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Mlody, B. and Lorenz, C. and Inak, G. and Prigione, A.

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Energy metabolism in neuronal/glia induction and iPSC-based modeling of brain disorders

Authors: Barbara Mlody, Carmen Lorenz, Gizem Inak, Alessandro Prigione[§]

Affiliation: Max Delbrueck Center for Molecular Medicine (MDC), Berlin, Germany.

[§]Contact information:

Alessandro Prigione, M.D. Ph.D.

Robert-Roessle-Str. 10, D-13125 Berlin-Buch, Germany,

Tel: 0049-30-9406-2871, Fax: 0049-30-9406-3696,

Email: alessandro.prigione@mdc-berlin.de.

Website: www.mdc-berlin.de/42289824/en/research/delbrueck_fellows/Alessandro_Prigione

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Abstract

The metabolic switch associated with the reprogramming of somatic cells to pluripotency has received increasing attention in recent years. However, the impact of mitochondrial and metabolic modulation on stem cell differentiation into neuronal/glial cells and related brain disease modeling still remains to be fully addressed. Here, we seek to focus on this aspect by first addressing brain energy metabolism and its inter-cellular metabolic compartmentalization. We then review the findings related to the mitochondrial and metabolic reconfiguration occurring upon neuronal/glial specification from pluripotent stem cells (PSCs). Finally, we provide an update of the PSC-based models of mitochondria-related brain disorders and discuss the challenges and opportunities that may exist on the road to develop a new era of brain disease modeling and therapy.

Mitochondrial remodeling in cell fate specification

The majority of cellular energy in form of ATP is provided through oxidative phosphorylation (OXPHOS) by mitochondria. Mitochondria are also involved in the metabolism of amino acids, fatty acids, and steroids, and contribute to cell signaling through the modulation of reactive oxygen species (ROS), calcium homeostasis, and apoptosis [1]. Furthermore, intermediate metabolites can cross-talk to the nucleus acting as epigenetic regulators [2].

In low oxygen environments, a typical conversion process of 1 molecule of glucose results into 2 molecules of ATP through glycolysis in the cytosol, which terminates with the secretion of lactate into the extracellular environment. Under normoxic conditions, the 2 molecules of pyruvate, generated through glycolysis, can enter the mitochondria and undergo further oxidation in the tricarboxylic acid (TCA) cycle, leading to the production of additional 34 molecules of ATP [3]. However, under conditions requiring high proliferative rates, this mitochondrial-based energy generation may be shut-down despite the presence of normal oxygen concentration [4]. This situation, known as aerobic glycolysis or Warburg effect, was first described by Otto Warburg in the context of cancer [5]. Recent studies demonstrated that a Warburg-like effect may also represent a defining feature of stem cells [6–8].

Since distinct cell types have different energy demands, regulation of mitochondria may represent an essential process allowing the cells to meet their biological requirements. The metabolic identity of cells may in fact be influenced not only by changes in the expression of metabolic genes, but also by modulation of mitochondrial dynamics and mitochondrial DNA (mtDNA) copy number [9,10]. In particular, energy metabolism is shifted towards glycolysis in stem cells, whose mitochondria appear round-shaped with poorly-developed cristae [11,12]. This is in sharp contrast to cells with high energy demands, like muscle cells and neurons, where mitochondria are abundant in number and exhibit tubular-like morphology and cristae-rich structures [13].

As a consequence, acquisition of a distinct metabotype may also modulate cellular identity. Accordingly, dysregulated TCA metabolites, so called oncometabolites, can contribute to cancer cell transformation [14,15]. This has also become evident in the process of reprogramming somatic cells into induced pluripotent stem cells (iPSCs), where early metabolic reconfiguration may dictate the changes in proliferative capabilities and epigenetic reconfiguration which ultimately enable the acquisition of a self-renewing pluripotent cellular state [16–18]. Indeed, inhibiting mitochondrial function promotes pluripotency [19–22], while stimulation of mitochondrial biogenesis induces stem cell differentiation [23–25].

Mitochondria are particularly crucial for the functionality of neuronal cells. Neurons are highly active post-mitotic cells that rely on localized bioenergetics and calcium buffering at presynaptic compartments to allow the firing of action potentials [26,27]. It is therefore not surprising that diseases affecting mitochondrial function mainly manifest in form of neurological conditions. This is the case for classical mitochondrial disorders, which are caused by mutations in the mtDNA [28,29]. Moreover, dysfunctional mitochondria are commonly observed in neurodegenerative diseases including Huntington’s disease, Parkinson’s disease, and Alzheimer’s diseases [30,31].

