Review

Neuroimmunometabolism: A New Pathological Nexus Underlying Neurodegenerative Disorders

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Neuroimmunometabolism is an emerging field that examines the intersection of immunologic and metabolic cascades in the brain. Neuroinflammatory conditions often involve differential metabolic reprogramming in neuronal and glial cells through their immunometabolic sensors. The impact of such bioenergetic adaptation on general brain function is poorly understood, but this cross-talk becomes increasingly important in neurodegenerative disorders that exhibit reshaping of neuroimmunometabolic pathways. Here we summarize the intrinsic balance of neuroimmunometabolic substrates and sensors in the healthy brain and how their dysregulation can contribute to the pathophysiology of various neurodegenerative disorders. This review also proposes possible avenues for disease management through neuroimmunometabolic profiling and therapeutics to bridge translational gaps and guide future treatment strategies.

Key words: **neuroimmunometabolism; neuroinflammation; neurodegeneration; immunometabolic sensors**

Significance Statement

Neuroimmunometabolism intersects with neuroinflammation and immunometabolic regulation of neurons and glial cells in the CNS. There is emerging evidence that neuroimmunometabolism plays an essential role in the manifestation of CNS degeneration. This review highlights how neuroimmunometabolic homeostasis is disrupted in various neurodegenerative conditions and could be a target for new therapeutic strategies.

Introduction

Neuroimmunometabolism is a broad umbrella term for an emerging area of research that involves understanding how reprogramming of cellular metabolism can alter immune responses in the CNS (Larabee et al., 2020). The interface of immune regulation and metabolic states is essential for maintaining dynamic cellular balance in an organism (Watts et al., 2018; Larabee et al., 2020).

Metabolic control (also conventionally referred to as neuroenergetics) is essential in the brain, where there is a high metabolic demand. Despite comprising ~2% of the body mass, the brain consumes ~20% of energy substrates at rest, mainly to reverse ion fluxes that mediate synaptic and action potentials; this demand is elevated during activity-dependent processes (Mink et al., 1981; Attwell and Laughlin, 2001; Harris et al., 2012). Neurons are responsible for most of these energy demands, while glial cells serve as energy suppliers (Jha and Morrison, 2018). Efficient energy shuttling requires metabolic flexibility in microglia, astrocytes, and oligodendrocytes (Philips and Rothstein, 2017; Morita et al., 2019; Bernier et al., 2020). This is achieved through robust regulation by metabolic sensors, such as receptors, transporters, and enzymes that allow glial cells to expend energy in response to elevated neuronal demands. These regulators also modulate glial inflammatory responses through crosstalk between metabolic and immune signaling pathways (Robb et al., 2020a).

Neuroinflammation is an important cellular defense mechanism that involves an immune response to noxious and harmful stimuli (Mitra et al., 2020). The triggering, activation, and persistence of inflammation, mediated by glial cells, are influenced by environmental factors and genetic predispositions (Lucas et al., 2006). Circadian rhythms, age, and lifestyle choices (diet, exercise, drug abuse, etc.) also affect the glial metabolic and

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inflammatory profile and thus influence glial function (Marpegan et al., 2011; Garcia-Caceres et al., 2012; Camandola and Mattson, 2017; Lacagnina et al., 2017; Chi-Castaneda and Ortega, 2018; Jin et al., 2020; X. Wang et al., 2020). Neuroinflammatory responses entail reprogramming of several transcriptional and translational pathways in glial cells, resulting in the production of inflammatory cytokines and reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Mitra et al., 2020). These cellular adaptations involving concerted action of metabolic and immune functions are essential in balancing immunometabolic changes in a metabolically active organ, such as the brain.

It is unclear whether alterations in neuroimmunometabolism in neurodegenerative conditions drive or oppose disease progression. Neurodegenerative diseases are debilitating disorders of the CNS that are characterized by progressive loss of neurons leading to abnormalities in behavioral domains associated with cognition, movement, and affective functions (Granholm et al., 2008; Bowman et al., 2011; Levenson et al., 2014; Dugger and Dickson, 2017; Gitler et al., 2017). With the lack of effective disease-modifying therapeutic interventions and the limited translational success of potential drug molecules, it is imperative to revisit these diseases with a renewed perspective to identify novel and effective therapeutic targets. Degenerative disorders are typically characterized by dysregulation in many cellular processes, which include imbalances in intracellular mechanisms, such as cellular stress, aberrant clearance of cellular debris by the proteasome and lysosomes, and abnormal immunometabolic activity (Gan et al., 2018).

In this review, we focus on how immunometabolic imbalances across CNS neurons and glia can be investigated to better understand the pathophysiology of neurodegenerative diseases. We discuss the regulatory roles of immunometabolic substrates and sensors in the brain and detail the immunometabolic aberrations occurring in particular neurodegenerative conditions. Finally, we introduce an integrative approach to devise effective therapeutic measures.

Neuroimmunometabolic sensors

The relationship between metabolism and immune functions in the CNS is tightly regulated by several sensors ("immunometabolic sensors") that form a critical regulatory hub for maintaining homeostasis in the metabolic and immune pathways. Sensors predominantly comprise energy substrates, such as sugars, amino acids, and lipids, along with transporters/receptors that sense fluctuations in these substrates and trigger metabolic and biosynthetic cascades that use the substrates. These sensors, expressed in neurons and glia, provide necessary signals to alter the metabolic and immune status based on the overall energy demand (Argente-Arizon et al., 2017; Saravia et al., 2020). Each cell type in the brain exhibits a unique metabolic profile based on its functions. Switching between metabolic states can have detrimental consequences in cells' structural and functional properties. In this section, we describe regulation of some of these sensors across CNS cell types.

Sugar sensors

Glucose is the most important sugar for generating energy in the brain, and it acts as an essential precursor for neurotransmitter synthesis (Mergenthaler et al., 2013). Glucose homeostasis in the brain is tightly regulated through neuro-glia metabolic coupling (Afridi et al., 2020). Glucose is sensed and transported across the cell membrane by a saturable transport system composed of various glucose transporters (GLUTs) (Navale and Paranjape, 2016). These transporters, based on sequence polymorphisms, exhibit differential affinity and distribution across cell types in the CNS (Mueckler and Thorens, 2013). Neurons primarily express high-affinity GLUT3 transporters, while oligodendrocytes, microglia, and astrocytes use GLUT1 and GLUT5. GLUT1 is also expressed in brain vasculature to enable glucose transport across the blood–brain barrier (BBB); but unlike in glial cells, the form expressed in the vasculature is highly glycosylated (Jurcovicova, 2014). Additionally, sodium/glucose cotransporters and the Kir6.2 subunit of an ATP-sensitive potassium channel sense and enable glucose transport in neurons and astrocytes (M. Liu et al., 1999; Vega et al., 2006; Yu et al., 2013; Koepsell, 2020).

Although neurons express a high-affinity glucose sensor (GLUT3), they have a low level of glycolysis because of the rapid degradation of the rate-limiting glycolytic enzyme 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase, isoform 3 (PFKFB3) (Herrero-Mendez et al., 2009; Bolaños et al., 2010). Therefore, it has been suggested that glial cells in the brain uptake and metabolize more glucose than neurons, and neurons depend on glucose metabolites, such as lactate released by glial cells (Chuquet et al., 2010; Fünfschilling et al., 2012; S. Lee et al., 2012). There are conflicting reports indicating that neurons rely on direct glycolysis rather than lactate from astrocytes (Díaz-García et al., 2017; Díaz-García and Yellen, 2019). These reports suggest that the mechanism underlying metabolic interchange between neurons and astrocytes is still unsettled.

Astrocytes provide metabolic sustenance to neurons by detecting circulating glucose and transporting it to neurons (Fig. 1) (Jurcovicova, 2014). Both GLUT1 and GLUT2 are critical for this astrocytic function. Astrocytes have low levels of the malate-aspartate shuttle, which is generally responsible for the reduction of NADH to NAD^+ during glycolysis. Instead, in astrocytes, NADH reduces pyruvate to lactate, leading to high levels of lactate production. The lactate is then shuttled into neurons by the monocarboxylate transporter MCT4 where it supports oxidative metabolism before being imported back to astrocytes by MCT1 (Roosterman and Cottrell, 2020).

There is emerging evidence that oligodendrocytes also shuttle lactate to neurons. Lactate produced in the mitochondria of oligodendrocytes is essential for local axonal support, and disrupting this function leads to elevated extracellular lactate. Lactate shuttling to neurons is blocked on inhibition of the lactate transporters MCT1/2 and GLUT1 (Fünfschilling et al., 2012; Meyer et al., 2018).

