Chapter 13
Emerging Approaches for Regenerative Rehabilitation Following Traumatic Brain Injury

Regenerative Rehabilitation in TBI

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Abstract The potential for rehabilitation to improve recovery after traumatic brain injury (TBI) is limited by a lack of inherent regenerative capacity in the brain as well as the chronic disabilities and ongoing pathologies of various injury endophenotypes. A large body of previous work has shown that traditional rehabilitative therapies in combination with dietary modifications and regular exercise can enhance brain plasticity and, in some cases, neurogenesis, but prolonged secondary injury and limits to plasticity and regeneration significantly limit the impact of rehabilitation. Therefore, there is an urgent need for therapeutic strategies to promote regeneration and complement rehabilitation efforts to maximize recovery from TBI. In the following chapter, we discuss the unique translational challenges for developing TBI therapeutics, existing approaches to rehabilitation, promising therapeutic targets for enhancing regeneration and plasticity, and emerging regenerative medicine approaches that could significantly expand attainable levels of functional recovery following TBI.

Keywords Traumatic brain injury · Regenerative medicine · Rehabilitation

13.1 Introduction

Traumatic Brain Injury (TBI) is a surprisingly common injury that can have devastating health consequences. According to a recent report from the Centers for Disease Control and Prevention, there were approximately 2.87 million TBI Emergency Department visits or hospitalizations in the USA in 2014—a 53% increase from 2006—of which 56,800 resulted in death (CDC 2019). Incidence has also increased in the modern military, with 22% of all combat casualties from Iraq and Afghanistan estimated to be TBIs compared to 12% from Vietnam (VA Office of R & D). While TBI is among the leading causes of death, survival can also be devastating as roughly 2% of the U.S. population currently lives with chronic TBI-related disabilities (Langlois et al. 2006; Wilson et al. 2017). Long-term disability along with increased risk for neurodegenerative disease, stroke, and other maladies have led many to view TBI as a chronic health condition (Wilson et al. 2017; Edlow et al. 2018). Thus, TBI has a tremendous impact on health and the overall economy, resulting from both direct medical expenditures and indirect costs totaling over $60 billion annually (Langlois et al. 2006). This underscores the fact that there are currently no targeted medical therapeutic agents to attenuate TBI-induced neural degeneration or to promote effective regeneration.

While TBI creates a chronic health condition, it begins with a physical event that generates injurious forces in the brain. More detailed descriptions of the mechanical forces of TBI and their translation to brain pathology can be found in several in-depth reviews (LaPlaca et al. 2007; Meaney and Smith 2015; Meaney and Cullen 2016; Keating and Cullen 2020). For the convenience of the reader, we are providing illustrations from the recent review by Keating and Cullen in Fig. 13.1. Mechanical loading in TBI can occur via direct impact, impulsive motion, blast pressure waves from an explosion, or a combination thereof (Fig. 13.1a). For example, while
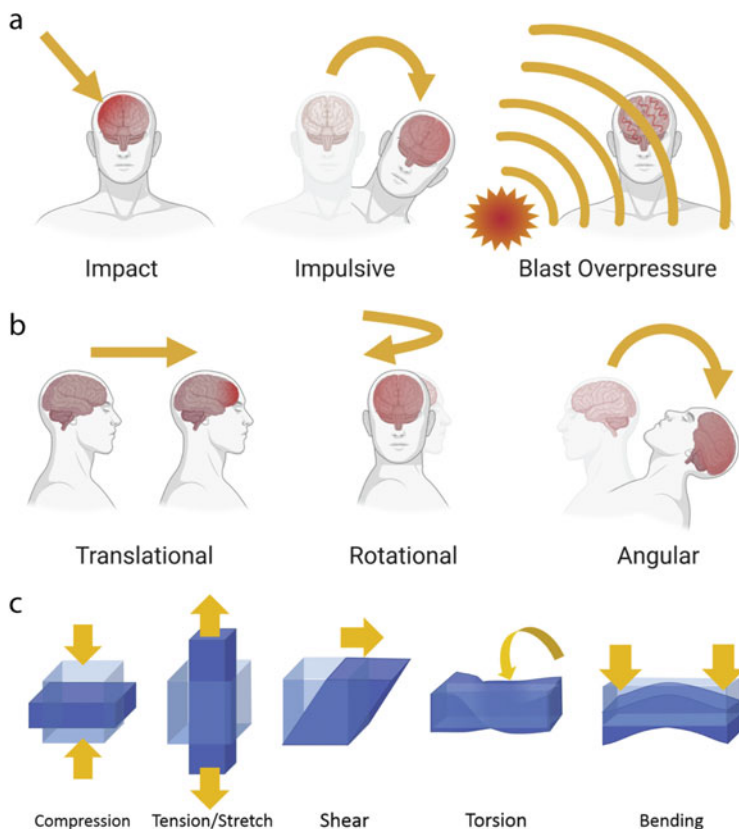
Fig. 13.1 Mechanical loading and deformation in TBI. Impact, impulse, and blast loading mechanisms of TBI are depicted (**a**). Head motion relative to the brain's center of mass affects impulse loading (**b**). Mechanical loading produces a variety of brain tissue deformations (**c**). Figure adapted with permission from Keating and Cullen (2020) (http://creativecommons.org/licenses/by-nc-nd/4.0/)

impulsive loading can be initiated without direct impact to the head (e.g., car accidents rapidly accelerating/decelerating the entire body), it most often occurs due to a direct impact to the head that sets the head in motion. Conversely, in the case of impulsive loading initiated by rapid body movement, the resulting head motion can also lead to impact loading due to the moving head encountering an object. Therefore impact-to-impulsive and impulsive-to-impact injuries are common (also impact-to-impulsive-to-impact). While primary impulsive loading with no focal impact lesion is common in mild TBI, impact to an immobilized head with no impulsive component is rare. The centrality of impulse loading to human TBI presents a challenge in preclinical studies, since the injurious forces are dependent on acceleration and brain mass, requiring large gyrencephalic animal models like non-human primates or swine to study mechanisms of injury and novel therapeutics in the context of impulse-generated TBI (Cullen et al. 2016; O'Donnell et al. 2019).

Table 13.1 Classification of TBI severity

(If a patient meets criteria in more than one category of severity, the higher severity level is assigned)			
Criteria	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness (LOC)	0–30 min	>30 min and <24 h	>24 h
Alterations of consciousness/mental state (AOC)[a]	Up to 24 h	>24 h; severity based on other criteria	
Posttraumatic amnesia (PTA)	0–1 day	>1 day and <7 days	>7 days
Glasgow Coma Scale (GCS) (best available score in first 24 h)[b]	13–15	9–12	<9

[a]Alteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be looking and feeling dazed and uncertain of what is happening, confusion, and difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

[b]In April 2015, the DoD released a memorandum recommending against the use of GCS scores to diagnose TBI. See the memorandum for additional information

Table reproduced from VA/DoD Clinical Practice Guideline for the Management of Concussion-Mild Traumatic Brain Injury

Despite the impractical accelerations necessary to account for the small brain mass of rodents, there have been attempts to apply impulse loading in small animal TBI models, but unfortunately, it does not appear possible to reach scaled thresholds with such disparate masses (Meaney et al. 2001; Sauerbeck et al. 2018). Blast TBI often also includes impulsive or impact loading components, contributing to the heterogeneity of the injury. Adding to this heterogeneity, the magnitude, distribution, and consequences of injurious forces generated by impulse loading vary based on the way the head moves relative to the brain's center of mass (Fig. 13.1b). Translational (a.k.a. linear) impulse loading occurs when the center of mass moves without rotation, and may be associated with brain surface injury that can occur due to the brain impacting the skull (sometimes referred to as contrecoup injury). Rotational loading involves head swivel around the brain's center of mass, and angular rotational loading involves rotational acceleration affecting the brain's center of mass. While injury at the surface of the brain from translational/linear loading can be a concern, there are far more injurious forces generated by angular rotational loading. Foundational work in non-human primates revealed that angular rotational loading (not translational/linear) was necessary and sufficient to produce extended loss of consciousness, a key element for clinical classification of TBI severity as shown in Table 13.1 (Denny-Brown and Russell 1941; Ommaya and Gennarelli 1974). Later work in the swine model utilizing pure impulse loading demonstrated that angular rotational head acceleration in the axial plane produced diffuse injury throughout the brain and prolonged coma, with lesions in the pons associated with coma duration (Smith et al. 2000; Cullen et al. 2016). The pons is a key branch point of the

Ascending Reticular Activating System (ARAS), and trauma to deep brain structures of the ARAS are associated with coma and prolonged Disorders of Consciousness (DoC) in humans following TBI (Edlow et al. 2012, 2013; Snider et al. 2019, 2020).

Direction of head rotation was a key determinant of outcomes such as duration of unconsciousness in a piglet model of TBI, and a more recent study suggests that properties of individual kinematic elements of head rotation (e.g., maximum negative velocity and peak-to-minimum acceleration time, both associated with more abrupt deceleration) influence recovery parameters in adult swine (Eucker et al. 2011; Wofford et al. 2021). These various mechanical loading parameters result in a variety of distinct types of tissue deformation determined by the type of loading as well as the physical properties and relative orientation of the material (in this case the brain) being deformed (Fig. 13.1c). Forces generated by mechanical loading will result in a combination of these deformations, with impact generally associated with direct compression at the brain's surface, and impulse generally associated with shear deformation throughout the brain. These deformation patterns may result in gross damage to vasculature and diffuse axonal injury (DAI), and at a sub-cellular level may cause cytoskeletal damage, loss of membrane potential due to opening mechanically-sensitive ion channels, plasma and organelle membrane permeabilization, disruption of the extracellular matrix and cell contacts, and other primary pathologies (Meaney and Smith 2015; Keating et al. 2020; Keating and Cullen 2020). The mechanical loading and tissue deformation of TBI is a rapid, high-energy event that typically lasts only milliseconds, but can produce pathological consequences that last a lifetime.

Following the initial mechanical TBI, secondary injury cascades produce waves of additional pathology and dysfunction over days, weeks, months, and even years. There are currently no approved therapeutics to mitigate this ongoing secondary injury. The varied consequences of the initial mechanical injury and the resulting multi-faceted secondary sequelae have been termed "endophenotypes." The concept of endophenotypes recognizes the heterogeneity of TBI and its consequences and allows a focus on treatment strategies and targeted therapeutics based on affecting specific phenomena. The heterogeneity of the primary injuries of TBI along with that of the patient population (e.g., age, sex, genetic background, medical history) contribute to the emergence of distinct endophenotypes—like microvascular injury and post-traumatic epilepsy (PTE)—with varying levels of contribution to the overall patient outcome (Diaz-Arrastia et al. 2009; Sandsmark et al. 2019). Endophenotypes that make major contributions to secondary injury cascades include inflammation, excitotoxicity, mitochondrial dysfunction, and oxidative stress at a cell/molecular level, and blood–brain barrier (BBB) disruption, microvascular injury, and PTE at the organ/systems level. Other endophenotypes of TBI exist as disabilities that impair rehabilitation and limit recovery but are not typically categorized as secondary injuries due to less-than-direct contributions to ongoing pathology. These include consequences such as sleep disturbances, confusion, and fatigue. Just as characteristics of the acute physical trauma are associated with—and indeed directly initiate—the subacute secondary injury cascades, the presence of various endophenotypes of secondary injury have been associated with increased

likelihood of chronic sequelae, such as pathological protein aggregation and neuroinflammation, potentially adding an additional layer of chronic neurodegenerative disease and disability. The line between injury and recovery is blurred following TBI due to prolonged secondary injury processes and ongoing neurodegeneration. Therefore, regenerative rehabilitation approaches to TBI must address both recovery and ongoing sequelae to be effective.

