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Chapter 4

Uncovering the Path to Neurodegeneration from Playingfield to Battlefield

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Additional information is available at the end of the chapter

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1. Introduction

It is becoming clear that a history of traumatic brain injury predisposes individuals to neurodegeneration later in life. Even mild recurrent brain concussions, often neglected, can have serious consequences. For example, people engaged in contact-sports such as American football, ice hockey or boxing, and also military personnel, suffer from recurrent brain concussions with no loss of consciousness and no need for hospitalization. However, these people face the possibility of long-term neurocognitive problems with increased risk of developing dementia, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis [1-7]. The mechanisms responsible for the post-traumatic neurodegenerative sequelae are not understood. Understanding the mechanisms, which render the traumatized brain susceptible to neurodegeneration, will guide the development of timed and targeted therapies to prevent the severe neurological decline seen in people at risk.

Recent hypothesis, based on post-mortem observations, attribute the mechanisms underlying the risk relationship between brain injury and neurodegeneration to disturbed metabolism, protein aggregation and axonal injury caused by the impact. Our hypothesis is that the increased susceptibility to neurodegeneration for people with a history of traumatic brain injury is caused by early injury-induced changes in the reactivity of highly specialized immune cells in the brain, called microglia. According to our hypothesis, microglia in the traumatized brain are sensitized to respond more vigorously to a subsequent injurious event. This phenomenon is named microglia priming [8]. Primed microglia are in a "ready-to-go" state which, if triggered by a challenge – for example a systemic infection, surgery or vaccination occurring even later in life –, may outburst in a severe pro-inflammatory event which results in prolonged delirium and cognitive deficit. The pathways that regulate microglia priming are largely unknown. Our group has recently demonstrated that activated complement, a part of the

innate immune system, is one of the triggers to switch the microglial phenotype from resting to primed, sensitizing the brain for accelerated pathology. It is apparent that knowledge of the regulatory pathways that control microglia priming will help to identify new therapeutic targets and guide in the development of novel strategies to treat patients at risk.

In this chapter we review the clinical evidence supporting the increased risk of many athletes and military personnel to develop a neurodegenerative disease. We report the neuropathological changes observed in the post-mortem brain tissue of donors who died of chronic traumatic encephalopathy, considered today as the disease which best represents the neuropathology of the concussive brain. We review the inflammatory changes which occur in the post-mortem brain. We present the current hypothesis of tau pathology and our novel hypothesis of microglia priming as putative mechanisms underlying the increased susceptibility of the traumatized brain to early on and accelerated neurodegeneration, and we discuss how these two hypotheses may co-exist. We focus on the candidate pathways, which may regulate the transition from the resting to the primed state and those, which may regulate the transition from the primed to the active state.

Our effort over the past 10 years has been directed to study the role of the complement cascade in the nervous system [8-14]. To date we have collected evidence which support a role for complement in microglia priming [8] as well as the protective role of inhibitors of complement activation in nerve damage [10,13]. Therefore, in this chapter we focus on the complement system as a potential target for therapy to fight neurodegeneration. We propose our conclusions and future directions towards which research should invest to identify targets, design drugs and test therapies to interfere with the changes occurring in the brain after recurrent trauma and prevent the neurodegenerative sequelae of events which take the life of many athletes and military forces.

2. Clinical evidence

Over the past decades, clinical studies have shown that traumatic brain injury (TBI) is a risk factor for the development of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), manifesting even decades after the trauma [15-19]. For example, a retrospective case-control study showed a link between head trauma with loss of consciousness and AD, with the strongest association in cases without a history of familial AD and in males [15]. Another study on 196 subjects, who developed PD, showed that the frequency of head trauma was significantly higher in cases than controls. Furthermore, the association was higher for men than women [20]. Also in studies performed on twins, the sibling with the onset of PD at a younger age was more likely to have sustained a head injury [16]. Another case-control study of 109 ALS cases and 255 matched controls found that multiple head injuries increased the risk of developing ALS by 11 fold [17].

Additional evidence suggests that also mild forms of TBI, including repetitive concussive injury without loss of consciousness, can trigger chronic neurological problems. The first

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description of traumatic chronic brain damage dates back to 1928 and was termed punch drunk syndrome, due to its association with boxing. In 1937, Millspaugh renamed this syndrome *dementia pugilistica* but only forty-five years later Corsellis et al [21] described the associated neuropathological changes in a case series of fifteen retired boxers. Their findings included cerebral atrophy, neurofibrillary tangles and hypopigmentation of the substantia nigra. More recent studies have shown that such neuropathological changes are not restricted to boxers but also occur in athletes who practiced other contact-sports such as American football, hockey, soccer and professional wrestling. In addition, the same neuropathological changes also occur in victims of physical abuse, in soldiers engaged in military operations and in circus acrobats repeatedly shot out of a cannon [1,6,22-25]. For example, a study in a case series of postmortem brains from U.S. military veterans exposed to blast and/or concussive injury, found evidence of neuropathology similar to that observed in young amateur American football players and a professional wrestler with histories of concussive injuries [26]. In addition, neuropathologically confirmed *dementia pugilistica* was found in American football players with asymptomatic concussions but who played positions, such as lineman, with the greatest exposure to repeated head blows [27], suggesting that also subconcussive trauma leads to chronic neurodegeneration [28].Therefore the neuropathological changes associated with *dementia pugilistica* are the general outcome for individuals with a history of repeated head trauma.