Sugar metabolism in microglia depends on their activation state. Microglia normally survey their environment for indications of damage or infection. This surveillance is powered by oxidative phosphorylation (OXPHOS). When damage is detected, however, it triggers microglial activation, which involves conversion to pro-inflammatory or phagocytic states. Like other immune cells (Warburg, 1956; Palsson-McDermott and O'Neill, 2013), activated microglia upregulate glycolysis and move away from oxidative phosphorylation to meet the inflammatory demand (Moss and Bates, 2001; Chénais et al., 2002; Gimeno-Bayón et al., 2014; L. Wang et al., 2019; Lauro and Limatola, 2020). This shift from OXPHOS to glycolysis in microglia is because of upregulation of GLUT1, which is concomitant with increased synthesis of hexokinase and PFKFB3 (the rate-limiting enzymes of the glycolytic pathway) and activation of mammalian target of rapamycin (mTOR), which regulates transcriptional control of glycolysis in a process involving hypoxia-inducible factor-1α (HIF-1α) (Yecies and Manning, 2011; Saxton and Sabatini, 2017; Li et al., 2018; Rubio-Araiz et al., 2018). In

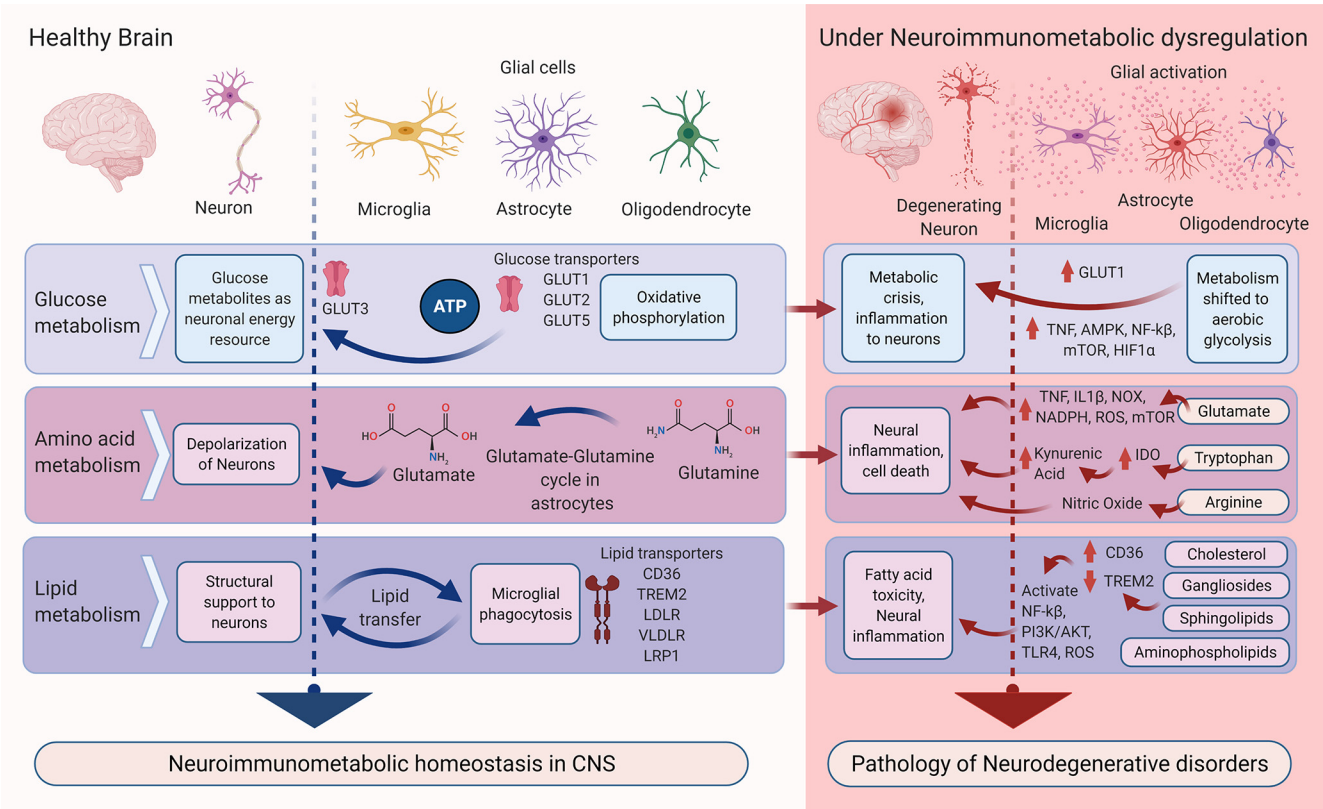

Figure 1. Predominant neuroimmunometabolic homeostasis in the healthy brain and its disruption in neurodegenerative conditions. In the healthy state (left, blue arrows), glucose, amino acid, and lipid metabolism occur in various cell types. Neuroimmunometabolism disrupts this homeostasis (right, red arrows) contributing to degenerative conditions. IDO, Indoleamine-2,3 dioxygenase; PI3K/AKT, phosphoinositide 3-kinases.

addition, activated microglia upregulate GLUT1 expression to promote glycolysis, which can be limited by inhibition of GLUT1 (L. Wang et al., 2019).

Although microglia are the primary inflammatory mediators of the brain, astrocytes also play an essential role. With their copious numbers and proximity to neurons, astrocytes can amplify inflammatory signals by releasing several proinflammatory chemokines and cytokines (Szepesi et al., 2018). This metabolically expensive inflammatory response requires astrocytes to rely on mitochondrial oxidation (Chao et al., 2019). Several *in vitro* studies have demonstrated that inflammatory challenges activate regulators of aerobic glycolysis, such as HIF-1α and AMP-activated protein kinase (AMPK) in astrocytes (Almeida et al., 2004; Brix et al., 2012). A similar metabolic switch occurs in the aging brain, where astrocytes decrease their trophic support to neurons and use energy substrates for their own metabolism (Jiang and Cadenas, 2014). An *in vivo* study in rats has shown that the switch to aerobic metabolism during aging is correlated with the activation of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), a regulator of innate and adaptive immunity (Jiang and Cadenas, 2014).

Outside the CNS, inflammation leads to uninterrupted glycolysis, which supplements the production of ATP to sustain the inflammatory mechanisms of macrophages and other immune cells (e.g., T cells), resulting in the amplification of pro-inflammatory chemokines and cytokines to fight the infection (Kaushik and Yong, 2020). This metabolic alteration in activated macrophages and T cells is linked to two major break points in the tricarboxylic acid (TCA) cycle, causing accumulation of citrate and succinate. The accumulation of succinate leads to the production of IL-6, IL-1β, and nitric oxide (NO), largely through a glycolytic flux from OXPHOS by activation of HIF-1α, while citrate accumulation reroutes the metabolism toward prostaglandin synthesis, the major metabolic pathway inducing inflammation in both the PNS and the CNS (Tannahill et al., 2013; Infantino et al., 2013; Jha et al., 2015; Ryan and O'Neill, 2017).

Overall, the results discussed above demonstrate that neurons and glia synergistically depend on glycolytic and substitute pathways of sugar metabolism for energy production to sustain metabolic homeostasis. Various sugar sensors can act as neuroimmunometabolic regulators, suggesting that sugars play an essential role in modulating several aspects of neuroimmunometabolic machinery and can be putative factors in disease pathologies.

Amino acid sensors

Although amino acids are not a primary energy precursor, they still play a critical role in neuroimmunometabolic programming (Xie et al., 2020). For example, the amino acid tryptophan is an essential precursor for coenzyme NAD^+ biosynthesis, which is critical for metabolic processes, such as glycolysis, the TCA cycle, and OXPHOS (Schröcksnadel et al., 2006). Tryptophan metabolism occurs through four different pathways, the most important being the kynurenine pathway (Kita et al., 2002; Gostner et al., 2020). Tryptophan is converted into kynurenine and downstream effector molecules by indoleamine-2,3 dioxygenase, a rate-limiting enzyme whose expression is elevated during inflammation, including the brain (Kwidzinski and Bechmann, 2007; O'Neill et al., 2016; Moffett et al., 2020). Tryptophan metabolic enzymes are expressed in both astrocytes and microglia. The key kynurenine metabolites quinolinic acid, 3-hydroxykynurenine, and kynurenic acid produce different inflammatory responses in

these glial cells. In astrocytes, kynurenic acid protects neurons by removing excess glutamate spillover, whereas quinolinic acid and 3-hydroxykynurenine inflict neurotoxic effects by activating the NMDAR NR2B subunit, which leads to excessive calcium influx (Guillemin et al., 2005; Tao et al., 2020).

Glutamate is another quintessential amino acid required for maintaining optimum metabolic performance of neurons and glia. In the healthy CNS, glutamate is the predominant excitatory neurotransmitter. After taking up glutamate via excitatory amino acid transporters (EAAT1 and EAAT2), astrocytic glutaminase hydrolyzes glutamate to glutamine, which is then transported to neurons (Fig. 1) (Yudkoff, 2017; Mahmoud et al., 2019). Glutamate also binds to glutamatergic receptors on microglia and acts as a chemotactic molecule to recruit microglia to sites of injury, where excess glutamate release catalyzes neural excitotoxicity (Domercq et al., 2013). Microglia produce ROS in response to glutamate stimulation via increased activity of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase (NOX) and NADPH. Microglia also release glutamate and exchange it with cystine through cystine/glutamate antiporter xCT (a membrane-bound Cl^--dependent antiporter) (Barger et al., 2007; Bridges et al., 2012; Mead et al., 2012; Domercq et al., 2013). Conversely, a neuroprotective role of glutamate has been reported in mixed cortical cultures, where estrogen receptor α and metabotropic glutamate receptor 1 interact to attenuate amyloid β ($A\beta$)-induced neurotoxicity (Spampinato et al., 2018). The precise downstream targets mediating these neuroprotective effects however remain to be investigated.

Glutamatergic homeostasis is disrupted under inflammatory conditions when the microglial inflammatory cytokines TNF and IL-1β impair the function of astrocytic EAATs (Domercq et al., 2007). In addition, conversion of glutamine to glutamate (glutaminolysis) in microglia activates mTOR signaling, halts autophagy, and creates a pro-inflammatory environment (Duran and Hall, 2012; Duran et al., 2012; G. Gao et al., 2020). Moreover, inhibition of glutamine synthetase, which catalyzes the reverse reaction of glutamate to glutamine, has been shown to enhance the inflammatory response of microglial cells (Palmieri et al., 2017). Based on these studies, one could speculate that astrocytes and microglia together play an essential role in maintaining the glutamine-glutamate balance, and any disturbance in this homeostasis can induce microglial neuroinflammation in the CNS.