13.2   Current Approaches to TBI Rehabilitation

As highlighted above, there is significant heterogeneity inherent with a clinical diagnosis of TBI (Zasler et al. 2007). This includes variations in the number and severity of possible TBI-induced endophenotypes (e.g., DAI, cerebral microvascular injury, intraparenchymal contusion, intracranial hemorrhage, cerebral edema) within one or more regions of the brain (e.g., focal, multifocal, or diffuse injury), depending on the mechanism of injury and direction of the applied mechanical force(s). Further, patients exposed to TBI often have a wide variety of pre-existing medical comorbidities, many of which further contribute to compromised neurocognitive function and/or predict a worse outcome. In an effort to parse this heterogeneity, current diagnostic guidelines classify TBI as "mild," "moderate," or "severe" based on specific diagnostic criteria at the time of injury, including the presence and duration of any loss of consciousness, the duration of an alteration in consciousness or mental state, the duration of post-traumatic amnesia, the presence or absence of pathological findings on traditional structural neuroimaging, and the best available Glasgow Coma Scale (GCS) within 24-h of the TBI exposure, as shown in Table 13.1 (VA/DoD 2016).

As a result of the considerable heterogeneity and the non-specific nature of TBI diagnoses, current neurorehabilitation interventions are not designed to target or mitigate specific neuropathological component(s) (e.g., DAI, microvascular injury, or persistent neuroinflammation), whether present in discrete regions of the brain or diffusely throughout the brain parenchyma. Rather, an individualized treatment/neurorehabilitation plan is developed for each patient by a Physiatrist (physician specializing in Physical Medicine and Rehabilitation, often sub-specializing in Brain Injury Medicine) centered around common physical, cognitive, and neurobehavioral symptoms and/or functional deficits, which occur across the spectrum of TBI severity (Zasler et al. 2007; VA/DoD 2016). The resulting individualized neurorehabilitation plan is generally implemented through collaboration with a multidisciplinary team, including Physical Therapy, Occupational Therapy, Speech-Language Pathology, Neuropsychology, and Neuro-Optometry, amongst others. For each component of the overall neurorehabilitation prescription (e.g., Vestibular Physical Therapy), there is an emphasis on goal-based interventions to improve specific neurological symptoms or functional deficits, which are continually

reevaluated to ensure the prescribed neurorehabilitation interventions are leading to symptomatic and/or functional improvement. Thus, neurorehabilitation interventions selected for each patient are modified throughout the rehabilitation course, based on their individual therapeutic response. Three of the most common neurological deficits seen throughout all severities of TBI for which neurorehabilitation interventions are prescribed include cognitive, oculomotor, and vestibular deficits.

13.2.1 Cognitive Deficits

Cognitive complaints are often the most concerning symptom for patients following TBI exposure, and the extent of objective cognitive deficits vary widely during the acute and sub-acute phase of TBI recovery, throughout the spectrum of TBI severity (Esslinger et al. 2007; VA/DoD 2016). Initial clinical evaluation includes screening for orientation, executive, visuospatial, naming, memory, attention, and language deficits. Depending on the findings and the overall clinical presentation, the cognitive rehabilitation plan may be to (1) monitor for natural recovery and re-assess at a future date; (2) prescribe specific cognitive rehabilitation with Speech-Language Pathology and/or Occupational Therapy; or (3) refer to Neuropsychology for in-depth cognitive evaluation. The decision for referral for comprehensive neuropsychological testing depends on both the severity of TBI and the time post-TBI exposure. When performed, neuropsychological testing involves extensive objective testing of multiple cognitive domains, such as memory, working memory, attention, executive and academic functioning, language, reasoning, processing speed, visual-spatial perception, visual-motor construction, and motor function (Lezak et al. 2004; Esslinger et al. 2007). Neuropsychological testing can be used to (1) identify the specific cognitive domains that demonstrate an impairment, weakness, or strength; (2) help guide the cognitive rehabilitation provided by Speech-Language Pathology and/or Occupational Therapy; (3) generate specific accommodation request(s) for school or work; and (4) perform longitudinal evaluations to evaluate for cognitive improvement or secondary cognitive decline. This last point is becoming especially important given the increasing numbers of epidemiological studies demonstrating an association between TBI exposure and an increased risk of age-related cognitive decline or dementia (Fleminger et al. 2003; Gardner and Yaffe 2014, 2015; Gardner et al. 2014), including a recent large cohort study involving over 350,000 Veterans which documented a dose–response relationship between the severity of TBI (from "mild" TBI without a loss of consciousness through "moderate-to-severe" TBI) and the cumulative incidence of dementia diagnosis as illustrated in Fig. 13.2 (Barnes et al. 2018).
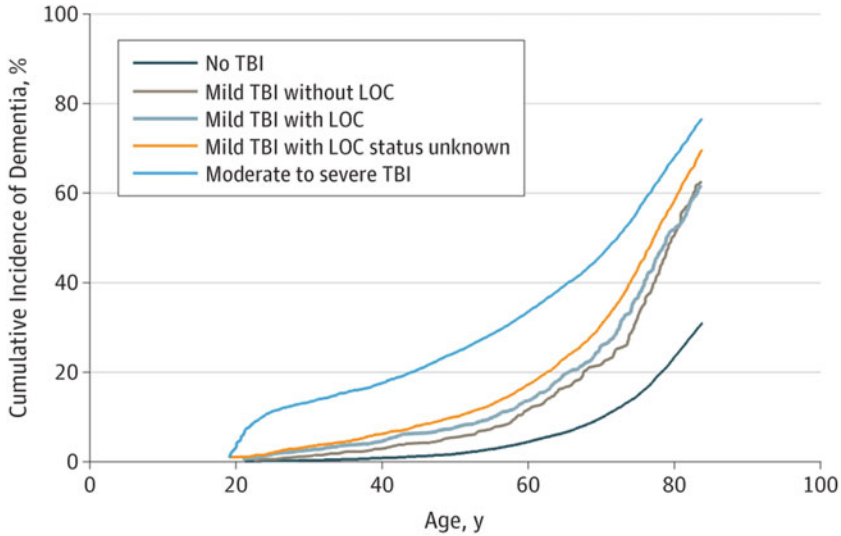
Fig. 13.2 Cumulative Incidence of Dementia by TBI Severity. The unadjusted cumulative incidence of dementia (age at dementia diagnosis) is shown as a function of TBI severity. After adjustment for demographics, medical conditions, and psychiatric disorders, there was a dose–response relationship between TBI severity and dementia diagnosis with hazard ratios of 2.36 (95% CI, 2.10-2.66) for mild TBI without loss of consciousness (LOC); 2.51 (95% CI, 2.29-2.76) for mild TBI with LOC; 3.19 (95% CI, 3.05-3.33) for mild TBI with LOC status unknown, and 3.77 (95% CI, 3.63-3.91) for moderate to severe TBI. Reproduced with permission from Barnes et al. (2018)

13.2.2 Oculomotor Deficits

Given that approximately half of the brain's neural networks are involved in binocular vision, abnormalities of oculomotor function are very sensitive to neurological insult and are commonly diagnosed throughout the spectrum of TBI severity (Padula et al. 2007; Ventura et al. 2014; VA/DoD 2016). Initial clinical assessment of oculomotor function often utilizes the validated Vestibular/Ocular Motor Screening (VOMS) assessment, which documents a patient's symptomatic response (headache, dizziness, nausea, and mental fogginess) when testing smooth pursuits, horizontal and vertical saccades, near point of convergence, the vestibulo-ocular reflex (VOR), and visual motion sensitivity (Mucha et al. 2014). When abnormalities are identified, patients are referred to Neuro-Optometry and/or Vestibular Physical Therapy for further sub-specialty evaluation and treatment (Padula et al. 2007; Scheiman and Wick 2008). Convergence insufficiency is then treated with either neuro-optometric rehabilitation or custom prism glasses when neuro-optometric rehabilitation is not indicated or available, while abnormalities of saccadic and smooth pursuit eye movements are treated by varied combinations of Vestibular Therapy, Occupational Therapy, and Neuro-Optometric Rehabilitation, depending

on the overall clinical presentation (Padula et al. 2007; Shepard et al. 2007; Scheiman and Wick 2008; Gallaway et al. 2017).

13.2.3   Vestibular Deficits

Vestibular deficits are commonly present throughout all severities of TBI and can be central and/or peripheral in origin (Shepard et al. 2007). Initial clinical evaluation often includes the validated Balance Error Scoring System (BESS) for static balance assessment, and components of a Functional Gait Assessment (FGA) for evaluation of dynamic balance (Wrisley et al. 2004; Bell et al. 2011; Iverson and Koehle 2013). Static balance screening with the BESS is a standardized assessment that evaluates a patient's stability during double limb stance, non-dominant single limb stance, and tandem stance, on both firm ground and a soft foam pad (Bell et al. 2011; Iverson and Koehle 2013). In contrast, dynamic balance screening with the FGA is a standardized gait assessment under ten conditions, including ambulation on level surfaces with changes in gait speed, horizontal and vertical head movements, eyes open versus closed, normal versus narrow base of support, pivot turns, stepping over obstacles, and ambulating backward (Wrisley et al. 2004). When abnormalities of static and/or dynamic balance are identified on initial clinical screening, referral is made to vestibular physical therapy for formal vestibular evaluation and treatment, where a more thorough assessment is conducted (Nashner 1993; Powell and Myers 1995; Shepard et al. 2007; Alahmari et al. 2014; Horn et al. 2015; VA/DoD 2016). Vestibular physical therapy evaluation commonly includes computerized dynamic posturography, which quantifies the ability to maintain postural stability through the use of visual, proprioceptive, and/or vestibular cues (Nashner 1993; Alahmari et al. 2014). TBI-induced static and/or dynamic vestibular deficits are then treated with a course of vestibular physical therapy, with the goal of retraining the vestibular system to maintain both static and dynamic postural control, utilizing a combination of visual and somatosensory substitution techniques, gaze stabilization exercises, saccadic and smooth pursuit eye movement exercises during both static stance and ambulation, and techniques to habituate the patient to chronic vestibular deficits which may remain despite targeted rehabilitation interventions (Shepard et al. 2007).

