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Stem cell therapy for central nervous system disorders: metabolic interactions between transplanted cells and local microenvironments

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Abstract

Stem cell therapy is a promising and rapidly advancing treatment strategy for a multitude of neurologic disorders. Yet, while early phase clinical trials are being pursued in many disorders, the mechanism of action often remains unclear. One important potential mechanism by which stem cells provide neuroprotection is through metabolic signaling with diseased neurons, glia, and other cell types in the nervous system microenvironment. Early studies exploring such interactions report normalization of glucose metabolism, induction of protective mitochondrial genes, and even interactions with supportive neurovasculature. Local metabolic conditions also impact stem cell biology, which can have a large impact on transplant viability and efficacy. Epigenetic changes that occur in the donor prior to collection of stem cells, and even during *in vitro* culture conditions, may have effects on stem cell biology that are carried into the host upon stem cell transplantation. Transplanted stem cells also face potentially toxic metabolic microenvironments at the targeted transplant site. Novel approaches for metabolically "preconditioning" stem cells prior to transplant harness metabolic machinery to optimize stem cell survival upon transplant. Ultimately, an improved understanding of the metabolic cross-talk between implanted stem cells and the local nervous system environment, in both disease and injury states, will increase the likelihood of success in translating stem cell therapy to early trials in neurological disease.

Graphical Abstract

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Author contributions

SAS and KSC both contributed to the Conceptualization; Funding acquisition; Project administration; Visualization; Writing - original draft; and Writing - review & editing

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SAS has no relevant disclosures

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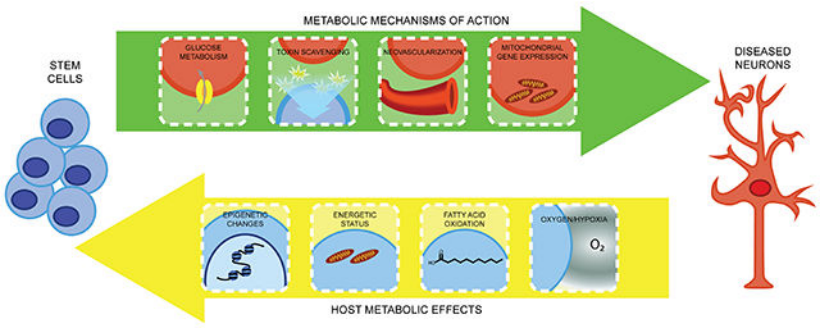
Search terms

A query in PubMed utilizing search terms "stem cell therapy" and "metabolism" and "nervous system" excluding "cancer" was performed, screening for manuscripts describing use of stem cells as a therapeutic in CNS disorders with a potential metabolic mechanism of action. In relevant articles, references were also screened for additional relevant papers.



Keywords

Central nervous system; metabolism; stem cell; transplantation

Introduction

Therapeutic options for neurologic disorders affecting the central nervous system (CNS) are at times hindered by the unknown or complicated mechanisms responsible for the underlying pathogenesis. While some CNS diseases have known genetic causes tied to a certain protein or pathway, many involve an intricate interplay between multiple cell types and metabolic processes within a complex microenvironment (Argueti-Ostrovsky et al., 2021; Guo et al., 2020; Le Gall et al., 2020; Mejzini et al., 2019). Similarly, traumatic brain and spinal cord injury, or vascular events such as stroke, induce a cascade of detrimental events that impact neurologic health (Delage et al., 2021; Mira et al., 2021; Uyeda and Muramatsu, 2020). As such, therapeutic approaches are required that offer multidimensional benefits to the diseased or injured nervous system.

Stem cell transplantation represents a promising opportunity to approach the treatment of CNS diseases and injury in a comprehensive, multifaceted manner. Many types of stem cells, including embryonic stem cells (ESCs), neural stem cells (NSCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs), are being evaluated *in vitro*, *in vivo*, and in translational clinical studies for their potential utility for a range of neurologic conditions (Chen and Feldman, 2017). These and other stem cell subtypes have entered the realm of early clinical trials for a variety of neurologic conditions, capitalizing on their proliferative capacity and adaptable biology. For amyotrophic lateral sclerosis (ALS), for example, intraspinal NSC transplantation has been evaluated in Phase 1 and 2 clinical trials (Feldman et al., 2014; Glass et al., 2016; Goutman et al., 2018). Additionally, several other stem cell types and delivery strategies are in various stages of development and clinical translation for ALS as well as a range of neurodegenerative conditions, including Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, and epilepsy (Bonaventura et al., 2021; De Gioia et al., 2020; Gonzalez et al., 2016; Goutman et al., 2019; Liu et al., 2021; Lunn et al., 2011; Reddy et al., 2020; Schweitzer et al., 2020; Zhao et al., 2021). Likewise, stem cell-based therapies are advancing for traumatic CNS injury (Bonilla and Zurita, 2021; Schepici et al., 2020; Silvestro et al., 2020; Younsi et al., 2021) and stroke (Azad et al., 2016; Hamblin and Lee, 2021; Kawabori et al., 2020).

