipose, bone marrow, umbilical cord, dental pulp, and olfactory sheath. Research has consistently shown that MSCs, similar to other stem cells, can ameliorate behavioral and memory dysfunctions, mHTT aggregation, striatal atrophy, ventriculomegaly, and enhance neurotrophic factors (Lescaudron et al., 2003; Lee et al., 2009; Edalatmanesh et al., 2012; Moraes et al., 2012; Sánchez et al., 2018; Yu-Taeger et al., 2019). Several injection routes have been explored, including intranasal, intravenous, intrastriatal, and intraventricular. Elbaz et al. (2019) reported positive outcomes from combining intravenous MSCs with intraperitoneal lercanidipine in 3-nitropropionic acid (3-NP) induced rats. The number of cell passages is a critical factor for graft viability, as shown by Fink et al. (2013), where high-passage MSCs reduced pathological deficits and temporarily improved memory function. Wenceslau et al. (2022) found that a single high dose of intravenous human immature dental pulp stem cells significantly increased brain-derived neurotrophic factor (BDNF) levels and DARPP-32 positive neurons compared to a triple low-dose regimen. Lastly, some stem cells are engineered to overexpress neurotrophic factors. Engineering stem cells to overexpress neurotrophic factors like BDNF and GDNF enhanced their therapeutic effects by improving neurogenesis, lifespan, and disease phenotypes (Sadan et al., 2008; Dey et al., 2010; Sadan et al., 2012; Zimmermann et al., 2016).

Unlike NSCs and NPCs, only a few clinical trials of MSCs in HD patients exist. Human dental pulp stem cells have

Table 7. Mesenchymal Stem Cells (MSCs)

Study Design	Cell sources	HD model	Route of administration	Outcome	Therapeutic effects	Articles
In vivo	hADSCs	QA-lesioned mouse	Unilateral intrastriatal implantation	↑Motor function ↓Striatum atrophy	Neurotrophic factors	(Hosseini et al., 2014)
		QA-lesioned rat and R/2 mouse	Unilateral/bilateral intrastriatal implantation	↑Motor function ↑Akt/cAMP-response element-binding proteins pathway ↓Lesion volume ↓Striatal apoptosis ↓mHTT aggregate	Neurotrophic factors	(Lee et al., 2009)
		YAC128 mouse	Bilateral intrastriatal implantation	↓Striatal atrophy No improvement in motor function	Neurotrophic factors	(Im et al., 2010)
	mBM-MSCs	R6/2 mouse	Intrastriatal implantation	High passage MSCs → ↑Motor function	Neurotrophic factors	(Rossignol et al., 2015)
		R6/2 mouse	Intranasal administration	↑Survival rate ↑Dopamine signaling ↓Circadian disruption ↓Inflammation	Neurotrophic factors, inflammatory modulation	(Yu-Taeger et al., 2019)
		N171-82Q HD mouse	Intranasal administration	↑Survival rate ↑Motor function ↑Genes in trophic, antioxidant, anti-apoptosis, cytokine/chemokine receptor migration, mitochondrial energy metabolism, and stress response signaling pathways ↓Striatal neuronal loss ↓mHTT aggregates	Neurotrophic factors	(Linares et al., 2016)
		QA-lesioned rat YAC128 and BACHD mouse/	Retro-orbitally injection	↑Cortical synapses ↑Serum IL-6, IL-10, CXCL1, and IFN-γ ↑Behavioral function ↓Brain pathology	Neurotrophic factors	(Wanda et al., 2012)
	rBM-MSCs, rNSCs	HD 51CAG transgenic rat	Bilateral intrastriatal implantation	MSCs have weaker immune response → ↑long-term benefit	MSCs modify local environment for NSCs differentiation and reduce immune response	(Rossignol et al., 2014)
	rBM-MSCs	QA-lesioned rat	Unilateral intrastriatal implantation	↑Working memory Poor differentiation	Neurotrophic factors	(Lescaudron et al., 2003)
		QA-lesioned rat	Unilateral intrastriatal implantation	↑Motor function ↑Glutamate concentration	Neurotrophic factors	(Sánchez et al., 2018)
		QA-lesioned rat/	Unilateral intrastriatal implantation	↑FGF-2 ↓Neuron degeneration ↓Ventriculomegaly	Neurotrophic factors	(Moraes et al., 2012)
		QA-lesioned rat/rBM-MSCs	Unilateral intrastriatal implantation	↑Motor function ↓Striatal atrophy	Neurotrophic factors	(Jiang et al., 2011b)
		QA-lesioned rat/rBM-MSCs	Unilateral intrastriatal implantation	↓Lateral ventricle enlargement ↓Striatal atrophy	Neuronal replacement, neurotrophic factors	(Amin et al., 2008)

Table 7. Mesenchymal Stem Cells (MSCs) (Continued)