13.2.4   Developing the Evidence-Base for Rehabilitation Interventions

Apparent in the above overview of neurorehabilitation following TBI is the fact that there is substantial heterogeneity not only in TBI exposure and diagnosis but also in the subsequent neurorehabilitation prescribed. Further, the current neurorehabilitation interventions prescribed are targeting resulting neurological

symptoms and functional deficits, rather than targeting specific underlying neuropathology. Perhaps that is one reason why—despite numerous clinical studies—it is not currently possible to distinguish the effectiveness of different rehabilitation approaches after TBI (Injury et al. 2012; Brasure et al. 2013; Oberholzer and Müri 2019). Available neurorehabilitation interventions, while better than doing nothing, have indistinguishable efficacy and are limited to mechanistically vague, minimally invasive interventions due to a lack of a clear translatable preclinical pipeline for research and development of novel therapeutics. The inability to distinguish between the efficacy of neurorehabilitation strategies also stems from a disconnect between the "active ingredients" and the "therapeutic targets" within the overall strategies (Whyte et al. 2014). New frameworks like the Rehabilitation Treatment Specification System (RTSS) seek to improve the design, reporting, replication, and synthesis of rehabilitation research by providing guidance on forming specific hypotheses based on clearly identified "ingredients" and "targets" being tested, enabling refinement of the underlying theories that comprise neurorehabilitation strategies by elucidating their mechanism of action (Van Stan et al. 2019). This precise and rigorous approach to evaluating the efficacy of neurorehabilitation treatments will be vital for measuring and comparing the efficacy of novel regenerative treatments when integrated into neurorehabilitation, as will establishing a viable translational pipeline for developing those novel regenerative treatments.

13.2.5 Exercise and Diet

Currently, various forms of exercise and diet constitute key "ingredients" of TBI rehabilitation strategies. Exercise is generally believed to enhance the expression of brain-derived neurotrophic factor (BDNF), reduce reactive oxygen species, and improve hemodynamics leading to improved cognitive recovery in humans and animals (Devine and Zafonte 2009; Lojovich 2010). Exercise-induced growth factor cascades enhance synaptic plasticity by instructing a change in synaptic structure and potentiation of synaptic strength (Cotman et al. 2007). Exercise has been shown to increase neural stem cell proliferation (i.e., neurogenesis) in the injured brain parenchyma, prevent neurodegeneration, and improve cognition following experimental TBI (Itoh et al. 2011a, b). Additionally, exercise was found to augment hippocampal neurogenesis and was associated with improved neurobehavioral recovery in a preclinical model of TBI (Karelina et al. 2021). Exercise-induced neurogenesis following TBI may therefore contribute to cognitive recovery by enhancing plasticity and compensatory rewiring, increasing neurogenesis, and/or by increasing resistance to insult via indirect improvements to learning and memory. While we still have much to learn and refine, the benefits of exercise during recovery from TBI are widely accepted and it is an active ingredient in most rehabilitation therapies. Dietary factors have been found to improve recovery from TBI through similar mechanisms, and have even been found to complement exercise during rehabilitation (Gomez-Pinilla and Gomez 2011; Wu et al. 2013). Omega-3 fatty

acids—particularly the essential fatty acid and neural membrane component docosahexaenoic acid (DHA)—have been shown to promote the restoration of energy homeostasis, reduce reactive oxygen species, and increase BDNF after brain injury (Wu et al. 2004; Gomez-Pinilla and Gomez 2011). Interestingly, unlike the benefits for improving recovery after injury, neuroprotective effects were not observed in rats administered a prophylactic diet rich in fish oil (high in omega-3s) prior to FPI, while a diet high in saturated fatty acids and cholesterol—associated with reduced plasticity and negative impact on recovery—was protective against acute permeabilization of neuronal plasma membranes and reduced lesion size; thus highlighting the importance of considering injury mechanism and phase when developing therapeutic strategies (Keating et al. 2021). Dietary administration of branched-chain amino acids (BCAAs) has enhanced cognitive recovery after TBI in several rodent studies, due in part to correcting neurotransmitter synthesis deficiencies (Cole et al. 2010; Elliott et al. 2018; Paterno et al. 2018). Lateral FPI in mice led to a significant reduction in brain BCAA concentrations that were corrected with dietary BCAA administration, as were deficits in contextual fear conditioning (Cole et al. 2010) and spatial memory (Paterno et al. 2018). Dietary BCAAs and physical exercise share mechanisms of action, such as PGC1α-mediated increases in BDNF expression (Blomstrand 2001; Samuelsson et al. 2016; Nasrallah et al. 2019). They have also both been shown to improve the sleep and cognitive deficits associated with damage to the ARAS after TBI (Devine and Zafonte 2009; Cole et al. 2010; Lojovich 2010; Lim et al. 2013; Elliott et al. 2018; Paterno et al. 2018). Furthermore, there is evidence that dietary BCAAs may reduce exercise-induced cognitive fatigue by competitively inhibiting increased tryptophan transport into the brain that typically occurs in response to exercise (Blomstrand 2001). Due to the limitations of small animal models, exercise and diet have not been thoroughly investigated in the context of neuronal loss associated with their therapeutic targets in humans. However, there appears to be some potential for local plasticity changes (i.e., new or strengthened local connections that can form and/or reinforce certain neural networks) and this plasticity may underlie improved recovery with contemporary rehabilitation strategies.

Developing effective regenerative therapeutics to pair with traditional rehabilitation approaches offers the greatest potential for improving outcomes. There are a variety of pathological TBI endophenotypes that can impair recovery, as well as secondary injury mechanisms that remain active during the rehabilitation/recovery phase of TBI. Different treatments and therapies should be based on the goals of the patient and adequately address underlying issues at the time via (1) neuroprotection: reduce ongoing sequelae to prevent ongoing cell death and axon loss, (2) plasticity: new or strengthened local connections/synapses that can form and/or reinforce neural networks involved in certain behaviors, and/or (3) regeneration: new neural cells and/or new long-distance connections. Traditional rehabilitation techniques and emerging regenerative rehabilitative techniques could be targeted to address one or more of these areas. In the following sections, we will discuss some of these pathological endophenotypes and how to target them, demonstrating the variety of potential strategies for providing regenerative rehabilitation following TBI, as well

as the urgent need for developing therapeutic approaches to target these mechanisms.

13.3 Removing Anti-regenerative Barriers

The brain's inherent lack of regenerative capacity along with dysfunction and ongoing pathology after TBI create an anti-regenerative environment. Therefore, any treatment that removes these barriers after injury is pro-regenerative, and mitigating dysfunction and secondary pathology following TBI is necessary to facilitate strategies intended to directly enhance underlying regenerative capacity. Beyond the broad categories of neuronal loss and inflammation (discussed in more detail in later sections), there are other endophenotypes present during the chronic phase of TBI that could present attractive targets for regenerative rehabilitation.

13.3.1 Post-Traumatic Epilepsy (PTE)

PTE has been reviewed elsewhere in much greater detail than what would fit within the scope of this chapter (Diaz-Arrastia et al. 2009), but we will provide a general summary of the etiology and need for regenerative treatments for this important endophenotype of TBI. Functional brain signaling is a product of coordinated and balanced excitatory and inhibitory signaling, but damage to brain circuitry due to the mechanical insult and secondary pathologies of TBI can result in disruption of excitatory/inhibitory coordination (Cohen et al. 2007; Wolf and Koch 2016; Wolf et al. 2017; Ulyanova et al. 2018, 2019; Koch et al. 2020). Ongoing secondary injury cascades along with aberrant neuroregeneration and reorganization can produce a discordant signaling imbalance that can in turn result in seizures that cause additional excitotoxic cell death and further exacerbate inflammation, metabolic distress, and other mechanisms of secondary pathology following TBI. Beyond secondary pathology, there also appears to be a connection to chronic neurodegenerative disease, as an association between seizure activity and tauopathy has been suggested by the increased prevalence of seizures in Alzheimer's disease patients and animal models (Yan et al. 2012; Sánchez et al. 2018). A recent study utilizing a model of blast TBI in tauopathy reporter zebrafish found that seizure-like activity was associated with increased accumulation of human tau in the brain, and blocking seizure activity after injury prevented that accumulation (Alyenbaawi et al. 2021). Inflammation-focused therapeutic approaches could be effective at mitigating PTE, as inflammation has been implicated in several studies investigating the mechanistic underpinnings of PTE (Webster et al. 2017; Sharma et al. 2019; Therajaran et al. 2020). Although surgical interventions can be effective (Hitti et al. 2020), many common anticonvulsants are ineffective against trauma-induced epilepsy, indicating a need to improve our mechanistic understanding of this unique condition via translational

modeling and data collection modalities (Diaz-Arrastia et al. 2009). PTE can significantly impair patients' ability to engage in exercise and cognitive rehabilitation activities. Therefore, it is imperative to develop regenerative rehabilitation strategies focused on managing post-traumatic epilepsy to maximize the effect of rehabilitation on recovery.

13.3.2 Vascular Injury

A recent study found that chronic BBB dysfunction and inflammation after TBI in rats and humans is associated with increased seizure susceptibility, suggesting that targeting these chronic endophenotypes may be effective for treating PTE (van Vliet et al. 2020). BBB disruption from mechanical and secondary injury is a persistent endophenotype of TBI that contributes to neuroinflammation and limits rehabilitation and recovery (Hay et al. 2015). In addition to BBB disruption, TBI also results in diffuse damage to microvasculature throughout the brain and in focal contusions. Beyond the direct consequences of disrupted circulation (e.g., ischemia), microvascular injury is also associated with inflammation and thrombosis via mechanisms that warrant further study (Hubbard et al. 2021). Microvascular injury, particularly in areas like the dorsal pons, can be predictive of long-term outcome (Izzy et al. 2017; Griffin et al. 2019). A recent review from Sandsmark and colleagues presents an in-depth discussion of the mechanisms and consequences of TBI-induced microvascular injury as well as the potential for therapeutic intervention (Sandsmark et al. 2019). Among treatments under investigation for addressing neurovascular dysfunction, there are several focused on the chronic phase of TBI that could be relevant for enhancing the impact of rehabilitation. For example, a study in mice 1 year after TBI found that administering the aminopropyl carbazole P7C3-A20 for 30 days restored BBB integrity, arrested axonal degeneration, and improved cognitive recovery (Vázquez-Rosa et al. 2020). Cerebrovascular reactivity—the change in cerebral blood flow in response to a stimulus—is commonly used as a measure of microvascular health, and a recent clinical study utilizing the phosphodiesterase-5 inhibitor sildenafil restored cerebrovascular reactivity in patients in the chronic phase of TBI (Kenney et al. 2018). As BBB and microvascular dysfunction are intricately linked to other endophenotypes of chronic TBI, these results suggesting that they are viable targets for therapy bode well for future research into regenerative rehabilitation.

13.3.3 Mitochondrial Dysfunction

Dysregulated metabolism and energy deficits are prominent characteristics of TBI and a critical component of the secondary injury cascade. Mitochondria are fundamental to cellular bioenergetics, and in addition to providing energy substrates, mitochondria also buffer Ca^{2+} and provide antioxidant support. Axons and astrocytic

processes are full of mitochondria moving to and from the soma, pausing at nodes of Ranvier or glutamate transporters servicing synapses, and engaging in constant dynamic fission and fusion to maintain mitochondrial health (Ohno et al. 2011; Genda et al. 2011; Youle and Bliek 2012; Schwarz 2013; Jackson et al. 2014). Axons and astrocytic processes are highly vulnerable to the diffuse shearing forces of TBI, producing cytoskeletal damage that disrupts or eliminates mitochondrial dynamics, and also leading to increased cytosolic Ca^{2+} that can exceed mitochondrial buffering capacities (Wang et al. 2021; Nguyen et al. 2021). The resultant mitochondrial dysfunction and energy failure lead to a collapse of ion gradients causing exacerbation of excitotoxicity due to reduced Ca^{2+} buffering capacity, a switch from providing protective antioxidants to producing damaging reactive oxygen species and, potentially, culmination in mitochondrial permeability transition that triggers programmed cell death. Cells that survive are often left with dysfunctional mitochondria, resulting in prolonged foundational impairments to energy production, neurotransmitter synthesis, Ca^{2+} signaling/buffering, and oxidative stress that negatively affect all downstream aspects of cell function and exacerbate the inflammatory extracellular environment. In addition to the central role of mitochondria during secondary injury after TBI leading to an anti-regenerative environment, they are also essential for cellular regeneration, making them a very attractive target for developing new neurotherapeutics (Wang et al. 2021).