For the majority of these clinical series, a precise mechanism of action for stem cells is not well established (Neal et al., 2018). Evidence is rapidly accumulating in support for metabolic drivers of pathology in nearly every neurologic disease, and thus metabolic pathways represent a promising window for stem cells to exert beneficial effects (Piers et al., 2020). Herein, we review the possible metabolic considerations associated with stem cell therapies, with particular emphasis on how stem cells impact the local environments and how metabolic implications of neurologic disease and injury states affect cell transplants.

Types of stem cells

Insight into the potential metabolic implications of the various stem cell classes used in transplantation research and translational applications first requires understanding of the origins and attributes of each stem cell type. ESCs are cells derived from the zygote or inner cell layer of the developing blastocyst, the former being totipotent (capable of differentiating to any cell type) and the latter being pluripotent (capable of differentiating to almost any cell type). In a similar vein, iPSCs are cultured cells (e.g., fibroblasts) that have been reprogrammed to express the Yamanaka factors (Oct3/4, Sox2, Klf4, c-Myc) and re-enter a state of pluripotency capable of differentiating into many cell types. NSCs, by contrast, are stem cells capable of proliferation but, upon differentiation, committed to neuroglial cell types. Similarly, MSCs are derived from a variety of tissues, such as bone marrow, and differentiate into mesodermal tissues, but have been coaxed into differentiating towards ectodermal and endodermal fates as well. Ultimately, the source and range of differentiation abilities should be considered when evaluating how stem cells may affect metabolic mechanisms in the host and vice versa.

Metabolic mechanisms by which stem cell transplants affect the host

The appeal of stem cells as a therapeutic tool is tied to the many complementary opportunities for neuroprotection made possible by their inherent properties. Stem cells proliferate, providing a self-renewing resource for therapeutic application. They can also differentiate into a range of cell types, and experimental paradigms are also now available to generate many neuronal subtypes from stem cells, such as motor neurons or GABAergic neurons (Ben-Shushan et al., 2015; Gupta et al., 2018; Ren et al., 2021; Shen et al., 2021). Another clear benefit of stem cell-based strategies is the ability to affect the host by a multitude of mechanisms, simultaneously and in a sustained manner (Chen et al., 2016; Pacheco-Herrero et al., 2021; Shinozaki et al., 2021; Wei et al., 2017a). Of course, the “holy grail” of regenerative approaches is replenishing a damaged cell population using stem cells. However, particularly in the nervous system, the ability to restore and rewire native neural circuits currently faces insurmountable challenges. Alternatively, stem cell differentiation into interneurons, glia, astrocytes, and other supporting cells offers a means to harness the full biological machinery of a complete cell to attenuate the progression of neurologic diseases. In this regard, stem cells can be employed to support neuromodulation, clear toxins, alter the extracellular matrix, facilitate vascular interactions, and regulate the immune system (Figure 1). Importantly, stem cells are also capable of direct cell-cell communication (gap junctions, synapses, etc.), offer paracrine signaling and trophic support via secreted proteins and extracellular vesicles, and can be readily manipulated *in vitro* or *in vivo*

to enhance expression of neuroprotective factors (Guy et al., 2019; Herman et al., 2021; McGinley et al., 2016; Willis et al., 2020).

One mechanism by which transplanted stem cells may benefit the host is by modulation or normalization of metabolic pathways. While the metabolic effects of stem cells have been explored in research fields such as cardiac, liver/pancreas, and hematopoietic stem cell transplants, they have not been well studied in the neurosciences. Limited reports, however, are beginning to provide insight into the implications of stem cells on glucose metabolism, mitochondrial function, and other neurovascular interactions.

Glucose metabolism

At a very basic level, the effect of stem cells on CNS glucose metabolism carries significant impact in the neurosciences. Neurons are known to rely chiefly on glycolysis and oxidative phosphorylation for their high energy demands, with minimal utilization of anaerobic forms of metabolism (Diaz-Garcia and Yellen, 2019). As a result, perturbations in glucose metabolism may have an outsized effect on neuronal function and survival. Transplanted stem cells, on the other hand, may normalize the glucose metabolism of neighboring cells and thus maximize neuronal survival in an otherwise hostile pathologic environment.

