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The role of oligodendrocytes and their progenitors on neural interface technology: A novel perspective on tissue regeneration and repair

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Abstract

Oligodendrocytes and their precursors are critical glial facilitators of neurophysiology, which is responsible for cognition and behavior. Devices that are used to interface with the brain allow for a more in-depth analysis of how neurons and these glia synergistically modulate brain activity. As projected by the BRAIN Initiative, technologies that acquire a high resolution, robust sampling of neural signals can provide a greater insight in both the healthy and diseased brain and support novel discoveries previously unobtainable with the current state of the art. However, a complex series of inflammatory events triggered during device insertion impede the potential applications of implanted biosensors. Characterizing the biological mechanisms responsible for the degradation of intracortical device performance will guide novel biomaterial and tissue regenerative approaches to rehabilitate the brain following injury. Glial subtypes which assist with neuronal survival and exchange of electrical signals, mainly oligodendrocytes, their precursors, and the insulating myelin membranes they produce, are sensitive to inflammation commonly induced from insults to the brain. This review explores essential physiological roles facilitated by oligodendroglia and their precursors and provides insight into their pathology following neurodegenerative injury and disease. From this knowledge, inferences can be made from the impact of device implantation on these supportive glia in order to engineer effective strategies that can attenuate their responses, enhance the efficacy of neural interfacing technology, and provide a greater understanding of challenges that impede wound healing and tissue regeneration during pathology.

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Keywords

Glial pathology; Microelectrode array; Brain injury; Inflammation; Demyelination; Foreign body response

1. Introduction

Neural electrode devices that can be used to study and interface with the brain have the potential to advance the field of neuroscience and improve the treatment of nervous system-related disorders and disabilities. The multi-potential use of these devices depends on the ability to transmit and receive electrical signals to and from neural tissue in a stable and reliable manner. In order to do so, the electrode contacts must be minimally impacted by protein biofouling and cellular encapsulation as well as remain in close proximity to active neurons that are integrated into the functional neural network. This level of integration at the electrode-tissue interface is necessary to maximize detected signal and reduce impedances, which can increase noise. However, on average, electrode-tissue interfaces degrade over time. Neural degeneration and glial scar formation reduce the functional performance of chronically inserted microelectrodes. Recent efforts aim to understand the biological mechanisms behind the onset of tissue inflammation and apply that knowledge toward effective therapies to attenuate this response and achieve the full potential of neural interfaces.

1.1 Obstacles encountered during neural interface design

The capabilities of neural interfaces as assistive devices for disabled or neurologically impaired individuals are limited by the gradual degradation in recording or stimulating performances over time [1–4]. Failure modes of chronically implanted neural electrodes can be divided into three major categories: mechanical, material, and biological sources of device failure [5, 6]. Mechanical failures involve a perturbation in the external connectors of the device that are responsible for transmitting signal from the implanted electrode to an external computer. Examples include electrode displacement from the tissue or severing of connector cables. Material failures include the degradation of the conductive, insulating, or specially coated interface that impedes the exchange of information between the electrode and surrounding tissue. This type of failure manifests in the conductor and insulating material chosen, as well as the size, geometry, and mechanical characteristics of the device which have respective influences on the severity of tissue inflammation. Biological failures are the result of endogenous tissue reactions to the physical implantation or presence of the device. Failure in either of these categories is not exclusive; for example, while delamination of the insulation results in recording failures, subsequent exposure of the underlying electroactive material can also lead to electrode dissolution, which negatively impacts tissue viability. The persistence of a degenerative foreign body response afflicts both biological tissue as well as the material interface, reducing the long-term recording quality of chronically implanted devices. Consequently, the design of neural interfaces becomes a multi-faceted approach and must take into consideration a wide array of design parameters to functionally integrate electrical materials with biological tissue [7]. Efforts to solve issues of performance reliability and variability by engineering solutions of one aspect of device

design prove insufficient when faced with multiple overwhelmingly complex and interconnected modes of failure. Furthermore, chronically implanted neural electrodes which avoid mechanical or material-induced mechanisms of failure ultimately succumb to the persistence of inflammation and degradation of neural tissue and lose quality in recording and stimulating performances [5].

A majority of investigations of the biological component of the electrode-tissue interface characterize the microglial and astrocyte reactivity around inserted devices and their impact on neural health (see review [8]). However, these studies neglect a variety of other cellular factors in the brain such as oligodendrocyte precursor cells, mature oligodendrocytes and their myelin components, mural cells such as pericytes and endothelial cells, and other immune system mediators such as monocytes, neutrophils, and leukocytes. Since each of these cells have their respective roles in maintaining brain health and may potentially deviate from their responsibility in homeostasis during disease and injury, careful characterization of their behavior around inserted neural devices is required to work toward effective device design. This review will detail the behavior of cells of the oligodendrocyte lineage as well as their myelin structures in both healthy and diseased states in an effort to predict the potential consequences of chronic microelectrode implantation on these cell types.

2. Current understanding of tissue response to injury

Normal physiology in the brain involves a variety of active signaling between neurons, glia, and vascular cells in order to perform functional activity and maintain tissue homeostasis. These sensitive connections are altered or compromised during injury, influencing neuronal output and tissue health [9]. The critical pathways that lead into the neurodegenerative insult induced by electrode implantation have been a subject of debate, however, major influences such as glial cell activation and blood-brain barrier permeability are widely accepted contributors to declining neuronal health [10, 11]. A brief review of the major constituents that exist within the parenchyma (neurons, glia, and the cells that support the blood-brain barrier) and their involvement in the foreign body response to inserted devices is required in order to contextualize the impact of implantation injury to other cell types within the brain.

2.1 Blood-brain barrier disruption on activation of the inflammatory tissue response

The blood-brain barrier actively regulates influx of nutrients and oxygen and efflux of waste products between CNS tissue and peripheral blood while providing protection to neuronal cells from toxins and pathogens that circulate throughout the body [12]. The insulating nature of this vascular membrane is the result of endothelial cells forming continuous intracellular tight junctions with one another, supported by astrocytes and pericytes that provide additional mechanical and trophic support to the blood-brain interface [13]. During brain injury, disrupting the endothelial cell-cell barrier can lead to vasogenic edema, loss of perfusion, activation of glia, and neurodegeneration [14]. Additionally, compromising the integrity of the BBB exposes the parenchyma to inflammatory plasma proteins and allows for the infiltration of inflammatory peripheral immune cells [14]. A review detailing the biochemical mechanisms behind the impacts of BBB disruption on degrading signal sensitivity of neural implants has been published previously [9]. Considering that

microelectrode arrays constantly shift due to breathing and pulsating micromotions within the body, random tears to the BBB can occur at any time throughout the lifetime of the implant. As a result, maintaining BBB integrity is required to minimize the impact of glial cell activation and surrounding tissue inflammation during chronic implantation.

2.2 Glial cells on noise

Gliosis is commonly observed in the context of chronically implanted microelectrodes which hinders recording and stimulating performances over time [15–18]. Glial scarring can interfere with the exchange of ions and charged solutes between neurons and the conductive surface of the electrode which increases the noise and impedes signal detection, ultimately leading to a decreased signal-to-noise ratio (SNR). *In vivo* imaging has been used to characterize the acute and immediate activation and encapsulation of microglia cells in response to microelectrode insertion [19]. The astrocytic scarring response is commonly characterized by an upregulation in glial fibrillary acidic protein (GFAP) around the device-tissue interface. As a result, the compacted glial scar creates a membrane-bound barrier that inhibits transmission of signal across the electrode-tissue interface. Gliosis can persist at chronic time points in part due to the continual secretion of pro-inflammatory factors and repeated disruption of the BBB whose ability to heal may be impaired by the implant, negatively impacting the viability of the surrounding neurons.

2.3 Neuronal sources of signal loss

Blood-brain barrier disruption, glial cell activation, and inflammation influence neuronal physiology and, ultimately, neuronal function. Direct correlations between increased BBB leakage and decreased neuronal activity have been observed at chronic time points [20]. The presence of a glial scar prevents the transmission of electrical signals and displaces nearby neurons further from the electrode interface. This effectively increases the distance to the nearest neuron making it difficult for an electrode to record or discriminate between single units due to the voltage drop off from increasingly distant neurons [21]. Furthermore, neurons are particularly susceptible to oxidative stress events which may occur when the BBB is disrupted, creating an ischemic event, or production of reactive oxygen species (ROS) from activated glia. Finally, reactive oxygen species and proinflammatory cytokines secreted by activated immune cells are notably toxic to neurons and have been characterized in other neurodegenerative disorders [22, 23]. Therefore, implementation of successful therapeutic strategies or improved device design could mitigate the blood-brain barrier or glial-induced insult on neuronal loss, improving the performance of chronically implanted neural electrodes [24].

2.4 Summary and current limitations on an integrated tissue response

The influence of blood-brain barrier disruption and activated glia on neuronal health are not mutually exclusive; effects of one insult can trigger inflammatory events in the other. Potential strategies aimed at mitigating the currently known biological reactions in an attempt to improve the biocompatibility of neural interfaces have been suggested and published elsewhere [7, 9, 25]. However, recent studies have proven that increased neuronal viability, decreased glial cell activation, or reduced BBB leakage are not exclusively accurate predictors of functional electrode performance [26]. This implies that other

endogenous tissue events which remain to be investigated could contribute to the degrading quality of neural microelectrodes, such as oligodendrocytes and their precursor cells, which share a more intimate relationship with neuronal cells compared to other glia.

