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Glial Biomarkers in Human Central Nervous System Disease

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Abstract

There is a growing understanding that aberrant GLIA function is an underlying factor in psychiatric and neurological disorders. As drug discovery efforts begin to focus on glia-related targets, a key gap in knowledge includes the availability of validated biomarkers to help determine which patients suffer from dysfunction of glial cells or who may best respond by targeting glia-related drug mechanisms. Biomarkers are biological variables with a significant relationship to parameters of disease states and can be used as surrogate markers of disease pathology, progression, and/or responses to drug treatment. For example, imaging studies of the CNS enable localization and characterization of anatomical lesions without the need to isolate tissue for biopsy. Many biomarkers of disease pathology in the CNS involve assays of glial cell function and/or response to injury. Each major glia subtype (oligodendroglia, astroglia and microglia) are connected to a number of important and useful biomarkers. Here, we describe current and emerging glial based biomarker approaches for acute CNS injury and the major categories of chronic nervous system dysfunction including neurodegenerative, neuropsychiatric, neoplastic, and autoimmune disorders of the CNS. These descriptions are highlighted in the context of how biomarkers are employed to better understand the role of glia in human CNS disease and in the development of novel therapeutic treatments.

Keywords

cerebrospinal fluid; inflammation; magnetic resonance imaging; neuroimaging; positron emission tomography

Introduction

Biomarkers are measurable indicators of a biological state indicative of normal or pathogenic biological processes, or a response to therapeutic intervention (FDA-NIH Biomarker Working Group, 2016). In medical research, biomarkers are often described in terms of endpoints that indicate changes in cellular metabolism, phenotype, or “activation” state of cells impacted by disease relevant pathology. In pharmaceutical research, this definition is expanded to include information about potentially therapeutic compounds

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including drug exposure at the site of action, drug-target interactions, and measurable physiological effects caused by the drug-target interaction. These were termed the “three pillars of survival” (Morgan et al., 2012), and by demonstrating all three one can reasonably predict that an observed drug effect is due to an action on the intended target. Furthermore, biomarkers are a cornerstone of modern drug discovery that can be used in selection or stratification of patient populations, establishing target engagement, demonstrating pharmacodynamic effects, and monitoring disease progression or outcomes.

In neuroscience research, validated biomarkers are critically important because most CNS cells of interest are not directly observable in intact systems in typical clinical settings. Instead, translatable biomarkers are needed to better understand what is happening at the cellular and neurochemical level within the brain. In an ideal world, biomarkers could be used to help diagnose patients as well as predict and track their response to treatments. Many disorders of the CNS are chronic and response to treatment does not yield detectable or rapid change in currently available biomarkers approaches such as neuroimaging endpoints. Thus, novel biomarkers are needed that will enable more efficient assessment of new therapeutic approaches.

One of the primary goals of personalized medicine is to identify disease specific biomarkers, whether genetic, neurochemical, or imaging endpoints, and use this information to determine the best treatment regimen for a given patient (Guest et al.,). A classic example in cardiovascular care is the use of low-density lipopolysaccharides as a risk indicator for atherosclerosis and the subsequent prescription of statin-class medications (Kastelein et al., 2003). It is important to understand that there are very few validated central nervous system (CNS) biomarkers (Marrer and Dieterle, 2007), and even fewer that are currently used to determine evidenced based patient care plans. These include diagnostic biomarkers such as identification of autoantibodies and specific imaging signatures using MRI or positron emission tomography (PET) as well as prognostic biomarkers of CNS recovery following cardiac arrest. This paucity in CNS biomarkers can be attributed to an insufficient understanding of disease pathology, but importantly also to limitations in access to the CNS compartment.

Evaluating biomarkers that originated in the CNS poses a unique challenge in that these signals must be measurable across the blood-brain-barrier to be easily accessible to researchers in most clinical settings. Certain factors produced by glia such as cytokines, chemokines, and microvesicles do cross into peripheral compartments and are measured in cerebrospinal fluid (CSF) or blood (serum/plasma). While these are promising, putative biomarkers of CNS neurochemistry, defining where and in what cell type the biomarkers originated is difficult since these biomarkers can originate from nonglial cell types including neurons. In addition, it is important to understand that peripheral immune cells and tissues produce many of the same chemical signals as microglia, including cytokines for example, which can obscure the origin of these signals. As such, it is important to be cautious in interpreting what biomarkers can be attributed to glial-derived sources. Since there are several potential cell types from which these disease markers may originate, the biology behind the disease marker and how it is modulated by a therapeutic intervention can be difficult to interpret. A more direct way of measuring glial phenotypes is through imaging

techniques such as PET. Although few ligands exist for specific glial targets, rapid advances are being made in imaging technologies.

In the following chapter, we will review biomarkers associated with glial dysfunction in human CNS disease, and the potential future uses of these biomarkers in defining patient segments that will be important for discovering and optimizing therapeutic treatments for CNS diseases.

Glia Biology Is a Key Resource for Biomarkers of CNS Pathology

The specific functions and properties of each glial cell type provide for a wide variety of ways to exploit how these cells react to, or participate in disease pathogenesis in a biomarker context. Glial cells influence numerous functions in the CNS, from determining action potential conduction velocity to modulating blood flow to regulating the concentration of neurotransmitters at the synapse. Thus, glia biology contributes to many currently used biomarkers of general CNS function. This includes a variety of chemical and physiological signals as well as the signals obtained in magnetic resonance imaging (MRI) and spectroscopy (MRS). In addition, each glial sub-type also has a distinct gene expression profile, a unique proteome and cell type specific responses to CNS injury and disease. When molecules expressed or synthesized specifically by glia are released into the extracellular space, they may be detected in CSF or serum and serve as both diagnostic and/or disease activity biomarkers referable to a specific glial cell response (examples are described in subsequent sections). Some of the unique properties of each CNS glial subtype can serve as biomarkers for CNS disorders that influence glia biology.

Oligodendrocytes and Myelin

Oligodendrocytes form myelin sheaths around CNS axons. While the majority of myelin is located within CNS white matter regions, oligodendrocyte cell bodies are observed throughout the CNS. The unique myelin forming function of oligodendrocytes has been used for decades as a CNS disease biomarker with demonstrable clinical utility. Fully functioning myelin is required for the normal conduction of action potentials. Specific sensory stimuli (visual, auditory, and somatosensory) will generate a compound action potential that can be measured using surface electrodes. The pattern of activity detected by the electrode is called an “evoked potential.” When myelin function is impaired, the velocity at which an evoked potential reaches the electrode is reduced. Abnormalities in evoked potential velocity have been employed as diagnostic biomarkers of myelin dysfunction for several decades (Galletta and Balcer, 2013). Evoked potential abnormalities were one of the earliest biomarkers of white matter pathology employed to diagnose multiple sclerosis (MS), optic nerve demyelinating disorders, and to assess the severity of anoxic brain injury.