Stem cell transplantation studies in neurologic diseases have benefitted from ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) assessment of metabolic integrity. In a study of subventricular zone stem cells transplanted into Sprague-Dawley rats, striatal stem cell transplants were associated in increased FDG-PET signal, although inherent stem cell metabolism versus impact on surrounding host cells could not be parsed (Cicchetti et al., 2007). Interestingly, in a mouse model of temporal lobe epilepsy in which human ESCs were compared to GABAergic neuronal progenitors, restoration of glucose metabolism was only seen in ESC-implanted animals (Du et al., 2019). This appeared to be associated with ESC ability to differentiate down an astrocyte/glial lineage, which may represent a therapeutic strategy for epilepsy and other conditions in which normalization of the neuronal microenvironment is a central goal. Similarly, in a rat model of Huntington's disease, transplanted mouse iPSCs resulted in improved FDG-PET signal, along with elevated expression of neuronal, astrocyte, and microglial markers (Mu et al., 2014). These studies highlight the advantages of generating diverse cell types to act on the metabolism of diseased host cells.

Evidence for metabolic benefits in the CNS are seen in a handful of studies focused on stroke. In a middle cerebral artery occlusion (MCAO) rat model of ischemic stroke, transplantation of mouse iPSC and ESCs as well as rat NSCs into the ventricular space resulted in improved glucose uptake as measured by FDG-PET within the ischemic region (Wang et al., 2013; Zhang et al., 2015a). In a similar study, human NSCs promoted a restoration of glucose metabolism as measured by FDG-PET signal, and these stem cells had better ability to reduce stroke volume when the ischemic area was more modest in size (Daadi et al., 2013). Metabolic imaging to assess stem cell transplantation in early human trials for stroke confirm transplant feasibility as well as use of FDG-PET as a promising, non-invasive method for probing transplant viability and efficacy (Kondziolka et al., 2000).

Stem cell-associated changes in glucose metabolism are also seen in traumatic conditions. In a model of traumatic brain injury, intraparenchymal injections of rat hippocampal NSCs demonstrated restoration of FDG-PET signal at the injury site (Zhang et al., 2008). By contrast, in a hemisection model of spinal cord injury, glucose content at and around the injury site more closely paralleled that of untreated controls. Instead, ATP and lactate levels appeared to diminish within the injury site in animals receiving NSC transplants (Mautes et al., 2004). These changes were hypothesized to be a result of the metabolism of the transplanted cells themselves and their adaptation to the hostile, traumatized microenvironment. It is apparent that much remains unexplored when considering the effect of stem cells on the complex metabolic cascades following traumatic injury.

In many of the above studies, it is unclear how much of the normalized PET signal is performed by the transplanted cells directly or due to effects on native tissue. Transplanted stem cells may themselves contribute to changes in metabolic readouts to some degree. Nevertheless, FDG-PET is often used as a marker for more large-scale regional brain metabolism, and restoration of this signal is suggestive of rescued neuroglial populations. This is supported by histological correlation in the above studies that demonstrate restoration of host neuron and glial counts, and that changes in FDG-PET are more globally measured when compared to cell-specific PET imaging (Daadi et al., 2013; Zhang et al., 2008).

Additionally, given that neurons are reliant on glucose and that perturbations in glucose metabolism are known to exacerbate pathology seen in most neurologic diseases, the changes in FDG-PET shown in these studies could be due to intrinsic metabolic changes induced by stem cell grafts. In other words, rather than being merely a byproduct of rescued host population cell numbers, elevated FDG-PET signal may result from stem cells altering gene expression to increase glucose uptake in a more greatly elevated, hypercompensatory manner. Further mechanistic explorations are needed to elucidate how glucose normalization is mediated (e.g., signaling that alters neuronal or glial metabolism, alteration in microvascular blood flow, induction of glucose transporters, etc.) and better understand what downstream cellular components (e.g., mitochondrion) are involved in metabolic normalization.