3. Oligodendrocyte and NG2 glia physiology in the brain

As some of the most metabolically active cells in the brain, oligodendrocytes and their precursors serve a variety of different homeostatic functions and interact with neurons, glia, as well as the blood-brain barrier in order to facilitate normal brain activity. Under normal physiological conditions, cells from the oligodendrocyte lineage experience four distinct phases throughout their life cycle: origin, migration, and proliferation of oligodendrocyte precursor cells (OPCs); differentiation into mature myelinating oligodendrocytes; initiation of neuronal contact and myelination of axonal fibers; and provision of trophic and metabolic support to neurons. Oligodendrocyte precursors are identified based a number of criteria involving morphology, antigen expression, and physiological functions. OPCs are defined as cells displaying a stellate-shaped morphology, extending processes radially about their cell soma [27]. These cells are increasing and more commonly referred to as NG2 glia due to their constitutive expression of the neural-glia antigen 2 marker [28]. However, other parenchymal cells such as pericytes and macrophages express the NG2 antigen as well, requiring the need for co-localization of multiple identification markers [29]. Additionally, the inherent heterogeneity of oligodendrocyte precursor-specific NG2 glia further complicates precise identification since physiological as well as pathological function may be dependent on embryonic origins or the resident tissue environment of the cell [30].

3.1 NG2 origin, migration, proliferation, and differentiation in the developing CNS

NG2 glia are highly proliferative and widely abundant (comprises 5–8% of the total glial population in adult brain) within the CNS. The earliest observations of NG2 in the developing CNS are from the ventricular zones (VZ) of the spinal cord at embryonic day 12.5 (E12.5) for mice and E14 for rats [31, 32]. In the rodent brain, NG2 glia originate in the medial ganglionic eminence and anterior entopeduncular area of the ventral forebrain, populating areas of the telencephalon such as the cerebral cortex from E16 until birth (~E18) [33]. After the initial influx of oligodendrocyte precursors, a second and third wave emerge from the lateral ganglionic eminence and postnatal cortex, respectively, to replace the first wave, with NG2 glia reaching a maximum density before birth within the spinal cord and by postnatal day 3 (P3) in the cortex [34]. Despite originating from different regions, NG2 glia retain similar characteristics such as the ability to spread over non-overlapping domains and fill vacant spaces in the event of cell migration, differentiation, or death *in vivo* [35]. Likewise, studies of oligodendrocyte precursors from gray and white matter regions showed no differences in proliferation rates or cell cycle lengths [36]. However, functional properties such as those involving membrane channels and receptors differ between NG2 glia populations in the mouse gray and white matter [37].

After diverging from radial glia progenitors, NG2 glia travel along blood vessels towards other regions of the developing CNS [38]. Migration of NG2 glia during development is determined by two different mechanisms, one of which is contact-mediated migration

involving extracellular matrix proteins (laminin, fibronectin) or cell surface proteins (cadherins, integrins) and the other involving the secretion of growth factors (PDGF, FGF-2, EGF, HGF), chemotactic molecules (netrins, semaphorins), or chemokines (CXCL1) [39]. More recently, it has been discovered that vascular and meningeal cells secrete growth factors (TGF- β and BMPs) that guide migration of NG2 glia into the cortex during development [40]. After migrating, NG2 glia evenly distribute throughout both gray and white matter and differentiate into mature myelinating oligodendrocytes. NG2 glia are commonly referred to as polydendrocytes due to their intrinsic ability to differentiate into neurons and astrocytes as well as oligodendrocytes (Figure 1) [41]. However, some NG2 glia do not differentiate into mature oligodendrocytes and maintain their precursor morphology throughout adulthood, consisting of ~4% of all cells in the adult cortex [42].

Through *in vivo* imaging of the mouse cortex, these cells are observed to be highly active exploring their surroundings through the extension and retraction of processes, maintaining a homeostatic distribution of cell bodies in a grid-like manner [35]. This local population of NG2 glia are thought to function as a reservoir of oligodendrocyte precursors in the event of demyelinating injury and as support cells for myelin maintenance and possible mediators of neuronal networks via formation of synaptic contacts [43].

3.2 Oligodendrocyte maturation and myelination

At post-natal day 2 (P2) in rodents, most cells are in the pre-oligodendrocyte phase where markers of differentiated oligodendrocytes (O4) begin to be expressed, markers for NG2 glia (NG2, PDGFR α) are downregulated, and a morphology indicative of branched, multipolar oligodendrocytes begins to take shape. During this maturation period, pre-oligodendrocytes lose the ability to migrate or proliferate [44]. The differentiation of NG2 glia into myelinating oligodendrocytes involves signaling between the Notch 1 receptor and the axonal ligand Jagged 1 [45]. The earliest occurrence of myelination in the white matter is not observed until postnatal day 7 where oligodendrocytes only have a brief time period, between 12 to 18 hours after differentiation, to form myelin sheaths around axons [46, 47].

Myelin is effective at transversely reducing the capacitance and increasing the resistance of a neuronal membrane, allowing for the saltatory propagation of action potentials along an axon fiber. The minimum axonal diameter required to be myelinated by oligodendrocytes is 0.2 μm [48]. Myelination by oligodendrocytes is most notably mediated by the presence of electrical activity from neurons [49], however myelin formation can also be regulated by oligodendrocyte precursors [50], astrocytes [51], microglia [52], and oligodendrocytes themselves [53]. Inhibition of electrical activity using voltage gated Na⁺ channel blockers or increased concentration of extracellular K⁺ prevents myelination [54]. Oligodendrocytes cultured *in vitro* by themselves display intracellular proteolipid protein (PLP) with membrane bound myelin basic protein (MBP) and GalC myelin proteins; however, when cultured with neurons, PLP is produced and transported to the cell surface via lipid rafts where it is normally observed around myelinated axons [55]. Secretion of LINGO-1 by neurons and oligodendrocytes, which is a ligand inhibitory to neurite outgrowth [56], prevents differentiation and myelination of axons *in vitro* through the activation of RhoA [53], a protein that regulates the cytoskeletal and morphological changes during

oligodendrocyte differentiation [57]. The presence of myelin solely on axonal fibers (and not dendrites or other cell structures) suggests cell surface markers specific to axons that regulate myelin, such as polysialic acid neural cell adhesion molecule (PSA-NCAM) [58, 59]. However, removal of negative PSA-NCAM modulation does not reverse the inhibition of myelination through use of voltage-gated Na⁺ channel blockers such as TTX *in vitro*, suggesting that both neuron cell surface moieties and electrical signaling are required to elicit the formation of myelin [59].

White matter consists of a high density of myelinated axons that are responsible for transferring information between the peripheral and central nervous system. Myelination in the gray matter was largely unknown until recent advances in high resolution neuroanatomy imaging have allowed researchers to visualize different myelination patterns of gray matter regions in the brain. Through the use of advanced electron microscopy (EM) techniques, it has been observed that patterns of gray matter myelination in the cortex are distinct from those commonly observed in white matter and myelination differs between different cortical layers, with a higher density of myelin covering deeper cortical layers (layers 5 and 6) compared to more superficial layers (layers 2 and 3) [60]. Interestingly, another study using EM combined with array tomography (AT) of the mouse neocortex observed a large portion of those myelinated cortical axons to be inhibitory interneurons (GABA-expressing neurons), specifically parvalbumin-positive (PV+) basket cells, comprising half of myelinated layer 2/3 axons and a quarter of myelinated layer 4 neurons [61]. The postsynaptic targets of these neurons are mainly the dendrites and neuronal soma of pyramidal cell neurons, which provide the large output of myelinated axons leading out of the CNS via white matter. Considering inhibitory neurons are only 10–20% of total neurons in the cortex, the myelination of these particular cells could play a critical function for neuronal viability and brain circuitry [62].

Lastly, there exists a different population of oligodendrocytes in the cortex, called satellite oligodendrocytes, distinct from their myelinating counterparts [63, 64]. These satellite oligodendrocytes, which reside in close proximity to the soma of neurons, are responsible for providing metabolic support, preventing cellular apoptosis, and assisting with remyelination following injury [65–67]. Whether there are heterogeneous differences in the reaction of satellite and myelinating oligodendrocytes to injury induced during chronic microelectrode implantation remains to be seen.

3.3 NG2 glia and oligodendrocyte mediate neuronal physiology

Demyelinating diseases and oligodendropathies such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) are characterized by chronic axon degeneration, emphasizing the dependence of neurons for oligodendroglial support [68, 69]. Previously, it has been shown that NG2 glia and oligodendrocytes both promote neuronal viability through the secretion of insulin-like growth factor 1 (IGF-1) *in vitro* [70]. Although both oligodendrocytes and NG2 glia maintain direct contact with axons through the extension of myelin sheaths and formation of synaptic contacts, respectively, their purpose and function are distinctly different. However, both contribute to overall neuronal health and are essential in maintaining tissue homeostasis during injury.