More recently, MRI to visualize regions of degeneration and/or blood brain barrier breakdown (gadolinium contrast MRI) has been the most frequently employed method for measuring biomarkers of white matter disease or injury. Standard structural MRI is often employed to measure white matter atrophy, edema, or loss of myelin in a wide variety of CNS disorders from autoimmune mediated disorders such as MS and neoplasm to genetic disorders of myelin formation in addition to all forms of acute CNS injury. In addition,

techniques to assess the development and maintenance of neural circuits (tractography) using diffusion tensor magnetic resonance imaging (DTI) have emerged. DTI approaches take advantage of the specific structure of white matter, where water molecule diffusion is directionally restricted by the organization of axon tracts relative to gray matter, where the direction of diffusion is more random. The biology of myelin contributes to this feature of white matter because myelin consists of hydrophobic macromolecules that substantially restrict diffusion. In addition, the specific properties of myelin also can be used to differentiate the myelin compartment from axons and other elements within white matter using a number of innovative techniques including myelin water weighted diffusion tensor imaging (Avram et al., 2010), measurements of myelin water fraction (MWF) and a more pragmatic estimate of MWF using a technique called multicomponent driven equilibrium single-pulse observation of T1 and T2 (Spader et al., 2013). Both approaches for measuring the MWF are based on the differential magnetic resonance signatures for water molecules in the intra and extra cellular spaces relative to water molecules relatively “trapped” within a myelin sheath. These novel approaches will likely enable the expanded use of MRI as a biomarker of both white matter disorders and oligodendrocyte dysfunction in the future.

In addition to MRI as an approach to measure alterations in myelin as a biomarker of disorders involving myelin degeneration, some have proposed employing PET approaches to make quantitative measurements of myelin. PET involves administering a radioactive ligand that specifically binds the compartment in question, then employing computed tomography to image and quantify the emitted particles. PET to measure myelin has been studied using radiolabeled compounds that bind myelin proteins, including N-methyl-4,4-diaminostilbens (MeDAS), which binds to myelin basic protein. MeDAS PET has thus far been employed in only in preclinical models of demyelination (Matthews and Datta, 2015), but may be a future approach to evaluate response to therapies aimed at myelin restoration.

Disorders impacting oligodendrocyte derived myelin can also be assessed by MRS. Myelin is composed of ~20% protein and 80% lipid. The lipid component includes cholesterol, glycosphingolipids and ~40% phospholipids, predominantly phosphatidylcholine. Alterations in the amplitude of spectral peaks for myelin lipid components serve as a biomarker of myelin degeneration. MRS demonstrating reduction of neutral lipid peaks and increased choline peaks due to degradation of phosphatidylcholine are often observed in demyelinating disorders (Laule et al., 2007). In addition, regions of active demyelination have evidence for increased glutamate concentration by MRS (Srinivasan et al., 2005) perhaps due to impaired glutamate uptake by injured oligodendrocytes.

Myelin proteins can also be biomarkers of injury and myelin degeneration. For example, myelin basic protein has been detected in the CSF of patients following ischemic strokes (Hjalmarsson et al., 2014), traumatic brain injury (TBI; Su et al., 2012), and the first clinical episode of autoimmune demyelination (Modvig et al., 2013). While the presence of MBP in CSF was correlated with future dissemination of lesions and diagnosis of MS, it is not yet clear if CSF-MBP is a biomarker with sufficient clinical utility to supplant other more established diagnostic modalities for MS (Greene et al., 2012). However, antigen array studies demonstrate that local synthesis of antibodies to myelin antigens within the CSF space is a potential biomarker of MS disease state that was highly responsive to anti-

inflammatory treatment (Quintana et al., 2012). These findings suggest that in autoimmune disease of the CNS, the presence of CSF antibodies directed at myelin antigens could serve as a biomarker of disease activity.

Astrocytes

Astrocytes are a heterogeneous group of non-myelin forming neuroectodermal glia. Astrocytes perform a wide variety of functions in the CNS, including regulation of metabolites and neurotransmitters in the extra-cellular space, generation of convective flux between the CSF and the vasculature and the local modulation of blood flow in response to synaptic activity (Thrane et al., 2014; Verkhratsky et al., 2015). Some of these functions can be assayed through measurement of metabolites or proteins in CSF, serum or both compartments. Other astrocyte functions can be detected using state of the art neuroimaging approaches. While astrocytes are infrequently the primary cell type involved in CNS pathology, CNS disease and injury can alter astrocyte function, making these measures of astrocyte function potential disease biomarkers.

The most extensively employed imaging clinical bio-marker that is often a direct read out of altered astrocyte function is MRI. Standard clinical MRI of the CNS primarily measures the relaxation time of water molecules, and astrocytes are the major cell type regulating both intracellular and extracellular water within the CNS (Xiao and Hu, 2014). Additionally, functional MRI fMRI studies that image regional synaptic activity actually image altered blood flow in those regions using a technique known as blood oxygen level dependent (BOLD) contrast imaging (Fox and Raichle, 2007). The BOLD signal is based on the differential magnetic susceptibility of oxyhemoglobin and deoxyhemoglobin. Astrocytes sense the metabolic needs of synaptically active neuronal populations and provide signals to vascular endothelial cells leading to vasodilation, a system generally referred to as the neurovascular unit. This leads to astrocyte-mediated augmentation of regional blood flow that is detected as an increased ratio of oxyhemoglobin to deoxyhemoglobin by fMRI. This technique has enabled the development of what is considered the default mode network of fMRI resting activity for healthy brain function and identification of disease specific variations in the default mode network (Sheline and Raichle, 2013). Numerous studies have employed fMRI in as both a diagnostic and disease activity biomarker of a wide variety of neurological and psychiatric disorders. Thus, even when not the primary cell type mediating pathology, astrocyte biology is still a critical component of useful imaging bio-marker studies.

Astrocytes respond to neuronal injury and disease with a change in morphology and gene expression profile. The pathological features observed when astrocytes respond to the injured CNS have been defined as astrogliosis. One molecular change associated with astrogliosis is increased expression of monoamine oxidase B (MAO-B), which can serve as a biomarker for CNS disease and injury using PET imaging for binding of radiolabeled deuterium-L-deprenyl (DED; Matthews and Datta, 2015). Increased DED binding has been observed in patients with epilepsy and neurodegenerative disorders (Carter et al., 2012; Gulyas et al., 2011; Johansson et al., 2007; Kumlien et al., 1995), two diseases known to promote astrogliosis. DED binding has also been demonstrated to negatively correlate with

hippocampal atrophy in patients with early stage Alzheimer's disease (AD) or minimal cognitive impairment (MCI; Choo et al., 2014) and to be increased in presymptomatic patients with autosomal dominant familial AD (Scholl et al., 2015). Thus, through this approach, disease associated change in astrocyte biology can serve as a biomarker of disease progression. Recently, newer radioligands for MAO-B that enable using longer half-life isotopes have been developed (Nag et al., 2015), which will greatly enhance the potential utility of this PET biomarker approach. Two additional approaches are under development for PET imaging of astrocytosis. These involve increased uptake of radiolabeled acetate through the monocarboxylase transporter and increased binding to the I2-imidazoline receptor, which like MAO-B is localized to astrocyte mitochondrial membranes (Matthews and Datta, 2015).