		QA-lesioned rat/rBM-MSCs	Unilateral intrastriatal implantation	↑BDNF levels	BDNF secretion	(Serrano Sánchez et al., 2014)
		QA-lesioned rat/rBM-MSCs	Single dose intravenous injection	↑Motor function ↑Cognitive function	Neurotrophic factors	(Edalatmanesh et al., 2010)
		3-NP induced rat/rBM-MSCs	Bilateral intrastriatal implantation	↑Behavioral function ↑BDNF, collagen type I, and fibronectin ↓Lateral ventricles enlargement No neural differentiation	Neurotrophic factors	(Rossignol et al., 2011)
		3-NP induced rat/rBM-MSCs	Single dose intravenous MSCs with daily intraperitoneal lercanidipine	Combined therapy → ↑Motor and behavior function ↑BDNF, FOXP3, Wnt, and β-catenin ↓Striatum tissue injury ↓Striatal cytosolic Ca2+, CaN, tumor necrosis factor-alpha, NFATc4 expression, and the Bax/Bcl2 ratio	Modulation of the Ca/calcineurin/NFATc4 and Wnt/β-catenin signalling pathways	(Elbaz et al., 2019)
	hBM-MSCs	QA-lesioned mouse and R6/2 mouse	Unilateral intrastriatal implantation	↑Motor function ↑Survival rate ↑Microglia and neuroblasts ↓Motor impairment	Neurotrophic factors	(Lin et al., 2011)
		N171-82Q mouse	Unilateral intrastriatal implantation	↑Endogenous NSCs proliferation/differentiation ↑NTFs signaling ↓Striatal atrophy Grafts rapidly disappeared	Neurotrophic factors, endogenous neurogenesis	(Snyder et al., 2010)
	hUC-MSCs	3-NP induced rat	Bilateral intrastriatal implantation	↑Motor function ↑Dendritic length ↑ROS protection ↓Gliosis ↓Striatal atrophy	Neurotrophic factors	(Ebrahimi et al., 2018)
		R6/2 mouse	Intrastriatal implantation, either a low-passage (P3 to 8) or high-passage (P40 to 50)	↑Spatial memory (temporary) ↓Pathological deficits No motor improvement	Neurotrophic factors	(Fink et al., 2013)
		BACHD mouse	Intravenous administration, combined with intraventricular antisense oligonucleotides (ASOs)	↑AQP-4 M23 isoform ↓Inflammation	Neurotrophic factors, immunomodulation, glymphatic recovery	(Wu et al., 2020)
	hIDPSC	3-NP induced rat	intravenously administered, either single high dose or three consecutive low doses with one-month intervals	Single high dose regimen → ↑BDNF, DARPP32, and D2R positive stained cells	Neurotrophic factors	(Wenceslau et al., 2022)

Table 7. Mesenchymal Stem Cells (MSCs) (Continued)

	DPSCs	3-NP induced rat	Bilateral intrastriatal implantation	↑Motor function ↓Striatal atrophy ↓Glial proliferation ↓Inflammatory ↓Caspase-3	Neurotrophic factors, immunomodulation	(Eskandari et al., 2021)
	hOE-MSCs	3-NP induced rat	Bilateral intrastriatal implantation	↑Locomotor activity ↑Motor coordination ↓Striatal atrophy ↓RIP3 and TNFα	Neurotrophic factors	(Bayat et al., 2021)
	BDNF-secreting MSCs	QA-lesioned, R6/2 and N171-82Q mouse	Unilateral intrastriatal implantation	↑Motor function	Neurotrophic factors	(Zimmermann et al., 2016)
	NTFs-secreting rBM-MSCs	QA-lesioned rat	Unilateral intrastriatal implantation	Graft migrated, differentiated into neurons and astrocytes NTFs secretion	Neurotrophic factors	(Sadan et al., 2008)
	BDNF/NGF-secreting mBM-MSCs	YAC128 mouse	Bilateral intrastriatal implantation	↑Motor function ↓Neuronal loss	Neurotrophic factors	(Dey et al., 2010)
		QA-lesioned rat	Unilateral intrastriatal implantation	↑Behavioral function ↓Striatal atrophy	Neurotrophic factors	(Sadan et al., 2012b)
	BDNF/GDNF-secreting hBM-MSCs	QA-lesioned rat	Intracerebral implantation posterior to the thalamus	Graft migrated to the lesion	Neurotrophic factors	(Sadan et al., 2009)
		R6/2 mouse	Bilateral intrastriatal implantation	Late transplantation → ↑Motor function (temporary) ↑Lifespan	Neurotrophic factors	(Sadan et al., 2012a)
	BDNF-secreting BM-MSCs	YAC128 and R6/2 mouse	Bilateral intrastriatal implantation	↑Neurogenesis ↑Lifespan ↓Striatal atrophy ↓Anxiety	Neurotrophic factors	(Pollock et al., 2016)
		YAC 128 and R6/2 mouse	Intrastriatal implantation	↑Neurogenesis ↑Lifespan ↓Striatal atrophy ↓Anxiety	Neurotrophic factors	(Wheelock et al., 2016)