Within the cortex, NG2 glia reside close to neuronal dendrites and soma where they receive synaptic input through glutamatergic and GABAergic activity [71, 72]. Depending on the cell fate of NG2 glia, some cells can possess voltage-gated sodium channels (Na_v) [73]. NG2 glia that differentiate into myelinating oligodendrocytes exhibit a downregulation of both glutamate receptors and Na_v channels, while undifferentiated glia maintain their excitability [74]. This is most likely due to the fact that neuronal activity can direct the migration, proliferation, and differentiation of mature NG2 glia, in which case differentiated oligodendrocytes would not require this excitability. Specifically, patterns of high frequency stimulation of callosum axons in the mouse brain promote an increased proliferation of NG2 glia while low frequency stimulation induces NG2 glia differentiation into myelinating oligodendrocytes [75]. NG2 glia have demonstrated neuronal modulation of network activity via cleavage of the NG2 proteoglycan, influencing alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) dependent activity in pyramidal cells [76], and secretion of known neuromodulatory factors [77]. The selective ablation of NG2 glia in the prefrontal cortex of mice induces altered glutamatergic signaling in neurons and subsequent expression of depressive-like behavior [78]. Another study involving the genetic ablation of adult NG2 glia *in vivo* observed induced neuroinflammation via activation of microglia, leading to neuronal cell death [29]. It was also found that hepatocyte-growth factor (HGF), which is an important anti-inflammatory factor that supports neuronal survival, is secreted by cultured NG2 glia [79]. During oligodendrocyte cell death, NG2 glia are responsible for the proliferation, differentiation, and initiation of myelination around demyelinated axons to preserve neuronal health. Thus, NG2 glia are critical for mediating neuronal communication and support through synaptic activity as well as providing precursors for oligodendrocyte differentiation and myelin development.

As well as providing electrical insulation via myelin ensheathment, oligodendrocytes provide neurotrophic support to neurons through the release of glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and IGF-1 [80–82]. Likewise, oligodendrocytes match the high metabolic demand of neurons through the provision of energy metabolites, glucose and lactate, via high expression of monocarboxylate transporter 1 (MCT1) [83]. MCT1 is predominantly localized to the myelin sheaths that surround axons and controls lactate export from oligodendrocytes [84]. Neurons also express their own form of monocarboxylate transporters (MCT2), allowing them to import energy metabolites secreted by astrocytes [85]. Additionally, through the release of glutamate that bind primarily to NMDA receptors, neurons instruct oligodendrocytes to transfer metabolite and antioxidant-loaded membrane vesicles, called exosomes, through the perineuronal space, which is the space between myelin and neuronal membranes [86]. As a result, in the condition in which oligodendrocytes are not able to establish contact with axons due to demyelination or via the physical blockade of trophic factors by an implanted device can have detrimental consequences to the health of neuronal tissue and the overall performance of neural interfaces in the brain.

3.4 NG2 and oligodendrocyte crosstalk with other glial cells

Astrocytes and NG2 glia are distinct types of glia that maintain differences in morphology and function despite originating from similar precursor cells during development [87]. However, both glia extend connections to nodes of Ranvier and synapses on neurons, indicating they may influence each other's physiology [88]. Astrocytes are important mediators of the migration, proliferation, and differentiation of NG2 glia during CNS development. Ncadherins present on the surface of astrocytes influence NG2 glia migration *in vitro* by anchoring them to their cell surface [89]. Additionally, the same way neurons elicit a calcium Ca^{2+} transient current within NG2 glia following glutamate secretion, astrocytes elicit a similar NG2 glia calcium transient through the release of adenosine and ATP [90]. Both secreted factors regulate NG2 glia differentiation; however, adenosine acts directly on the NG2 glia while ATP acts indirectly by prompting astrocytes to express leukemia inhibitory factor (LIF) [91, 92]. Astrocytes also promote the proliferation and differentiation of NG2 glia by secretion of platelet-derived growth factor AA (PDGF-AA). Likewise, different cytokines that are normally expressed during injury influence astrocyte-induced migration of NG2 glia [93]. Chemokine receptors CXCR1 and CXCR2 expressed by oligodendroglia during development are known targets for astrocyte-secreted CXCL1, which stimulates NG2 glia proliferation *in vitro* via a PDGF-AA signaling mechanism [94]. Astrocytes also secrete soluble factors that protect NG2 glia from oxidative stress via ERK and Akt signaling pathways [95]. However, during insertion injury reactive astrocytes may secrete alternative pro-inflammatory factors that supersede this protective effect. Lastly, it has been observed *in vivo* that NG2 glia can develop into protoplasmic astrocytes within gray matter regions of the brain [96]. However, NG2 glia also possess a limited ability to differentiate into scar-forming astrocytes during injury, prompting the question about their role during the development of an inflammatory glial scar and overall disease pathology.

Like NG2 glia, oligodendrocytes also share a close spatial relationship with astrocytes. Astrocytes create a "glial syncytium" or glial network with oligodendrocytes through the formation of gap junctions [97]. This glial syncytium is hypothesized to re-distribute potassium ions from axons following neuronal activity [98]. Astrocytes play a significant role in differentiation and myelination of oligodendrocytes throughout maturation and during injury. Through physical contact alone, astrocytes can promote oligodendrocyte maturation via interactions with integrins [99]. Additionally, a variety of astrocyte-secreted factors such as neuregulin-1, gamma-secretase, ciliary neurotrophic factor (CNTF), insulin-like growth factor 1 (IGF-1), osteopontin, and neurotrophin-3 (NT3) are known to influence myelination [100]. Bone morphogenetic proteins (BMPs) secreted by reactive astrocytes negatively regulate the differentiation of NG2 glia into mature oligodendrocytes *in vitro*, inhibiting the expression of myelin proteins during differentiation [101]. Hyaluronan, fibronectin, platelet-derived growth factor (PDGF), fibroblast-derived growth factor 2 (FGF-2), and tenascin C also expressed by reactive astrocytes can impair remyelination [100]. This indicates that the pathological state of astrocytes is a strong determinant for the promotion or inhibition of myelination following injury.

Depending on the activation state of microglia, they can either secrete pro-inflammatory or anti-inflammatory molecules which differentially modulates NG2 glia and oligodendrocytes.

During normal physiology, microglia are known to promote NG2 viability and oligodendrocyte maturation via upregulation of transcription factor NF κ B as a result of PDGF- α receptor stimulation [102]. A reduction in tumor necrosis factor alpha (TNF- α) secretion has been shown to reduce NG2 glia proliferation and delay remyelination [103]. However, TNF- α also reduces NG2 glia differentiation into myelinating oligodendrocytes [104]. Binding of TNF- α to tumor necrosis factor receptor 2 (TNF-R2) as opposed to tumor necrosis factor receptor 1 (TNF-R1) induces this reparative effect following demyelination [105]. Microglia can modulate the differentiation of NG2 glia into oligodendrocytes via expression of galectin-3 but not galectin-1 [106]. However, galectin-1 attenuates the loss of myelin and neurodegeneration in animal models for MS [107]. Interestingly, non-reactive microglia and astrocytes influence NG2 glia differently [108]. Astrocyte-derived medium, which consists of increased PDGF-AA, FGF2, CNTF, and growth hormones, promotes proliferation of NG2 glia while microglia-derived medium, consisting more of IGF-1, CX3CL1, IL-2, and IL-5, promotes the differentiation of NG2 glia, indicating different fundamental roles in regulating the fate of oligodendroglia [100]. During injury, TGF- β instructs microglia to secrete hepatocyte growth factor (HGF), which is a chemotactic molecule that recruits NG2 glia for proliferation and differentiation into remyelinating oligodendrocytes [109]. Using two-photon microscopy to observe NG2 glia and microglia dynamics in response to probe insertion *in vivo*, there was a 12 hour delay in the activation of NG2 glia after microglia activation which may be representative of a temporal, chemotactic response between the two glial cells [110]. Similarly, activated microglia inhibit the proliferation of NG2 glia and promote their cell death [108, 111].

Microglia are a primary source of iron for oligodendrocytes. Prior to the differentiation of NG2 glia, microglia accumulate iron in preparation for myelination by mature oligodendrocytes [112]. Oligodendrocyte viability is dependent on the supplementation of ferritin by microglia. When microglia become activated during injury they produce many pro-inflammatory mediators such as glutamate, matrix metalloproteinases, and reactive oxygen and nitrogen species that make oligodendrocytes vulnerable to excitotoxic or oxidative stress [113]. Lipopolysaccharide-induced activation of microglia via the toll-like receptor 4 (TLR4) pathway has shown to induce oligodendrocyte cell death as well as hypomyelination [114]. However, activated microglia can still produce trophic factors such as insulin-like growth factor 2 (IGF-2), which supports oligodendrocyte viability [115]. Reverting microglia from a pro-inflammatory phenotype to an anti-inflammatory phenotype improves oligodendrogenesis and myelin formation during remyelination [116]. Likewise, oligodendrocytes under duress are known to produce several chemotactic factors (CXCL10, CCL2, and CCL3) that recruit microglia to areas of injury [117].