There are numerous pharmacological approaches under investigation to mitigate mitochondrial dysfunction after TBI. A recent study utilizing focal TBI in swine found that a new lipid emulsion formulation of cyclosporine—a drug that functions in part via inhibiting the formation of the mitochondrial permeability transition pore and has significant preclinical evidence for mitigating TBI pathology—preserved fractional anisotropy as measured by diffusion tensor imaging (DTI) and reduced concentrations of neurofilament light (NF-L) in cerebrospinal fluid (Karlsson et al. 2020). These results are significant not only for providing evidence that this cyclosporine formulation reduces white matter pathology from TBI in a large animal model but also for validating DTI and NF-L as translational endpoints for future neurotherapeutic studies. A more unconventional and early-stage regenerative strategy involves the transfer of healthy mitochondria into cells with damaged mitochondria (McCully et al. 2016; Chang et al. 2019; Chen et al. 2020). Preliminary clinical studies in cardiac arrest have yielded encouraging results (Emani and McCully 2018). While models of ischemia/reperfusion injury have produced mitochondrial damage and autophagic degradation in astrocytes, other brain injury models have demonstrated that astrocytes transfer healthy mitochondria to neurons in distress (O'Donnell et al. 2016; Hayakawa et al. 2016; Quintana et al. 2019; English et al. 2020). Seeking to emulate this endogenous phenomenon on a larger scale, therapeutic vehicles for mitochondrial transfer currently under investigation include synaptosomes and mesenchymal stem cell-derived exosomes (Zhang et al. 2020; Lu et al. 2020; Picone et al. 2021). Mitochondria are both essential for cellular function and central to mechanisms of cell death, making them an ideal therapeutic target for reducing secondary injury after TBI and for facilitating plasticity and regeneration to maximize the effect of rehabilitation on recovery.

13.3.4 Astrocytic Dysfunction

Astrocytes are the most abundant cell type in the brain, where they are responsible for ion gradient homeostasis, facilitating anabolic and catabolic metabolism, providing antioxidant protection, fixing NH_4, incorporating nitrogen into biological molecules, preventing edema, removing glutamate from the extracellular space, coupling neuronal activity to changes in blood flow and glucose uptake, regulating breathing in response to changes in brain oxygenation, directly participating in signaling and plasticity, and many other vital functions. Not surprisingly, disruptions of each of these functions, often in combination, have been implicated in acute trauma and neurodegenerative disease (for reviews, see (Chen and Swanson 2003; Rossi et al. 2007; Sheldon and Robinson 2007; Barreto et al. 2011; Lange et al. 2012; Brambilla et al. 2013; Stary and Giffard 2015; Nguyen et al. 2021)). Historically, the vast heterogeneity of astrocytes and their wide variety of responses to pathological conditions have been inappropriately classified into a single "reactive" phenotype, and a recent consensus statement drawing attention to this oversimplification emphasized the need to move away from a cursory quantification of "astrogliosis" to study pathological responses of astrocytes in vivo in the context of multiple molecular and functional endpoints (Escartin et al. 2021).

Astrocytes are vital for brain metabolism, a myriad of essential homeostatic functions, stemming the perpetual threat of excitotoxicity, and communicating between brain and body. As such, they provide an excellent therapeutic target for rescuing distressed neurons and directly facilitating regeneration. One particular endophenotype following TBI—elevated intracranial pressure—has been mechanistically linked to the disrupted homeostatic function of astrocytes leading to cerebral edema, and as a result, the astrocytic water channel aquaporin 4 has emerged as a potential therapeutic target, at least in the acute/subacute phase of injury and recovery (Shields et al. 2011). Indeed, loss of aquaporin 4 and other astrocytic responses to TBI such as clasmatodendrosis were recently described in an in-depth histological and transcriptomic analysis in mice and were also found to be exacerbated with age (Early et al. 2020). Although astrocytes possess significant glycolytic capacity that contributes to their ability to survive pathological conditions, their mitochondria are involved in nearly all of the essential functions that astrocytes provide to the rest of the brain. As described in the previous section, these astrocytic compartments and the mitochondria therein appear to be uniquely susceptible to pathological conditions. Studies examining astrocytic mitochondria in primary culture have revealed depolarization and dysfunction in response to various pathological conditions as well as a few techniques to prevent that dysfunction (Stary and Giffard 2015). Heat shock proteins involved in mitochondrial Ca^{2+} handling have been implicated in mitochondrial dysfunction in primary astrocytes, and pharmacological or genetic induction is neuroprotective in in vitro and in vivo models of ischemia (Ouyang et al. 2005, 2006; Sun et al. 2006; Xu et al. 2010; Li et al. 2021). Astrocyte-targeted reduction of microRNAs that have been implicated in mitochondrial homeostatic mechanisms is neuroprotective in in vivo models of ischemic

stroke (Ouyang et al. 2011, 2012a, b, 2013; Xu et al. 2015b). Purinergic signaling plays a prominent role in astrocytic communication during health and disease (Franke et al. 2012). Calcium-mediated stimulation of mitochondrial metabolism in astrocytes via activation of purinergic P2Y1 receptors provides neuroprotection against oxidative stress in primary co-cultures (Wu et al. 2007) and reduces edema and infarct size in an in vivo photothrombotic stroke model in mice (Zheng et al. 2010, 2013). Compared to the often-fatal consequences in neurons, mitochondrial dysfunction and other secondary injury mechanisms are far less severe and very rarely fatal for astrocytes. During the chronic phase of TBI, astrocytes are intimately involved in angiogenesis and BBB repair, as well as neurogenesis, synaptogenesis, and synaptic remodeling (plasticity), and they simultaneously perform pro- and anti-regenerative functions that should be specifically targeted to improve recovery (Zhou et al. 2020). Since astrocytes are capable of rescuing neurons from a multitude of pathways simultaneously, a therapeutic approach that targets the less-severe dysfunction in astrocytes may offer greater chances of success compared to therapies focused on a single neuronal target. Astrocytes are also entangled in the processes of neuroinflammation, and anti-inflammatory strategies are therefore also likely to affect astrocytic dysfunction, providing additional benefits for enhancing regeneration during rehabilitation.

13.4   Current and Future Approaches to Mitigate Inflammation

Neuroinflammation encompasses myriad mechanisms by which the immune system responds to events in the central nervous system (CNS). These complex mechanisms involve central and peripheral cellular activity such as resident microglial activation and peripheral recruitment of neutrophils, lymphocytes, and monocyte-derived macrophages, as well as molecular components such as cytokine and chemokine signaling. Under normal conditions, neuroinflammation provides vital physiological functions, but in the case of TBI, this response is often pushed beyond homeostatic parameters to become pathological and can contribute to a lifetime of disability and neurodegenerative disease. This critical need for inflammation is exemplified by the numerous failed anti-inflammatory therapy clinical trials. Therefore, a new framework has been proposed to optimize targeted interventions and the immune response to TBI: acute proinflammatory response should be limited to levels needed for debris clearance and danger signaling; anti-inflammatory and pro-regenerative immune cell phenotypes should be promoted; and the development of chronic neuroinflammation should be prevented (Simon et al. 2017). This framework addresses the critical role inflammation plays in neuroprotection, fostering plasticity (synaptic remodeling), and facilitating regeneration. In the sections below, we will outline current and future therapeutic approaches that can be utilized within these framework guidelines to modify the neuroinflammatory response to TBI.

13.4.1 Complement Activation

The complement system is a vital part of the innate immunological response and plays a key role in various functions of the immune system. Classically described as having three distinct activation patterns—the classical, alternative, and lectin pathways—all leading to a cascade-like enzymatic process that converges on common end products as depicted in the schematic in Fig. 13.3 from a recent review by Dalakas, Alexopoulos, and Spaeth (Dalakas et al. 2020). Unlike the regulated complement activation that occurs in response to infection and autoimmune processes, an exaggerated complement response follows a traumatic injury. The cleavage of complement components initiates the subsequent steps and produces activated complement cleavage products that act as anaphylatoxins both locally and systemically. As a result, complement components comprise a large proportion of circulating blood proteins and play an important role in a multitude of processes.

While the CNS is generally considered to be immune-privileged due to the BBB, emerging evidence has demonstrated that the innate immune system functions
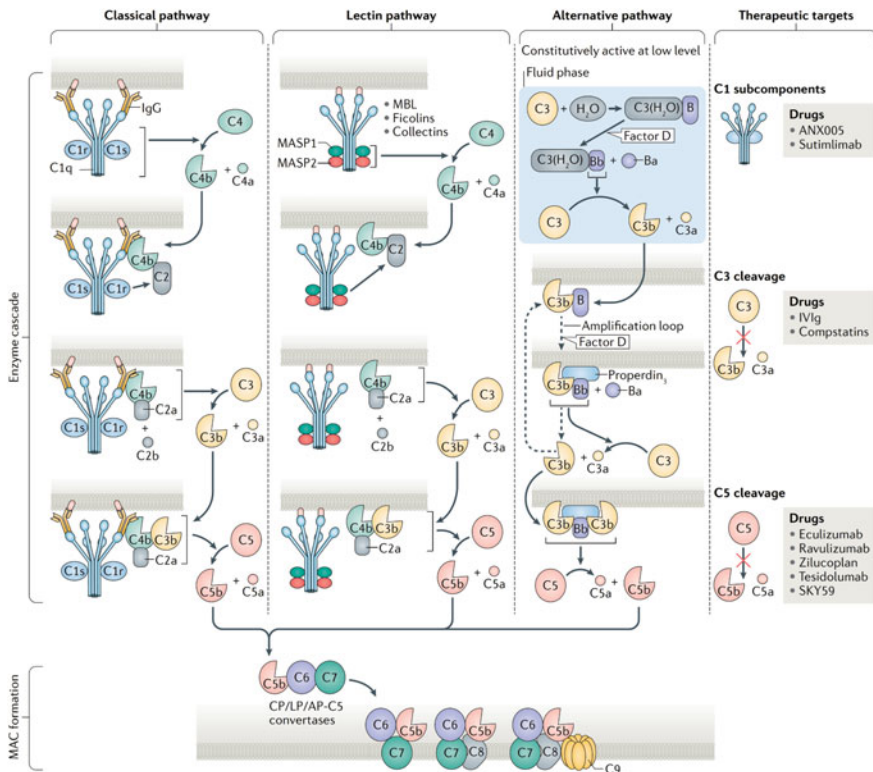

Fig. 13.3 Complement activation pathways and emerging therapeutic targets. Schematic reprinted with permission from Springer Nature (Dalakas et al. 2020)

within CNS. Cells of the brain can indeed produce complement components. Likewise, neurons, astrocytes, oligodendrocytes, and especially microglia express complement receptors (Orsini et al. 2014). Complement plays an important function in homeostasis, helping to clear protein debris and damaged cells as well as neuronal pruning during development (Veerhuis et al. 2011). Consequently, complement has been implicated in neurodegenerative diseases such as Alzheimer's and autoimmune diseases like Multiple Sclerosis. Indeed, increased complement component deposition has been found in hippocampi of aged mice, an indicator of the function of complement in senescence (Krukowski et al. 2018).