Mitochondrial function

Stem cells may mediate normalization of glucose metabolism by altering mitochondrially expressed proteins in resident host cells. Using the MCAO stroke model in rats, a proteomic analysis identified 39 differentially expressed proteins upon treatment with mouse iPSCs. These included many mitochondrial proteins, such as TOMM20 (translocase of outer mitochondrial membrane 20) and GALE (urine diphosphate (UDP)-galactose 4-epimerase) (Chen et al., 2021). TOMM20 is a member of the mitochondrial translocase of the outer membrane, which functions to shuttle mitochondrial-targeted proteins to the mitochondrial matrix (Omura, 1998) and has been implicated in pathophysiology of Parkinson’s disease (Franco-Iborra et al., 2018; Teixeira et al., 2016). GALE participates in the interconversion of UDP-galactose and UDP-glucose (Frey and Hegeman, 2013), important in the metabolism of galactose and generation of glucose substrates. Thus, transplanted iPSCs appear to directly affect mitochondrial physiology of host cells.

Similarly, in the APP/PS1 mouse model of Alzheimer's disease, murine NSCs increased mitochondrial DNA and normalization of PGC-1α (peroxisome proliferator-activated receptor-gamma coactivator 1α), NRF-1 (nuclear respiratory factor 1), COXIV (cytochrome c oxidase subunit 4), and other mitochondrial proteins (Zhang et al., 2015b). PGC-1α and NRF-1 are central transcriptional regulators of mitochondrial biogenesis and cellular energy metabolism (Li et al., 2017), and this is confirmed by electron microscopy in NSC-treated animals showing normalized mitochondrial morphology and numbers. Parallel findings were likewise found using a model of Huntington's disease treated with human adipose stem cells. Here, although mostly GABAergic neurons were formed, there appeared to be a restoration of Akt and CREB (cAMP response element-binding protein) signaling as well as PGC-1α (Lee et al., 2009). While further studies are required to identify factors mediating these stem cell-associated changes in mitochondrial function, these studies provide insight into the mechanisms by which stem cells promote neuroprotection by influencing metabolic pathways.

Neurovascular and other interactions

Stem cells may exert beneficial effects by modulating the metabolic response to pathologic injury in many other ways. For example, in a rat model of neonatal hypoxic-ischemic brain injury, transplanted MSCs appeared to attenuate the proliferation and activation of reactive astrocytes (He et al., 2019). This effect appeared to be mediated by stem cell secretion of IL-6, which suppressed 5' adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) signaling in astrocytes. Importantly, these and the above discussed metabolic interactions could all occur simultaneously in a stem cell transplant treatment paradigm.

Transplanted stem cells may also exert beneficial effects indirectly, by first chiefly affecting neurovascular structures and blood flow, with metabolic changes a secondary benefit. In Alzheimer's disease models, many studies have shown that stem cells are associated with increased vascular endothelial growth factor (VEGF) expression (Li et al., 2018). In turn, higher VEGF levels are associated with greater glucose metabolism and neuroprotective effects (Wang et al., 2018), which may be mediated by neovascularization (Garcia et al., 2014). Hence, secreted factors derived from transplanted cells impact the supportive structures of neuronal metabolism, and stem cells can thus provide neuroprotection by both direct and indirect mechanisms simultaneously.

While the CNS is traditionally viewed as a privileged vascular environment, the benefits of stem cell transplants may have impact systemically as well. Metabolomic analysis in the MCAO model of ischemic stroke demonstrated that improvements after rat ESC transplants were associated with increased consumption of N,N-dimethylglycine, glucose, and formate, together with reduced excretion of lactate, alanine, glutamate, 3-hydroxybutyrate, glutathione, methionine, aspartate, fatty acyl chain, choline, glycerol, myoinositol, and glycerophosphocholine, as measured in peripheral serum (Gao et al., 2020). Whether these changes result from the stem cells directly and have a downstream impact on host neurons or whether these changes simply reflect rescue of native neuronal/

glial populations is unclear, but these findings represent a metabolic signature which may have value as an accessible peripheral biomarker of disease and treatment response.

Host effects on stem cell transplant metabolism

While it is often the expressed goal for stem cell transplants to impact physiology of the host, the converse is emerging as an increasingly important area of study. With this in mind, the metabolic circumstances of donor tissue from which stem cells are derived become of great importance to the transcriptional and epigenetic signatures that are carried along with cell transplants. Once stem cells reach their destination, another consideration is how stem cells are impacted by the challenging microenvironment present in neurologic injury or disease (Frederiksen et al., 2020; Nguyen et al., 2019). While they can aid in detoxifying a potentially hostile disease microenvironment and confer several additional advantages, as mentioned above, stem cells must first be amenable to surviving within the immunologic and metabolic milieu that comprises that environment. Metabolic perturbations of the host, whether due to environmental factors (diet, exposures, etc.) or intrinsic neuropathologic disease processes, likewise impact the physiology of transplanted cells. Here we will summarize early work in understanding how destination metabolic microenvironments impact transplanted cells (Figure 2), and approaches that build upon this knowledge to maximize the survival and therapeutic benefit of cell-based therapy.