The amino acid arginine has also been reported to influence immunometabolic mechanisms. Arginine is the starting substrate in the NO synthetic pathway, which involves the conversion of arginine to citrulline by the enzyme nitric oxide synthase 2 (Forstermann and Sessa, 2012). NO, the final product of this pathway, is an essential immunometabolite: it inhibits OXPHOS (Tengan and Moraes, 2017), thus shifting the balance toward the glycolytic pathway, a phenomenon that occurs in microglia exclusively during inflammation.

Lipid sensors

Brain lipid metabolism relies on both *de novo* local synthesis and peripheral lipid reserves. Lipids provide structural support to neurons, and intercellular exchange of lipids through microvesicles, lipoproteins, and nonesterified fatty acids (FAs) modulates energy and redox status (Tracey et al., 2018). Additionally, lipid sensing is essential for myelination by oligodendrocytes and debris clearance by microglia. After glucose metabolism, the brain draws a considerable amount of energy from lipid metabolism. Among many lipid sources, FA oxidation provides 20% of its total metabolic energy to the brain (Panov et al., 2014)). It is believed that FA oxidation occurs largely in astrocytes, but other glial and neuronal cells also use FAs, such as oleate and palmitate for oxidative metabolism (Ebert et al., 2003; Chausse et al., 2019). FA oxidation homeostasis also plays a major role in inflammatory responses in microglia. Polyunsaturated FAs can induce an anti-inflammatory phenotype in microglia, whereas saturated FAs can produce an inflammatory state (Namgaladze et al., 2014; X. Chen et al., 2018).

Microglia express several lipid-sensing receptors that remodel the microglial lipidome during cellular stress. Pattern recognition receptor cluster of differentiation 36 (CD36) is an essential lipid sensor that recognizes low-density lipoprotein (LDL) and $A\beta$ (El Khoury et al., 2003; Kim et al., 2008; D. Gao et al., 2010). Upon activation, CD36 influences inflammatory remodeling through uptake of palmitate, which is a ligand of Toll-like receptors (TLRs). TLR activation results in phagocytosis, and production of ROS (Li et al., 2019; Tzeng et al., 2019). CD36-containing microglia also express LDL receptor (LDLR), very-LDL receptor (VLDR), and LDL-receptor-related protein 1 (LRP1). These receptors regulate the endocytosis of different isoforms of apolipoprotein (APOE2, APOE3, and APOE4). APOEs act as a hub for lipid transfer between neurons and microglia (Loving and Bruce, 2020). Although APOE is thought to be a negative regulator of inflammation (Rebeck, 2017), its isoforms (APOE2, APOE3, and APOE4) perform a dual role in inflammatory mechanisms. While APOE3 and APOE4 attenuate $A\beta$-induced inflammatory responses in glial culture, both isoforms exert an inflammatory response in the absence of $A\beta$ (Guo et al., 2004). Further, the $\varepsilon 4$ allele of APOE4 is the most common risk factor for persistent neuroinflammation underlying cardiovascular and neurodegenerative diseases (Sullivan et al., 1997; Tu et al., 2009; Mannix et al., 2011; Zhu et al., 2012; Rodriguez et al., 2014). Concomitantly, inflammatory cytokines can regulate the levels of APOE (H. Zhang et al., 2011).

Another lipid sensor expressed in microglia is triggering receptor expressed on myeloid cells 2 (TREM2), which recognizes APOE, $A\beta$, and aminophospholipids for phagocytosis and autophagy in microglial cells (Hsieh et al., 2009). There is a lack of consensus regarding the role of TREM2 during inflammatory responses. A soluble form of TREM2 has been found to stimulate the production of inflammatory cytokines by activating phosphoinositide 3 kinase/protein kinase B (Zhong et al., 2017). On the other hand, loss of TREM2 mitigates neuroinflammation in a mouse model of Tau-mediated neurodegeneration (Leyns et al., 2017).

Cholesterol is yet another important substrate in immune signaling involving lipid metabolism (Fig. 1). Astrocytes synthesize cholesterol in the endoplasmic reticulum, and it is shuttled to the membrane by ATP-binding cassette transporters (Nieweg et al., 2009). Membranes enriched in cholesterol act as platforms for effective dimerization of TLR4, which promotes inflammation (Varshney et al., 2016). Depletion of membrane cholesterol can therefore alter the neuroinflammatory status of astrocytes. An increase in brain glucose metabolism has been reported after astrocyte-selective knockdown of sterol-regulatory-element-binding protein 2, a receptor-bound transcription factor that regulates genes involved in cholesterol biosynthesis and uptake (Ferris et al., 2017).

Sphingolipids are also key components of astrocytic lipid reserves. Neurons, astrocytes, and microglia act in concert to sustain sphingolipid metabolism in the brain; and in the inflammatory state, this homeostasis is disturbed by production of

inflammatory mediators through sphingolipid intermediate metabolites, such as ceramide and sphingosine-1-phosphate (J. Y. Lee et al., 2020). On the other hand, gangliosides, a class of glycosphingolipid, are produced by astrocytes in abundance and can regulate inflammatory status by triggering astrocytic autophagic pathways (Hwang et al., 2010).

Lipid metabolic coupling with neurons is tightly regulated by astrocytes. This is essential to avoid FA toxicity in neurons (Ioannou et al., 2018). Neurons typically have a low capacity to house the lipid droplets that store FAs to thwart toxicity and loss of mitochondrial membrane integrity. The lipid droplets act as an alternative energy source during stress and nutrient depletion (Jarc and Petan, 2019). Under constant stimulation, neurons produce ROS that catalyze the oxidation of FAs and thus build up lipid-induced toxicity. Astrocytes host lipid droplets and are able to clear FAs expelled from neurons. Additionally, astrocytes regulate transcription of putative targets that participate in energy metabolism and neutralization of oxidative species (Reynolds and Hastings, 1995; Unger et al., 2010; Rambold et al., 2015; Nguyen et al., 2017). Overall, this indicates that lipid biosynthetic and metabolic sensors have an essential role in regulating immunometabolic status of the CNS.

Neuroimmunometabolism and neurodegenerative disorders

Neurodegenerative diseases differ in multiple attributes, such as the brain regions affected, underlying molecular pathways, associated genetic and immunologic aberrations, and specific symptoms (Dugger and Dickson, 2017). The molecular mechanisms implicated in these diseases often include protein aggregation and associated neurotoxicity in the brain, for example, tau neurofibrillary tangles and amyloid plaques in Alzheimer's disease (AD), α-synuclein-containing Lewy bodies in Parkinson's disease (PD), and polyQ protein aggregates in Huntington's disease (HD) (Dugger and Dickson, 2017). Advances in brain imaging and systematic recording of clinical symptoms have contributed to better understanding of different stages of disease progression. But because of the complex and multifactorial etiologies of these diseases, the precise neurobiological underpinnings remain elusive. Although studies have elucidated the role of genetic and environmental factors that trigger neuroinflammatory conditions in these diseases, the contribution of neuroimmunometabolic factors to neurodegenerative pathophysiology is not well examined. Perhaps, that is why translational success in these diseases is limited. In this section, we look at different neurodegenerative disorders from the neuroimmunometabolic angle to highlight potential targets for better disease management (Fig. 2).

AD: a neuroimmunometabolic disorder?

Extracellular amyloid plaques and intracellular neurofibrillary tau tangles are the central pathologic hallmarks of AD. But therapies targeting amyloid and tau pathology have generally failed to exert any positive outcomes in clinical trials, suggesting that multiple associated cofactors play roles in disease manifestation (Banik et al., 2015). Recent reports show a correlation between inflammatory and immunometabolic pathways and amyloid and tau pathologies in AD models (Holland et al., 2018; McIntosh et al., 2019). There is accumulating evidence that metabolic disturbance plays an important role in the underlying microglial mediated neuroinflammation (Devanney et al., 2020). Furthermore, age-related decline in cerebral glucose metabolism (hypometabolism) is associated with cognitive loss in mild cognitive impairment and AD patients (Mosconi et al., 2008; Lin and Rothman, 2014), along with amyloid deposition and white matter disruption (Schilling et al., 2019). Glucose hypometabolism in AD brains is largely linked to mitochondrial calcium dysregulation in neurons, which may subsequently lead to cell death (Moreira et al., 2010). The presence of Aβ peptides in mitochondria may be another causative factor in neuronal death (Cha et al., 2012). Notably, some evidence, albeit limited, suggests that hypometabolism in AD is linked with disturbed homeostasis of GLUT1 and GLUT2, which is mostly expressed in glial cells, and GLUT3, which is predominantly expressed in neurons. While GLUT1 and GLUT3 levels are decreased in the cerebral cortex, the levels of GLUT2 are increased to compensate for the reduction in ATP production (Szablewski, 2016).

A role for astrocytes and microglia in disruptive metabolism has also been identified in the experimental models of AD. In cultured astrocytes derived from transgenic AD mice, exogenous Aβ can reduce glycolytic capacity by decreasing GLUT1 levels. This impairs glucose uptake and lactate production by astrocytes. Further, decreased levels of MCT1 reduce lactate transport to neurons (Merlini et al., 2011). In addition, calcium dysregulation in astrocytes may activate several pro-inflammatory regulators through NF-κB and HIF-1 pathways, responsible for ROS and NO production (Abramov et al., 2004; Hsiao et al., 2007; Schubert et al., 2009; Mesquita Dá et al., 2016; Shigetomi et al., 2019; Robb et al., 2020b). These studies strongly suggest a central role of glucose metabolism coupled with inflammation in inducing pathophysiological states in AD.