In addition to its role in homeostasis, complement is activated in times of injury and cerebral distress. TBI is often devastating due to the multifactorial nature of injury mechanisms leading to acute and long-lasting damage. While several processes contribute to the clinical manifestations of TBI, neuroinflammation and complement activation specifically play a critical role. Following TBI, the immune reaction is vast, with both systemic and localized activation, changes in epigenetic transcription, and enzymatic expression (Orsini et al. 2014). Activated complement components act as anaphylatoxins and lead to immune cell activation and recruitment in the injured brain, endothelial damage, and BBB breakdown. In addition to exogenous cell recruitment, an important function of complement anaphylatoxins is the activation of glial cells and recruitment of microglia specifically to the site of injury. This in turn can lead to localized cytokine release with pathologic consequences. Breakdown of the BBB results in a further influx of systemic complement components in addition to locally produced proteins. The complement cascade has been shown to contribute to both acute and subacute secondary injury following TBI through anaphylatoxin release, immune cell recruitment and activation, and directly causing neuronal death. Both the classical and the lectin pathways have been implicated in TBI-related secondary injury (Ciechanowska et al. 2020). In addition, the interplay between neuroinflammation and platelet activation has pointed to the role of complement in post-TBI hypercoagulability and microthrmobosis (Fletcher-Sandersjöö et al. 2020). Complement has likewise been linked with long-term disability and cognitive decline following TBI (Alawieh et al. 2021).

The vast majority of research into the role of complement in TBI has been performed in rodent models using gene knockout techniques and small molecule complement inhibitors. Not surprisingly, complement blockade has emerged as an attractive target for TBI therapy in preclinical rodent models with studies investigating the efficacy of complement inhibition as a therapeutic strategy following TBI (Leinhase et al. 2007; Rostami et al. 2013; Fluiter et al. 2014; Ruseva et al. 2015; Bambakidis et al. 2016; Alawieh et al. 2018; Rowe et al. 2018; De Blasio et al. 2019; Weiss et al. 2020). C1 inhibition has shown improved motor function at 4 weeks following TBI, as well as significant behavioral improvement and decreases in injury volume (Longhi et al. 2009). C3 knockout mice demonstrated decreased edema and microglial activation after TBI. Likewise, neutrophil recruitment was significantly reduced following TBI in the knockout animals (You et al. 2007). In addition, C3 knockout animals show decreased proinflammatory gene expression, lesion size, and vascular damage (Sewell et al. 2004). Studies show that inhibiting C3 cleavage

reduces post-injury activation of microglia and astrocytes, C3 deposition, and neuronal cell death, leading to improvements in cognitive and functional recovery (Rich et al. 2016; Alawieh et al. 2018). Likewise, evidence points to C3 convertase inhibition as a potent inhibitor of blood–brain barrier breakdown and neutrophil recruitment to the CNS, mirroring evidence in knockout experiments (Kaczorowski et al. 1995). Furthermore, overexpression of C3 convertase inhibitor demonstrated improvements in behavioral outcomes following TBI, both acutely at 4 and 24 hours after injury, as well histopathological evidence of less neuronal loss in key anatomic areas (Rancan et al. 2003). In longer-term studies, C3 activation promotes a sustained degenerative state through microglial and astrocyte activation for several weeks following injury, resulting in long-term effects (Alawieh et al. 2018). The resultant neuroinflammation is longer lasting and seems to be a key driver of negative outcomes. Mice deficient in C4 also demonstrated attenuated damage and improved recovery following TBI (You et al. 2007).

Further down the complement cascade, C5 has also emerged as a potential target for intervention, although less potent due to the downstream position in the activation sequence (Sewell et al. 2004). The administration of a C5-binding protein inhibitor was shown to reduce neurologic deficits after TBI (Fluiter et al. 2014). Direct C5a blockade has also been shown to improve outcomes in mice (Sewell et al. 2004; Yang et al. 2006). Inhibiting the formation of the membrane attack complex (MAC, a.k.a. C5b-9), the end product of the complement cascade and downstream of C5 cleavage, has likewise been studied as a potential intervention strategy with results suggesting a reduction in the accumulation of microglia and macrophages as well as reduced neuronal death and axonal pathology (Fluiter et al. 2014). Downregulation of CD59 in knockout animals resulted in increased neurologic deficits and neuronal damage, further evidence that the role CD59 plays in MAC inhibition is potentially impactful for attenuating traumatic injury (Stahel et al. 2009). C3a and C5a receptor antagonists (C3aRA and C5aRA respectively) have been investigated in rodent models of TBI and stroke and found to be effective in suppressing the complement response, decreasing the expression of complement receptor, and decreasing secondary brain injury (Fattouch et al. 2007; Ducruet et al. 2008; Kim et al. 2008; Rynkowski et al. 2009; Széplaki et al. 2009; Garrett et al. 2009; Banz and Rieben 2012).

While the majority of evidence supporting the critical role of complement in TBI is from rodent studies, a significant body of work has shown complement up-regulation in humans following TBI. Studies examining the CSF of TBI patients identified a significant increase of activated C3 (Kossmann et al. 1997; Morganti-Kossmann et al. 2001a). Brain injured patients have increased levels of complement activation products in CSF (Lindsberg et al. 1996; Mocco et al. 2006; Széplaki et al. 2009; Elvington et al. 2012; Manek et al. 2018; Si et al. 2019). Pathologic studies have also demonstrated expression of complement receptor and deposition of complement components on injured brain tissue including the MAC, the convergent end-product of all three complement pathways, and an effector of direct cellular damage (Rostami et al. 2013). Likewise, pathological studies demonstrated increased deposition of complement in perilesional and peri-vascular regions. This

is supported with rodent evidence of increased mannose-binding lectin (MBL) deposition in perivascular and perilesional space in injured mice resulting in activation of the lectin pathway (Longhi et al. 2014). In longer-term studies, increased expression of complement protein has been described up to 6 months post-injury with implications for amyloid homeostasis and chronic sequela (Bao et al. 2018).

With significant animal model evidence indicating therapeutic efficacy, attention is turning to complement inhibition as a therapy in human neurological diseases including TBI. Unfortunately, the TBI field has failed to translate any therapies strongly supported by rodent preclinical data despite over 30 clinical trials (Loane and Faden 2010; Xiong et al. 2013; Kabadi and Faden 2014; Vink 2018). To address the weaknesses in the translational pipeline and bridge the gap between rodents and humans, swine appears to be a viable preclinical model for complement research. Swine studies of severe TBI resuscitation with valproic acid led to a down-regulation of complement activation, and a resultant decrease in injury severity (Dekker et al. 2014; Bambakidis et al. 2016). Complement-directed therapeutics such as eculizumab (Soliris, Alexion, USA) have gained significant traction with a well-established safety profile and have been proposed as a potential therapy in TBI (Roselli et al. 2018). Likewise, small molecule complement receptor antagonists, specifically for C3a and C5a, are entering human trials and will likely move on to TBI as a disease target (Ducruet et al. 2009; Garrett et al. 2009). The complement system appears to be integral to the acute and chronic inflammatory response following TBI, offering promising therapeutic targets for neuroprotection, improved plasticity, and increased regenerative potential to enhance rehabilitation and improve outcomes.

13.4.2   Microglial Activation

One of the earliest inflammatory cellular responses after TBI is the activation of microglia, the primary immune cells of the CNS. Microglia in the healthy adult brain survey the local environment and monitor synapses, while microglia after TBI (and in other disease pathogenesis) engulf cellular debris and promote both regeneration and inflammatory cytokine release (Salter and Stevens 2017; Wofford et al. 2017). This activity may have both beneficial and detrimental effects, as prolonged or uncontrolled activation may contribute to more serve cognitive impairments and neurodegenerative disorders (Simon et al. 2017). Indeed, microglial activation can persist for weeks, years, or decades after injury as demonstrated in human TBI and preclinical animal models of injury (Gentleman et al. 2004; Johnson et al. 2013a; Loane et al. 2014; Lafrenaye et al. 2015; Grovola et al. 2020, 2021).

Recent therapeutic advances have attempted to target the mechanisms responsible for neuroimmune dysregulation using a variety of approaches. Unfortunately, many clinical trials targeting inflammation TBI have failed to demonstrate beneficial effects on neurological outcomes. These failed trials include corticosteroids, such as hydrocortisone and methylprednisolone, hypothermia therapy, and hypertonic

saline infusion (Roberts et al. 2004; Hutchison et al. 2008; Bulger et al. 2010; Asehnoune et al. 2014). Other anti-inflammatory drugs, such as minocycline, have had mixed results; in a clinical trial of 15 patients, minocycline administered for 12 weeks reduced chronic microglial activation after TBI but increased neurodegeneration (Scott et al. 2018). These minocycline trial results suggest that microglia play a reparative role in the chronic phase of TBI and drug treatment may need to be employed at specific time points post-injury.

One promising method that allows finer control over microglia involves inhibiting the microglia colony-stimulating factor 1 receptor (CSF1R). CSF1R is expressed by microglia, macrophages, and osteoclasts, and knocking out the CSF1R gene eliminates the brain's microglia population (Patel and Player 2009; Erblich et al. 2011). To determine the role of CSF1R signaling in microglial homeostasis, Elmore et al. (2014) tested the effectiveness of CSF1R inhibitors in adult mice. After initial compound selection experiments, PLX3397 displayed the greatest decrease in brain microglia by demonstrating a 50% reduction after just three days of administration in standard rodent chow and greater than 90% reduction after 7 days of administration. Furthermore, remaining microglia stained for active caspase-3, a marker for apoptosis, indicating that CSF1R inhibition initiates microglial cell death. Researchers then withdrew drug administration and made two remarkable discoveries. First, microglia began to repopulate the brain within 3 days, though these microglia were hypertrophied with short stubby processes compared to sham. Second, microglia density and morphology mirrored sham specimens 14 days after drug withdrawal. Therefore, microglia repopulation occurs through rapid increase in cell number followed by stabilization of their morphology. Finally, profiling of 86 immune-related genes lead to a reduction of these genes after microglial depletion (Elmore et al. 2014). Overall, CSF1R inhibitors allow for highly-selective microglial depletion through non-invasive administration and lacks a cytokine inflammatory response.

Recently, Spangenberg et al. (2019) developed the next generation of CSF1R inhibitors for microglial elimination (Spangenberg et al. 2019). These researchers sought to create a CSF1R inhibitor that is orally bioavailable, brain-penetrant, and depletes microglia for an extended time period. After several key changes to the chemical structure of PLX3397, PLX5622 was synthesized. Thorough pharmacokinetic investigation in mice, rats, dogs, and monkeys revealed a 20% brain penetrance for PLX5622 compared to 5% for PLX3397. This improved penetrance can be attributed to PLX5622's lower molecular weight, higher lipophilicity, and better cell permeability, thus allowing PLX5622 to cross the BBB more easily. Additionally, PLX5622 caused a 90% reduction in microglia within 5 days of administration in standard rodent chow at doses as low as 1200 ppm. Importantly, withdrawal of PLX5622 also allows for microglial repopulation, potentially offering a means to reset a predominantly pathological microglial phenotype after injury.