Metabolic contributors to stem cell quiescence, pluripotency, proliferation, and differentiation

Metabolic disturbances can impact gene expression profiles of stem cells, and can thus influence the delicate balance between quiescence, self-renewal, and terminal differentiation. Interestingly, seemingly opposite dietary modifications, including both ketogenic/restricted calorie diets and high-fat diet, appear to increase stem cell self-renewal by convergent signaling onto common pathways engaged in fatty acid oxidation and peroxisome proliferator-activated receptors (Novak et al., 2021). However, high-fat diet or models of the “Western diet” appear to also impart a tendency towards inappropriate stem cell proliferation and carcinogenesis.

It is also clear that metabolic alterations have significant impact on stem cell epigenetic factors (Fawal and Davy, 2018; Ryall et al., 2015). Factors involved in oxidative phosphorylation act to modulate epigenetic changes (Tay et al., 2021). Sirtuin 1 activity, for example, is crucial for maintenance of pluripotency, participates in histone deacetylation, and is regulated by nicotinamide adenine dinucleotide (NAD+) concentrations that reflect stem cell metabolism (Correia et al., 2017; Fang et al., 2019). Histone and DNA methylation/demethylation by DNA methyltransferases and lysine-specific demethylase 1 also depends on one-carbon metabolism and the concentrations of flavin adenine dinucleotide (FAD), again impacting expression of pluripotency versus differentiation genes (Castex et al., 2017; Ryall et al., 2015). Also, embryonic exposure to hyperglycemia appears to promote chromatin reorganization, histone H3 lysine 9 trimethylation, and global DNA methylation in NSCs (Shyamasundar et al., 2013). Thus, it is important to consider this metabolic “baggage” when establishing stem cell cultures or iPSC lines. Moreover,

understanding the metabolic history of cell lines may lead to optimized transplantation paradigms and downstream studies.

Metabolic pathways additionally directly contribute to stem cell survival, maintenance of pluripotency, and the switch from quiescence to proliferation (Wanet et al., 2015). Signaling that involves forkhead box class O (FOXO), mTOR, AMPK, and sirtuin signaling pathways maintain a quiescent stem cell "pool" and minimize oxidative stress; however, the signaling of these pathways may be disrupted by changes in energy availability (Rafalski et al., 2012). Interestingly, fatty acid metabolism also appears to play a central role in stem cell biology. Malonyl-CoA reduces fatty acid oxidation which then promotes exit from quiescence into proliferation (Knobloch et al., 2017), and activity of fatty acid synthase also appears to promote adult neurogenesis and proliferation (Knobloch et al., 2013). The complexities of this area of study are only just beginning to be revealed, but knowledge of metabolic contributions to proliferation and differentiation may maximize stem cell survival and could be harnessed to improve treatment outcomes.

The stem cell niche and metabolic responses to culture and transplantation

The very act of *in vitro* culture and manipulation can impact stem cell metabolism and subsequent performance. Endogenous stem cells appear to exist in a specific niche with defined environmental factors and metabolic pathway utilization (Ottoboni et al., 2017; Rafalski et al., 2012). For example, certain stem cell populations appear to rely on glucose and preferentially utilize glycolysis over oxidative phosphorylation (Salazar-Noratto et al., 2020). This occurs in the face of relative hypoxia, whereas the switch to oxidative phosphorylation is linked to terminal differentiation in normoxic settings (De Filippis and Delia, 2011). The ability to expand and manipulate stem cell cultures *in vitro* prior to implantation is often cited as an advantage for stem cell-based approaches. However, keeping in mind the metabolic switch to oxidative phosphorylation is critical when considering that most *in vitro* culture of stem cells occurs at atmospheric oxygen levels. This exposure to elevated oxygen levels and switch to aerobic respiration may result in fundamental changes that might prove detrimental when cells are transplanted again into damaged, hypoxic host tissues and expected to proliferate (Sandvig et al., 2017).