Exogenous introduction of Aβ or inflammatory stimuli, such as LPS, reduce oxidative metabolism of macrophages and microglia through activation of inflammatory cascades, and this leads to metabolically inefficient glycolysis (Rubio-Araiz et al., 2018; Finucane et al., 2019). A change in neuro-glial glycolytic flux was also found in a 76-year-old individual: magnetic resonance spectroscopy data revealed that there was a 28% decrease in TCA-cycle activity in neurons and a 30% increase in TCA-cycle activity in astrocytes compared with a 26-year-old individual (Boumezbeur et al., 2010). Finally, cultured microglia isolated from APP/PS1 mice, a transgenic model of AD, exhibit disrupted phagocytosis and chemotactic activity in tandem with an increased rate of glycolysis (Holland et al., 2018; McIntosh et al., 2019). This suggests that microglia adopt an altered neuroimmunomodulatory phenotype in AD, which may influence disease pathology.

Genome-wide association studies (GWASs) have revealed several predisposing genetic risk factors for AD, including variants of APOE4, TREM2, and TLR4, which are linked to metabolic functions and are highly expressed in microglia. It is demonstrated that APOE can trigger the formation of Aβ peptides in the brain of transgenic AD mice by using astrocytic cholesterol. APOE promotes two-way traffic of neuronal amyloid precursor protein from intracellular lipid clusters to increase the insoluble Aβ burden in the brain (H. Wang et al., 2021). The APOEε4 allele is one of the most investigated genetic risk factors for AD with a 15-fold increased risk for AD in people homozygous for this allele (Mosconi, 2013; Lumsden et al., 2020). Positron emission tomography (PET) studies of young adults (20-39 years of age) carrying APOEε4 alleles show reduced glucose metabolism in the cerebral cortex, similar to the pattern seen in the cortex of AD patients at progressive stages of the disease (Reiman et al., 2004; Mosconi, 2013). Hexokinase, one of the key cytosolic enzymes in glucose metabolism, was reported to be downregulated in the brains carrying an APOEε4 allele (compared with APOEε2 and APOEε3) leading to a deficiency

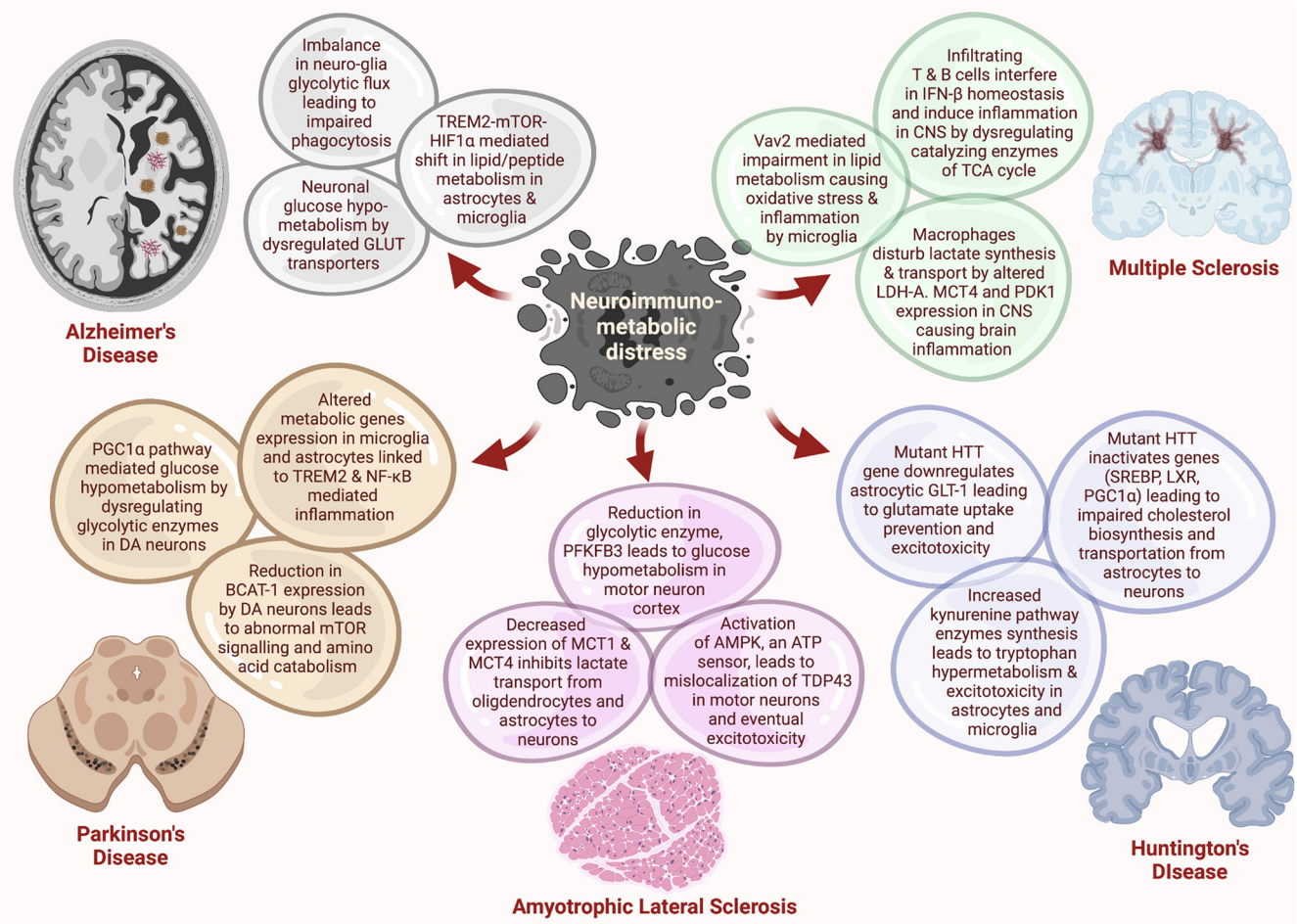

Figure 2. Major neuroimmunometabolic imbalances in neurodegenerative disorders. Several glucose, peptide, and lipid metabolic pathways are hindered in neurons and glia in these neurodegenerative diseases. These perturbations potentiate altered synthesis and transportation of different metabolites, leading to excitotoxicity, impaired phagocytosis, and inflammation in the CNS.

in glucose metabolism (Ding et al., 2013). This glucose hypometabolism is linked to the inhibition of PPAR-γ/PGC-1α (peroxisome proliferator-activated receptor γ/coactivator-1α), implicating this signaling pathway in AD pathophysiology (L. Wu et al., 2018).

TREM2, an immune receptor expressed on microglia, actively binds to Aβ oligomers and maintains phagocytic clearance of amyloid peptides from the healthy brain (Zhao et al., 2018). A deficiency or functional mutation in TREM2 increases the risk of AD (Jonsson et al., 2013). Recently, TREM2 deficiency was found to increase levels of cholesterol ester, which exacerbates inflammation and increases clearance burden on microglial phagocytic machinery (Nugent et al., 2020). Microglia from TREM2$^{-/-}$/5XFAD mice also exhibit a reduced rate of glycolysis and decreased production of ATP that is linked to defective mTOR signaling and leads to increased autophagy. The impairment in TREM2-mTOR signaling is associated with fewer activated microglial cells migrating to surround amyloid plaques in AD patients and TREM2-deficient AD-model mice. RNA-seq data reveal downregulation of genes related to metabolic and bioenergetic pathways in TREM2-deficient mice, which likely causes autophagic abnormalities (Ulland et al., 2017). Additionally, genetic variants of *TREM2* disrupt autophagy by impairing mTOR signaling in AD brains (Ulland et al., 2017; Zhou et al., 2018). Interestingly, TREM2 KO results in elevated tau phosphorylation leading to microglial activation in AD mice (Audrain et al., 2019). Surprisingly, TREM2 haploinsufficiency increases tau pathology and inflammatory responses more than complete knockdown of TREM2 in a mouse model of tauopathy, suggesting a dynamic role of TREM2 in regulating neuroinflammation by a probable compensatory mechanism in microglia (Sayed et al., 2018).

Hypoxia signaling pathways are also linked to metabolic distress and pro-inflammatory induction in the AD brain (Bazan et al., 2002; Baik et al., 2019) A recent report highlights the role of TLR4 in the immunometabolism of Aβ-treated microglial cells through the mTOR-HIF-1α hypoxia signaling pathway. Aβ induces phosphorylation of mTOR and higher expression of HIF-1α in primary microglia, activating proinflammatory cascades (Baik et al., 2019). A higher rate of mTOR-HIF-1α signaling is associated with decreased oxygen consumption rate and increased extracellular acidification rate, critically shifting the glycolytic balance in these cells (Ulland et al., 2017). Overall, these findings suggest a strong neuroimmunometabolic dysregulation pertaining to lipid and sugar metabolism that may mediate pathologic conditions associated with AD (Fig. 2).

PD: a neuroimmunometabolic anomaly?