Here, we review the recent developments in the study of mitochondrial and metabolic regulation in the establishment of neuronal identity and provide an overview of the mitochondrial-related phenotypes that have been observed using stem cell-based models of neurological disorders.

Brain energy metabolism

Sufficient brain energy supply is probably the most unneglectable task of the human body. The human brain consumes up to 20% of total body energy even though it accounts only for 2% of the total body weight [32]. It was shown already over 60 years ago that glucose is the obligatory energy substrate for the brain, where it is almost fully oxidized [33].

However, some part of glucose entering the brain also yields lactate following aerobic glycolysis [34,35].

At the cellular level, aerobic glycolysis and lactate production are considered to be metabolic features of glia cells [36]. In fact, down-regulation of glycolytic genes has been found to specifically impair glial physiology [37]. According to the astrocyte-neuron-lactate shuttle (ANLS) hypothesis [38], the lactate produced through astrocytic glycolysis is taken up by neurons, which can convert it into pyruvate for ATP generation in the mitochondria through OXPHOS [37]. The employment of lactate-derived energy generation may allow neurons to re-route glucose into the pentose phosphate pathway (PPP), which generates nucleotide precursors and contributes to antioxidant defense through the production of glutathione [39–42].

Oligodendrocytes might also be metabolically coupled to the axonal compartment to provide lactate to myelinated axons [36,43]. The same may be true also for Schwann cells, which provide peripheral axons with energy-rich metabolites independently from the presence of myelin [44]. A recent work of Mächler et al. employed a genetically encoded FRET sensor in combination with two-photon microscopy to monitor lactate *in vivo*, which confirmed the presence of a lactate gradient existing between astrocytes and neurons [45].

The reason underlying this metabolic compartmentalization between neuronal and glial cells was originally thought to be related to the morphological features of neurons. The long and complex axon extension and branching was believed to require energy-consuming transport processes to balance the metabolic costs of impulse conduction and membrane repolarization [46]. However, the majority of the energy usage seems to occur locally at the level of synapses [47]. On the other hand, the conductance of the action potential through the axons has been found to cause only minimal dissipation of energy [48]. The synaptic compartment may thus represent the major site of mitochondrial respiration within neurons, thereby accommodating its specific expenditure. Mitochondria within synapses may

additionally exert a key role of calcium buffering. In fact, tight calcium regulation is critical for neuronal firing and its excessive influx may trigger the apoptotic cascade [27,49]. Conversely, local glycolysis-derived bioenergetic support may take place within the axons [50]. Finally, glycolysis-derived bioenergetics may be important during neurogenesis, early neural development, and synaptic plasticity [34,35].

Other important energy metabolites released from astrocytes to neurons are ketone bodies, which are derived from fatty acids [51] or leucine [52]. Under particular conditions, such as fasting, uncontrolled diabetes, or maternal milk diet in newborns, ketone bodies are responsible for sustaining the energetic requirements of the brain [32]. Astrocytes have also an important role in lipid metabolism, and the cholesterol pathway in particular. The central nervous system contains 25% of the total-body cholesterol [53]. Brain cholesterol is produced in the astrocytic compartment, bound to apolipoprotein E, and eventually carried to the neighboring neuronal cells [54].

Finally, the heterogeneity of mitochondria in the brain is important for ensuring correct neuron-astrocyte interactions with respect to nitrogen metabolism, which is connected to the glutamine-glutamate-cycle and the antioxidant response via glutathione [55]. Excess ammonia is toxic to the central nervous system and its concentration in the brain must be kept low. This is accomplished by the high activity of glutamine synthetase, which is localized in astrocytes [56] and which permits efficient detoxification of incoming or endogenously generated ammonia. On the other hand, glutamine is released from astrocytes to be taken up by neurons, where it is converted back to glutamate by the action of glutaminase [57].

Taken together, brain cells exhibit unique metabolic hallmarks, due to their specific biological requirements, morphological properties, and inter-cellular coupling. These features need to be taken in consideration for the appropriate generation of neuronal and glial derivatives from stem cells and for the development of stem cell-based models of neurological disorders (**Figure 1**).