Understanding how these glial cells function during injury is obscured by the fact that multiple phenotypes, or “polarizations”, can arise under different circumstances. Based on simplified *in vitro* analysis, microglia have historically been categorized as either ‘M1’ pro-inflammatory or ‘M2’ anti-inflammatory phenotypes primarily on exposure to different cytokine stimuli [118]. However, these are isolated states and fail to account for the assortment of signaling molecules that are secreted during injury *in vivo* [119]. Additionally, these distinct inflammatory profiles are being refuted by investigators as further information is uncovered about the complexity of microglia polarization [119]. Microelectrode insertion

injury induces both pro-inflammatory and anti-inflammatory microglia states and administration of therapeutics can modulate microglia activation [120]. Similarly, astrocytes demonstrate varying phenotypes during inflammation ('A1'/'A2' polarizations) that complicate understanding of their roles following injury. For example, astrogliosis is traditionally viewed as neurodegenerative and detrimental to the surrounding tissue, however, evidence suggests that reactive astrocytes can provide neuronal protection via inhibition of apoptosis, neurotrophic support, and homeostatic balance [121]. Activation of microglia and astrocytes, while commonly seen as perpetuators of inflammation, are required for tissue repair and regeneration. Activated microglia are responsible for myelin debris clearance and promotion of oligodendrogenesis whereas reactive astrocytes secrete factors that modulate NG2 glial responses [122]. Thus, a more thorough understanding of these pro-inflammatory and anti-inflammatory glial phenotypes is required to determine the true nature of their functions and interactions with other cells during CNS injury.

3.5 Perivascular NG2 cells interact with the BBB

In the developing CNS, angiogenesis and foundation of the BBB occurs around E11, before the appearance of NG2 glia, where oligodendrocyte precursors use the vascular endothelium to migrate away from their sites of origin [38, 123]. From there, NG2 glia either distribute throughout the parenchyma (parenchymal NG2 glia) or reside in close proximity to endothelial-bound pericytes (perivascular NG2 glia). Previous studies suggest a bidirectional relationship between NG2 glia and pericytes, where exposing conditioned media of one cell type has a proliferative effect on the other [124]. Interactions between NG2 glia and endothelial cells also occur. NG2 glia prevent the permeability of the BBB by secreting transforming growth factor beta (TGF- β) which binds to TGF- β receptors on the surface of endothelial cells, upregulating the expression of tight junction proteins (claudin-5 and ZO-1) via MAPK/ERK pathways [125]. Likewise, endothelial cells secrete fibroblast growth factor-2 (FGF-2) and brain-derived neurotrophic factors (BDNF) which have an influence on the survivability and proliferation of NG2 glia via Akt and Src signaling pathways [126]. Endothelial cells also secrete vascular endothelial growth factor (VEGF-A) which promotes the migration of NG2 cells, but not their proliferation, through VEGF-receptor 2 (Flk-1) signaling [127]. VEGF induced migration of NG2 glia is mediated through cytoskeletal rearrangement in an ROS- and FAK-dependent manner [128]. In contrast, VEGF-C reportedly influences the proliferation of NG2 glia via VEGF-receptor 3 signaling cascades [129].

3.6 Summary of oligodendroglial role in brain homeostasis

Due to their inherent spatial relationships with neurons, oligodendrocytes and their precursor cells are critical regulators of brain physiology. Unlike other glia, oligodendrocytes and NG2 glia are direct sources of neurotrophic and metabolic support, and each cell type has specific roles in modulating neuronal activity. As a result, they must maintain high energy demands to keep up the constant metabolic activity of active neurons. This presents opportunities for severe trauma during injury such as microelectrode implantation, which induces oxidative stress and excitotoxic shock. Additionally, oligodendrocytes and NG2 glia share functional relationships with other constituents of the brain such as microglia, astrocytes, and mural cells that support the blood-brain barrier. Impairment in their normal physiological behavior

could trigger a cascade of neuroinflammatory events involving different cell networks within the brain. Oligodendrocytes and NG2 glia may react similarly during injury, succumbing to inflammation-induced cell death, which would increase demyelination injury, impair the potential of remyelination repair, and deprive neurons of neurotrophic and metabolic support, ultimately impairing recording and stimulating capabilities using chronically implanted neural electrodes. However, NG2 glia may take on other roles such as possibly differentiating into scar-forming astrocytes and contributing to proinflammatory tissue events. As such, it is important to investigate these cell types during trauma and determine their influence in the foreign body reaction to implanted neural interfaces and their overall role in progressive neurodegenerative disease.

4. Role of oligodendroglia in acute tissue inflammation

The onset of acute inflammation following injury has a purpose to protect against foreign pathogens and repair damaged tissue. Immediate activation of phagocytotic microglia triggers removal of cellular debris and continual secretion of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α), chemokines (MCP-1, CXCL-1), reactive oxygen species (NADPH oxidase, MPO), and coagulation factors. Microglia also secrete neurotrophic factors such as BDNF upon activation, which indicates a parallel role in the reactive tissue response to repair tissue [130]. However, BDNF has been shown to increase the number of activated microglia *in vivo*, suggesting it may amplify microglia reactivity and persist in a chronic inflammatory response [131]. Reactive astrocytes increase expression of glial fibrillary acidic protein (GFAP), an intermediate filament involved in modulating the cell's structure and mechanical strength, and encapsulate foreign bodies within a glial scar. Cells within this scar express axon growth inhibitory CSPGs that prevent the functional recovery of tissue [132]. Oxidative stress from microglia and astrocyte reactivity impairs function of tight junction proteins in endothelial cells, increasing BBB permeability [133, 134]. Endothelial cells express a variety of cell adhesion molecules (E-selectin, P-selectin, VCAM, ICAM) which promote the recruitment of leukocytes and neutrophils to the site of injury [135]. Pericytes, whose primary function is to help clear metabolic waste and maintain EC viability, are also known to promote entry of immunologic T cells and monocytes into the brain parenchyma [136]. These infiltrating cells produce harmful oxidative species, secrete BBB-degrading MMPs, and release pro-inflammatory cytokines such as IFN- γ which further exacerbates glial cell activation [137]. As a result, neuronal viability is compromised and the formation of a glial scar prevents the diffusion of neurotrophic factors, ions, and charged solutes, impairing tissue physiology.

The acute foreign body response to implanted neural devices is characterized by a mechanically-disrupted BBB, reduction in perfusion of oxygen and nutrients, impairment in waste removal, increase in mechanical strain due to tissue displacement and edema, and biofouling of the electrode surface [9]. Penetrating electrodes expose sensitive neural tissue to inflammatory pathogens through the disruption of the BBB [138, 139]. Due to the hydrophobicity of the electrode, plasma proteins adhere easily to the electrode surface and incite glial cell reactivity [24], which can persist over chronic time periods [140]. Chronic hypoxia as a result of occluded or damaged vasculature eventually promotes angiogenesis and the foundation of a new vascular network around sites of injury [141]. Indeed, vascular

pericytes, which promote angiogenesis through the release of VEGFs and MMPs, have been observed near implanted electrodes [26, 142, 143]. Insertion causes dimpling of the surface of the brain, displacing and compressing cells and blood vessels, and can persist for hours after insertion [10, 19, 144–146]. Increased strain has been correlated with increased cell death in neurons and astrocytes as well as production of IL-1 β via ERK signaling pathways in astrocytes [147–149]. Tissue movement due to stress and strain forces as well as biological micromotions are reflected in the performance of implanted electrodes, where detection of individual neurons come and go as tissue is displaced [150]. These initial tissue events following electrode insertion set the stage for a chronic inflammatory response and the severity of damage incurred during implantation is reflected at later time points in the form of exacerbated glial scar formation and neuronal loss. Thus, it is important to understand the consequences of acute inflammation during the implantation of neural interfaces into the brain.

4.1 Oligodendrocyte and NG2 glia susceptibility to oxidative stress

Oxidative stress is a primary effector of the acute inflammatory response to microelectrode failure, impacting neuronal viability and blood-brain barrier integrity [151, 152]. Oligodendrocytes and their precursors are particularly sensitive to oxidative stress after injury via multiple mechanisms of cell death (Figure 2). In order to meet the high-energy demands of myelin output oligodendrocytes must produce a substantial amount of myelinrelated proteins, requiring high metabolic rates [153]. While continuous myelin deposition does not occur in the adult brain, newly matured remyelinating oligodendrocytes could sustain increased susceptibility to oxidative insults following injury. As a result, potentially toxic byproducts of cellular metabolism are formed, such as hydrogen peroxide and reactive oxygen and nitrogen species, which can cause DNA damage, lipid peroxidation, and apoptosis of oligodendrocytes if not metabolized properly [154, 155]. Mitochondria of oligodendrocytes are targets for oxygen and nitrogen radicals, interfering with the essential proteins involved in cellular respiration. Indeed, toxic models of demyelination involve the use of cuprizone, a copper-chelator known to disrupt complex IV of the mitochondrial respiratory chain [156]. Both oligodendrocytes and NG2 glia contain low amounts of the antioxidant glutathione, which makes them even more vulnerable to oxidative damage than other glial cells in the brain when trying to cope with oxidative stress [157, 158].