PD impacts ~7-10 million people around the world, making it the second most common neurodegenerative disease (Beitz, 2014). The pathologic features of PD include the loss of dopaminergic neurons in the substantia nigra pars compacta and

accumulation of α-synuclein in intracellular inclusions known as Lewy bodies (Kalia and Lang, 2015; Maulik et al., 2017). Although genetic alterations and environmental exposures are thought to trigger PD, the exact molecular mechanisms linking the risk factors to PD pathology are unclear (Trinh and Farrer, 2013). Postmortem analyses of human PD samples and animal studies have demonstrated the presence of activated astrocytes and microglia in the brain (McGeer et al., 1988; Yamada et al, 1992; Q. Wang et al., 2015). The pro-inflammatory cytokines released by these cells can exacerbate degeneration of midbrain dopaminergic neurons (Hirsch et al, 2003). It can be predicted that neuroimmunometabolic modulators play certain passive roles in the neuroinflammatory characteristics of PD by altering the metabolic status of neurons and associated glial cells.

Glucose hypometabolism has been implicated in PD pathogenesis using MRI and fluorodeoxyglucose (18F) PET (Borghammer, 2012; González-Redondo et al., 2014). Moreover, reduced glucose metabolism in the cortex of PD patients is linked to the development of PD dementia (Firbank et al., 2017). Associations between glucose metabolism, changes in cell bioenergetics, and neurodegenerative pathology in PD may be mediated in part by PD-related risk factors linked to glucose and amino acid transporters, metabolic enzymes, and transcription factors that regulate metabolic pathways (Dunn et al., 2014; Y. Zhang et al., 2016; Anandhan et al., 2017). Nuclear receptors, such as peroxisome proliferator-activated receptor (PPAR), which is known to regulate inflammation and energy metabolism in the brain, are linked to several neurodegenerative disorders, including PD (Chaturvedi and Beal, 2008). Upon activation, PPARγ/PGC-1α promotes transcription of genes encoding mitochondrial respiratory subunits in the substantia nigra, thus regulating glucose metabolism in dopaminergic neurons (Zheng et al., 2010). Branched-chain amino acid transferase (*BCAT1*), which catalyzes degradation of branched-chain amino acids, is downregulated in the substantia nigra of sporadic PD patients (Yao et al., 2018). Knockdown of *BCAT1* increases mitochondrial respiration and results in oxidative damage in neurons through mTOR-independent pathways (Mor et al., 2020). Finally, dysregulation of several glycolytic enzymes, including GLUT, MCT1, MCT4, pyruvate dehydrogenase kinase 1 (PDK1), LDH-A, and pyruvate kinase M2, has been reported to produce a hypometabolic state in the PD brain (Vallée et al., 2019). Knockdown of at least one of these genes MCT4 (*SLC16A3*) also results in impaired motor function in experimental mice (Lundquist et al., 2021).

Many PD-associated genes are expressed in glial cells, indicating that dysfunction of the encoded proteins in microglia and/or astrocytes could contribute to PD etiology (Joe et al., 2018). For example, the microglial receptors TREM2 and sialic acid-binding Ig-like lectin 3, which are associated with AD risk, are also related to PD risk (Rayaprolu, 2013; Chan et al., 2016). The recycling of microglial TREM2 at the plasma membrane is suggested to be regulated by the vacuolar protein sorting 35, which is often implicated in late-onset autosomal-dominant familial PD (J. Yin et al., 2016). Activation of microglia via TREM2 signaling also results in neuroinflammation in the environmental-toxin-induced model of PD (Belloli et al., 2017). However, there are conflicting reports regarding the association between TREM2 and PD pathology (Mengel et al., 2016; Ren et al., 2018); therefore, further investigation is warranted.

PD-related genes that are highly expressed in astrocyte include cytosolic ubiquitin-E3-ligase *PARK2, PARK7*, PTEN induced kinase 1, leucine-rich repeat kinase 2, α-synuclein, and glucocerebrosidase. These proteins play vital roles in astrocytic functions, such as inflammatory responses, uptake of glutamate, oxidative stress responses, and neuroprotection (Sonninen et al., 2020). Studies using astrocytes derived from induced pluripotent stem cells obtained from PD patients have shown dysfunction in α-synuclein clearance and downregulation of matrix metallopeptidase 2 and *TGF* genes. Furthermore, leucine-rich repeat kinase 2- and glucocerebrosidase-deficient astrocytes exhibit elevated levels of α-synuclein, increased reactivity to inflammatory stimulation, greater Ca^{2+} release from the endoplasmic reticulum, and altered polyamine metabolism: crucial hallmarks of PD pathophysiology (Sonninen et al., 2020).

Loci related to NF-κB signaling, such as methylcrotonyl-CoA carboxylase 1, DDRGK domain-containing protein 1, ras like without CAAX 2, and scavenger receptor Class B member 2 (Xi et al., 2013; Cao et al., 2016; van der Poel et al., 2019) have been identified in GWAS meta-analysis from PD patients (Jimenez-Ferrer and Swanberg, 2018). Similarly, metabolic genes, such as transmembrane glycoprotein NMB, sterol regulatory element-binding protein 1, and aminocarboxymuconate semialdehyde decarboxylase, that induce inflammatory signaling have been associated with PD pathology (Ivatt et al., 2014; Murthy et al., 2017; Vilas et al., 2017). Overall, these findings show the potential contribution of neuroimmunometabolic genes in PD pathogenesis (Fig. 2).

Multiple sclerosis (MS): intersecting peripheral and central immunometabolism

MS is an autoimmune disorder affecting sensory, motor, and autonomic functions in patients. It is a progressive neurodegenerative condition in which autoreactive immune cells (T and B lymphocytes) infiltrate the CNS, triggering a cascade of neuroinflammatory responses that cause demyelination, gliotic scarring, and axonal loss (Doshi and Chataway, 2017). In the disease state, the pro-inflammatory subsets of T and B cells (T helper cells, monocytes/macrophages, and dendritic cells) are activated in the peripheral immune system. The regular metabolic resources for energy production in these cells, on activation, are found to be shifted from the TCA cycle to glycolysis once they cross the BBB and reach the CNS.

The treatment for MS so far is heavily dependent on variants of IFN-β to reduce inflammation in the brain by shifting the balance of T and B cells toward an anti-inflammatory state. Although INF-β treatment significantly improves the medical care for MS patients, the mechanism of action is still unclear, raising doubts about its long-term responsiveness and associated risks versus benefits (Jakimovski et al., 2018). The involvement of IFN-β in targeting catalyzing enzymes of the TCA cycle links its effects to immunometabolic mechanisms of immune cells (Kaushik and Yong, 2020). Consistent with this, IFN-β treatment restores the metabolic enzymes related to glycolysis and mitochondrial respiration in relapsing-remitting MS patients (La Rocca et al., 2017). Hence, a renewed angle of investigation is warranted to identify the immunometabolic components of MS progression.

The interplay between the peripheral immune system and neuroinflammatory cascades in the pathophysiology of MS makes MS a unique degenerative disorder of the CNS. Immune-reprogramming moves from blood to brain, integrating peripheral and central immunometabolic mechanisms. Postmortem brain tissues from MS patients and mouse models have revealed the presence of brain-infiltrating macrophages that exhibit an elevated glycolytic state, suggesting a peripheral immune role in regulating metabolic homeostasis and neuroinflammation in the MS brain. Such compromised metabolic and neuroinflammatory

states are most likely because of a leaky BBB that enables infiltration of the macrophages into the CNS (Popescu et al., 2013). These infiltrating macrophages express high levels of LDH-A and MCT4, which are responsible for lactate synthesis and transport. When LDH-A and MCT4 are knocked down in cultured macrophages from MS-model mice, their migration is restricted (Kaushik et al., 2019). Another study reports accumulation of lactate in infiltrating macrophages in the parenchyma of the mouse brain, and this lactate accumulation is correlated with high levels of PDK1. Increased PDK1 leads to production of lactate that triggers the inflammatory M1 phenotype in macrophages (Tan et al., 2015. This confirms an immunometabolic switch in the CNS toward the activation of proinflammatory cascades (Guglielmetti et al., 2017).

Several gene array studies have identified potential metabolic targets in the pathogenesis of MS. One potential candidate identified in GWAS of MS is the guanine nucleotide exchange factor *Vav2*, which, in microglia stimulated with fibrillar Aβ, activates NADPH oxidase by activating Rho-family GTPases, which in turn upregulate the NLRP3 inflammasome leading to oxidative stress (Wilkinson et al., 2006; Conley et al., 2017). Interestingly, *Vav2* functions downstream of *TREM2* (Y. Wang et al., 2015), indicating a possible involvement of Vav2 in lipid metabolism underlying MS pathology.

An independent transcription profiling study in microglial cells isolated from human MS postmortem brains reported higher transcription of genes related to lipid metabolism, iron metabolism, and regulation of the NF-κB pathway (van der Poel et al., 2019). These findings demonstrate the parallel immunometabolic changes occurring in neuroimmune cells along with peripheral immune cells in the MS brain (Fig. 2). How the resident immune cells of CNS metabolically react to the infiltrating peripheral immune cells is still not clearly understood and warrants further investigation.

Amyotrophic lateral sclerosis (ALS): neuroimmunometabolic swing between spinal cord and motor cortex

ALS is a fatal and aggressive neurodegenerative disorder affecting motor neurons. It is characterized by rapid progression of neuronal loss, brain and spinal cord atrophy, active astrogliosis, and a self-perpetuating inflammatory cycle. Motor neuron degeneration leads to muscle degeneration, eventual respiratory failure, and death (Brown and Al-Chalabi, 2017). Treatments for the disorder remain elusive.