The protoplasmic astrocyte, the common astrocyte type located within the CNS gray matter, is the most abundant cell type in the human brain, making degradation products derived from astrocytes potentially more sensitive biomarkers of brain injury than neuron specific molecules. For example, glial fibrillary acidic protein (GFAP) has been reported to be elevated in the CSF of patients with both acute (Yang and Wang, 2015) and chronic (Ishiki et al., 2015) forms of brain injury. Additionally, GFAP and GFAP break down products have been detected in serum following acute CNS injury including TBI and stroke (Yang and Wang, 2015). Access to a glial derived biomarker in serum dramatically enhances the practical utility of that biomarker, especially in the setting of acute CNS injury when quick clinical decision-making is often needed. Recent research has demonstrated that GFAP and S100 β , another astrocyte derived biomarker of TBI migrate from the CNS to the blood via the recently described glymphatic system. The glymphatic system involves active flux through the moving solutes from blood to CNS interstitial fluid to the CSF (Plog et al., 2015). This finding suggests potential means by which the sensitivity of serum biomarkers of CNS injury could be enhanced through manipulating glymphatic flux. In addition, since astrocyte localized aquaporin 4 water channels are a major molecular contributor to generating glymphatic flux, the movement of GFAP and S100 β from injured astrocytes into the vascular space also involves a critical function of astrocytes.

Microglia and Inflammation

Microglia have a well-described role in responding to CNS disease or injury. Microglia are yolk sac derived cells of mesodermal origin that enter the CNS very early in embryogenesis (Ginhoux et al., 2010). Based on ontogeny and molecular phenotype, microglia most closely resemble tissue macrophages of the CNS. As such, they are the primary innate immune responders, sensing pathogens or neural injury through a variety of signaling systems including chemokine, purinergic, and Toll-like receptors. When those signals are received, microglia respond rapidly with changes in morphology, function and gene expression. The behavior of microglia in response to inflammatory signals has been labeled microglia activation. While the diversity of microglia responses and the time course along which these responses develop and resolve vary according to stimulus intensity and identity, some features of microglia inflammatory activation can be detected as biomarkers of neural injury or disease.

One extensively studied biomarker of the microglia response to inflammatory activation is PET imaging using radiolabeled ligands that interact with the 18kD translocator protein (TSPO). Ligands for TSPO were initially identified as binding to a receptor the peripheral benzodiazepine receptor (PBR; Benavides et al., 1983; Le Fur et al., 1983). The canonical ligand, PK11195 demonstrated increased in response to neural injury and proinflammatory stimuli and within the CNS, and the increased binding was localized to a mitochondrial binding site in microglia (Altar and Baudry, 1990; Banati et al., 1997; Gehlert et al., 1997; Stephenson et al., 1995). Using PET imaging of PBR ligand binding, several seminal studies demonstrated evidence for microglia activation in a variety of neurological disorders (Banati et al., 2001; Cagnin et al., 2001a,b; Goerres et al., 2001; Pappata et al., 2000). After the receptor was molecularly identified as TSPO, a protein involved in cholesterol transport into mitochondria a second generation of ligands have been developed, further enhancing the potential utility of PET for the study of microglia activation. TSPO ligands labeled with longer half-life isotopes such as Fluorine¹⁸ will enable broader clinical utility for TSPO based PET imaging, since the labeled ligands can be transported at greater distance from the cyclotron employed for isotope generation. With this advance, it is likely that TSPO-PET will be used as an important biomarker of disease progression and/or response to therapy in a number of disorders where neuroinflammation is a critical readout of the underlying disease process.

Activated microglia also release soluble inflammatory mediators into the extracellular space, and these molecules can then be detected in CSF or the peripheral circulation. Microglia derived signaling molecules have been suggested as potential biomarkers of inflammatory activation for a variety of neurological disorders that involve an inflammatory response. Microglia release several classes of inflammatory mediators that can be employed as CSF biomarkers of neurological disease such as secreted cytokines and small molecule utilized to signal inflammation (e.g., prostaglandins). Many CSF cytokines have been explored as potential biomarkers for neurological and psychiatric disorders. Promising data have suggested the CSF cytokines can serve as prognostic biomarkers following ischemic and traumatic CNS injury (Kwon et al., 2010; Stockhammer et al., 2000) and are correlated with cognitive impairment in neurodegenerative disease (Yu et al., 2014). However, the use of CSF cytokines as prognostic biomarkers has not yet entered into common clinical practice. Some CSF cytokine biomarkers have been used to stratify subjects (Aalbers et al., 2012; Bornsen et al., 2011) or to serve as a surrogate marker of response to treatment in clinical trials (Bartosik-Psujek and Stelmasiak, 2006; Kivisakk et al., 2014; Møllergaard et al., 2010; Romme Christensen et al., 2014). In addition to cytokines, small molecules associated with the inflammatory response such as prostaglandins, arachadonic acid, and reactive oxygen species have been studied as biomarkers of brain injury and neurodegeneration (Bjork et al., 2013; Clausen et al., 2012; Hu et al., 2015; Yu et al., 2014). However, as with CSF cytokines, the use of small molecule inflammatory mediators as biomarkers currently remains a research tool.

Chemokines are one class of inflammatory mediator with broad potential utility as biomarkers. These small peptide mediators of the inflammatory response were initially identified as molecules that promote cellular migration (chemo = molecules/kine= kinesis). Several studies have demonstrated increased chemokine levels in the CSF of patients with

neurodegenerative disorders (Baron et al., 2005; Kuhle et al., 2009; Semple et al., 2010), suggesting them as potential biomarkers of inflammatory activation secondary to chronic neuronal injury or degeneration. In addition, the lymphocyte attracting chemokine CXCL13 is a biomarker of outcome and treatment response in the autoimmune disorder Anti-N-methyl-D-aspartate receptor encephalitis (Leypoldt et al., 2015). Increased CSF chemokines may also directly contribute to disease pathogenesis, thus have potential to serve as a direct readout of disease activity. For example, HIV associated neurocognitive disorder is a consequence of HIV infection of CNS myeloid cells, leading to chronic inflammatory activation. In this setting, increased chemokine levels have been reported, and the specific chemokines observed correlate with imaging biomarkers for neurodegeneration as well as contribute to neurodegeneration in model systems (Letendre et al., 2011; Mehla et al., 2012). Thus, chemokine biomarkers derived from microglia may signal both the degree of inflammation as well as the coincident neurodegeneration.