Oligodendrocytes store high amounts of iron and ferritin subunits relative to other cells in the brain to account for the amount of oxygen consumed and ATP produced during myelin formation [159]. Binding of ferritin to iron occurs coincidentally with the formation of myelin in the developing brain and it has been suggested that oligodendrocytes are responsible for regulating iron throughout the CNS [160, 161]. Oxidative stress has been linked to iron dysfunction in oligodendrocytes and, when exposed to hypoxic conditions, iron accumulates inside the cell and induces endoplasmic reticulum (ER) stress and mitochondrial dysfunction resulting in cell death [162]. Likewise, excess levels of iron can result in the formation of hydroxyl radicals, a toxic reactive species implicated in DNA, lipid, and protein disruption [163]. Interfering with the ability for oligodendrocytes to maintain iron homeostasis in the brain can have detrimental effects on microelectrode performance. For example, transferrin, an iron transport protein, is synthesized by

oligodendrocytes and is responsible for transporting iron into neurons [164]. Increased ferritin levels have been observed around microelectrodes with poor electrode performance [165]. Hemosiderin, an iron-binding molecule, is hypothesized to result from the interaction of iron and free-radicals. Hemosiderin-laden macrophages have been observed next to implanted electrodes, suggesting possible phagocytosis of iron-containing cells such as oligodendrocytes or iron-bound myelin debris [151]. Dysregulation of iron has been observed alongside neurodegeneration and demyelination in a variety of neurodegenerative diseases, which can allude to a role in the loss of neuronal signaling around chronically implanted electrodes [166–168].

4.2 Glutamate-mediated excitotoxicity of oligodendrocytes and their precursors

Oligodendroglial cells express glutamate-binding receptors AMPA, kainate, and NMDA [169, 170]. Both mature oligodendrocytes and NG2 glia have shown excitotoxicity during prolonged glutamate exposure *in vitro* [171, 172]. One mechanism of action leading to cell death via glutamate excitotoxicity involves increased production of free radical species in mitochondria responding to an increase in intracellular calcium [173]. It has been shown that varying the activation of kainate and AMPA receptors leads to apoptosis of oligodendrocytes in either caspase-dependent or –independent manners [173]. Likewise, oligodendrocyte cell death can occur indirectly through glutamate signaling via the release of pro-inflammatory cytokines TNF- α and IL-1 β from activated microglia [174, 175]. Elevated expression of glutamate transporters has been observed acutely around inserted devices, which may precede NG2 glia and oligodendrocyte excitotoxic cell death, subsequently leading to demyelination and degeneration of axons around chronically implanted microelectrodes and impairing their recording and stimulating potential [176].

4.3 Oligodendrocytes and myelin susceptibility to BBB disruption

Although penetration of major blood vessels is preventable using vascular mapping techniques, damage to smaller vessels and capillaries can be difficult to avoid especially with multi-shank electrodes [10]. BBB disruption can persist throughout the lifetime of the implant in cases where microelectrode steric blockade prevents repair of the vasculature membrane or angiogenesis. Additionally, biological micromotion (i.e. breathing) or mechanical impact to the electrode can rupture vessels, resulting in secreted cytokines, which increase the permeability of endothelial cells and exposure of brain tissue to both inflammatory plasma proteins and coagulation factors that are known to contribute to neurodegeneration and demyelination [177]. Fibrin, the insoluble form of the plasma protein fibrinogen, is observed in active and chronic lesions of multiple sclerosis prior to the vasculature infiltration of T cell leukocytes and demyelination [177]. Direct correlation between the exposure of fibrin on the CNS and the recruitment of myelin-targeting Th1 cells has been demonstrated *in vivo*. In this study, fibrin promoted the secretion of chemokines CCL2 and CXCL10 via CD11b binding of activated microglia, which induced recruitment of T cells and macrophages, respectively [178]. Fibrin signaling also provokes T cell differentiation toward myelin antigen-specific Th1 cells via upregulation of IL-12 [178]. Thrombin, another inflammatory factor originating from vascular spillover, is responsible for converting fibrinogen into fibrin deposits. Thrombin acts as a suppressor of ERK1/2 and AKT-mediated CNS myelination via activation of protease-activated receptor 1 (PAR1) on

oligodendrocyte precursors [179]. PAR1 is also expressed in T cells, endothelial cells, glial cells, and neurons [180]. PAR-1 activation by thrombin exerts direct neurophysiological effects at the nodes of Ranvier *in vivo*, inducing conduction block in rat sciatic nerves [181]. Thrombin can have both neuroprotective and neurodegenerative effects depending on its concentration, protecting hippocampal neurons and astrocytes at low concentrations yet mediating cell death at higher concentrations [182, 183]. As a result, disruption of the blood-brain barrier via microelectrode-induced mechanisms can have a negative impact on the myeloarchitecture which is responsible for the exchange of neuronal information to and from the implanted device, impairing performance output.

5. Oligodendroglia pathophysiology during the chronic foreign body response

The physiological functions of oligodendrocytes and NG2 glia are compromised during chronic disease. In MS, it is widely accepted that NG2 glia persist in chronic demyelinated lesions without differentiating into new, myelinating oligodendrocytes. However, the cause for this differentiation block is still unknown. Since NG2 glia are responsible for replenishing depleted oligodendrocytes after injury and oligodendrocytes themselves express membrane receptors for a variety of cytokines and chemokines produced by activated glia, their behavior in the context of chronically implanted electrodes can broaden the perspective of the foreign body response to inserted devices [184].

The damages sustained from chronic implantation of intracortical electrodes are most clearly demonstrated in stab wound studies. Immediately implanting and removing a probe results in a decreased activation of glial cells as well as a reduction in neuron loss over time, compared to a chronically implanted probe [185]. Following the physical removal of the implant, signs of neurogenesis in the lesion site begin to show owing to the limited capacity for the brain to regenerate after injury [186]. Long-term damage due to electrode implantation is thus characterized by persistent glial scarring and neurodegeneration leading to continual pro-inflammatory cytokine release and tissue degradation, which generates a “kill zone” radially around the implant [185]. Both gliosis and neurodegeneration are attributed to the tissue failure of chronically implanted microelectrodes via increases in noise and impedance and a loss of recordable signal [9]. Hypertrophic astrocytes and reactive microglia accumulate around the implant and displace neurons from the surface of the electrode, which reduces the ability to yield high SNRs [187]. These same activated microglia and astrocytes secrete a multitude of inflammatory cytokines that perpetuate BBB breakdown, further glial cell reactivity, and activate apoptotic signaling cascades in neurons [9]. Due to their influence on neuronal health, both NG2 glia and oligodendrocytes may contribute to degrading quality in performance on microelectrodes overtime and its apparent inability to recover from glial scarring and loss of neurons.

5.1 NG2-glia activation during glial scar formation

NG2 glia and astrocytes both divide from radial stem cells during development before migrating and proliferating throughout the CNS [188]. Use of NG2-Cre mice for genetic fate mapping of NG2 glia *in vivo* show their differentiation into protoplasmic astrocytes (as well

as oligodendrocytes) during development [96]. During glial scar formation, astrocytes proliferate, become hypertrophied, release intermediate filaments GFAP and vimentin, and secrete cytokines, chemokines, and inhibitory CSPGs [189]. Similar to astrocytes, NG2 glia display a hypertrophied morphology and increase expression of inhibitory CSPGs within 24 hours after injury (Figure 3) [190]. Likewise, similar to microglia, NG2 glia extend processes and migrate towards the lesion site, however, at a slower rate [35, 110]. One of the characteristic features of the tissue response to electrode insertion into the brain is the gradual development of a glial scar that persists throughout the lifetime of the implant, impairing neuronal function and altering exchange of electrical signals [2, 185, 191]. NG2-Cre mice used to observe differential fate after cortical stab injury show only 8% of NG2 glia express astrocytic GFAP after 10 days, decreasing to 2% of NG2 glia that are GFAP-positive after 30 days post-lesion. However, in the case of spinal cord injury, 25% of NG2 glia are immunoreactive for GFAP at 7 days post injury, decreasing to 8% of NG2 glia that express GFAP by 4 weeks. It has been suggested, with respect to spinal cord injury where secondary damage is more likely to occur and gliosis is more prevalent, that the severity of injury modulates the astrocytic potential of differentiating NG2 glia under pathological conditions in the CNS [192]. Since the foreign body reaction to intracortical microelectrodes has been characterized as having acute and chronic inflammatory events persisting throughout the lifetime of the implant, the astrogliogenic potential of NG2 glia could be amplified under these conditions. However, that has yet to be observed.

5.2 NG2-glia as neural growth inhibitors

Expression of CSPGs by NG2 glia is upregulated and localized around the lesion during CNS injury with notable inhibition of neuronal regeneration [189, 194, 195]. Indeed, expression of CSPGs was observed up to 135 μm around implanted microelectrodes at 1 week post-insertion, coinciding with the proliferation of astrocytes and generation of the glial scar [196]. During development, neurites actively avoid CSPG dense regions, implying CSPGs are “negative” regulators of axon growth [197]. *In vitro* neurite extension does not occur on substrates coated with purified NG2, a transmembrane CSPG expressed on the surface of oligodendrocyte precursors [198]. Use of antibodies to neutralize NG2 on oligodendrocyte precursors only partially reverses the inhibitory effect of the proteoglycan, due to the fact that NG2 glia express other growth-inhibitory molecules such as semaphorin 5A [199]. However, some studies suggest that NG2 expression promotes axon growth after injury [200, 201]. NG2 glia form synaptic connections with neurons, a feature unique amongst glia cells of the CNS. They express voltage-gated sodium channels as well as post-synaptic receptors for glutamate and GABA, demonstrating the ability to generate action potentials and sense activity from neurons [202]. NG2 glia also express fibronectin and laminin on their membrane surface, two ECM molecules that promote neurite outgrowth and are expressed in the lesion core after CNS injury [203]. After spinal cord injury, axons become dystrophic and “die back” from the lesion, associating with nearby NG2 glia [192]. In NG2 null mice, fewer synaptic connections are made after SCI and damaged axons retreated to farther distances than normal controls.