Mitochondrial and metabolic reconfiguration in neuronal/glia commitment

The differentiation of stem cells into neurons occurs rapidly and globally during the development of the nervous system. In the adult brain, neurogenesis can still take place within specific brain regions [58,59]. In particular, residual populations of multipotent stem cells exist in the subgranular zone of the dentate gyrus in the hippocampus and in the subventricular zone of the cortex [60,61]. These multipotent stem cells, defined as neural stem cells (NSCs) or neural progenitor cells (NPCs) retain the potential to give rise to the three cellular identities comprising the mammalian central nervous system, i.e. neurons, astrocytes, and oligodendrocytes.

The commitment of stem cells towards the neural lineage is accompanied by defined chromatin remodeling [62–64]. Accordingly, distinct post-translational histone modifications, such as methylation, acetylation, deacetylation, phosphorylation, each occurring at specific sites and amino-acid residues, have been associated with specification of neuronal and glial cell types [65,66]. Hence, during neural induction, multiple cellular mechanisms need to be simultaneously regulated, requiring finely-tuned metabolic adaptations.

NPCs reside in their niches under hypoxic conditions and therefore have to rely on a metabolic state allowing the maintenance of stemness. The transcription factor FoxO3 has been found to influence the state of NPCs *in vivo* and to be necessary for their self-renewal by regulating genes involved in oxidative stress response and glucose metabolism [67,68]. During neuronal differentiation, a switch towards normoxia occurs, leading to FoxO3 repression and consequent elevation of ROS levels. Accordingly, increased ROS concentrations are believed to prime NPCs for differentiation by activating the eicosanoid pathway [69].

Within NPCs generated *in vitro* from pluripotent stem cells (PSCs), mitochondrial structure and functionality appeared indistinguishable from that of brain-derived NPCs [70].

During neural induction of PSCs into NPCs, globular-like mitochondria convert into elongated-like structures with clearly developed cristae and dense matrices [70] [Lorenz et al, unpublished]. This is paralleled by an increase in mitochondrial mass and mitochondrial DNA content [71]. In addition, the remodeling of mitochondrial morphology during neural induction is accompanied by changes in the energy metabolism. Highly proliferative NPCs derived from human embryonic stem cells (ESCs) were found to exhibit low ATP turnover possibly due to high glycolytic rates [72]. However, our unpublished results suggest that, in spite of these low ATP levels, human PSC-derived NPCs rely more on OXPHOS-based metabolism and show decreased lactate production and reduced expression of glycolytic genes as compared to undifferentiated PSCs (Lorenz et al, unpublished).

Regulation of mitochondrial biogenesis may also impact neural differentiation. NPCs and newly generated neurons have been found to express elevated levels of PGC1 α (peroxisome proliferator-activated receptor gamma coactivator 1 alpha) [73], which is a master regulator of mitochondrial biogenesis [74]. Moreover, knockout of PGC1 α in mice causes cellular vacuolization in several brain regions [75], further implying PGC1 α in the dynamic process of neuroplasticity.

Importantly, neural differentiation and neural development may also be dependent on mtDNA integrity. The mitochondrial genome is notably susceptible to oxidative damage due to ROS which are common by-products of OXPHOS and concentrate in the mitochondrial matrix [76]. Oxidative damage may in turn interfere with mtDNA transcription and replication and therefore impact the activity of the electron transport chain (ETC). In fact, failure to maintain mtDNA integrity has been found to lead to impaired neuronal maturation [77]. Therefore, it is of utter importance to verify the mtDNA sequence during *in vitro* reprogramming and further differentiation into neuronal cells. Using Sanger-based whole mtDNA sequencing, we observed that the mitochondrial genome sequence, including

individual variants, is entirely retained during iPSC generation from patient fibroblasts as well as during the conversion of iPSCs into NPCs (Lorenz et al, unpublished).

During differentiation of human NPCs into motor neurons, mitochondrial biogenesis is elevated while mitochondrial mass remains unchanged [78]. Differentiating cells increase their mitochondrial components, leading to enhanced bioenergetic capacity. Hence, the generation of motor neurons from NPCs requires ATP synthesis coupling and low glycolytic flux [78].

Similarly, neuronal differentiation of mouse ESCs into dopaminergic neurons has been shown to fail when mitochondrial complex III was inhibited with Antimycin A [20]. Following this inhibition, the expression of pluripotency-associated protein OCT4 remained elevated and was accompanied by a concomitant increase of HIF1a protein. Therefore, blocking mitochondrial respiration may lock stem cells in their glycolysis-dependent undifferentiated state, thereby preventing the acquisition of an OXPHOS-dependent neuronal identity.