Neurodegenerative Disorders

The role of glia in the pathology of neurodegenerative disorders has been extensively studied (Jebelli et al., 2015; Verkhatsky et al., 2014), particularly the production of cytokines, chemokines, and neurotoxic species such as kynurenine metabolites and reactive oxygen species produced by microglia and astrocytes. In addition, phenotypic and morphological changes are described that are associated with altered glial activation and progression of disease states. The following section will highlight recent findings in glial biomarkers that are prevalent in some of the most common neurodegenerative diseases.

Glial Biomarkers in AD

AD is the leading cause of dementia in elderly patients. It progresses from memory loss and cognitive dysfunction in the early stages known as MCI to dementia along with a wide variety of additional symptoms in terminal stages. Diagnosis of AD typically occurs at advances stages of the disease after substantial neurological damage has already occurred which may limit treatment outcomes. Thus, there is a critical need to identify biomarkers for early detection. Extensive research implicates accumulation of amyloid- β -containing (A β) plaques in the brain as well as tau-rich neurofibrillary tangles in the development and progression of AD. In spite of the neurocentric nature of most AD research, human genetics demonstrate that several risk alleles are largely or even exclusively expressed by glia in the CNS. This strongly supports a meaningful role for glia in the development of AD, either through production of neurotoxic species that contribute to disease progression, aberrant amyloid clearance mechanisms, or lack of homeostatic support (Dzamba et al.,).

A wide variety of glia-derived biomarkers that can be accessed through peripheral compartments such as CSF and/or blood are found in AD including cytokines, chemokines, and kynurenine pathway (KP) metabolites. In fact, activation of microglia is correlated with disease progression and levels of dementia (Arends et al., 2000). AD patients demonstrate an imbalance in pro- and anti-inflammatory cytokines, as well as irregular tryptophan metabolism associated with activation of microglia and astrocytes. Among these effects, IFN- γ , TNF- α , IL-1 β , IL-2, and IL-8 are elevated along with increased kynurenine levels in

serum and/or CSF samples from AD patients (Alsadany et al., 2013; Delaby et al., 2015; Niranjani, 2013; Widner et al., 1999). In addition, quinolinic acid, a product of microglial kynurenine metabolism, is elevated in AD brain tissue (Guillemin et al., 2005), which could act as a priming event in tau hyperphosphorylation (Rahman et al., 2009). Nevertheless, detection of reliable changes in peripheral compartments for use as a biomarker has been elusive. Indeed, microglia and astrocytes also are sensitive to priming by $A\beta$ resulting in greater responses to IL-1 β stimulation such as increased IL-6 and IL-8 (Gitter et al., 1995). However, it is important to note that differences in cytokine patterns may be seen in CSF where TNF- α and IL- β were reportedly decreased in elderly patients with mild cognitive impairment (Rizzi and Roriz-Cruz,) suggesting that either cytokine profiles are differentially regulated across compartments or that these cytokine patterns change over the course of the disease. In either event, further research is needed to better understand the relationship between glia-mediated cytokine production and progression of AD, with a particular focus on method validation, sample collection, and storage procedures to ensure comparability across studies.

Another potential source for glia-related biomarkers in AD are chemokines. Several changes in blood and CSF chemokines were reported in AD, most notably MCP-1 and its receptor CCR2 (Delaby et al., 2015; Solfrizzi et al., 2006; Westin et al., 2012; Zhang et al., 2013). MCP-1 was associated with severity of disease, rate of cognitive decline, and reactivity of monocytes making it a particularly interesting biomarker for future studies. Of note, while MCP-1 was increased in blood, CCR2 was reportedly decreased (Zhang et al., 2013) suggesting differential regulation of the ligand and receptor under pathological conditions relevant for AD. An additional chemokine associated with AD is fractalkine, the ligand for CXCR3. Preliminary evidence indicates that fractalkine is reduced in the serum of MCI and AD patients (Kim et al., 2008). Interestingly, levels of serum fractalkine were also associated with the severity of cognitive impairment. It is of course important to bear in mind that altered chemokine patterns observed in peripheral blood may reflect systemic immune function imbalance. However, it is becoming clear that this imbalance is both a reflection of and a contributor to altered inflammatory regulation in the CNS (Liu et al., 2014). This suggests that while circulating chemokines may or may not originate from glia, it is nevertheless a biomarker of neuroinflammatory change, suggesting glial dysfunction in brain that warrants further research.

While many potential glial biomarkers have been reported in blood and/or CSF with associations to AD, most are the result of single, or very few, studies. A great deal of research is needed to confirm and validate these findings before they will be considered useful to help confirm AD diagnosis, prognosis, or response to experimental therapy.

Glial Biomarkers in Parkinson's Disease (PD)

PD is a progressive neurodegenerative disorder characterized by loss of dopamine neurons and the presence of α -synuclein protein inclusions called Lewy bodies in the substantia nigra pars compacta (Zinger et al., 2011). The etiological pathogenesis of PD has yet to be elucidated, but several contributing mechanisms have been proposed including mitochondrial dysfunction, glutamate excitotoxicity, and excessive production of reactive

oxygen species. The presence of activated microglia in PD brain, as well as production of cytokines and neurotoxic kynurenine metabolites, suggest that neuroinflammation may be linked to the genesis of PD.

Many studies support the presence of widespread microglia activation in PD (Vila et al., 2001). In two such studies, MHC class II expression, a marker of microglial activation, was higher in the substantia nigra and putamen as well as in the hippocampus, transentorhinal cortex, cingulate cortex, and temporal cortex of PD brains (Imamura et al., 2003; McGeer et al., 1988). In addition, MHC class II was frequently in proximity to α -synuclein-positive Lewy neurites and monoaminergic neurites, and were also positive for TNF- α and IL-6 in the putamen of PD brain (Imamura et al., 2003).

Further support for a role of activated microglia in the pathology of PD comes from biomarker studies in living patients. *In vivo* imaging of activated glia with [11C](R)-PK11195 PET in PD patients revealed wide-spread binding to brain regions including the pons, basal ganglia, and frontal and temporal cortex (Gerhard et al., 2006). In addition, levels of several cytokines including TNF- α , IL-1 β , IL-2, IL-4, IL-6, and TGF- α were also elevated in the CSF and striatum of PD brain (Mogi et al., 1994a,b; Nagatsu et al., 2000). In the periphery, serum levels of IL-6 and CCL5 (RANTES) were expressed at higher levels in PD patients compared to healthy controls (Tang et al., 2014) including a mild correlation between CCL5 expression level and the duration of PD. Although it is unclear whether these markers directly reflect primary glial pathology, they strongly suggest disrupted inflammatory regulation in the CNS that inherently involves the biology of glia.

In PD patients, IDO activity, as measured by the ratio of kynurenine to tryptophan, was increased in both serum and CSF compared with controls (Widner et al., 2002). Furthermore, changes in glial kynurenine metabolism are reported in postmortem PD brain. Kynurenic acid levels were decreased in PD postmortem brain (Ogawa et al., 1992). In contrast, levels of 3-hydroxykynurenine were elevated in the frontal cortex, putamen, and pars compacta of the substantia nigra in PD brain (Ogawa et al., 1992). Taken together, these data indicate that in PD kynurenine metabolism is stimulated by a proinflammatory environment and may be tipped in favor of neurotoxic species produced by microglia.