reached clinical phases I and II, including the SAVE-DH, ADORE-DH, and ADORE-EXT trials (Macedo et al., 2021). These trials indicated that intravenous dental pulp stem cells are well tolerated and lead to significant improvement in motor symptoms in moderate HD patients. The STAR trial, a phase III clinical trial, is currently ongoing. The PRE-CELL trial from the University of California Davis is exploring engineered MSCs to overexpress BDNF in early HD patients (Wheelock et al., 2016) but is still in the participant recruitment stage.

Two primary mechanisms in neural stem cell transplantation for HD amelioration have been identified: the secretion of neurotrophic molecules and neural replacement. Previous studies have found that neural stem cells secrete various neurotrophic factors, such as NGF, BDNF, GDNF, and ciliary neurotrophic factor (CNTF), which enhance endogenous neurogenesis and reduce neuroinflammation, a key pathogenesis of HD (Conforti et al., 2018). The goal of neural replacement is to reconstruct the damaged striatum, focusing on the MSNs of the caudate/putamen, the primary neuronal population degenerating in HD (Ferrante et al., 1985). Research has convincingly shown MSN differentiation and integration into host brain circuits, indicating their regenerative potential. Furthermore, MSCs are free from ethical concerns, unlike ESCs and other fetal tissues (Kim and Park, 2017). However, possible complications highlight the need for further safety profile development.

Extracellular Vesicles (EVs)

Multiple studies have explored the use of culture media from healthy cells to reverse HD phenotypes in vitro, highlighting the potential of EVs as cell-free alternatives to stem cell therapy. Human fibroblast-derived EVs increase GABAergic synapses and transmission when added to culture media of HD iPSCs and neurons (Beatriz et al., 2021; Beatriz et al., 2023). Culture media from NSCs and NPCs mitigates mHTT aggregation and prevents neuronal apoptosis in HTT knock-in cell models (Heon-Chang et al., 2008; Ma et al., 2012). Furthermore, EVs from adipose tissue-derived stem cells (ADSCs) improve mitochondrial function, phospho-cAMP response element-binding protein, and PGC-1α expression alongside disease phenotypes (Lee et al., 2009; Lee et al., 2016).

In vivo studies further affirm the positive impacts of EVs. Lee et al. (2021) conducted an experiment that established a surgical connection of blood circulation between young wild-type mice, old wild-type mice, and R6/2 HD mouse models. This simulated parasymbiosis demonstrated that blood serum from young healthy mice could enhance survival rates

Table 8. Extracellular Vesicles

Study Design	EV sources	HD model	Route of administration	Outcome	Therapeutic effects	Articles
In vitro	HDF-EVs/CM	HD human dermal fibroblast-derived iPSCs	Added in culture media	↑GABAergic synapses and transmission	Neurotrophic factors	(Beatriz et al., 2023)
		HD iPSCs-derived MSNs	Added in culture media	↑GABAergic currents	Neurotrophic factors	(Beatriz et al., 2021)
		HD iPSCs-derived GABAergic neurons	Added in culture media	↑GABAergic transmission	Neurotrophic factors	(Beatriz et al., 2022)
	Blood serum of young and old WT mice	R6/2 mouse SVZ-derived NSCs	Added in culture media	↓mHTT aggregation ↓Cell death ↓Cell proliferation	Neurotrophic factors	(Lee et al., 2021)
	hNPCs-CM	mHTT-transfected cerebral hybrid neurons (A1)	Added in culture media	↓Inclusions ↓N-terminal cleavage ↓Annexin-V+PI+ and Annexin-V+PI− neurons	Neurotrophic factors	(Heon-Chang et al., 2008)
	DNAJB6-enriched NSCs-EVs	HTT-Q74-RFP/EGFP transfected HEK293T cells	Added in culture media	↓mHTT aggregation	Neurotrophic factors Neurotrophic factors	(Joshi et al., 2021)
	hADSCs-CM	mHTT-transfected cerebral neuroblastoma	Added in culture media	↑PGC-1α expression ↓N-terminal mHTT Apoptosis	Neurotrophic factors	(Lee et al., 2009)
	ADSCs-exosome	R6/2 mouse derived NSCs	Added in culture media	↑Mitochondrial function ↑Phospho-CREB and PGC-1α ↓mHTT aggregates ↓Cell apoptosis	Neurotrophic factors	(Lee et al., 2016)
In vivo	Blood serum of young and old WT mice	R6/2 mouse	Surgically connected parabiosis between mice	↑Survival rate ↑Mitochondria function ↑Cognitive function ↑Cleaved caspase-3 ↓Weight loss ↓mHTT aggregation ↓Cell death	Neurotrophic factors	(Lee et al., 2021)
	DNAJB6-enriched NSCs-EVs	R6/2 mouse	Intrathecally weekly for 3 times	↓mHTT aggregation	Neurotrophic factors, gene therapy (DNAJB6 inhibit mHTT aggregration)	(Joshi et al., 2021)
	ADSCs-EVs	R6/2 mouse	Intraperitoneally, two times a week for 6 weeks	↑Motor function ↑CREB-PGC-1α pathway ↓Weight loss ↓Striatal atrophy ↓mHTT aggregation	Neurotrophic factors	(Im et al., 2013)
	hAMSCs	R6/2 mouse	daily intraperitoneal injection, 6 days a week for 9 weeks	↑Motor function ↓Striatal atrophy ↓Inclusions ↓Microglia activation ↔BDNF level	Immunomodulation	(Giampà et al., 2019)