5.3 Demyelination and remyelination of axons during oligodendrocyte pathology

Changes to the myelin structure around implanted microelectrodes have only been briefly investigated previously (Figure 4). One study observed acute changes to the myelin membrane as early as 1 hour following microelectrode insertion via the formation of “myelinosome” perturbations [204]. Likewise, only one investigation observed potential demyelination around chronically implanted microelectrodes, visualizing demyelinated axons 12 weeks post-implantation in the rat cortex [11]. Usually demyelination occurs when the viability of the oligodendrocyte cell is compromised, referred to as primary demyelination, and is different from myelin degradation due to neuronal or axonal loss, referred to as secondary demyelination [205]. Following a demyelinating incident, remyelination does not occur from existing myelinating oligodendrocytes but from a reservoir of previously quiescent and mature NG2 glia which differentiate into new myelinating oligodendrocytes [206]. Activated microglia and astrocytes are responsible for prompting recruitment, proliferation, and transformation of these inert precursor cells into differentiating NG2 glia. Specifically, anti-inflammatory microglia promote remyelination after ethidium bromide induced demyelination via activation of TGF β ligand receptors that are involved in GTPase, Akt, and mTOR signaling pathways implicated in NG2 glia differentiation and myelination [207, 208]. However, newly remyelinated sheaths are thinner than they were before injury as indicated by the g-ratio (the inner axon diameter divided by the total outer diameter) and the difference is more apparent in larger diameter axons than small diameter axons [207, 208]. Loss of oligodendrocytes and axonal demyelination lead to impairments in signal propagation and deprive neurons of essential neurotrophic factors for survival. Since signal conduction is dependent on the insulating structure of myelin, the consequence of demyelination around chronically implanted microelectrodes could result in an impairment in electrophysiological signals obtained from neurons. Additionally, the capacity for demyelinated axons to be remyelinated following injury could potentially be compromised due to the tissue response to implanted devices.

5.4 Lack of oligodendrocyte support leads to axonal loss

Oligodendrocyte dysfunction is observed not just in demyelinating diseases such as MS, but in neurodegenerative disorders such as Alzheimer’s and ALS as well, implicating their involvement in the degradation of neurons. For example, aggregates of mutated insoluble tau protein have been observed in oligodendrocytes alongside axon degeneration [210]. Additionally, MCT1, which is responsible for transport of metabolic factors into axons, was markedly reduced in mouse models of ALS [211]. Specific ablation of oligodendrocytes, which exclude any influence of other activated glial cells or infiltrating immune cells, has demonstrated secondary axonal damage. Studies in which myelin proteins such as PLP, are overexpressed or depleted via genetic mutation are complemented by severe degeneration of neurons [212–215]. However, PLP is a protein primarily localized to the myelin sheath while CNP is exclusive to the surface of oligodendrocyte cell bodies. Studies involving the mutation of CNP demonstrated functional motor deficits alongside neuron pathology, while the amount and structure of other myelin proteins remained intact between experimental and wild-type controls [213]. This indicates a myelin-independent support of neurons by oligodendrocytes, such as through the production and secretion of neurotrophic and metabolic products.

6. Potential strategies to mitigate oligodendrocyte/NG2 glia pathophysiology

NG2 glia, oligodendrocytes, and myelin are all negatively susceptible to both acute and chronic injury events. Mediating the response of oligodendroglia during injury is the primary focus of oligodendrocyte and myelin-affected diseases such as MS, ALS, Alzheimer's and more. Therapeutic strategies are either designed to be preventative, attempting to prevent oligodendrocyte/oligodendrocyte precursor cell loss and demyelination, or reparative, rehabilitating injured tissue following injury through the promotion of oligodendrocyte differentiation and remyelination. Additionally, a materials-based approach at influencing oligodendrocyte and oligodendrocyte precursor responses during injury is observed.

6.1 Preventing oligodendrocyte cell death and demyelination

As metabolically demanding cells, oligodendrocytes are easily susceptible to oxidative stress and excitotoxicity during injury-induced inflammation. Antioxidants such as NADPH help prevent oxidative stress-induced death in both oligodendrocytes and their precursors. For example, administration of dehydroepiandrosterone (DHEA) protects NG2 glia lacking NADPH during metabolic stress [216]. As an endogenous neurosteroid, DHEA is also known to protect against NMDA-mediated excitotoxicity and hydrogen peroxide-mediated cytotoxicity [217, 218]. Additionally, DHEA promotes neuronal survival in stroke models [219]. The upregulation of reactive oxygen and nitrogen species during inflammation due to activation of reactive glia poses a threat to oligodendrocytes by impacting mitochondrial metabolism. An anti-inflammatory agent such as methotrexate (ITMTX), which is commonly used to treat MS patients, can mitigate the immune response and alleviate the insult to oligodendrocytes and myelin. Methotrexate is an immunosuppressant that has demonstrated effective results in MS patients [220]. However, in cuprizone-treated animals, ITMTX mitigates the formation of gliosis and inhibits demyelination, demonstrating that it acts more specifically to preventing demyelination without systemic immunosuppression [221]. Recently, we have shown a novel role of GSK3b in cuprizone induced oligodendrocyte apoptosis [222]. Conditional depletion of oligodendrocytic GSK3b protects oligodendrocytes from caspase-dependent apoptosis and leads to significant attenuation of demyelination with preservation of myelin thickness and has broad effects on the surrounding glia, resulting in decreased glial activation. Inhibitors of GSK3b may be exploited to preserve oligodendrocyte viability and myelin integrity. Lastly, recent work has demonstrated a protective effect of the antioxidant resveratrol on oxidative stress-induced cell death of oligodendrocytes and NG2 glia [223, 224]. Resveratrol has previously been used to improve neuronal density surrounding chronically implanted neural electrodes and the apparent effect on neuronal viability could be a consequence of preserved oligodendrocyte and NG2 glia health. However, their viability around inserted microelectrodes remains to be seen.

6.2 Promoting oligodendrogenesis of NG2-glia and remyelination

The natural response following demyelination is for NG2 glia to migrate, proliferate, and differentiate into myelin-forming oligodendrocytes around the lesion site. However, when the demyelinating injury is severe and chronic, as is the case in MS, remyelination is impaired leading to progressive neurodegenerative symptoms. Deficiencies in axon remyelination are less attributed to the reduction of NG2 glia and more a result of an impairment in the proliferation, migration, and differentiation that allows NG2 glia to transform into myelinating oligodendrocytes [225]. Region-dependent differences were found to influence oligodendrocyte differentiation; with oligodendrogenesis more likely to occur in a white matter-derived environment compared to gray matter [226]. This presents different possibilities for potential therapies, whether it is promoting differentiation by implantation of cells into the white matter or utilizing the specialized environmental or molecular cues that promote differentiation for gray matter cells. A common way to promote oligodendrogenesis is to manipulate the mammalian target of rapamycin, also known as mTOR, which is a downstream mediator of NG2 glia differentiation and oligodendrocyte myelination and acts through the phosphatidylinositol-3-phosphate kinase (PI3K/Akt) signaling pathway [227]. Rapamycin is an inhibitor of mTOR, and is known to impair myelination via reduced Akt signaling [228]. The mTOR kinase also has the ability to reduce T-cell activation and modulate other glial functions making it an emerging therapeutic target in MS research [229]. Another important pathway responsible for myelin growth involves extracellular signal regulated protein kinases 1 and 2 (ERK1/ERK2), which are downstream mediators of mitogen-activated protein kinases (MAPK) [230]. This pathway is responsible for regulating myelin thickness and mutant mice deficient in this pathway display normal NG2 glia differentiation and initiation of myelin formation, yet no observable increase in myelin thickness that normally follows axonal contact. Whether the PI3K/Akt pathway and ERK1/ERK2 pathway are independent or dependent pathways of one another remain to be seen. Acting independently of these two growth factor pathways is a third mechanism which controls oligodendrogenesis of NG2 glia via canonical Wnt-signaling, which is negatively regulated by endogenous GSK3 β [231]. Application of inhibitors of GSK3 β have successfully improved oligodendrocyte regeneration and remyelination within demyelinating lesions [232]. Due to their anti-apoptotic influence on cell death pathways, GSK3 β inhibitors could have a dual advantage of enhancing the differentiation of oligodendrocyte precursors and protecting mature oligodendrocytes. Finally, recent work to promote cortical repair following injury involves converting other cells into functional neurons due to their inherent neurogenic potential. NG2 glia maintain the genetic machinery to be reprogrammed through the induced expression of specific transcription factors (*Sox2*, *Ascl1*) into functional neurons in the context of injury [233]. Regenerating lost neurons following injury may be an effective first step in tissue repair before NG2 differentiation into oligodendrocytes and initiation of remyelination, promoting a more innervated neural network to restore brain circuitry and function. However, if demyelination is a primary mode of failure for chronically implanted neural interfaces, restoring oligodendrocytes, their precursors, and the myelin structure may be essential to support neuronal physiology and improve device performances.