While a variety of glial biomarkers have been established in PD, further research into early phenotypic markers will be important to better understand what role glia play in the etiology and progression of PD. These studies are critical for early detection of PD as well as hopefully helping to evaluate novel treatment paradigms to slow or arrest the progression of the disease.

Glial Biomarkers in Amyotrophic Lateral Sclerosis (ALS)

ALS is a non-cell-autonomous progressive neurodegenerative disease that affects the upper and lower motor neurons, leading to loss of motor function, respiratory paralysis, and death within a few short years. The etiology of ALS is largely unknown with ~90% of cases presenting as sporadic ALS and the remaining 10% linked to a variety of specific gene mutations (e.g., SOD-1, TDP-43, FUS, OPTN, VCP, UBQLN2, PFN1, and C9ORF72; Brites and Vaz, 2014). Compelling evidence support a causal role in motor neuron loss by

microglia and possibly astrocytes. Indeed, microgliosis at sites of motor neuron injury is a pathological hallmark of ALS (Lasiene and Yamanaka, 2011). Although the exact interaction and course of events is unknown, microglia are thought to provide protection and support for neuronal health early in the course of the disease, followed by a shift toward more neurotoxic phenotypes and rapid neuronal loss.

A number of peripheral and central biomarkers have been identified that may be related to glial function in ALS. Recent advances in imaging technologies have allowed researchers to directly assess neuroinflammation and glial activation markers in the living brain (Cistaro et al., 2014; Radford et al., 2015). The first PET imaging studies using the TSPO ligand, [^{11}C]-PK-11159, confirmed wide-spread glial activation in ALS patients (Turner et al., 2004). More recently, TSPO PET ligands such as [^{18}F]-DPA-714 were developed that have less background and lower signal-to-noise ratios producing more detailed images of glial activation. Increased TSPO binding was subsequently confirmed in the brain and reported in the primary motor cortex, supplementary motor area as well as temporal cortex of patients (Corcia et al., 2012). Activated microglial receptors or astrocytic metabolites have been observed throughout the course of ALS and in fact demonstrate a relationship between gliosis and disease progression (Cagnin et al., 2004; Chio et al., 2014). Together, the rapid advancements of imaging agents provide powerful tools to evaluate disease progression and perhaps may offer a way to monitor treatment responsiveness.

In addition to TSPO PET imaging evidence for neuroinflammatory activation of glia in ALS, CSF, and blood based biomarkers of inflammatory activation that may reflect glial dysfunction have been reported in ALS. While the precise cell type to release each inflammatory mediator that is increased in the setting of ALS pathology is not known, the detection of these markers in CSF and serum is likely to be a surrogate marker of glial pathology and disease activity. In ALS patients, CSF IL-4, IL-7, IL-10, IL-17, and G-CSF were significantly elevated (Furukawa et al., 2015). It was noted that titers of IL-4 and IL-10 were particularly higher in patients with mild symptoms suggesting a potential unique cytokine signature in patients with a slower progressing disease. Interestingly, S100 β , a protein primarily expressed in astrocytes, was reportedly decreased in CSF (Sussmuth et al., 2003). This suggests decreased astrocyte contribution to CSF proteins, even though postmortem tissues confirm astrogliosis and elevated GFAP in ALS (Philips and Robberecht, 2011). In fact, similar decreases in S100 β were also reported in serum (Otto et al., 1998).

Although a variety of preclinical studies predict increases in cytokines and chemokines, few reports have noted circulating glia or immune-related biomarkers in plasma or serum of ALS. In a study, examining the interleukin-1 family of cytokines, Italiani et al. reported elevated serum levels of IL-18 and its endogenous inhibitor, IL-18BP, in patients with sporadic ALS, but no changes in IL-1 β , IL-33, or IL-37 (Italiani et al., 2014). In another study, G-CSF and TNF- α were also significantly increased in serum (Furukawa et al., 2015). Finally, IL-17 and IL-23 were reportedly elevated in both serum and CSF (Rentzos et al., 2010; Saresella et al., 2013) suggesting a contribution of Th17 cells to the immunological milieu of ALS.

Research into the pathology of glia in ALS has resulted in a variety of accessible biomarkers for translatable studies including a burgeoning imaging field along with well-defined soluble biomarkers that could be suited to evaluate patient phenotype and disease progression.

Acute CNS Injury

The evaluation of acute CNS injury secondary to trauma, hemorrhage, or ischemia has involved the use of imaging biomarkers for many years. Currently employed clinical imaging modalities are capable of defining the anatomic extent of pathology, determining whether or not the injury involves extravasation of blood from the vascular space to the CSF parenchyma, and differentiating between acute and chronic injury. Nevertheless, many clinical scenarios would benefit from improved biomarker availability. For example, biomarker that would distinguish between patients with a good vs. poor prognosis could be extremely helpful in the acute care setting. In addition, imaging biomarkers require extensive infrastructure and are relatively time intensive. As such, some critically ill patients are not easily evaluated using imaging biomarkers because they cannot be safely moved away from the intensive care setting or from a low infrastructure setting to one with full imaging capabilities. Therefore, novel biomarkers based on serum or CSF samples would both enhance clinical management and enable more effective evaluation of novel therapeutic approaches in clinical trials.

Glial cells are concurrently injured in all types of acute CNS injury. Thus, factors released from injured glia can serve as biomarkers of disease activity in the acute CNS injury setting. While serum and CSF biomarker are not yet commonly employed in clinical practice, they have been well studied in clinical research settings. This has included extensive study of the astrocyte protein S100 β in both serum and CSF. In the setting of TBI serum S100 β is elevated in patients with the worst long term outcomes and demonstrated greater predictive power than serum concentrations of markers of neuronal injury (Herrmann et al., 2001). Another astrocyte protein, GFAP, is elevated in serum following TBI and both GFAP and S100 β are accurate prognostic biomarkers of the degree of injury observed by MRI (Pelinka et al., 2004). When compared with serum ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1), a serum protein released from injured neurons, high serum GFAP/UCH-L1 ratio predicted focal mass lesions after TBI while high UCH-L1 was associated with diffuse axonal injury and elevations in both serum proteins were associated with higher mortality (Mondello et al., 2011, 2012). Additionally, recent studies have reported that TBI patients develop auto-antibodies to GFAP that can be detected in serum (Wang et al., 2015; Zhang et al., 2014). Higher titers of anti-GFAP antibodies were negatively correlated with outcome measures following TBI (Zhang et al., 2014), suggesting that the release of glial proteins following TBI may be sufficient to initiate an adaptive immune response that could serve as a prognostic biomarker.