While Spangenberg et al. initially applied PLX5622 to plaque formation in preclinical models of Alzheimer's disease, Henry et al. (2020) investigated the elimination of microglia utilizing a controlled cortical impact injury in rodents (Henry et al. 2020). At 28 days after injury, Henry et al. administered PLX5622 to

mice for 1 week to potentially mitigate posttraumatic neurodegeneration and neurological dysfunction. This delayed depletion of microglia improved motor function recovery in beam walk and rotarod tests, as well as improved cognitive function recovery in Y-maze and Morris Water maze tasks. Additionally, PLX5622 treated mice had decreased lesion volume and attenuated cortical and dentate gyrus neuron loss. Histological examination of microglia in PLX5622 treated animals showed an increase in resting, ramified microglia in the injured cortex compared to TBI + vehicle-treated animals. Finally, PLX5622 altered cortical transcription patterns of oxidative stress, neuroinflammation, neuroplasticity, and apoptosis (Henry et al. 2020). These findings suggest that functional recovery after TBI may occur at chronic time points, thus expanding the therapeutic window for post-TBI interventions. Furthermore, CSF1R inhibitors did not cause cognitive or motor impairments despite the critical role of microglia in brain surveillance and synapse monitoring (Salter and Stevens 2017).

While CSF1R inhibitors are showing increasing potential as a therapy for TBI and a range of other neurological disorders, it should be noted that CSF1R inhibition by PLX5622 also affects peripheral immune cells. Lei et al. (2020) administered PLX5622 to adult mice for 3 weeks, then ceased treatment for 3 weeks before assessing bone marrow, spleen, and blood for immunological changes (Lei et al. 2020). PLX5622 administration resulted in the suppression of select monocyte progenitor cells, bone marrow-derived macrophages, hematopoietic stem cells, and hematopoietic progenitor cells. Importantly, these cell populations did not recover by this 3-week post-treatment experimental timepoint (Lei et al. 2020). Therefore, research focusing on peripheral and circulating macrophages in addition to microglia is necessary to understand the consequences—positive and/or negative—of administering PLX5622 following TBI.

Despite the need for further investigation into the impact of depleting peripheral immune cells, PLX5622 remains the best available tool to deplete microglia in vivo—both to investigate their functions in TBI and a myriad of other conditions, and also for proof-of-concept TBI therapeutics studies. Thorough characterization of all immune cell types at extended time points should be monitored across various factors, such as subject age, sex, mechanism and degree of injury, and secondary insults to determine the full effectiveness of CSF1R inhibitors as a potential therapy for TBI. Targeted modulation of microglia continues to garner significant research interest due to their potential to mitigate specific drivers of neurodegeneration and dysfunction following TBI, and though it may seem extreme to some, short-term depletion of microglia may yet prove to be a powerful non-invasive therapy to mitigate neurodegeneration and dysfunction following TBI, providing a more regenerative environment for rehabilitation. Future studies will need to discern if temporary microglia removal/repopulation or a more sustained and targeted modulation of detrimental microglia behavior will yield superior therapeutic benefits.

13.4.3   Macrophage Infiltration

In addition to resident cells of the CNS, the peripheral immune system can also have profound effects on the extent of regeneration and recovery following TBI. In healthy conditions the BBB limits interactions between the CNS and the peripheral immune system. However, following trauma, the BBB can become mechanically and chemically altered, thereby reducing the impedance between the peripheral whole blood and the CNS. Of course, penetrating TBIs and focal TBIs result in mechanical trauma to cerebral vasculature, affecting the neurovascular unit integrity. Furthermore, changes in signaling molecules can affect the stability of astrocytic endfeet, endothelial cell tight junctions, and pericyte support (Cash and Theus 2020), all of which can affect vasculature integrity after trauma. These changes to BBB integrity have been described in focal, diffuse, and closed-head TBI and have been noted in clinical TBI cases (Hay et al. 2015; Li et al. 2016; Johnson et al. 2018; van Vliet et al. 2020).

It is therefore unsurprising that peripheral immune cells, which are primed to identify tissue damage, can infiltrate into the brain when the BBB becomes leaky. Within hours of the injury, neutrophils, the first responders of the peripheral immune system, infiltrate into the brain tissue (Liu et al. 2018). Once inside the brain, they can contribute to pathological progression by secreting neutrophil extracellular traps (NETs) and altering the cerebral blood flow rate (Vaibhav et al. 2020). Following the neutrophils, monocyte-derived macrophage numbers in the brain begin to significantly increase approximately three days after trauma (Alam et al. 2020; Hazy et al. 2020). Lastly, adaptive immune cells, including B cells and T cells have been reported to infiltrate brain tissue several days after TBI (Morganti-Kossmann et al. 2001b; Ling et al. 2006; Alam et al. 2020).

Research efforts aimed at mitigating pathology and behavioral deficits after TBI have turned to controlling monocyte-derived macrophages because of the convenient timing, magnitude of infiltration, and association of monocyte-derived macrophage infiltration into the brain with neurotoxicity and neurological deficits in animal models (Hsieh et al. 2014; Gyoneva et al. 2015; Morganti et al. 2015). Over the last couple decades, much attention has been garnered to attempt to understand, remove, or reprogram monocyte-derived macrophages in the CNS after trauma (Lee et al. 2016; Chan and Viswanathan 2019). Here, we will briefly review the contributions of monocyte-derived macrophages to TBI and some therapeutic approaches that employ these cells to provide a more regenerative environment for rehabilitation.

Monocyte-derived macrophages are unique because they can exhibit a wide range of behavioral phenotypes that can amplify inflammation, promote angiogenesis, remodel extracellular matrices, or stimulate phagocytosis (Mosser and Edwards 2008; Wynn et al. 2013; Brown et al. 2014; De Paoli et al. 2014; Graney et al. 2020). As a result of the environmental cues in the injured brain, infiltrating monocyte-derived macrophages generally promote a chronic inflammatory phenotype and exacerbate neuroinflammation (Wofford et al. 2019b; Hazy et al. 2020).

This preserved inflammatory phenotype is distinct from the phenotype progression that monocyte-derived macrophages typically present in other models of healthy tissue regeneration (Kim et al. 2016). Typically, monocyte-derived macrophages will exhibit a transient inflammatory phenotype followed by a tissue remodeling phenotype (Snyder et al. 2016; Spiller and Koh 2017). It is theorized that this temporal sequence encourages clearance of necrotic and infectious material, wound closure, and tissue remodeling. To avoid or overcome the chronic inflammatory processes in the brain after TBI, several strategies have emerged to control monocyte-derived macrophages that broadly fall into three categories: (1) keeping monocytes and macrophages out of the CNS, (2) employing monocyte-derived macrophages to deliver therapeutics to the CNS, or (3) controlling monocyte-derived macrophage phenotype in the CNS.

Preventing infiltration of monocyte-derived macrophages in animal models of TBI lessened neuropathology and behavioral deficits (Hsieh et al. 2014; Makinde et al. 2017). These studies suggest that preventing monocyte-derived macrophage infiltration into the injured brain may be a logical treatment strategy. In line with this premise, researchers developed a drug-free microparticle-based treatment strategy that directs monocyte homing toward the spleen instead of sites of damage or disease (Getts et al. 2014). This team found that intravenous infusion of negatively charged microparticles would be rapidly phagocytosed by circulating monocytes. Thereafter, the particle-loaded cells would preferentially home to the spleen, where they subsequently undergo apoptosis, rather than traffic to the sites of inflammation (the brain, peritoneum, bowel, or heart in several models of disease or damage). Building on this work, researchers have administered similar negatively charged particles intravenously to mice following a closed head or a focal TBI (Sharma et al. 2020). Particles were administered 2–3 h, 24 h, and 48 h after a TBI and resulted in reduced myeloid cell infiltration, decreased lesion volume, decreased GFAP intensity, attenuated edema, and preserved long-term motor behavior (Sharma et al. 2020). These studies utilized FDA-approved materials and a reasonable treatment timeline that is promising for the field of neurotrauma. This strategy is a novel way to selectively suppress detrimental immune functions and suggests that the depletion of peripheral macrophages along with microglia via CSF1R inhibition may provide additive therapeutic benefits. Indeed, other attempts to broadly suppress the peripheral immune system have resulted in poor long-term neurological outcomes and also increase the risk of secondary infections (Lim and Smith 2007; Hazeldine et al. 2015). Targeting circulating monocytes without broadly suppressing immune function could have utility as a TBI treatment, although this needs to be tested in other species and in clinical situations.

In contrast to preventing monocyte homing to the injured brain, other researchers are attempting to leverage the convenient homing behavior of monocytes to enhance the delivery of therapeutics into the CNS. Indeed, delivery of therapeutics to the injured brain is notoriously challenging. Employing monocytes to carry and deliver therapeutics to injured brain could be a strategic way to locally increase the concentration of beneficial therapeutics in the CNS after TBI. For example, reactive oxygen species are especially detrimental to neuronal health and are a major driver of

secondary injury progression after TBI. Indeed, because the brain's baseline oxygen consumption is much higher than other organs it is especially vulnerable to reactive oxygen species and free radicals. Administration of antioxidants has emerged as a potentially promising therapeutic strategy (Corps et al. 2015). However, these treatment strategies typically require antioxidant administration prior to the injury, within minutes of the injury, or direct injection into the CNS. A more translational approach was employed by the Batrakova lab where they loaded the redox enzyme, catalase, into phagocytosable nanoparticles (Klyachko et al. 2014). These "nanozymes" were taken up by macrophages, were stable intracellularly, and preserved catalase activity. When nanozyme-loaded macrophages were administered intravenously 48 hours after a CNS injury, they reduced neuroinflammation and increased neuronal survival. Additionally, other groups have attempted to use monocytes to deliver other types of therapeutics to the injured brain, including viral vectors (Tong et al. 2016). Other researchers are working to enhance monocyte delivery of therapeutics to peripheral tissues and organs. For example, recent studies suggest that monocytes can carry hypoxia-activated pro-drugs to sites of hypoxia (Evans et al. 2019). Additionally, others are working to develop monocyte "backpacks" that adhere to the surface of homing cells (Anselmo and Mitragotri 2014; Anselmo et al. 2015). These loaded monocytes can home to sites of inflammation and reduce off-target delivery. While these results are promising, much work still remains to determine if the homing potential of loaded monocytes is conserved and the therapeutic efficacy can reduce secondary injury cascades following TBI.