6.3 A materials-based modulation of oligodendrocyte and oligodendrocyte progenitor responses

While biomaterials have had a widespread use in an attempt to promote neural regeneration within the injured central and peripheral nervous system, oligodendrocyte regeneration using similar materials-based approaches are not as common or understood. The chemical composition of the substrate can have distinct modulating effects on NG2 glial maturation and differentiation. For example, chitosan-based biomaterials have been used in the past to promote oligodendrocyte survival and attachment [234], as well as differentiation into oligodendrocytes [234–237]. Materials that influence oligodendrogenesis from oligodendrocyte precursors include fibrin, HA-methylcellulose, poly(lactic-co-glycolic) acid (PLGA), and methacrylimde, while materials that promote myelination from mature oligodendrocytes include fibrin, PLGA, chitosan, and HA-gelatin [238]. The topographical cues and fiber diameters of varying materials also influence oligodendrocyte generation [239, 240]. Random or unaligned polycaprolactone fibers favored oligodendrocyte adherence and survival compared to aligned fibers [241], as well as promote oligodendrogenesis from NG2 glia [242]. Topographical cues provided by nanofiber alignment of varying biomaterials also positively support myelin production and remyelination of axons *in vitro* [243–245].

Previous studies demonstrated that substrate stiffness modulated oligodendrocyte and NG2 glial responses. Substrates of lower stiffness contributed more to NG2 glial sprouting of processes and proliferation [246, 247], while substrates of higher stiffness contributed more to NG2 glia-mediated oligodendrogenesis [247, 248].

Migration of oligodendrocyte progenitors is also dependent on the modulus of the substrate, with the optimal range for migration of NG2 glia appearing on gels with an elastic modulus around 0.7 kPa, near the modulus for soft brain tissue [248]. Many *in vitro* studies demonstrated that the potential application for neural progenitor cells (NPCs) to differentiate into oligodendrocytes also depends on the mechanical properties of the environment; however, the results are more material-dependent. NPCs cultured on softer hyaluronic acid (HA)-methacrylate hydrogels differentiated into oligodendrocytes, whereas stiffer HA-methacrylate gels generated more NPC-derived astrocytes [249]. Alternatively, NPC differentiation into oligodendrocytes favored stiffer methacrylamide chitosan substrates [235]. The implications of these results can have significant effects on the oligodendroglial response considering the field of neural interface engineering is moving toward softer, more flexible biomaterials [250, 251]. As a result, the increased compliancy of these materials may be favoring increased NG2 glia recruitment and proliferation, whereas stiffer substrates would promote oligodendrocyte generation from neuronal and oligodendrocyte progenitors alike [248].

Finally, use of nanoparticles (NPs) for delivery of modulating drugs are also being investigated as potential therapeutic approaches to improving oligodendroglial function. NPs targeted toward oligodendrocyte progenitors specifically (for example, via surface-coated antibodies against NG2 antigen) can be used to deliver promyelination factors such as leukaemia inhibitory factor (LIF) or oligodendrocyte-generating transcription factors Olig1 and Olig2 [252, 253]. Similar methods can be applied to the potential delivery of pro-

oligodendrocyte and pro-myelination factors, such as BDNF, neuregulin, and/or neurotrophin-3 [254–257]. Surface functionalization or hydrogel encapsulation of nanoparticles around devices could help facilitate this method of therapy.

7. Attenuating reactive tissue response of implanted devices: new insights

A variety of approaches to intervene during the inflammatory reaction of neural interfaces have been investigated to improve their long-term stability and functionality. Historically, these approaches are evaluated on their ability to mitigate the activation of glial cells and reduce chronic neurodegeneration in an attempt to improve recording performances following chronic implantation. Given the newly acquired knowledge of oligodendrocyte and NG2 glia susceptibility to inflammation-induced injury, alternative and novel approaches should be considered to account for their potential role in the biological failure mode of implanted devices.

7.1 Reducing the accumulation of oxidative stress following probe insertion

Hypoxic and ischemic insults due to BBB disruption and the accumulation of reactive oxygen species due to glial cell activation contribute to the oxidative stressors that mediate some of neuroinflammatory responses of implanted microelectrode arrays [258]. Previously, anti-oxidants have been used to reduce the build-up of ROS through either localized drug delivery, systemic administration, or surface modification [152, 259, 260]. Oligodendrocytes and oligodendrocyte precursors are particularly susceptible to these stressors in an ER-mediated manner, which is a common method of oligodendroglial loss in neurodegenerative diseases such as MS, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, and Parkinson's disease [261, 262]. Using guanabenz for pharmacological inhibition of IFN- γ which phosphorylates PERK, a common ER-stress associated protein, has demonstrated increased oligodendrocyte viability both *in vitro* and *in vivo*, reducing clinical symptoms in chronic MS models [263]. Additionally, protecting oligodendrocytes from ER-stress directly with salubrinal rescued hypomyelination and oligodendrocyte cell death in oligodendrocyte cultures exposed to IFN- γ directly [264]. Further methods to reduce the onset and build-up of oxidative species production would be to minimize damage to the blood-brain barrier, reducing hypoxic and ischemic inflammatory events, as well as reducing glial cell activation, which can lead to increased ROS and free radical production.

7.2 Attenuating glutamate-mediated excitotoxicity around neural probes

Insertion of a microelectrode array into the brain induces cortical spreading depression in neurons, a global calcium activating event that can lead to neuronal injury and cell death [265]. Although the impact of CSDs on oligodendrocytes and their precursors are unknown, spreading depolarizations in the cortex are accompanied by glutamate-induced excitotoxic events that can be detrimental to oligodendrocyte viability [266]. Reducing or attenuating glutamate-induced excitotoxicity in oligodendrocytes and NG2 glia may protect against myelin loss and inflammation following CNS injury. Ionotropic glutamate receptors, AMPA and kainite, on the surface of oligodendrocytes and their precursors mediate glutamate-induced excitotoxicity. Antagonists of these ionotropic receptors have attenuated

neurodegeneration in models of MS [267, 268]. On the other hand, activation of metabotropic glutamate receptor, attenuates hypoxic/ischemic-induced excitotoxicity in NG2 glia *in vitro* via protein kinase C alpha (PKC α) activation, which reduces intracellular ROS and maintains antioxidant glutathione levels [269]. Use of agonists to activate metabotropic glutamate receptor pathways or antagonists to inhibit AMPA/kainite-mediated excitotoxicity such as with TNF- α inhibitors could protect cells of the oligodendrocyte lineage from excitotoxic consequences of CNS injury that can occur during microelectrode implantation.

7.3 Minimizing the insult to the blood-brain barrier

Severe permeability of the blood-brain barrier has been correlated to the decreasing recording performance of chronically implanted neural electrodes [20]. Due to the micromotions of a fixed, mechanically stiff device within the brain, disruptions to the BBB can persist throughout the lifetime of the implant. Vascular mapping using twophoton microscopy prior to microelectrode implantation allows for insertion in regions devoid of large penetrating vessels, reducing the amount of BBB disrupted [10]. Minimizing the severity of blood-brain barrier leakage can provide multiple benefits to the viability and integrity of oligodendrocytes, their precursors, and the myelin structures they form. First, reducing the exposure of pro-inflammatory plasma proteins to the parenchyma will mitigate glial cell activation, decreasing the amount of reactive species and harmful cytokines produced. This includes the activation of NG2 glia and their potential differentiation into scar-forming astrocytes. Secondly, less BBB permeability will result in reduced infiltration of peripheral immune cells, some of which are programmed to target myelin specifically.

7.4 Probe surface functionalization to reduce glial cell activation

Activation of microglia and astrocytes is at the center of many neuroinflammatory pathways either directly or indirectly due to their secretion of pro-inflammatory cytokines, upregulation of BBB disrupting proteinases, and formation of an inhibitory glial scar. Engineering the surface of the probe to reduce glial cell activation or promote anti-inflammatory glial cell phenotypes is an important first step toward designing biocompatible neural interfaces. One way of mitigating glial activation is by modifying the surface of the probe to reduce the absorption of microglia and astrocyte activating plasma proteins following rupture of the vasculature. This can be done by decreasing the hydrophobicity of the device through chemical surface coatings in order to prevent biofouling. A recent strategy is to coat the probe in a bioactive compound, the cell adhesion molecule L1, which reduces the pro-inflammatory activation of microglia *in vivo* [270]. The additional benefit of promoting neuronal integration and reducing microglia activation is the possibility of supporting oligodendrocyte viability and myelin integrity around implanted microelectrodes. Extracellular matrix-derived proteins functionalized on the surface of the probe is also another strategy to modulate glial cell phenotype [271]. ROS scavengers to minimize oxidative damage, extracellular proteins to promote neuronal cell adhesion, and glial cell modulating proteins are also being explored. Lastly, functionalizing the surface of the probe in compounds that manipulate the pathways influencing NG2 glia and oligodendrocyte cell death, differentiation, or myelination discussed in the previous section are potentially new approaches to improving the tissue response to chronically implanted devices as well.