Efforts to develop serum and CSF biomarkers for ischemic stroke have involved some of the same proteins as have been employed in TBI studies. S100 β is elevated in serum following ischemic stroke and can be used to predict malignant infarction of the middle cerebral artery (Foerch et al., 2004). Elevation of S100 β in CSF was also predictive of poorer long-term outcome after stroke (Petzold et al., 2008). In addition, the myelin protein

MBP also peaks in serum at 24 h following an ischemic stroke and both higher S100 β and MBP are predictive of a larger stroke and worse clinical outcome (Jauch et al., 2006). While these findings have been replicated, MBP was not as strong a predictor of white matter damage as CSF neurofilament light chain (Hjalmarsson et al., 2014), suggesting that neuronal proteins may be a better bio-marker of axonal injury. In addition, microglia factors galectin-3 and quinolinic acid have been measured in the CSF of newborns exposed to perinatal asphyxia and demonstrated that poor outcome was associated with higher concentrations of these microglia factors in the CSF (Savman et al., 2013). While these studies suggest that measurement of glial proteins in serum or CSF could provide important biomarkers in ischemic stroke or cerebral hypoxia, prospective clinical trials are needed to determine if these biomarkers provide clinical benefit either for critically ill patients or patients in low infrastructure settings where imaging studies are difficult to access.

Neuroinflammatory Disorders

Autoimmune attack on CNS tissue is a common mechanism of neurological disease. The spectrum of nervous system disorders caused by acquired autoimmunity is broad, but the most prevalent of this class of disease is MS. There are several defined subtypes of MS with the most frequently observed being relapsing-remitting MS (RRMS). The phasic nature of this disorder leads to additional challenges for diagnosis, treatment and the development of novel therapies. Effective biomarkers of disease activity can greatly assist in the effort to meet these challenges, both for improving patient care and for the development of novel therapeutics. Biomarkers that reflect glial pathology are extensively used to guide MS diagnosis and treatment. MS diagnosis involves demonstration of disease separated in time and space, meaning a patient needs to have experienced two clinical events separated in time that involve two different regions of the CNS. In addition, an MS diagnosis should include one objective measure confirming demyelination. As described above, one clinically useful bio-marker of CNS demyelination is demonstration of delayed evoked potentials. Currently, MRI is the most frequently employed objective measure of disease activity in RRMS both for diagnosis and to monitor treatment response. However, MRI lesion burden does not correlate with symptoms and does not provide strong information regarding prognosis for progression of disability or transition to the secondary progressive phase of MS (Daumer et al., 2009). Thus, there remains a need for prognostic biomarkers in MS.

Pathological lesions in MS include evidence for astrocyte damage as well as reactive astrogliosis, suggesting that astrocyte proteins may be elevated in CSF of MS patients. One early study of CSF GFAP and S100 β in a cohort of MS patients compared to control demonstrated that elevated S100 β was more strongly associated with RRMS than progressive forms of MS while elevated GFAP was associated with neurological disability regardless of MS subtype (Petzold et al., 2002). The finding that elevated CSF GFAP was associated with worsening disability has been confirmed by multiple independent studies (Malmstrom et al., 2003; Martinez et al., 2015). In addition, CSF biomarkers studies done concurrently with MRI studies demonstrate that while CSF MBP correlates with the presence of active lesions on MRI during relapse, CSF GFAP increases with time and persists after CSF MBP and MRI abnormalities have normalized (Burman et al., 2014).

Taken together, these studies suggested that CSF GFAP could be a biomarker for disease progression in MS, reflecting increasing astrogliosis with advancing disease burden.

The very highest levels of CSF GFAP have been observed in a discrete subtype of CNS autoimmune demyelinating disease, known as neuromyelitis optica (NMO). The identification of autoantibodies directed against aquaporin 4 in association with the clinical presentation of a syndrome of demyelination predominantly localized to the spinal cord and optic nerves has led to the understanding the NMO may result from pathophysiology that is distinct from MS. Patients with NMO demonstrate up to several thousand times higher levels of GFAP in the CSF compared to MS patients (Misu et al., 2009; Takano et al., 2010). Since the autoantibodies that define NMO are directed against an astrocyte protein, it is possible that CSF GFAP in this disorder is a direct bio-marker of antibody mediated astrocyte injury in NMO patients and a reflection of reactive astrocyte activation in MS patients.

As mentioned above, there has been a substantial effort to develop biomarker evidence for oligodendrocyte injury and/or regeneration. This is a critically important task for the use of biomarkers to determine if novel therapies aimed at myelin restoration are impacting the intended biological target. Several myelin proteins including MBP, Tubulin Polymerization Promoting Protein/p25 (Vincze et al., 2011), and myelin oligodendrocyte glycoprotein (Avsar et al., 2012) have been explored in CSF and serum as potential biomarkers for MS. Some studies have demonstrated that anti-inflammatory or immunosuppressive treatment leads to normalization of these myelin derived biomarkers. However, no clear path to identification of a biomarker for myelin regeneration has yet emerged.

Psychiatric Disorders

There is a growing recognition that glia influence human behavior in subtle ways beyond overt neurodegeneration. Glia are involved in maintenance of homeostatic synaptic stability as well as mediating immune-neural communication. When these functions are disrupted by immune stimuli, stress, or other signals, normal synaptic function may become impaired, leading to adaptive or maladaptive behaviors. The following section will highlight recent findings in glial biomarkers that are prevalent in some of the most common psychiatric disorders.

Glial biomarkers in Depression

Depression is the most common neuropsychiatric disorder with ~1 in 5 adults experiencing at least one depressive episode in their lifetime (Kessler et al., 2005). The causes of depression are myriad with contributions from genetic, environmental, and socioeconomic factors. Because only ~1/3 of patients fully respond to their first course of antidepressant treatment, there is a pressing need for novel biomarkers to help customize the initial treatment in major depressive disorder (MDD) to an intervention most likely to be effective in each individual patient. In recent years, the role of inflammation and consequent glial functions have received substantial in the literature due to the common co-occurrence of depressive symptoms and inflammation (Lichtblau et al., 2013; Schmidt et al., 2011). Evidence indicates that a subset of MDD patients develop symptoms secondary to systemic inflammation or neuroinflammation that may trigger depressive episodes. Patients receiving

immune-stimulating therapeutic treatments (e.g., IFN- α to treat hepatitis C; (Bonaccorso et al., 2002a, 2002b) or in experimental endotoxin paradigms (Eisenberger et al., 2010) have a high incidence of developing depressive symptoms. It is clear that peripheral activation of the immune system can have an impact on neural function, but in addition has direct measurable effects on glial activation states. The mechanism by which this occurs is not clear but could be mediated by type 1 cytokines such as TNF- α , IFN- γ , and IL-1 β that can both enter and influence the physiology of the CNS.