There is abundant evidence indicating a role for immunometabolic dysregulation in ALS. Metabolic and energy perturbations have been observed in both clinical populations and preclinical models of ALS (Vandoorne et al., 2018; Kirk et al., 2019). PET scanning of ALS brains has shown hypometabolism of glucose in the motor cortex and frontal lobe, while the midbrain, occipital cortex, hippocampus, and spinal cord exhibit a hypermetabolic profile (Ludolph et al., 1992; Claassen et al., 2010; Pagani et al., 2014). Hypermetabolism in the spinal cord is congruent with elevated glucose levels in the cerebrospinal fluid of patients (Toczylowska et al., 2013). Conversely, postmortem analysis from ALS brains has demonstrated twofold attenuation in cortical mRNA content of the glycolytic enzyme PFKFB3 (X. S. Wang et al., 2006). Given that glia are more glycolytic than neurons, it is plausible that the increased glycolysis in the CNS of individuals with ALS could be largely because of glial cell activation (Vandoorne et al., 2018). This is corroborated by clinical studies showing downregulation of MCT1 transporters in oligodendrocytes of ALS patients (S. Lee et al., 2012; S. H. Kang et al., 2013; Philips et al., 2013), whereas expression of glutamate transporter EAAT2 is reduced in astrocytes of postmortem samples (Rothstein et al., 1995). MCT1 expression is also reduced in oligodendrocytes of ALS-model mice, and this occurs alongside cell degeneration, leading to reduced trophic support of lactate to neurons (S. Lee et al., 2012; S. H. Kang et al., 2013; Philips et al., 2013). Meanwhile, increases in synaptic glutamate resulting from reduced expression of glutamate transporter 1 (GLT-1) in astrocytes might lead to excitotoxic cell death (Lasiene and Yamanaka, 2011).

Certain kinases regulate energy metabolism through downstream immunometabolic mediators (Salminen et al., 2011). AMPK, a crucial energy regulatory kinase, is activated in motor neurons, and this causes mislocalization of TAR DNA-binding protein 43 (TDP43) in ALS patients and in an ALS mouse model expressing mutant SOD1 (Lim et al., 2012; Y. J. Liu et al., 2015). Reducing AMPK activity reverses these pathologic features (Lim et al., 2012). Interestingly, metabolic imbalances are often concomitant with neuroinflammatory aberrations. Microglial upregulation of NOX and NO synthase leads to exacerbated production of ROS and RNS in a process involving the prostanoid synthesis pathway (Almer et al., 2001; Beers et al., 2006; D. C. Wu et al., 2006; Boillée and Cleveland, 2008). Microglia also amplify NF-κB signaling in the mutant-SOD1 mouse model of ALS (Frakes et al., 2014). On the other hand, astrocytes from ALS patients, when cocultured with neurons, exhibit neurotoxicity by an unknown mechanism (Haidet-Phillips et al., 2011) that might involve the upregulation of chemokines and cytokines (Haidet-Phillips et al., 2011) or insufficient astrocytic metabolic support to neurons (Ferraiuolo et al., 2011; Philips and Rothstein, 2014). Overall, these reports suggest a contribution of neuroimmunometabolic pathways to ALS (Fig. 2), but further scrutiny will be required to establish any causative links to the disease pathology.

HD: susceptible genes linked to neuroimmunometabolism

HD is an autosomal dominant disease characterized by progressive deficits in motor function. It is caused by expanded repeats of glutamate residues at the N-terminal of the huntingtin gene (*HTT*). Inflammation is common in the brains of HD patients, having been identified in both presymptomatic and postmortem HD patients (Sapp et al., 2001; Tai et al., 2007; Vonsattel et al., 2008, 2011). Cell-autonomous expression of dysfunctional mHTT in the microglia results in its activation (Crotti et al., 2014; H. M. Yang et al., 2017), whereas selective expression of mHTT in astrocytes causes motor and transcriptional dysfunction (Bradford et al., 2009; Wood et al., 2019). The *HTT* gene is also reported to dysregulate several genes involved in cholesterol metabolism. For example, inhibition in SREBP (*SREBF1*), LXR (*NR1H3*), and PGC1α (*PPARGC1A*) genes results in impaired synthesis and transport of cholesterol from astrocytes to neurons in HD (Leoni and Caccia, 2015). These findings indicate immunometabolic imbalance induced by several genetic risk factors in HD (Fig. 2)

Molecules related to amino acid metabolism are also involved in the inflammatory cascade in HD brains. For example, studies have indicated that mHTT can downregulate GLT-1 in astrocytes, preventing uptake of glutamate and causing excitotoxicity (Lievens et al., 2001; Shin et al., 2005; Khakh et al., 2017). Another notable example is kynurenine-pathway metabolites, which induce neuroinflammation and neuroexcitotoxicity by activating microglia and astrocytes (Satyasaikumar et al., 2010; Campesan et al., 2011; Palpagama et al., 2019). Multiple lines of

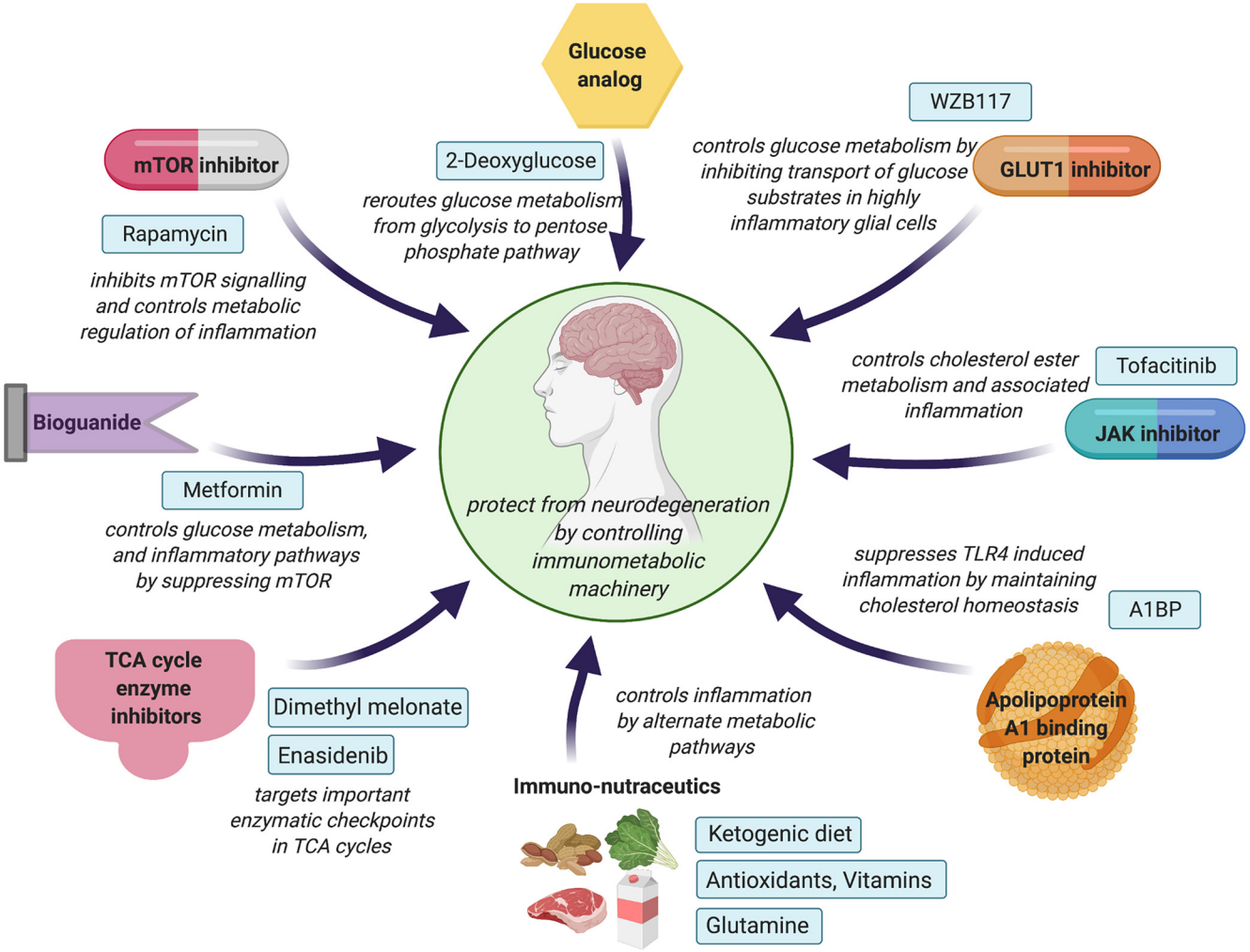

Figure 3. Novel therapeutic strategies to control immunometabolic machinery in neurodegenerative disorders. Glucose analogs, inhibitors of GLUT1 and TCA-cycle enzymes, act on essential regulators to sustain or control glycolytic homeostasis in the brain. While bioguanides and mTOR inhibitors control glucose metabolism, JAK inhibitors and A1BP maintain cholesterol homeostasis and associated neuroinflammation. Immuno-nutraceutics, such as ketogenic diet, antioxidants, vitamins, and glutamine supplements, can also influence neuroinflammatory events in neurodegenerative conditions by fulfilling the brain's energy requirements through alternative metabolic pathways.

evidence point toward reduced kynurenine levels and increased quinolinic acid, an intermediate of the kynurenine pathway, in the early stages of HD (Beal et al., 1992; Guidetti et al., 2004; Giorgini et al., 2008; Crotti et al., 2014). Indeed, genetic ablation of kynurenine 3-monooxygenase, an enzyme that converts kynurenine to toxic 3-hydroxykynurenine, suppresses huntingtin-mediated excitotoxicity in a yeast model system (Giorgini et al., 2005). Further, both *in vitro* and *in vivo* studies have shown that mHTT can cause activation of NF-κB signaling, an important immunometabolic pathway in the CNS, via the IκB kinase of the IκB kinase complex. (Khoshnan et al., 2004; Träger et al., 2014). These studies also strengthen the plausibility that NF-κB-mediated increases in kynurenine-pathway activity play a role in HD (Ligam et al., 2010).