Brunet et al. (2004) investigated changes in phenotypic and metabolic markers upon differentiation of mouse NPCs into astrocytes. Together with the acquisition of glial marker expression and associated morphological transformation, the authors observed increased expression of the glutamate transporter GLAST and the monocarboxylate transporter MCT1, which is needed for appropriate lactate release and is thus in agreement with the ANLS hypothesis [79].

In addition to rapid neuronal differentiation from PSCs [80], mature neurons/glia may also be generated through direct conversion from adult/somatic cells [81–83]. This can be achieved by forced over-expression of key neuronal/glial-associated transcription factors which can enable the conversion of both human and mouse fibroblasts into neurons or astrocytes [81,84]. Moreover, astrocytes may also be directly converted into neurons *in vivo* [85]. Importantly, Gascón et al. recently revealed that the starting metabotype of the cells is a

key modulator of the direct conversion of mouse fibroblasts and astrocytes into neurons [86]. In fact, metabolic restructuring and ectopic expression of the mitochondrial anti-apoptotic protein Bcl-2 were found to promote neuronal differentiation. These findings suggest that modulation of energy metabolism may represent a central mechanism enabling the acquisition of a novel cellular identity not only in the case of reprogramming towards pluripotency or differentiation into mature cells, but also during trans-differentiation. Further studies will be required to molecularly dissect the mitochondrial and metabolic modifications, and their associated epigenetic regulation, taking place during the direct generation of neurons and astrocytes from somatic cells.

iPSC-based modeling of brain disorders

Human diseases associated with mitochondrial impairment commonly cause neurological dysfunction. Indeed, although single symptoms may differ, mitochondrial disorders mostly affect the nervous system [28]. Mitochondrial disorders are particularly challenging since mitochondria are under combined genetic control of both nuclear and mitochondrial genome [31,87]. Mutations in either genome may lead to altered function of the proteins or RNA molecules residing in the mitochondria directly or indirectly. Furthermore, because of the multi-copy nature of mtDNA, the expression and severity of mitochondrial disease symptoms may depend on the level of mutation heteroplasmy (amount of mutated mtDNA molecules over wild-type molecules). Additionally, there exist a number of neurological conditions associated with impaired mitochondrial function, including more frequent neurodegenerative disorders such as Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis [88].

In all these diseases, the modeling systems may not fully recapitulate the human neural phenotypes [89]. In fact, given the inaccessibility of the affected human neural cells, the advances in understanding the underlying molecular mechanisms are particularly hampered

for neurological diseases. This is particularly true for mitochondrial disorders, for which no animal model exist and for which cellular models, such as cybrids [90], fail to reproduce the metabolism of the susceptible neural cells and the patient-specific nuclear/mitochondrial genome match. Hence, the development of novel therapeutic options for mitochondria-associated neurological diseases is highly needed, together with the establishment of innovative strategies to achieve this goal.

Modeling neurological disorders via iPSCs holds great promise. In the context of mitochondrial-related diseases, the most striking property of iPSCs is that they would enable the generation of disease-relevant cell types carrying both the mitochondrial and nuclear genetic background of the patients. This critical feature would enable the investigation of genotype-phenotype correlation within the appropriate cellular environment, thereby allowing the dissection of the disease pathways and the specific contribution of neuronal/glial cells in the pathogenesis.

Nonetheless, key challenges and limitations still exist when using patient-specific neural cells for the study of brain disorders, as discussed in a recent opinion piece [91]. Critical aspects include the derivation of fully mature human neuronal and glial subtypes in a cost-effective and time-efficient manner, the achievement of pure populations, and the establishment of an *in vitro* system able to recapitulate the complex brain-specific metabolic interplay between the different brain populations. Moreover, epigenetic factors and somatic mosaics may add additional layers of complexity that may further hinder successful PSC-based modeling of brain disorders [91,92] (**Figure 1**).

iPSC models of mitochondrial neurological diseases

To date, a few iPSC-based models of mitochondrial DNA disorders have been reported. MELAS (Mitochondrial myopathy, Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes) [93] was recently investigated using iPSCs. This was accomplished by

several groups [93–98]. A common feature identified by these studies was that the original heteroplasmy level present in the patient fibroblasts can undergo changes before or during reprogramming. This phenomenon may thus lead to mutation-rich and mutation-free iPSC lines, as we had previously predicted when we performed whole-mtDNA pyrosequencing of control fibroblasts and related control iPSCs [99].