Furthermore, the destination for cell transplants is often hostile, with altered blood flow, impaired nutrient and toxin shuttling, and inflammatory changes. A demonstration of these interactions was demonstrated using NSC transplants performed in a compression-based model of spinal cord injury in mice (Zhang et al., 2022). At baseline, transplanted NSCs tended to differentiate towards astrocytes in the presence of an M1 proinflammatory phenotype of surrounding microglia. By contrast, spinal cord injury in aldose reductase inhibition or in aldose reductase deficient mice favored an M2 microglial phenotype, associated with differentiation of NSCs toward a neuronal phenotype and improved motor function. Aldose reductase catalyzes the conversion of excess glucose to sorbitol in the polyol pathway, and has been implicated in activation of microglia (Chang et al., 2019). Thus, metabolic factors in stem cell transplant recipients clearly influence the inflammatory milieu, which in turn impacts the differentiation and survival of transplanted stem cells. These studies underscore the need for understanding stem cell interactions with host

metabolic microenvironments in order to optimize the efficacy and translation of cell-based therapies.

Stem cell preconditioning

One domain in which metabolic contributors to stem cell performance, and indeed metabolic manipulation, has had greater study is in the realm of ischemic stroke (Bernstock et al., 2017; Yu et al., 2013). It is known that stem cells enter a hostile environment of hypoxia, excitotoxicity, and inflammation when transplanted acutely after stroke. As a result, there is a high degree of cell death for both endogenous and exogenous stem cells (Othman and Tan, 2020). Efforts to combat this are described as stem cell "preconditioning" using approaches such as genetic modifications (Wei et al., 2017a; Xue et al., 2019) or engineered biomaterials (Moshayedi et al., 2016). Alternatively, simple exposure to hypoxic culture conditions appears to result in transcriptional changes that improve metabolic profiles (Wei et al., 2017b). The mechanism underlying this observation is currently under investigation and may be multifactorial. Certainly, the activation of hypoxia inducible factors HIF-1α and HIF-1β is logical, with many potential downstream metabolically active targets, including VEGF, erythropoietin (EPO), sodium-calcium exchanger-1, protein kinase D1, lactate dehydrogenase A, and uncoupling protein 2 (Dehne and Brune, 2009; Greer et al., 2012; Semenza, 2011; Zhang et al., 2019). Interestingly, given the central role of glucose in stem cell and neuronal metabolism, the glucose transporters GLUT3 and glucose-6-phosphate transporter are also induced by HIF-1α after hypoxia (Thamotharan et al., 2013). Other mediators of stem cell preconditioning include EPO (Theus et al., 2008; Wei et al., 2012) or involve an increase in the formation of connexin hemichannels and ATP release (Jaderstad et al., 2010).

Further methods to induce stem cell preconditioning include exposure to compounds such as minocycline (Sakata et al., 2012b), doxycycline (Malik et al., 2013), interleukin-6 (Sakata et al., 2012a), adjudin (Zhang et al., 2017), resveratrol (Yao et al., 2021), or sodium butyrate/nicorandil (Hosseini et al., 2018), or even direct electrical stimulation (George et al., 2017). Again, growth factor secretion and/or angiogenesis appears to be engaged in these processes and are under further study. Notably, the AMPK activator metformin also appears to impart a beneficial effect on stem cell transplants. In an endothelin-1 rat model of stroke, co-treatment with metformin and human iPSC-NSCs resulted in improved proliferation, differentiation, and reduction of human leukocyte antigen (HLA)-A expression in stem cells (Ould-Brahim et al., 2018). Reduction in HLA-A or other antigen presenting molecules may help prevent graft rejection. While detailed metabolic studies of metformin and effects on transplanted stem cells were not performed, this study underscores the complex interplay between metabolism in the periphery, the CNS, injured tissue, and stem cells.

Conclusions

Stem cell therapies for neurologic conditions impart a range of metabolic effects for the CNS as well as for the stem cells themselves (Figures 1 and 2). At baseline, the interaction between normal metabolism, impaired metabolism, and neurologic diseases is complex and poorly understood. Adding in stem cells, with their metabolic interactions with both local

microenvironments as well as systemic processes, increases the combinatorial complexity of underlying metabolic and pathologic pathways. However, achieving therapeutic impact on host metabolism using the cellular capabilities of stem cells is a promising paradigm to address a wide range of neurologic conditions. Furthermore, emerging understanding regarding local environmental effects on stem cell metabolism may optimize the efficacy of stem cell treatments. It is apparent that much more detailed, high-quality research in this field is needed, and ongoing study is certain to yield great steps forward in enabling the translation of stem cell therapy for neurologic diseases and injury states. With this increased understanding of the interplay between stem cells and metabolic parameters in the brain, the success of stem cell therapy can ultimately be improved.