Finally, new strategies are emerging that attempt to control macrophage phenotype as a therapeutic strategy for TBI treatment. As previously mentioned, when not assuming an inflammatory phenotype macrophages can perform a variety of functions that are required for tissue regeneration and stability including angiogenesis, extracellular matrix remodeling, and clearing damaged tissue. Indeed, there are a number of problems in TBI-induced secondary injury that monocyte-derived macrophages are uniquely poised to remedy. Macrophages cultured with CNS slice cultures subjected to oxygen-glucose deprivation rescued hypoxic neurons (Desestret et al. 2013). Macrophages can secrete essential neuronal growth factors including brain-derived neurotrophic factor (BDNF) (Kerschensteiner et al. 1999). Additionally, macrophages may be more capable of clearing toxic components including myelin debris and erythrocytes compared to other brain cells (Hikawa and Takenaka 1996; Kroner et al. 2014; Nairz et al. 2017). Indeed, a number of clinical trials have attempted to deliver monocytes or macrophages to the brain, spinal cord, and other peripheral organs (Chan and Viswanathan 2019). However, methods to control an ideal phenotype over time are necessary for these approaches to reach their full potential.

To address this need, our group has co-developed a strategy to exogenously reprogram monocytes with drug-loaded microparticles. Phagocytosed microparticles degrade over time releasing immunomodulatory drugs into the cytosol of the monocyte-derived macrophages, thus controlling their phenotype over time (Wofford et al. 2019a, 2020). Intracellular microparticles were able to mitigate gene expression and protein secretion related to inflammation when the cells were

cultured in both regular and inflammatory environments. Experiments validating the efficacy of this cell reprogramming strategy in vivo after a TBI are necessary to determine if controlling monocyte-derived macrophage phenotype could have therapeutic efficacy. Moreover, modulating inflammation to a constructive magnitude and duration is likely the first step toward implementing these cells as a therapy. Controlling the extent of homing, phagocytosis, and cytokine secretion will also be imperative if they are to become a clinical treatment. This strategy along with other macrophage-directed TBI therapies offers promising avenues to provide a pro-regenerative environment that can improve the efficacy of rehabilitation and maximize recovery.

13.5   Current and Future Approaches to Mitigate Neuronal and Axonal Loss

Despite the heterogeneity of brain injury, all forms of TBI—whether mild or severe, focal or diffuse—are thought to result in some form of neuronal and/or axonal loss (Meaney et al. 2014; Dixon 2017; Kaur and Sharma 2018). While the location and extent of neuronal or axonal loss depend on the specific injury mechanisms, the presence of such degeneration appears to be ubiquitous. The initial event resulting in TBI causes mechanical tissue deformation that may lead to relatively rapid necrotic cell death (Kaur and Sharma 2018). In focal brain injuries such as hematomas, hemorrhages, and contusions, a large proportion of the initial neuronal loss is concentrated around the injury site (Kaur and Sharma 2018). In diffuse brain injury, inertial impulse loading leads to widespread axonal damage throughout the brain (DAI), as well as acute plasmalemma permeabilization affecting soma in the gray matter (Singleton and Povlishock 2004; Cullen et al. 2011; Johnson et al. 2013b; Meaney et al. 2014; Kaur and Sharma 2018; Keating et al. 2020). The disruption of axonal integrity caused by DAI leads to structural, metabolic, and neurochemical impairments that in turn initiate Wallerian degeneration of the axons, a series of hallmark pathologies that begins with disrupted axonal transport and ultimately leads to complete degeneration and self-destruction (Johnson et al. 2013b; Koliatsos and Alexandris 2019). This pathology generally develops quickly but can persist chronically following even a single injury event in the human brain (Povlishock and Christman 1995; Johnson et al. 2013b). Additionally, across both focal and diffuse TBI, the primary insult that results in initial neuronal death is followed by secondary (or indirect) injury that is driven by events including neuroinflammation, excitotoxicity, oxidative stress, and mitochondrial dysfunction (Wang and Jin 2015; Russo and McGavern 2016; Wofford et al. 2019b; Ladak et al. 2019). This secondary injury further exacerbates the initial neuronal loss resulting from the primary injury, causing a continual neuronal loss for weeks, months, and even years after the initial injury. Thus, acute pathology can lead to widespread axonal degeneration and programed neuronal loss that may greatly exceed any necrotic cell

death that occurs at the time of the initial injury. In addition, the adult CNS has an extremely limited capacity to regenerate following injury (Fry 2001; Illis 2012), owing to an extremely limited capacity for neuronal replacement, an inability of axons to regenerate on their own absent directed guidance, coupled with an inflammation-induced inhibitory environment that further limits regenerative potential (Fry 2001; Kyritsis et al. 2014). The meager regenerative capacity of CNS neurons limits the potential for recovery from TBI. This deficiency has inspired research into the development of a variety of therapies specifically designed to promote neuronal replacement and/or axon regeneration following brain injury.

As described in the previous section on current approaches to rehabilitation, diet and exercise can enhance plasticity—and to some degree neurogenesis—in the brain, facilitating compensatory rewiring to achieve functional recovery. In addition to these contemporary approaches for enhancing plasticity, there are currently three advanced regenerative strategies being explored to replace lost neuronal populations following TBI (Grade and Götz 2017): (1) transplantation of exogenously-sourced stem cells, or differentiated neurons derived from stem cells (Kassi et al. 2018; Clervius et al. 2019; Liao et al. 2019), (2) direct reprogramming of existing cell populations in the brain (Torper and Götz 2017; An et al. 2018; Wang and Zhang 2018), and (3) redirection of endogenous neural stem and/or progenitor cells (NSPCs) into an injured brain region (Bellenchi et al. 2013; Rolfe and Sun 2015; Hayashi et al. 2018; Purvis et al. 2020). The majority of neuronal replacement techniques have been designed to repopulate areas afflicted by focal injury such as cerebral ischemia or focal TBI. Indeed, the first thing that comes to mind for most people when they hear "regenerative therapy" is stem cell transplantation. This technique involves transplanting a bolus of stem cells either directly into or nearby a region of brain injury. Transplanted stem cells have been shown to reduce cognitive and motor deficits caused by experimental TBI (Haus et al. 2016; Spurlock et al. 2017) and to offer neuroprotection in the penumbra by reducing inflammation, mitigating chronic glial activation, and augmenting endogenous neurogenesis in preclinical models of TBI (Kassi et al. 2018; Clervius et al. 2019). While exogenous stem cells have the ability to survive, integrate, and fire action potentials following transplantation into the brain (Tennstaedt et al. 2015; Falkner et al. 2016), differentiation and functional integration to restore lost neural circuitry remains a challenge, and benefits observed in preclinical studies are primarily attributed to release of neurotrophic factors from the transplanted cells (Rolfe and Sun 2015; Yamashita et al. 2017; Xiong et al. 2018). Furthermore, the efficacy of mesenchymal stem cell-derived exosomes for improving functional recovery in a preclinical model of TBI coupled with a lack of differentiation of transplanted cells shows that the benefits of exogenous stem cell transplantation are independent of differentiation or neuronal replacement (Zhang et al. 2020). In fact, one of the most difficult challenges in stem cell transplantation is promoting and ensuring survival and functional integration of the transplanted cells (Liu and Huang 2007; Uemura et al. 2010). Limited cell survival indicates that the beneficial effects of transplanted cells (i.e., growth/neurotrophic factors released from stem cells into the injury site) are likely short-lasting, suggesting that multiple transplants would be required to promote enduring

neuroprotection and regeneration over time. In addition to a lack of cell differentiation and low neuronal survival rates, exogenous stem cell transplantation often comes with the risk of immune rejection (Barker and Widner 2004) and retention of epigenetic memory of the transplanted cells (Kim et al. 2010).

Current regenerative treatments are not limited to exogenous stem cells. Another widely investigated neuronal replacement approach is direct in vivo reprogramming of one somatic cell type (e.g., fibroblasts, astrocytes, NG2 glia, reactive glial cells, early post-mitotic neurons) into another (i.e., a specific neuronal phenotype lost due to injury) without intermediately generating induced pluripotent stem cells (Xu et al. 2015a; Torper and Götz 2017; An et al. 2018; Wang and Zhang 2018). A variety of techniques have been used to induce reprogramming including lineage-specific regulatory transcription factors (Guo et al. 2014; Heinrich et al. 2014) and microRNAs (Ambasudhan et al. 2011; Yoo et al. 2011). Small molecules have also been used for direct reprogramming, bypassing the need for invasive genetic manipulation techniques (Hu et al. 2015; Li et al. 2015). While direct cell reprogramming circumvents issues of immune rejection and tumor formation caused by exogenous transplants, this approach has the potential to introduce dangerous genetic mutations causing deleterious side effects and inherently relies on reducing the quantity of other cell types presumably necessary to brain function. Additionally, although conversion efficiencies have improved over time and have fairly high efficacy (Guo et al. 2014; Gascón et al. 2016), current reprogramming techniques still struggle to reliably generate sufficient numbers of functional, subtype-specific neurons (Torper and Götz 2017; Wang and Zhang 2018).

A third class of neuronal replacement techniques has focused on endogenous NSPCs as a source to replace neurons lost due to brain injury. There is a substantial body of research detailing a variety of different experimental technologies that are designed to redirect endogenous NSPCs in the brain from their site of origin into a site of brain injury (recently reviewed by Purvis et al. 2020) (Purvis et al. 2020). Endogenous neuroblasts are a particularly attractive cell source to replace lost neuronal populations because there is no risk of immune rejection as occurs with exogenous stem cell transplants and there is no requirement for invasive reprogramming techniques for cells to acquire a neuronal phenotype (Bellenchi et al. 2013). Most endogenous neuronal replacement techniques target NSPCs that arise from the subventricular zone as these cells already possess the inherent ability to depart from their site of origin and migrate toward regions of neuronal injury (Ramaswamy et al. 2005; Thored et al. 2007; Lindvall and Kokaia 2015; Kaneko et al. 2018), an observation that has also been reported in the human brain (Jin et al. 2006; Minger et al. 2007). However, the quantity of endogenous neuroblasts that mature into functional neurons in injured regions is insufficient to improve functional recovery without experimental intervention (Kojima et al. 2010; Kernie and Parent 2010; Hayashi et al. 2018). Various pharmacological strategies, biomaterial scaffolds, and emerging tissue-engineering techniques have been created to enhance the migration of subventricular zone-derived NSPCs and promote survival and integration following their arrival into regions of neuronal injury.

Pharmacological strategies include utilization of neurotrophic factors such as epidermal growth factor (Teramoto et al. 2003), stromal-derived factor 1 (Ohab et al. 2006), or BDNF (Schäbitz et al. 2007) to augment NSPC production within the subventricular zone and migration of these cells into injured regions. The majority of pharmacological techniques have administered neurotrophic factors directly into the lateral ventricles (Teramoto et al. 2003; Kolb et al. 2007; Schäbitz et al. 2007), but subcutaneous (Ohab et al. 2006; Popa-Wagner et al. 2010) and intranasal (Ma et al. 2008) administration methods have also shown efficacy at augmenting NSPC migration into regions of injury. The efficacy of neurotrophic factor administration for promoting endogenous NSPC infiltration can be further augmented when the factors are administered in biomaterial hydrogels (Wang et al. 2012). However, such pharmacological interventions have overall shown limited efficacy for altering endogenous NSPC arrival into regions of injury, and the transient effectiveness indicates that repeated administration over time is likely needed to produce clinical efficacy. There is also limited research demonstrating whether these pharmacological techniques can lead to actual functional recovery following experimental TBI. Additionally, while compounds such as growth and neurotrophic factors do provide chemoattractive cues that guide NSPCs toward regions of injury, cells must migrate through harsh, unfamiliar territory to reach distant locations in the brain. For instance, NSPCs often migrate along blood vessels, with branching blood vessels often leading NSPCs astray and preventing a majority of cells from reaching their destination (Kojima et al. 2010; Grade et al. 2013; Hayashi et al. 2018).