Importantly, the investigation of MELAS mutation during iPSC differentiation into neural-like cells demonstrated impaired mitochondrial dynamics and active complex I degradation through an autophagy-mediated mechanism [96]. These data indicate that the cellular context may actively modify mtDNA segregation and manifestations, and that complex I may be specifically down-regulated within neurons carrying the MELAS-causing mtDNA mutation m.3243A>G [96]. Furthermore, the metabolic defects of NPCs derived from mutation-rich MELAS iPSC lines were found to be corrected within NPCs that were obtained from mutation-free iPSC lines [97]. This further implies iPSC-based studies as a powerful system for dissecting the molecular mechanisms of neural dysfunction associated with mtDNA mutations.

Leigh syndrome (LS), the most detrimental mitochondrial disorders causing infantile subacute necrotizing encephalomyelopathy, has also been recently being tackled using PSCs [97]. iPSCs derived from patient fibroblasts contained unaltered levels of the homoplasmic mutation 8993T>G. Using somatic cell nuclear transfer (SCNT), the authors replaced the patient mitochondrial genome and therefore enabled the correction of the metabolic phenotype identified in differentiated cells carrying the mutation. This implies that stem cell-related technologies may not only allow the dissection of disease mechanisms but also potentially enable cellular replacement applications using genetically corrected PSC-derived cellular progeny.

A mitochondrial gene replacement technology-based work has also been undertaken in the context of Leber's Hereditary Optic Neuropathy (LHON), which is due to homoplasmic

mtDNA mutations in the complex I and causes degeneration of retinal ganglion neurons and blindness in young adults [28]. Iyer et al. (2012) introduced LHON pathogenic mutation into human ESC-derived NPCs [100]. Further studies using this model for the derivation of various neuronal and glial cell types may enable the investigation of disease-associated mechanisms.

Nuclear mutations of mitochondrial proteins may also cause mitochondrial brain disorders. Mouse ESCs have been recently generated from blastocysts harboring a deletion of the nuclear gene *NDUFS4* [101], which encodes for a Complex I protein whose mutation has been associated with Leigh syndrome [102]. Interestingly, the generated ESCs displayed aberrant gene expression patterns during embryoid body (EB)-based differentiation and astrocytes induction. Further detailed analysis using this system may allow identifying the bases for the mutation-associated neurological defects.

Hick et al., (2013) generated iPSCs from patients with Friedreich's ataxia (FRDA), a recessive neurodegenerative disorder caused by expanded GAA trinucleotide repeats within the gene encoding for the mitochondrial protein frataxin [103]. Neurons derived from FRDA-iPSCs recapitulated the characteristic features of the disease terms of GAA expansion as well as FRDA instability. Importantly, impaired mitochondrial function could be observed in derived neuronal cells, including decreased mitochondrial membrane potential and progressive mitochondrial degeneration. Hence, the iPSC system may represent a promising tool for advancing the understanding of the mechanisms of action and brain targeting of mitochondrial disorders due to both nuclear and mitochondrial mutations.

Mitochondrial impairment in iPSC models of brain disorders

The mitochondrial state has also been investigated within neuronal cells differentiated from iPSCs derived from patients affected by classical neurodegenerative disorders. Cooper et al. (2013) analyzed iPSC-derived neural cells carrying mutations in the PINK1 (PTEN-

induced putative kinase 1) and LRRK2 (leucine-rich repeat kinase 2) genes causing Parkinson's disease (PD) [104]. Interestingly, they observed dysfunctional mitochondrial dynamics that could be rescued with coenzyme Q10, rapamycin, or the LRRK2 kinase inhibitor GW5074, emphasizing the importance of oxidative stress and mitochondrial dysfunction in the pathogenesis of PD. Likewise, Nguyen and the colleagues (2011) showed that LRRK2 mutant iPSC-derived midbrain dopaminergic neurons were susceptible to oxidative stress [105].