and mitochondrial function while reducing HD symptoms, phenotypes, and cell death (Lee et al., 2021). Extracts from MSCs and ASCs improved disease activity and motor function in the R6/2 mouse model (Im et al., 2013; Giampà et al., 2019). Joshi et al. (2021) advanced this approach by engineering NSCs to overexpress DNAJB6. Post-intrathecal administration of NSCs-derived small EVs in R6/2 mice resulted in decreased mHTT aggregation, a benefit also observed in HTT-Q74 transfected cells (Joshi et al., 2021).

The clinical trial landscape for EV therapy in HD is still in its infancy, with only an observational study by the University of Central Florida investigating the role of EVs as blood-based biomarkers for brain HTT, aiming for application in future HTT-lowering clinical trials (NCT06082713, 2023).

EVs exhibit several properties that make them particularly suitable for treating neurodegenerative diseases (D'Egidio et al., 2024). Firstly, EVs can naturally traverse the blood-brain barrier thanks to their phospholipid composition (Alvarez-Erviti et al., 2011). EVs can also protect their cargo from enzymatic degradation, ensuring that therapeutic molecules remain biologically active upon reaching their target cells. Secondly, EVs demonstrate low immunogenicity and toxicity. They can be administrated intravenously, significantly reducing the risk of procedural complications. Additionally, the potential for tumor growth is minimized because EVs primarily facilitate the delivery of neurotrophic factors instead of actual stem cells. Lastly, EVs can be specifically engineered to target distinct cells or tissues, thereby increasing the specificity and effectiveness of the treatment. These benefits set EV therapy apart from direct stem cell transplantation, presenting a cell-free option that

reduces risks inherent in cell-based therapies while leveraging the advantageous effects of stem cell secretomes.

Conclusion

HD represents a profound neurological challenge, currently without effective treatment options. Cell and EV therapies have emerged as promising avenues as treatment for neurodegenerative diseases such as Alzheimer's disease (Duan et al., 2023; Garcia-Contreras et al., 2023), Parkinson's disease (Upadhya et al., 2021; Shastry et al., 2023), multiple sclerosis (Islam et al., 2023; Barabadi et al., 2024), and stroke (Park et al., 2020; Zhao et al., 2023). In the HD context, these approaches can potentially shift the focus from mere symptomatic relief to a reversal of HD. The literature of the last decades depicts the effects of cell therapy in HD models well, describing the complex interconnection between stem cell properties and the cellular and molecular contexts in the recipient. Indeed, the content of the stem cell secretome can positively modulate the diseased environment, causing, for instance, reduced oxidative stress, eventually via mitochondrial transfer, and neuroinflammation via secretion of inflammatory mediators that also potentially impact the surrounding glial cells. Moreover, cell therapy can be exploited to improve neurogenesis, and eventually, the stem cell secretome can improve the functional and electrical integration of neuronal cells. However, cell therapy brings significant risks, including surgical complications, alloimmunization, and the development of overgrowing masses, highlighting the necessity for safer therapeutic alternatives. EV therapy offers a promising cell-free alternative, potentially mitigating the risks associated with cell transplantation while leveraging the benefits of cellular communication for therapeutic purposes. In fact, EVs represent the principal actors mainly responsible for the assessed therapeutic effects within all the components of the stem cell secretome. Moreover, the possibility of optimizing engineered EVs as carriers of therapeutic molecules underscores their potential as therapeutic instruments in HD and beyond. Although there are many stem cell transplantation studies, clinical trials for EVs have not yet been performed. More studies of EVs' safety profile and efficacy in HD are needed before moving to the next stage.

The journey towards effective treatments for HD is complex and requires further extensive research to address these gaps. As research continues, there is hope for developing therapies that can manage or even cure HD, offering new possibilities for those affected by this debilitating condition.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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