Elevated peripheral cytokines are commonly observed in MDD patients, with increased levels of TNF- α and IL-6 consistently reported (Dowlati et al., 2010; Howren et al., 2009; Kahl et al., 2006). Similarly, elevated levels of IL-1 β are reported (Diniz et al., 2010; Thomas et al., 2005). However, increased serum IL-1 β has been less consistently associated with MDD (Jazayeri et al., 2010), possibly due to differences in detection methodologies or patient populations. Recently, a panel of RNA transcripts measured in the blood, including TNF- α and IL-1 β , were shown to correlate to antidepressant treatment response (Belzeaux et al., 2012) indicating a potential means to predict, which patients will respond to current therapies. Indeed, a similar panel of biomarkers (TNF- α , IL-1 β , and MIF) was reported to predict lack of treatment response to traditional antidepressant medications (Cattaneo et al., 2013). Interestingly, a study of infliximab in depressed patients demonstrated reversal of depressive symptoms, but only in patients with a high inflammation tone (serum CRP >5 mg/dL; Raison et al., 2013) further validating the role of proinflammatory cytokines in mediating depressive symptoms. However, the source of peripheral proinflammatory cytokines is not likely to be from glia within the brain, but do seem to act on these cells none the less. One consequence of peripheral immune stimulation is induction of KP enzymes within microglia including IDO and KMO (Corona et al., 2010; O'Connor et al., 2009). The consequence of this is elevated conversion of tryptophan to kynurenine and subsequent production of neurotoxic metabolites such as quinolinic acid. Induction of IDO activity is predicted by measuring kynurenine/tryptophan (K/T) ratios. Elevated K/T is commonly found in depressed patients and is associated with increased anhedonia (Gabbay et al., 2012) and severity of depression in children (Gabbay et al., 2010). Furthermore, quinolinic acid is elevated in the anterior cingulate cortex of depressed patients, but only in severely depressed individuals (Steiner et al., 2011). In addition, studies have now demonstrated that, along with increased plasma kynurenine (Sublette et al., 2011), QUIN and IL-6 are increased in the CSF of suicide attempters (Brundin et al., 2015; Erhardt et al., 2013). Finally, plasma levels of tryptophan, kynurenine, and 3-HAA were correlated to treatment response to fluoxetine across a broad range of clinical scales (Mackay et al., 2009). Together these data suggest that a subset of MDD patients with high levels of underlying inflammation are associated with disruption in kynurenine metabolism that may relate to depressive symptoms. However, it is unclear as of yet whether the dysregulation of kynurenine metabolism by inflammatory mediators in MDD patients is driven primarily through peripheral metabolic pathways, since kynurenine and some metabolites can be transported across the blood-brain-barrier (Fukui et al., 1991), or whether central neuroinflammation systems also contribute to this effect.

MDD has heterogeneous biology, and at least a subset of patients develops elevated inflammatory tone in the brain and periphery, as well as increased microglial activity. Some discrepancies, possibly due to methodological differences, exist within the literature.

Nevertheless, the molecules involved in these signaling processes such as TNF- α , IL-1 β , IL-6, and various kynurenine metabolites make good accessible biomarkers in both the CSF and blood. These markers may be useful for segmenting patient populations for specific treatments, or possibly as indicators of treatment response. However, further research is needed to validate these hypotheses in studies using large patient sample sizes and standardized methods.

Glial Biomarkers in Schizophrenia

Schizophrenia is a debilitating neuropsychiatric disorder that affects ~1% of the world population. It is characterized by positive (delusions, hallucinations, disordered thoughts), negative (anhedonia, alogia, asociality) and cognitive (deficits in attention, executive function, and memory) symptoms (Harrison and Weinberger, 2005; Lewis et al., 2005). The role of glia is unclear in the development or progression of schizophrenia, though genome-wide association studies predict that altered astrocyte and oligodendrocyte genes are linked to an increased risk of developing schizophrenia (Goudriaan et al., 2014). In addition, a recent meta analysis (Miller et al., 2011) supports a role for immune signaling molecules in schizophrenia and confirmed that several cytokines are elevated in blood including both state-dependent (IL-1 β , IL-6, and TGF- β) and trait-dependent (IL-12, IFN- γ , TNF- α , and sIL-2R) markers. More limited findings were demonstrated in the CSF including decreased IL-1 β and with no change in IL-6 (Schwieler et al., 2015). These changes may be due to altered peripheral immune states (Schwarz et al., 2001; Smith and Maes, 1995) or microglial responses (Monji et al., 2009). Another recent study found that the ratios of serum IFN- γ /IL-4, IFN- γ /IL-10, IL-2/IL-4, and TNF- α /IL-4 were reduced in schizophrenic patients compared with controls (Chiang et al., 2013). These data support an emerging, although still controversial hypothesis which proposes that schizophrenia is associated with a shift from the production of Th1 cytokines, such as IFN- γ , IL-2, and TNF- α , toward the production of Th2 cytokines, such as IL-4, IL-10, and IL-6 (Muller et al., 2012; Schwarz et al., 2001). Thus, the etiology and/or pathogenesis of schizophrenia may be influenced by aberrant immune function and further research into understanding whether similar glia-related effects occur within the CNS.

One hypothesis for the underlying cognitive deficits associated with schizophrenia involves chronic hypoglutamatergic signaling in the cortex. From a biomarker standpoint, the KP may offer substrates to measure a biological link to this hypothesis. Kynurenine and kynurenic acid are elevated in CSF from schizophrenic patients compared with healthy controls (Linderholm et al., 2012). In addition, the ratio of quinolinic acid to kynurenine acid was reduced (Kegel et al., 2014). Since kynurenic acid is reported to antagonize NMDA and other glutamate receptors, while quinolinic acid is an NMDA excitatory agent, it has been speculated that these glial-derived neuroactive agents may contribute to the cognitive dysfunction in schizophrenia. Indeed, preclinical studies in rats demonstrated that inhibiting KAT II, the primary kynurenic acid producing enzyme in the brain, improved spatial memory and attention in both rats and non-human primates (Kozak et al., 2014). While no study has evaluated the direct impact of kynurenic acid on cognitive performance in humans, it could be used as a putative marker of astrocyte-mediated regulation of neuronal signaling.

Although the role of glia in schizophrenia is yet uncertain, a number of biomarkers that could be derived from glia or have a direct impact on glia function have been deduced. State- and trait-dependent cytokines offer opportunities to identify patient endophenotypes and perhaps assess response to medications. Further research is needed to determine the role of elevated kynurenic acid in schizophrenia, although if a role in cognition in patients is determined, it may offer a direct astrocyte-derived biomarker to identify patients with cognitive dysfunction.

Neuro-Oncology

Oncological diagnosis of CNS tumors remains primarily based on the use of pathological samples obtained during biopsy or surgical resection. However, biomarkers are occasionally used for diagnosis and extensively employed to examine disease progression and response to treatment in both clinical practice and research settings. The clinical utility of biomarkers for neuro-oncological diagnosis is most prominent when tumor location makes surgical access extremely risky. In this setting diagnosis is occasionally made using primarily imaging approaches, with or without MRS. When CSF can be safely obtained, tumor cells may be detected in the CSF and enable definitive diagnosis without need for surgery to obtain tumor tissue. However, the sensitivity of CSF cytology in brain tumors is low and new biomarkers would greatly enhance both current clinical care as well as in clinical trials of new therapeutic interventions.