GWASs have also implicated many neuroimmunometabolic genes in relationship to HD. One of these is Autophagy related 7 (*ATG7*), a gene associated with defective autophagy (Squitieri et al., 2003; Metzger et al., 2010). Atg7 has been linked to (*CRTC1*) activity and glycolysis (Wei et al., 2016), suggesting a neuroimmunometabolic role in driving autophagy. Mechanistically, *ATG7* deletion results in disrupted autophagy and activation of (*CRTC1*) and the glycolytic pathway. Inhibiting mTORC1 reverses the metabolic dysregulation caused by Atg7-mediated autophagic deficits (Wei et al., 2016).

Cofactors triggering neuroimmunometabolic switching

Aging and lifestyle choices, such as stress, diet, exercise, and substance abuse are some of the critical modulators of immunometabolic processes. In this section we aim to highlight how the process of aging and lifestyle factors may lead to an imbalance in immunometabolic homeostasis in the CNS (Fig. 3).

Aging

Aging is a major risk factor for neurodegenerative diseases. There is a gradual decrease in neuronal viability in brain regions related to memory, motivation, and locomotion with age (Fearnley and Lees, 1991; Umegaki et al., 2008; Kusindarta et al., 2018; Maxwell et al., 2018). Aging may contribute to neurodegeneration in multiple, complex ways. Aging is associated with hyperactivation or hypoactivation in certain brain regions; this has been supported by PET scanning showing increased or decreased glucose metabolism in cortical regions and hippocampus of aged compared with young brains (Prvulovic et al., 2005; Kaup et al., 2014; F. Yin et al., 2016; Nyberg et al., 2019).

Hypometabolism is manifested by metabolic shifts involving decreased neuronal glucose uptake and alterations in mitochondrial TCA cycle (Boumezbeur et al., 2010; Winklhofer and Haass, 2010; Jiang and Cadenas, 2014; J. Yin et al., 2016). Hyperactivated states are thought to be associated with drastic immunometabolic shifts, as excessive excitation can induce glutamate spillover leading to neurotoxicity (Esposito et al., 2013; Assefa et al., 2018). Further, aging is associated with increases in reactive astrocytes and microglia in the frontal cortex and the hippocampus (Rodríguez et al., 2016; Muddapu et al., 2020). In the aging brain, increased signaling by prostaglandin E2 in microglia promotes glucose sequestration into glycogen, reducing glucose flux and mitochondrial respiration. This hypometabolic state is compounded by the dependence of myeloid cells on glucose. Inhibiting prostaglandin E2 signaling in myeloid cells of aged mice reverses these deficits, improving synaptic plasticity and spatial memory (Minhas et al., 2021).

Diet

A century of industrialization and mass urbanization have led to a steady decline in the intake of fruits, vegetables, and fibers and increased consumption of animal products, saturated fats, and refined sugars (Popkin and Gordon-Larsen, 2004; Popkin et al., 2012). This, coupled with a modern sedentary lifestyle, has increased the incidence of metabolic syndromes that have gained a pandemic status (Bray et al., 2004; Bray and Popkin, 2014). There is compelling evidence that diets rich in fat and sugars adversely influence the metabolic and inflammatory profile of brain cells (Beilharz et al., 2015; Chianese et al., 2018). Apart from FAs synthesized in the brain, dietary FAs can cross the BBB (Freund Levi et al., 2014) and modulate cellular processes in the brain. It is unknown how central versus peripheral lipid pools distinctly modulate neuroimmunometabolic mechanisms, necessitating further investigation.

Disturbances in immunometabolic signaling and day/night rhythmicity because of hypercaloric diet have been demonstrated in microglia (Milanova et al., 2019). Dietary habits influence microglial phenotypic polarization, a morphologic adaptation driven by cell surface receptors. These receptors recognize harmful stimuli that lead to transcriptional changes necessary for the phenotypic switch. High-fat diet induces region-specific inflammatory states and metabolic imbalances in microglia, astrocytes, and oligodendrocytes (Valdearcos et al., 2014; Guillemot-Legris et al., 2016; Guillemot-Legris and Muccioli, 2017; Jin et al., 2020), mainly as a result of saturated FAs activating putative immunometabolic mediators, such as myelin disruption, and pathways linked to NF-κB, TLR receptors, IFN-γ, TNF, and IL-33 (Buckman et al., 2015; Guillemot-Legris et al., 2016; Ng and Say, 2018; H. T. Huang et al., 2019). Additionally, high-fat diets attenuate the positive effects of nutraceuticals, such as Alaskan bog blueberries, on neurodegenerative pathophysiology by microglial activation (Maulik et al., 2019). In contrast, unsaturated and ω3 FAs, abundantly present in foods, such as fish oils, attenuate anti-inflammatory phenotypes in microglia (Inoue et al., 2017). Omega-3 FAs also help in eliminating myelin debris and extracellular Aβ peptides by glial phagocytosis (Oksman et al., 2006; S. Chen et al., 2014; Dong et al., 2018).

Exercise

There is accumulating evidence for a role of exercise in regulating neuroinflammation and glial activation. Exercise releases anti-inflammatory myokines, such as IL-6, from skeletal muscles, and this increases the production of IL-10, an anti-inflammatory cytokine. Myokines can travel across the BBB, bind to microglial receptors, and promote a quiescent phenotype as opposed to a more active inflammatory phenotype (Cianciulli et al., 2015; Kelly, 2018; Vecchio et al., 2018; Pederson, 2019). Long-term treadmill exercise elevates neuronal expression of CD200, a Type 1 membrane glycoprotein. CD200 binds to the CD200R receptor expressed on the microglia and leads to glycosylation of CD200R (N-glycosylated at asparagine 44). This CD200-CD200R interaction checks on the microglial activation in PD mice, sustaining metabolic homeostasis (Sung et al., 2012; C. Liu et al., 2018).

BDNF, a ubiquitous modulator of neurogenesis, synaptic plasticity, and inflammation, is produced by neurons, microglia, and astrocytes and is upregulated by exercise (Wrann et al., 2013; Sleiman et al., 2016). The precise mechanisms by which BDNF reduces inflammation is unknown. The most likely target is the cholinergic system where an imbalance in neuroimmune communication may lead to inflammation through phosphoinositide 3-kinases/GSK-3β-mediated pathways (Papathanassoglou et al., 2015; Halder and Lal, 2021). Notably, acute bouts of exercise have positive impact on BDNF levels and inflammatory status in both healthy individuals and PD patients (Małczyńska-Sims et al., 2020).

Finally, exercise produces antioxidants, such as GSH and SOD, which play a vital role in maintaining redox balance and anti-inflammatory status in astrocytes and microglia (Radak et al., 2001), as well as attenuating TLR activation on microglial cells by high-fat diets (E. B. Kang et al., 2016).

Substance abuse

Substance abuse and stress can also significantly influence the immunometabolic status of the brain. Longitudinal studies have shown progressive changes in brain metabolic activity in cocaine abusers (Volkow et al., 2011) and in animals after abstinence from cocaine self-administration (Nicolas et al., 2017). Similarly, alcohol decreases brain glucose metabolism in heavy drinkers (Volkow et al., 2015), and methamphetamine and 3,4-methylenedioxymethamphetamine abuse causes oxidative stress, metabolic compromise, and inflammation (Yamamoto and Raudensky, 2008). Both 3,4-methylenedioxymethamphetamine and methamphetamine elicit acute decreases in glucose utilization, and this is linked to long-term impairment in energy metabolism and increased inflammation in different brain regions. These neurotoxic effects were found to be selective and long-lasting or irreversible (Pontieri et al., 1990; Y. H. Huang et al., 1999; Quate et al., 2004).

Neuroimmunometabolic therapeutics: time to change the course of disease management?

Designing treatment strategies centered around optimizing neuroimmunometabolic aberration could be challenging but may lead to effective therapeutic intervention for these neurodegenerative disorders (Fig. 3). Most current clinical treatments serve to cope with symptoms rather than addressing the underlying pathophysiology (X. Chen and Pan, 2015). Further, most of these drugs (e.g., Levodopa, amantadine, galantamine, memantine, etc.) carry severe side effects, such as gait disturbances, tremors, hives, headache, drowsiness, etc. (Duraes et al., 2018). There remains a huge opportunity in using drugs that target the metabolic and immune machinery to halt the progression of these diseases.

Metformin

Metformin is a biguanide that controls glucose metabolism and inhibits mitochondrial electron transport and ROS production. Metformin activates the AMPK pathway by activating serine–threonine liver kinase B1, inhibiting mTOR and its coupling to downstream mediators (Kalender et al., 2010; Y. Wang et al., 2018), which are disrupted in degenerative conditions. Moreover, metformin significantly reduces mitochondrial distress caused by BCAT-1 deficiency, thus reversing neurotoxicity, improving motor function, and enhancing neuronal viability in *Caenorhabditis elegans* models of PD (Mor et al., 2020). Furthermore, clinical trials are currently recruiting ALS and AD patients to test the efficacy of metformin in altering the pathophysiology in these disorders (www.clinicaltrials.gov, NCT04098666, 2020; NCT04220021, 2020).