The work by Kiskinis et al. (2014), which combined stem cell reprogramming and genome engineering, shed light on the mechanisms at the bases of the selective cell death of motor neurons in patients with Amyotrophic Lateral Sclerosis (ALS) [106]. In particular, they showed that mutant SOD1 iPSC-derived motor neurons exhibited altered mitochondrial morphology and motility, suggesting a disruption of the delicate balance between ER signaling and neuronal excitability. In accordance, a reduction in voltage-activated sodium and potassium currents, which may be linked to deregulated calcium homeostasis, has been observed in ALS iPSC-derived motor neurons [107].

Recently, mitochondrial and metabolic alterations have been also demonstrated in iPSC-derived neural cells from patients with Huntington's disease (HD). In fact, NPCs carrying extended CAG repeats displayed disease-associated changes not only in electrophysiology and cell adhesion but also in energy metabolism, as shown by decreased intracellular ATP content and ATP/ADP ratio [108]. A proteomics-centered study by McQuade and colleagues (2014) compared unaffected and affected human HD-ESCs as well as terminal differentiated neural cells and found key differences in the expression levels of components of ETC complexes as well as loss of NADPH and fatty acid oxidation capacity and aberrant mitochondrial dynamics [109].

Finally, mitochondrial-associated alterations have also been detected in iPSC models of neurodevelopmental and psychiatric disorders. Robicksek et al. (2013) investigated iPSCs

from patients with schizophrenia and demonstrated that dopaminergic neurons failed to differentiate, whereas glutamatergic cells were not able to fully mature [110]. Impaired mitochondrial respiration was observed in both neuronal types as well as dissipation of mitochondrial membrane potential and disturbances in mitochondrial network structure. These mitochondrial phenotypes may possibly contribute to the identified loss of neuronal differentiation and connectivity. Accordingly, altered oxygen metabolism has been associated to the neurogenesis of iPSCs derived from a schizophrenic patient [111]. Although future studies are warranted to address the connection between neural differentiation and mitochondrial function in schizophrenia, the studies so far conducted highlight the potential that iPSC-based studies may bring to the dissection of the molecular mechanisms underlying complex psychiatric disorders.

Conclusion

Energy metabolism plays a key role in directing cell proliferation, differentiation, and reprogramming, as well as on the maintenance of stemness [112–114]. Given the high energy demand and the complex distribution of mitochondria in the brain, mitochondrial dysfunction can strongly affect neuronal/glial differentiation [77,115]. It is therefore not surprising that disturbances in mitochondrial energy metabolism are among the prominent causative factors in neurodegenerative and neurodevelopmental disorders.

Insufficient understanding of brain disease mechanisms may be due to the lack of appropriate model systems capable of recapitulating the human brain complex multi-cellular metabolic environment. In fact, when compared with other human diseases, such as cardiac-based dysfunctions, almost no novel therapeutic targets of brain disorders have been discovered in the past twenty-five years [116], making neurological diseases a huge burden for society.

In order to enable a new era of brain disease therapy, stem cell research should aim on establishing multi-cellular 3D *in vitro* systems coupled with nuclear and mitochondrial genome targeting that would take into account the specific metabolic features of the cells. This may potentially allow the generation of faithful modeling systems which could ultimately lead to the discovery of novel therapeutic targets and specific counteracting actions. In particular, detailed investigations of the connection between cell fate and metabolism should in future provide strategies for targeted differentiation from pluripotent stem cells and unveil novel opportunities for metabolic and pharmacological approaches against debilitating brain disorders.