The majority of human adult malignant CNS tumors arise from glial cell types. Glial tumor biomarkers in general are based in the biology of the glial cell of origin. As described above, the most frequently employed biomarker of CNS tumors is MRI. The MRI findings in brain tumors are in part due to the manner in which tumor biology alters the biology of surrounding glial cells. For example, highly malignant glioblastoma multiforme causes extensive accumulation of extracellular water in the interstitial space surrounding the tumor leading to increased signal on MRI. The source of the increased interstitial water may be secondary to increased capillary influx or decreased glymphatic efflux. Since most glial tumors are associated with increased accumulation of contrast agents delivered through the vascular system, it has long been assumed that increased water signal in the surrounding tissue is due to capillary leak. However, the volume of tissue demonstrating so called “vasogenic” edema is typically substantially larger than the volume of tissue demonstrating infiltration of contrast agents from the vasculature. Glymphatic flux is a recently described means of moving water through the CNS interstitial space and is predominantly regulated by astrocyte aquaporin-4 channels (Plog et al., 2015). Identification of glymphatic flux and demonstration that it is regulated by both physiological and pathological change suggests that glial tumors may influence interstitial water accumulation at least in part through by impairing glymphatic flux.

While MRI is the standard clinical biomarker employed to follow both disease progression and response to therapy in CNS tumors, it may not be the most sensitive measure of residual disease after treatment and it has little prognostic value for long-term disease recurrence. Thus, development of novel CNS tumor biomarkers is an active area of research. One potential biomarker of persistent disease that may enhance the sensitivity of CNS imaging

for tumors is TSPO-PET. While TSPO is predominately expressed by activated microglia relative to all other nontransformed cells in the CNS, glial tumor cells substantially increase TSPO expression, and high grade gliomas can be visualized as increased TSPO ligand binding using PET (Su et al., 2015). In addition, tumors that metastasize to the CNS from other tissues cause glial activation that can also be imaged using TSPO-PET with potentially greater sensitivity and resolution than contrast MRI (O'Brien et al., 2014). Thus using TSPO-PET to image glial activation can be a viable biomarker of both primary and metastatic tumor invasion.

In addition to imaging modalities, there is substantial effort underway aimed at identifying CSF based biomarkers for prognosis and/or monitoring response to therapy. For example, oxidative metabolites such as citric, isocitric, and lactic acids are substantially increased in patients with high grade gliomas and statistically associated with a poorer prognosis (Nakamizo et al., 2013). In addition, CSF proteomic studies of glioma patients have lead to the concept of the liquid biopsy for the future treatment of patients with these tumors. Multiple studies have demonstrated altered levels of proteins associated with the tumors and/or the inflammatory response that can aid in diagnosis as well as prognosis and response to treatment (Best et al., 2015). One exciting new area of biomarker discovery for glial tumors is in the identification of microvesicles (exosomes) and/or microRNAs residing within those exosomes in serum, CSF, or both fluid compartments (Qu et al., 2015; Tumilson et al., 2014). Future studies are likely to generate high levels of diagnostic accuracy by using a combinatorial biomarker strategy to bring the promise of non-surgical liquid biopsies to fruition in the near future (Kros et al., 2015).

Primary CNS lymphoma is another malignant tumor of the CNS for which would benefit from the development of effective biomarkers. Primary CNS lymphoma is a hematopoietic malignancy that can be diagnosed either by pathological examination of a biopsy or resection specimen or through the use of combinatorial biomarkers of disease. Typically, this involves diagnostic imaging in combination with the identification of malignant lymphoma cells in the CSF or vitreous chamber of the eye. Additional CSF and serum biomarkers with potential diagnostic utility for primary CNS lymphoma are also under development (Turetsky et al., 2015; Viacoz et al., 2015). As with glial based tumors, altered serum or CSF miRNA concentrations have been reported (Baraniskin et al., 2011; Mao et al., 2014; Wei et al., 2015) and the levels of some CSF cytokines or chemokines are sufficiently elevated to provide a high degree of diagnostic specificity (Fischer et al., 2009; Sasagawa et al., 2015). Development of effective and specific biomarkers in serum or CSF may enable noninvasive means of distinguishing between CNS lymphoma and glioma (Scott et al., 2013). In addition, a strongly predictive serum biomarker for residual disease and/or response to treatment could be a very useful adjunctive component to future clinical trials.

Conclusions

The discussion above illustrates the growing understanding of the role that glia play in psychiatric and neurological disorders, and highlights the importance of developing glia-associated biomarkers to help support diagnosis, prognosis, and assessing response to therapy for a wide variety of CNS disorders. The biological responses of glia are accessed in

all modalities of biomarkers including molecular markers, electrophysiological assessments, and neuroimaging approaches. Most currently employed CNS disease biomarkers are based in glial responses to the specific disease. This includes both anatomical and functional MRI, which is the current standard approach used to monitor response to treatment in clinical trials for acute injury, neuroinflammatory disorders, and CNS neoplasms.

Several themes emerge from the CNS biomarker field regarding the potential for novel biomarkers that will streamline therapeutic development for neurological and psychiatric disorders. First, several functions of glia make them likely to serve as a potential window into pathophysiological processes within the CNS. Astrocytes regulate many features assayed by current neuroimaging approaches. In addition, microglia activation can be visualized by PET imaging. These approaches have sufficient anatomic resolution to enable identification of specific CNS regions involved in the pathology. In addition, since these glia based neuroimaging approaches are assaying reversible processes, they are likely to be used as biomarkers of response to treatment in a variety of chronic CNS disorders. Second, glia based inflammatory responses, whether precipitating or responding to CNS pathology, will alter the composition of serum and CSF, yielding biomarkers of disease activity. Some therapeutic development efforts aimed at modifying CNS inflammation may use biomarkers of CNS inflammation as evidence of target engagement in addition to a potential means to monitor disease activity. A third theme involves the need to develop enhanced understanding of normal glia functions and how they interact with glia based biomarkers. For example, CNS disease and injury states likely alter glymphatic transit of solutes from blood to CSF. How altered glymphatic transit influences the relative concentration of molecular biomarkers in each compartment remains to be determined.

In summary, biomarkers are critical adjunctive components that substantially assist in the development of novel clinical interventions. For CNS disorders, biomarkers are frequently based on the physiology of glia. As novel therapeutic ideas are tested, glia based biomarkers will be used to help determine if these novel therapeutic approaches successfully engage they predicted target and/or modify the natural history of the disorder to provide therapeutic benefit. Further clarification of glia biology in the setting of CNS disease will enhance the utility of currently available biomarkers as well as aid in the development of novel biomarkers to improve patient stratification and more efficiently assess response to treatment.

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