7.5 Drug delivery

Drug delivery around microelectrode arrays has yielded beneficial tissue responses in the past. Administration of anti-inflammatory agents such as dexamethasone and minocycline has reduced the reactive glial response elicited around inserted devices. Using retrodialysis techniques, dexamethasone was shown to attenuate acute microglial activation *in vivo* [272]. Additionally, dexamethasone attenuates glial scar formation as well as reduces ischemic insult around inserted electrodes [273, 274]. Minocycline administered orally was shown to significantly increase the recording performance of chronically implanted microelectrodes compared to controls as well as significantly attenuate the reactivity of astrocytes around the implant [275]. In experimental autoimmune encephalomyelitis (EAE), animals treated with minocycline experience reduced inflammation and demyelination [276]. Minocycline is also known to inhibit matrix metalloproteinases (MMPs), which are responsible for tissue inflammation, neurodegeneration, and demyelination [277]. A reduction of microglia activation has the potential to reduce pro-inflammatory insults on oligodendrocytes, myelin, and oligodendrocyte precursors by reducing the secretion of harmful cytokines, chemokines, and reactive oxygen and nitrogen species. However, this approach is a double-edged sword since activated glia are responsible for the clearance of myelin debris and tissue remodeling that are necessary for wound repair and regeneration [278]. Finally, using neutralizing antibodies against Lingo-1, to direct modulation of oligodendrocytes and oligodendrocyte precursors, or myelin protein Nogo-A, to improve neuronal growth inhibition, hold promising potential to regenerate lesions following CNS injury [279, 280]. Specifically, Lingo-1 neutralizing antibodies are beginning to undergo clinical trials to treat MS patients [281, 282]. Before microelectrode-directed pharmacological interventions can be evaluated on the response of oligodendroglia, however, a time course of microelectrode-induced insult to myelinating oligodendrocytes and their precursors should be investigated in order to optimize potential therapeutic approaches.

8. Conclusion

The role of oligodendrocytes and their precursors are key components missing in the series of events that constitutes the tissue response to chronically implanted neural interfaces (Figure 5). The myelin produced from mature, differentiated oligodendrocytes is responsible for the electrical conduction of neuronal signals, the critical component of information transfer between neurons and implanted microelectrode technology. Oligodendrocytes and the NG2 glia responsible for replacing myelinating oligodendrocytes are highly susceptible to oxidative and excitotoxic injury, key characteristic events in the foreign body reaction to inserted devices. The dependence that neurons have on these two cell types for their survivability and physiology prompt the question of their individual fates during implantation injury and to what extent, if any, are they responsible for the characteristic increase in neurodegeneration around chronically implanted devices. Defining a spatial and temporal time course of the viability of oligodendrocytes, their precursors, and their myelin structures around chronically implanted neural electrodes will reveal a clearer understanding of the biological mechanisms that result in the reduced recording and stimulating performance of these devices. This knowledge can then be applied to alternative therapies to

increase the longevity and stability of chronic neural interfaces implanted in the body and increase their lifespan of usability for the patients afflicted with neurological deficits.

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Figure 1. Development and cell fate of oligodendrocyte precursor cells.

Oligodendrocyte precursor cells maintain various paths of cell fate depending on tissue conditions. (a) Histological stain of NG2+ glia (green) and cell nuclei (blue) in horizontal sections of the adult mouse cortex. Scale bar = 100 μ m. Olig2+ oligodendrocytes (green) can be perineuronal (white arrow), residing in close proximity to NeuN+ neuron cell bodies (red) in both the (b) cortex and (c) dentate gyrus of coronal sections of the adult mouse brain. Scale bar = 25 μ m. (d) Confocal image of cortical CC1+ myelinating oligodendrocytes (green) and cell nuclei (blue) in horizontal sections of the adult mouse. Scale bar = 100 μ m. Oligodendrocyte precursors have been observed in certain regions of the brain to transdifferentiate into neurons and, under specific injury conditions, into reactive astrocytes.

Figure 2. Molecular mechanisms of NG2 glia and oligodendrocyte cell death.

Both NG2 glia and oligodendrocytes are susceptible to oxidative and excitotoxic cell death.

Low levels of glutathione render each cell vulnerable to reactive oxygen and nitrogen species that lead to mitochondrial-induced stress. Due to their high metabolic rates,

oligodendrocytes have increased susceptibility to iron accumulation within their cell bodies and myelin membranes. Cell death pathways of greater severity are emphasized in bold.

NMDA: N-methyl-Daspartate receptor, AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, TNFR: tumor necrosis factor receptor; NO: nitric oxide; Cyt c: cytochrome c; Apaf-1: apoptotic protease-activating factor 1; AIF: apoptosis-inducing factor, PARP-1: poly [ADP-ribose] polymerase 1, PERK: protein kinase R (PKR)-like endoplasmic reticulum kinase, ROS: reactive oxygen species; RNS: reactive nitrogen species; OGD: oxygen glucose deprivation.

Figure 3: NG2 glia physiology and pathology.

(a) Proliferation of NG2 glia shown *in vivo* using two-photon microscopy on CSPG4-eGFP mice. Dividing cells can be identified by individual somas (yellow arrowheads) migrating in opposing directions. (b) NG2 glia turnover is identified as changes in cell morphology and decrease in fluorescence intensity. (c) NG2 glia can be observed differentiating into myelinating oligodendrocytes via distinct changes in the morphology of their cellular processes into more stratified myelin extensions and gradual loss of fluorescence intensity due to the downregulation of the NG2 promoter. (d) NG2 glia respond to photoablation

injury via extension of processes and migration of cell somas. Reprinted by permission from Springer Nature: Nature Neuroscience [35], © 2013. (e) A ramified, or non-activated, NG2 glial cell identified by the extension of processes radially in equal directions around the cell body. (f) A transitional, or activated, NG2 glia cell in response to injury or perturbation in its surroundings. Activated NG2 glia are identified by preferential extension of processes in a particular direction relative to their cell soma. Scale bar = 25 μm . Reprinted from [110], with permission from Elsevier © 2018. NG2 glia become activated in response to electrode insertion (blue outline) and can be seen extending processes at 2 hours (g), 12 hours (h), and 24 hours (i) before making contact with the electrode surface. Scale bar = 25 μm . Reprinted with permission from [193]. © 2017 American Chemical Society. Visualization of the electrode surface via cross-sectional views of the probe (blue outline) implanted for 72 hours in mouse models labeling NG2 glia (j) and microglia (k) for comparison. A red fluorescent dye was used to label the vasculature. Scale bar = 25 μm . Adapted from [110], with permission from Elsevier © 2018. (l) Area of tissue coverage was measured as a function of distance from the probe surface showing the distribution of NG2 glia and microglia near the vicinity of the electrode. Counts were binned every 2 μm .

Figure 4. Gross morphological changes to oligodendrocyte and myelin structure following microelectrode implantation.

Acute myelin damage in the form of myelinosomes (yellow ellipses) can be observed within the vicinity of the electrode (blue outline) at 1 hour (a) and 6 hours (b) post-insertion using *in vivo* two-photon microscopy of CNP-eGFP mice. Oligodendrocyte cell bodies can be identified as adjacent somas (cyan arrowheads). Reproduced with permission from IOP Publishing [145]. Scale bar = 100 μ m. Large scale damage to the myelin architecture has been observed at 12 weeks post-insertion of an electrode in the rat cortex. (c) A stain for myelin basic protein (green) shows demyelination in a discrete area of unmyelinated axons

(red) in a horizontal section. Reprinted from [11], with permission from Elsevier. Scale bar = 100 μm . (d) A coronal section of the implanted electrode shows a similar characteristic reduction in myelin around the insertion site. Reprinted from [209], with permission from Elsevier. Scale bar = 100 μm . (e) A stain for APC/CC1 oligodendrocytes (red), platelet-derived growth factor β pericytes (PDGF β , green), immunoglobulin IgG (white), and cell nuclei (blue) in white matter region CA1 of the adult mouse brain. Scale bar = 100 μm . (f) Similar stain, implant duration, and implant region as in (e) in an apoptosis-resistant Caspase-1 knockout mouse. Scale bar = 100 μm . Reprinted from [26], with permission from Elsevier.

Figure 5. Schematic representation of the physiological consequences of microelectrode implantation in the brain.

The presence of the microelectrode has the potential to alter critical cellular functions that help maintain normal tissue homeostasis. NG2 glia are responsible for supporting neuronal health and modulating neuronal activity while maintaining a reservoir of oligodendrocyte precursors in the event of demyelination injury. Oligodendrocytes also support neuronal viability and produce insulating myelin sheaths that are necessary for signal propagation between neurons throughout the brain. Following electrode insertion, NG2 glia, along with microglia and astrocytes, become activated, proliferating and migrating toward the surface of the device. NG2 glia maintain the potential to differentiate into reactive astrocytes and participate in the encapsulation of the electrode via a glial scar. Scarring, which increases electrical impedances within the tissue (resistance and capacitance of the tissue, R_t and C_t), coupled with the impedance formed by the electrode-electrolyte layer (R_e and C_e) as well as the electrode access resistance (R_a) impair ion exchange and reduce transfer of signal. Oligodendrocytes, which are easily susceptible to oxidative and excitotoxic injuries, succumb to inflammation and perish. The myelin structures they established begin to degrade leaving axons demyelinated, which can result in reduced signal amplitudes and latency delays in the exchange of electrical signals. The simultaneous increase in impedance due to glial scar formation and reduced neuronal viability or function due to lack of oligodendrocyte or myelin support can affect the recording and stimulating potential of the tissue surrounding the electrode. Chronic injuries will leave tissue unreparable as remyelination or regeneration of axons fails to occur.