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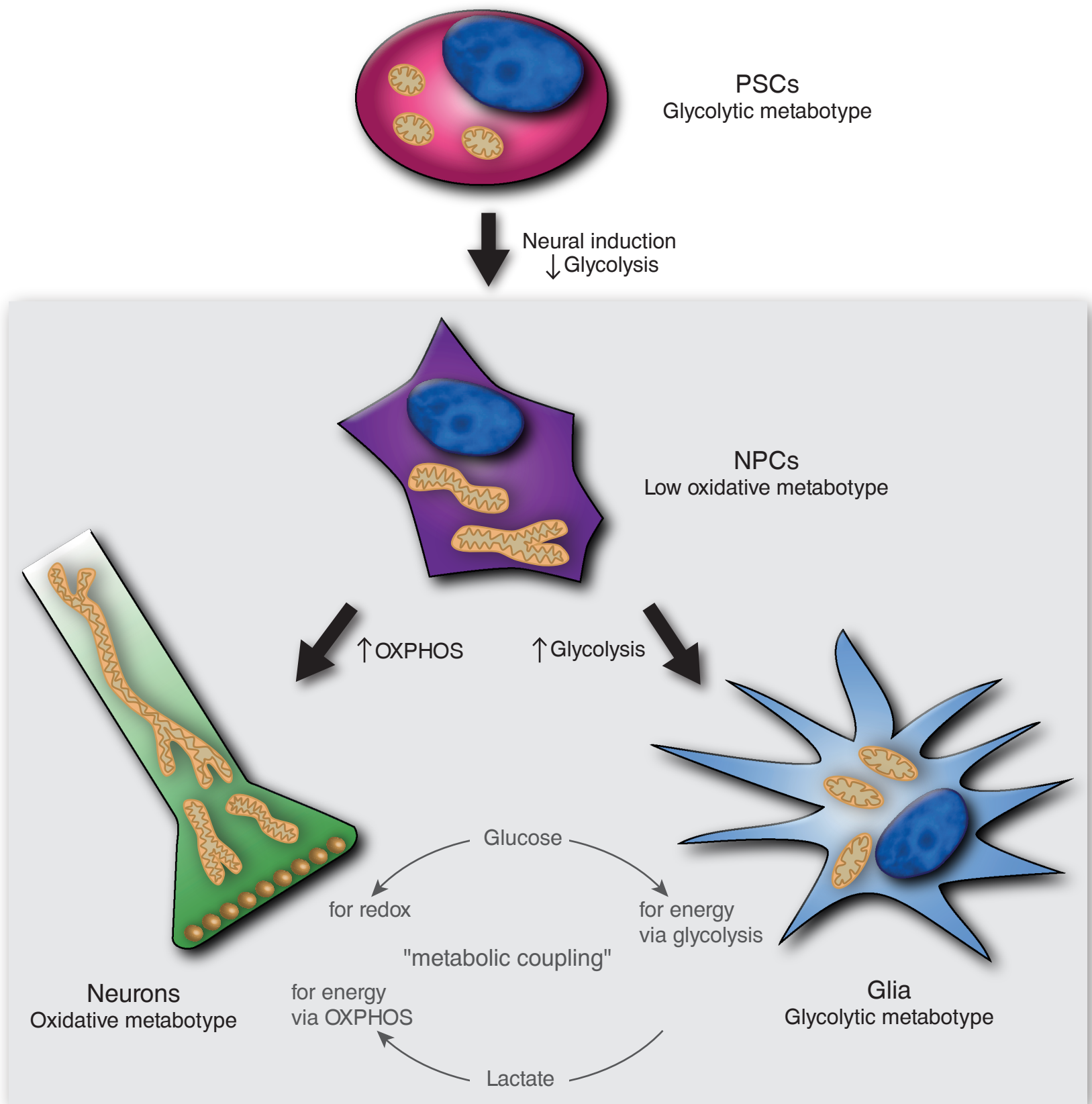
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Figure legend

Figure 1: Stem cell-based modeling of brain disorders

Pluripotent stem cells (PSCs) mainly rely on glycolytic metabolism and exhibit low rate of oxidative phosphorylation (OXPHOS), as identified by immature-like fragmented mitochondria. Upon conversion into neuronal progenitor cells (NPCs), mitochondrial maturation takes place, which is marked by organelle fusion and elongation and increased cristae complexity. Simultaneously, the glycolytic rate decreases, giving rise to a cellular metabotype mainly dependent on OXPHOS, although to a lower level compared to post-mitotic neurons. Mature neurons strongly rely on OXPHOS metabolism and utilize astrocyte-derived lactate for energy production. This leaves glucose neuronal consumption free to be employed for redox balance through glutathione generation via the pentose phosphate pathway. Glia cells, on the other hand, take up the majority of glucose for glycolytic-based energy derivation. This division of labor and metabolic compartmentalization is also reflected in the mitochondrial physiology. Neurons display a more complex mitochondrial network, especially within the regions with high energy demands like synapses, which also require the mitochondrial presence for local calcium buffering. PSC-derived NPCs, neurons and glia may serve as excellent models for brain diseases and could represent important platforms for the development of innovative treatment strategies.



Brain disease modeling & therapy

- Capture disease-relevant phenotypes ↔ Genetic/functional phenotypic correction
- Maintain complex interactions ↔ Dissect cell type-specific contributions
- Cellular replacement therapies ↔ Phenotypic screens for drug discovery