This challenge has led to the development of a variety of acellular biomaterial scaffolds designed to directly intercept the subventricular zone neurogenic niche and span directly into an injured brain region, providing a pathway to guide endogenous NSPC migration and circumventing the need for NSCPs to travel along inefficient, indirect routes to reach injured destinations (Oliveira et al. 2018; Purvis et al. 2020). One concern with using endogenous NSCPs to replace lost neurons is that these precursors are multipotent, meaning that they have the potential to differentiate into neurons or glial cells once they arrive at a site of injury (Lim and Alvarez-Buylla 2016). To circumvent this problem, biomaterial hydrogels are often engineered to contain neurotrophic factors to encourage neuronal differentiation upon arrival at an injury site (Fon et al. 2014a, b; Zhou et al. 2016; Clark et al. 2016). Some of the most efficacious of these acellular scaffolds are constructed from laminin, mimicking the material properties of blood vessels that traditionally support endogenous NSPC migration toward regions of injury (Ajioka et al. 2015; Fujioka et al. 2017; Gundelach and Koch 2018). These biomaterial scaffolds have effectively augmented the delivery of new, mature neurons into neuron-deficient brain regions (Wang et al. 2012; Gundelach and Koch 2018; Jinnou et al. 2018; Motamed et al. 2019) and have contributed to behavioral recovery following preclinical brain injury (Clark et al. 2016; Jinnou et al. 2018). These scaffolds are an attractive strategy for endogenous NSPC redirection as they offer an enhanced level of spatial control for cell migration and they can be engineered to mimic signaling mechanisms that typically support endogenous NSPC migration.

An alternative technology that seeks to further enhance NSPC migration from the subventricular zone into injured brain regions is the tissue-engineered rostral migratory stream (TE-RMS) (O'Donnell et al. 2018, 2021; Purvis et al. 2020). This "living scaffold" contains living astrocytes encapsulated within a preformed three-dimensional hydrogel column and is designed to emulate the structure and function of the endogenous rostral migratory stream, thus providing an "implantable highway" that recapitulates the mechanisms with which subventricular zone-derived NSPCs naturally migrate in the adult brain (Winter et al. 2016; O'Donnell et al. 2018, 2021; Katiyar et al. 2018). Similar to the acellular scaffolds discussed above, the TE-RMS is intended for implantation to span from the subventricular zone neurogenic niche toward a region of brain injury. It is predicted that this scaffold will integrate into the brain following implantation, becoming enwrapped by blood vessels that surround and support the scaffold. While further research is needed to demonstrate the ability of this emerging technology to promote functional recovery following injury, the TE-RMS is predicted to be particularly effective at NSPC redirection and functional integration due to the ability of NSPCs to actively communicate with cells contained within the scaffold, thus recapitulating both the physical (e.g., glial tube structure (Gengatharan et al. 2016)) and chemical (e.g., Slit/Robo signaling (Kaneko et al. 2017)) cues that traditionally guide subventricular-zone derived NSPC migration (O'Donnell et al. 2018, 2021). Additionally, by replicating the mechanisms with which NSPCs migrate endogenously, the TE-RMS is designed to *slowly* introduce new neurons into regions of injury over time (rather than introducing a large quantity of new cells all at once as occurs with exogenous stem cell transplantation). It is hypothesized that providing slow, sustained delivery of NSPCs over time will increase cell survival and augment the ability of redirected cells to functionally integrate into existing circuitry as compared to traditional cell transplantation or reprogramming techniques.

In addition to repopulating neuron-deficient brain regions with single neurons, strategies are being explored to replace long-distance axonal tracts that have been lost or damaged as a result of brain injury. Axons are generated early during embryonic development when neuronal targets are close to one another (Tau and Peterson 2010). As the brain develops, the length of axonal pathways increases simultaneous with the growth of bone and connective tissue, leading to the establishment of long-distance "stretch-grown" axonal tracts throughout the brain. Following injury, the adult CNS is generally unable to re-grow long-projecting axons due to a combination of an inhibitory environment, limited intrinsic neuronal growth capacity, and insufficient directed axon guidance to appropriate distant targets (Fawcett 2002; Curinga and Smith 2008; Fitch and Silver 2008; Huebner and Strittmatter 2009). Due to this lack of axon regeneration, the effects of widespread axonal loss in white matter following TBI can be devastating and permanent. Cell transplantation and replacement strategies cannot sufficiently restore the anatomical features of long, damaged axonal pathways. Strategies to encourage targeted and long-distance axon re-growth encompass two broad techniques: reducing the inhibitory environment that prevents axon regrowth (Stichel et al. 1999; Bradbury et al. 2002; Mingorance et al. 2006) and increasing the intrinsic regeneration ability of

axons (Jain et al. 2004; Yip et al. 2010; Liu et al. 2010). Various biomaterial-based tubular conduits have been developed that promote axon regeneration following spinal cord injury in vivo (Tsai et al. 2004; Moore et al. 2006; Silva et al. 2010). While these strategies have demonstrated some success at eliciting axon regeneration, achieving sufficient axonal growth rates and proper targeting in vivo remain major challenges. Therefore, these strategies have had minimal success at functionally restoring lost axonal connections.

In addition to repopulating neuron-deficient brain regions with single neurons, another emerging tissue engineering approach seeks to replace entire circuits that have been lost due to brain injury. For example, micro-tissue engineered neural networks (micro-TENNs) are implantable living scaffolds consisting of neurons and preformed axonal tracts contained within a hydrogel structure that are designed to re-establish long-distance neuronal connections in the brain (Struzyna et al. 2015a, b, 2017). This is the first technology created to simultaneously replace multiple discrete neuronal populations *and* their long-distance axonal connections, introducing the possibility of targeted neurosurgical reconstruction designed to facilitate functional axonal replacement and/or regeneration following brain injury (Struzyna et al. 2015a, b, 2017; Harris et al. 2016). Micro-TENNs have been created with both unidirectional and bidirectional architectures (Struzyna et al. 2015a) to recapitulate specific neuronal tracts including the nigrostriatal (Struzyna et al. 2018) and corticothalamic (Struzyna et al. 2015b) pathways. Notably, micro-TENNs have been shown to exhibit functional connectivity (Dhobale et al. 2018) and have been successfully engineered from human embryonic stem cells (Struzyna et al. 2018). Further advancements in this technology may introduce significant potential to restore functional neuronal connectivity following TBI.

Patients that suffer a severe TBI may experience damage to connections between the deep brain areas that constitute the ARAS—such as those between pons and thalamus or pons and basal forebrain—resulting in prolonged Disorders of Consciousness (DoC) (Edlow et al. 2012, 2013; Snider et al. 2019, 2020). The resultant disruption of activation of higher-order brain circuitry and lack of awareness of self or environment can render traditional cognitive and exercise rehabilitation approaches unworkable. DoC patients require specialized rehabilitative approaches focused on restoring awareness (Schnakers and Monti 2017; Provencio et al. 2020; Edlow et al. 2021). In the future, it may be possible to replace lost connections between select areas of the ARAS, and micro-TENNs for replacing ponto-thalamic afferents offer a focused, promising target for initial testing, with thalamocortical reconstruction as a secondary goal. While these new approaches are exciting, it should be stressed that these technologies are many years away from clinical application. Investigating tissue engineering approaches to regenerative rehabilitation from traumatic DoC will require preclinical studies, and while a preclinical model of traumatic DoC does not currently exist, efforts are underway to make these studies possible (O'Donnell et al. 2019).

In general, there are several questions and challenges that remain to be addressed regarding the ability of the abovementioned technologies to restore lost neuronal populations to regions of brain injury (Aboody et al. 2011; Purvis et al. 2020). One

of the biggest challenges for all neuronal replacement techniques is the ability to generate a sufficient number mature, phenotype-specific neurons to effectively restore function to an injured brain region. Across all neuronal replacement technologies, more research is needed to demonstrate that new neurons appropriately mature, differentiate (i.e., express relevant synaptic structures and synaptic markers), and functionally integrate with preexisting circuitry. There are also numerous manufacturing, safety, and regulatory considerations as these technologies move toward clinical utilization. While significant hurdles remain, these evolving technologies demonstrate considerable potential for neuronal and/or axon tract replacement following TBI.

13.6 Conclusions and Future Directions

Current efforts to promote plasticity and regeneration during rehabilitation from TBI are limited in their potency, specificity, and efficacy. Diet and exercise have been found to provide some improvement to regenerative potential during rehabilitation, but the ceiling is unfortunately low compared to other regenerative therapies under preclinical investigation. Emerging strategies for regenerative rehabilitation, from more traditional therapeutic approaches intended to mitigate anti-regenerative TBI endophenotypes, to more innovative approaches like tissue engineering and microglial depletion/replacement, offer significant potential for removing limits to rehabilitation to maximize functional recovery. Of course, spurring neurogenesis is only part of the challenge—new neurons need to end up where they are needed, integrate within appropriate 3D architecture, mature into correct phenotypes, and form functionally meaningful connections. Just as these nascent regenerative therapies are intended to enhance traditional rehabilitative therapies, those traditional rehabilitative therapies may help to improve the microenvironment of new neurons and therefore indirectly aid in addressing these challenges. For example, exercise and diet can reduce harmful inflammation, promote neurotrophic factor release, and improve plasticity, creating a more favorable environment for the survival and functional integration of implanted neural networks and/or re-routed endogenous neurons. As such, next-generation pro-regenerative therapies should be integrated with the existing—and effective—framework for cognitive rehabilitation after TBI.

Despite the lack of any approved treatment for mitigating neurodegenerative cascades and/or improving recovery from TBI, there are many potential therapeutics and even more potential therapeutic targets under preclinical investigation. For example, device-based plasticity (e.g., transcranial direct current stimulation, transcranial magnetic stimulation) may have a role as an adjunct to traditional rehab but is beyond the scope of the current article. We only discussed a fraction of these potential therapeutics and targets in this chapter, while illustrating the chronic challenges limiting recovery from TBI and the various ways in which regenerative rehabilitation strategies could be employed to maximize recovery. Unfortunately, neurotrauma therapeutics have a history of translational failure, due

in part to the heterogeneity of TBI, but also largely due to an overreliance on rodent models that do not sufficiently recreate the mechanisms and manifestations of the injury to provide reliable efficacy testing. Small animal models of TBI are essential to study specific endophenotypes, identify potential therapeutic targets, and test mechanisms of action for novel therapeutics. However, large animal models that better represent the mechanisms of biomechanical injury, neurophysiological sequelae, and neuropathological distribution of human TBI must be utilized to bridge the gap between small animal models and clinical trials to establish a viable translational pipeline for neurotrauma. By engaging in research addressing the challenges of both plasticity and ongoing injury, targeting specific endophenotypes based on the heterogeneity of TBI, and progressing through a carefully considered translational pipeline from small animals to large gyrencephalic animals, emergent strategies for regenerative rehabilitation can be brought to bear to maximize recovery after TBI.

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