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Abbreviations

ALS	amyotrophic lateral sclerosis
AMPK	AMP-activated protein kinase
CNS	central nervous system
COXIV	cytochrome c oxidase subunit 4
CREB	cAMP response element-binding protein
EPO	erythropoietin
ESC	embryonic stem cell
FAD	flavin adenine dinucleotide
FDG-PET	fluorodeoxyglucose-positron emission tomography
FOXO	forkhead box class O
GALE	urine diphosphate-galactose 4-epimerase
GLUT	glucose transporter
HIF	hypoxia-inducible factor
HLA	human leukocyte antigen
iPSC	induced pluripotent stem cell
PGC-1α	peroxisome proliferator-activated receptor-gamma coactivator 1α
mTOR	mammalian target of rapamycin

NAD+	nicotinamide adenine dinucleotide
NRF-1	nuclear respiratory factor 1
NSC	neural stem cell
TOMM20	translocase of outer mitochondrial membrane 20
UDP	urine diphosphate
VEGF	vascular endothelial growth factor

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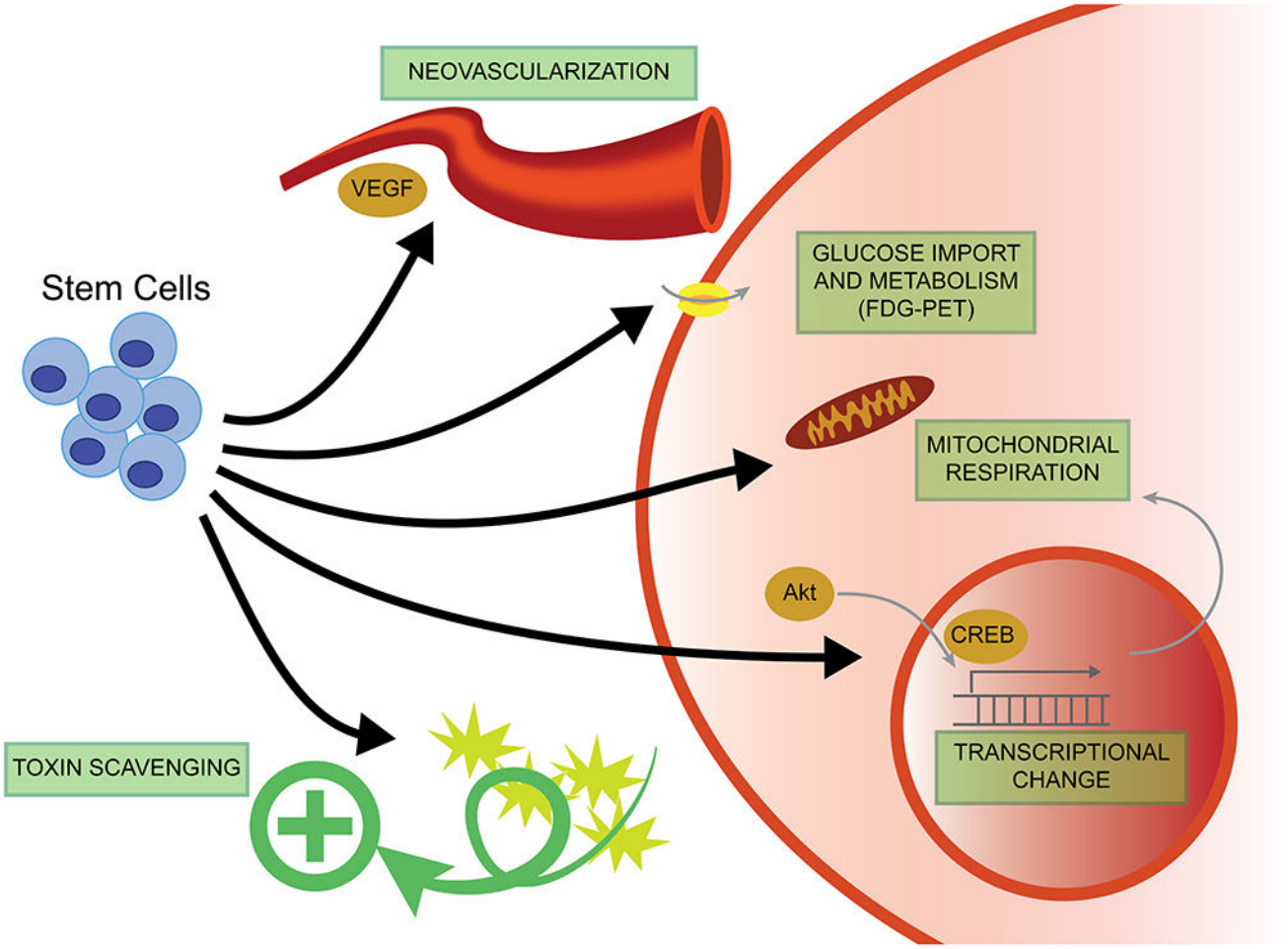

Figure 1: Metabolic implications of stem cell therapies in the CNS.