Rapamycin and inhibitors of glucose metabolism

Given the plethora of evidence implicating mTOR in the metabolic regulation of inflammation, the mTOR inhibitor rapamycin may be an effective therapeutic to combat immunometabolic imbalances. Rapamycin, sold under the trade name Sirolimus, exhibited efficacy in clinical trials of inflammatory disorders, such as systemic lupus erythematosus (Lai et al., 2018).

The glucose metabolism inhibitor, 2-deoxyglucose, which is used as a noninvasive diagnostic tool in PET scanning, can inhibit excessive glycolysis alone or in combination by rerouting glucose metabolism into the pentose phosphate pathway involving hexokinase (Maher et al., 2004; Pajak et al., 2019), and this might be able to attenuate the excessive glycolytic surge observed in several pathologic conditions. Another drug, WZB117, inhibits the glucose transporter GLUT1 and thus reduces inflammation by suppressing metabolism (Y. Liu et al., 2012). Furthermore, drugs, such as dimethyl malonate (a succinate dehydrogenase inhibitor) and enasidenib (an isocitrate dehydrogenase inhibitor) that target the TCA cycle at various enzymatic steps, may ameliorate immunometabolic dysregulation by regulating energy metabolism (Stein et al., 2019).

Tofacinib

Like drugs targeting glucose metabolism, drugs targeting lipid substrates are under clinical investigation for immune and metabolic disorders. Dysregulation of the JAK/STAT signaling pathway and the resulting disruption of lipid metabolism is evident in several metabolic disorders (Xu et al., 2013; Gurzov et al., 2016; Bharadwaj et al., 2020). Tofacitinib, an FDA-approved drug for rheumatoid arthritis (RA) and other immune disorders, is a JAK inhibitor, and it ameliorates macrophage-induced inflammation in RA patients by controlling the metabolism of cholesterol esters (Fleischmann et al., 2012; Kremer et al., 2012). In a rabbit model mimicking the lipid paradox in RA (a high cardiovascular risk despite low levels of LDL), tofacitinib treatment reverses inflammation-induced inhibition of reverse cholesterol transport (Perez-Baos et al., 2017). Although the precise mechanism is unknown, tofacitinib is believed to influence reverse cholesterol transport by upregulating ATP-binding cassette A1 transporters that promote phospholipid and cholesterol transport on pre-high-density lipoprotein (Perez-Baos et al., 2017). This drug could be further investigated for treating neurodegenerative disorders, such as AD and PD, where pathways related to lipid metabolism are disrupted. Notably, a recent nonrandomized clinical trial is registered to test the efficacy of tofacitinib in AD and other dementias. Further, a tofacitinib trial is currently underway in RA patients (www.clinicaltrials.gov, NCT04529876, 2020).

Apolipoprotein A-I binding protein (AIBP)

AIBP helps to maintain cholesterol homeostasis in lipid rafts in immune cells by removing excess cholesterol. AIBP is reported to promote cholesterol efflux from macrophages by binding to ATP-binding cassette A1, the key transporter involved in cholesterol metabolism (M. Zhang et al., 2016). Further, AIBP can inhibit inflammatory responses in macrophages by inhibiting the formation of foam cells in the circulation through a process involving the activation of MAPK and NF-κB signaling pathways (M. Zhang et al., 2018). Furthermore, AIBP inhibits LPS-induced TLR4 dimerization and inflammatory cytokine production in microglial lipid rafts (Woller et al., 2018).

A role for AIBP has also been tested in other degenerative models, such as glaucoma. Glaucoma involves apoptosis in retinal ganglion cells, and glia-driven neuroinflammation. In a mouse model of glaucoma, the level of AIBP in retinal ganglion cells was significantly reduced, and exogenous administration of recombinant AIBP protected retinal ganglion cells from glaucomatous neurodegeneration and associated inflammatory responses (Choi et al., 2020).

Immuno-nutraceutics

Another new line of research has been the development of immuno-nutraceutics. This field explores the possibility of using nutritional intervention and physical activity to improve neuroimmunometabolic balance. For example, carbohydrates influence immune responses to chronic intense exercise. Further, data from exercise-immune studies have revealed positive benefits of using antioxidants, vitamins, amino acids, such as glutamine, and other nutraceuticals in exercise-induced immunometabolic restoration (Gould and Pazdro, 2019).

In the 1920s, the ketogenic diet was formulated for the treatment of drug-resistant epilepsy (Wheless, 2008). This carbohydrate-depleted and fat-enriched diet shifts metabolic pathways from glycolysis to the TCA cycle, pushing the body into a state of ketosis that involves burning fat for energy production. The ketogenic diet has also been shown to exert anti-inflammatory effect in several experimental models and clinical cohorts of AD, PD, HD, and other disorders (Ruskin et al., 2011; J. Y. Chen et al., 2016; Phillips et al., 2018; Brenton et al., 2019; Rusek et al., 2019; Bahr et al., 2020; Koh et al., 2020). There is growing evidence that the ketogenic diet suppresses potential pro-inflammatory pathways, such as the NRLP3, PPARγ, and mTOR cascades (Huttenlocher, 1976; Koh et al., 2020).

While such dietary interventions could hold potential in treating neuroimmunometabolic pathologies, it is also important to understand that there are confounding factors that influence success of such therapeutic strategies. This includes the stage of diagnosis, potential side effects, specificity of action, and individual responses to these therapies or interventions. Moreover, adjuvant or combinational treatment involving immunonutrition and multiple drugs could be an alternative intervention. This hypothesis, however, remains to be tested in different models of CNS neurodegenerative disorders and thus warrants further investigation.

Neuroimmunometabolic profiling to bridge the translational gap

As described above, neurodegenerative diseases are affected by multiple genetic and nongenetic factors, including neuroimmunometabolic sensors. They differ in their disease manifestation but share numerous features, including scarce availability of efficient tools for early diagnosis and managing disease progression.

Preclinical evaluation of pathways related to genes implicated in these diseases has usually failed to produce drugs that prove effective in clinical trial. The complexity of the diseases lies in the involvement of multiple risk genes, each of which imposes only modest risk on its own. Moreover, the encoded genes may have roles in complex pathways, the disruption of which may affect numerous other pathways in various cell types. For example, metabolic aberration in glial cells may induce a recalibration of immune responses, which might lead to reconfiguration of neural connectivity, thus resulting in an array of neuronal abnormalities. Such a network of events can initiate at any node, resulting in a unidirectional or bidirectional effect. Thus, functional studies are essential to evaluate the role of risk genes and verify their involvement in discrete biological cascades. The gap between preclinical and clinical findings suggests that a more holistic preclinical approach is necessary.

Understanding disease mechanisms is contingent on identifying all the implicated genes, verifying their roles, and testing for therapeutic potential. This can be achieved by approaches, such as genomics (genotype arrays, GWAS, whole genome, and exome sequencing), epigenomics, transcriptomics, proteomics, and metabolomics. GWASs are unbiased, as they have often shown association of completely unrelated genes previously considered to be remotely associated with the disease.

For example, screening of AD-associated genes expressed in CNS cell types has led to the discovery of many hits in microglia, such as *TREM2* and *APOE*, as potential risk factors for AD (Andreasson et al., 2016; Jansen et al., 2019). Comparing the results of studies of one disease with those from another disease can reveal risk factors that affect more than one disease. Cross evaluation of multiple conditions will not only expand our understanding of diseases, but will also aid in designing informed therapeutic interventions.

Epigenomics, involving epigenome wide association studies, addresses reversible or irreversible modification of DNA and histones, including methylation and acetylation (Hasin et al., 2017). Differentially methylated immunometabolic factors can serve as indicators of disease status (Piunti and Shilatifard, 2016). Similarly, transcriptomics measures genome-wide RNA levels using various advanced RNA sequencing techniques (Z. Wang et al., 2009; Lowe et al., 2017), whereas proteomics quantifies peptide expression, interaction, and clearance using mass spectroscopy-based and mass spectroscopy-independent methods (Hasin et al., 2017; Timp and Timp, 2020). Metabolomics, on the other hand, quantifies small molecules and metabolites, which can be used to determine neuroimmunometabolic reprogramming (Johnson et al., 2016).

Seldom are all risk genes produced by any single one of these approaches translatable. Further, evaluating therapeutic potential of each risk gene in a global framework might be time- and resource-intensive. Thus, a combinatorial approach to verify risk genes may help bridge therapeutic gaps. After omics evaluation, risk genes can be studied *in vivo* or *in vitro* to examine in detail how they contribute to various cascading effects that disturb neuroimmunometabolism. This will aid in unraveling more therapeutic hits. Some of the common techniques for studying the onset of neuroimmunometabolic shifts include examination of metabolic changes through colorimetric techniques, specialized biosensor imaging, mass spectroscopy, PET and imaging, as reviewed previously (Bernier et al., 2020). Given the flood of data available in individual fields, such as immunological, neurodegenerative, and metabolic diseases, the neuroimmunometabolic gene profiles in animal models identified by omics have great potential to increase translational success. The omics databases of risk genes can be used by the health care system to track individual health for personalized treatment. At this point, the cost of generating individual omics data is too expensive for the payers to appreciate, but as the technology advances, these problems can be overcome.

Conclusion

In conclusion, we have provided an overview of the immunometabolic mediators and mechanisms that play critical roles in regulating energy balance in the CNS. Abnormalities in neuroimmunometabolic functioning linking cellular intermediates and pathways can lead to neurodegenerative conditions. Unraveling the cellular mediators underlying such pathways in these disorders can provide a basis for future therapeutic intervention. Further, translating these preclinical findings may help us in synergizing personalized treatment for many currently untreatable neurodegenerative disorders.

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