Although precise mechanisms have yet to be delineated, stem cells appear to have multimodal beneficial effects on neuronal metabolism. Stem cells may directly affect glucose metabolism and transport, which is often visualized using fluorodeoxyglucose-positron emission tomography (FDG-PET). Stem cells may also scavenge toxic metabolic byproducts. Mitochondrial proteins, which could mediate normalization of glucose metabolism and other pathways, represent a further downstream target of stem cell signaling. Secreted growth factors, such as VEGF, may also mediate metabolic repair via vascular remodeling.

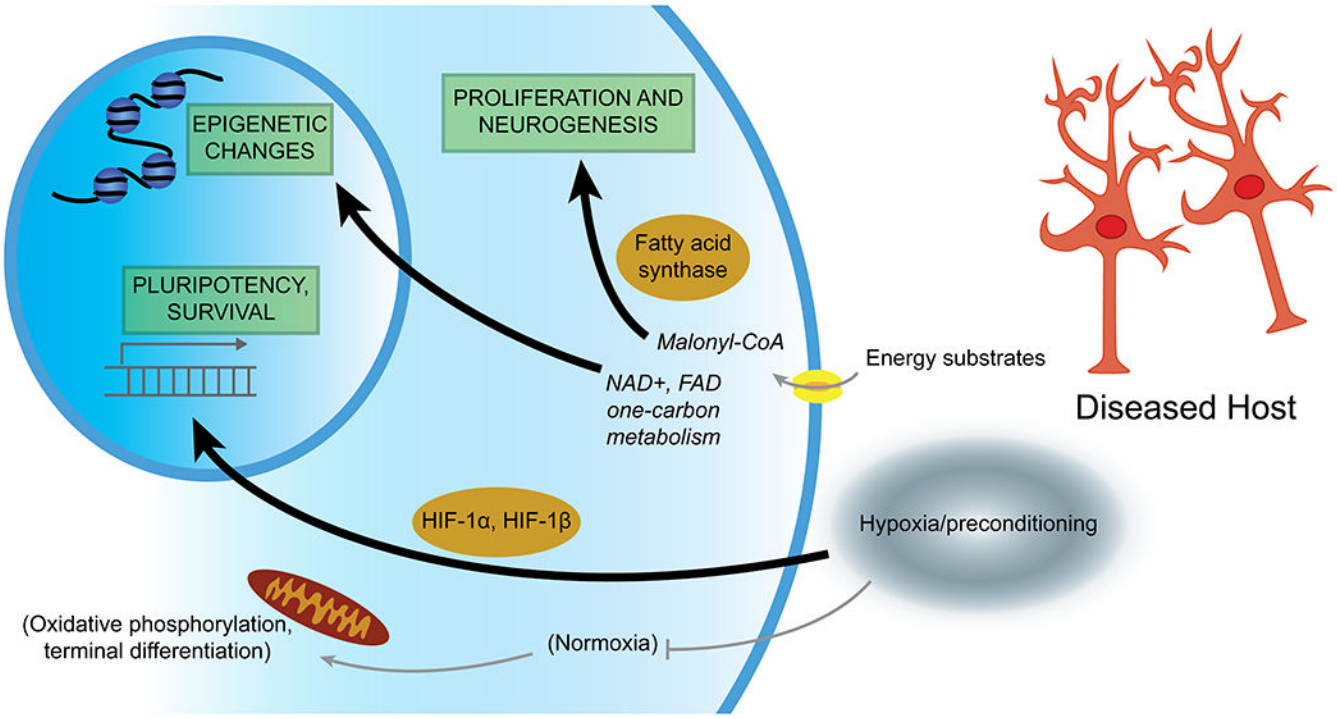

Figure 2: Environmental and host metabolic influence on stem cells.

Stem cells are affected by metabolic processes both from their source (carrying resultant epigenetic changes), metabolic changes resulting from *in vitro* culture, and also face pathologic metabolic signaling in the target tissue. Relative levels of energy substrates appear to influence the biology of proliferation and maintenance of a pluripotency, versus commitment towards terminal differentiation. Many epigenetic alterations resulting from metabolic conditions may also be carried with transplantation and may influence downstream efficacy. “Preconditioning” of stem cells prior to transplant, for example using relative hypoxia, may be a way to improve resilience of transplanted cells and maximize therapeutic benefits.