Over the last decade, the chronic brain damage caused by multiple concussive injuries has been renamed chronic traumatic encephalopathy (CTE). CTE is defined as a neurodegenerative disorder, which occurs years or decades after concussive head trauma. In the case of athletes, it often manifests when the sporting career has already ended [22]. The clinical symptoms of CTE vary from mild behavioral changes, such as apathy, to severe cognitive deficits accompanied by movement disorders (e.g. parkinsonism) and neuropsychiatric problems such as disinhibition, aggressiveness and hypomania, often culminating in violent behavior [29] and suicidal acts [22-24]. The heterogeneity of the symptoms is likely reflective of the brain regions affected. Because of the heterogeneity of clinical symptoms of CTE, its extensive overlap with other causes of dementia and the lack of definite guidelines for a clinical diagnosis of CTE, it has been difficult to distinguish between CTE, AD, frontotemporal lobar degeneration (FTLD) or aging, especially in advanced disease. Therefore, the prevalence of CTE in the demented population has been difficult to establish. Early studies suggest that the prevalence of CTE in professional boxers is about 20% [30]. More recent MRI studies showed brain abnormalities, including atrophy, dilated perivascular spaces and diffuse axonal injury, in 76% of professional boxers [31]. Another recent study in a sample of 513 retired players of the American National Football League (NFL) Association, indicated possible cognitive impairment in 35.1% of retirees [32]. A large study completed on 2552 retired players of the American NFL Association found that retired players with three or more reported concussions (34.4%) had a threefold prevalence of significant neuropsychiatric problems compared with retirees without a history of concussion. They also observed an earlier onset of AD in the retirees than in the general American male population [4]. Overall, these findings suggest a link between recurrent concussions and increased risk of dementia. However, definite guidelines for the clinical diagnosis of CTE and future prospective longitudinal studies on

large populations would probably provide more accurate incidence and prevalence of CTE over the coming years.

3. Neuropathological changes

Fourty years ago, Corsellis *et al.* [21] performed the first series of autopsies in professional boxers with *dementia pugilistica* and reported neuropathological changes which were confirmed in 2005 by Omalu *et al.* in the first autopsy from a NFL player [6]. In 2008, the Center for the Study of Traumatic Encephlopathy (CSTE) at Boston University School of Medicine established the CSTE brain bank at the Bedford VA Hospital to collect post-mortem brain and spinal cords of athletes, military veterans and civilians who experienced repetitive concussive injury. In 2009, McKee *et al.* at the CSTE performed a retrospective study on the archival literature and the three new cases available at the brain bank at that time. They verified the neuropathological findings by Corsellis and Omalu in 49 additional cases of confirmed CTE [22]. Today the CSTE collected over 100 brains with histories of repetitive mild traumatic brain injury. Of these, over 60 cases have been fully analyzed and diagnosed with neuropathologically confirmed CTE [33]. Overall, the neuropathological findings are consistent and together make CTE a disorder distinctive from other forms of neurodegeneration.

3.1. Gross pathological changes

Macroscopic examination of the CTE brain shows generalized atrophy of the frontal and temporal cortices, median temporal lobe, diencephalon and mammillary bodies; thinning of the corpus callosum and atrophy of the cerebral subcortical white matter; pallor of the substantia nigra and locus coeruleus. Frequent findings also include cavum septum pellucidum with fenestrations; dilation of the lateral and third ventricles [22]. These latter changes are probably caused by the mechanical shearing forces of the traumatic impact, which produce a fluid wave through the ventricular system.

3.2. Microscopic neuropathological changes

Microscopically, CTE is characterized by abundant neurofibrillary inclusions in the form of neurofibrillary tangles (NFTs), neuropil threads (NTs) and glial tangles (GTs) [22,34-36]. Tangles are intracellular thread-like aggregates of hyperphosphorylated tau protein[37]. Tau is an axonal protein whose normal function is to promote microtubule assembly and stability by binding to microtubules via its microtubule-binding domains conserved in all of its six isoforms. Hyperphosphorylation of tau at its several threonine or serine phosphorylation sites makes tau prone to aggregation in the form of tangles, thereby reducing microtubule binding. This causes disassembly of the microtubules, ultimately resulting in impaired axonal transport and compromised neuronal function [38].

Like in CTE, also in AD and other tauopathies, tau is found in a hyperphosphorylated form and tangle aggregates [38]. In addition, the specific tau isoforms found in CTE are indistinguishable from those found in AD [35]. However, tau deposition in CTE is topographically

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and quantitatively distinct from AD. In CTE NFTs deposition is often found in greater densities compared to severe AD. The distribution of tau NFTs in CTE is irregular and affects primarily the superficial cortical layers with foci at the depths of the sulci, in the diencephalon, basal ganglia and brainstem, and surrounding blood vessels [5,22]. By contrast, NFTs in AD are preferentially distributed in the hippocampus and in large projection neurons in layers III and V of the cortex [39].

Deposition of β-amyloid (Aβ), a major feature of AD pathology, is only found in 40-45% of CTE cases [22]. Furthermore, Aβ deposits in CTE are generally found in the form of diffuse plaques rather than neuritic plaques typically present in the AD brain. Aβ is generated from amyloid precursor protein (APP) by the action of β- and γ- secretases [40]. APP is highly expressed by neurons and is thought to promote axonal sprouting, neurite outgrowth and synaptogenesis, critical for axonal survival after damage [41-44]. However, APP rapidly accumulates in neurons and axons after injury, especially in truncated axonal bulbs [45]. This may stimulate overproduction of Aβ and accumulation in the extracellular space in the form of diffuse plaques [46].

The TAR-DNA-binding protein 43 (TDP-43) is another protein, which aggregates in the neurodegenerative brain. It was initially considered to be a specific neuropathological feature of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) and ALS [47] but it is now apparent that TDP-43 accumulation occurs in several other neurodegenerative diseases including AD [48], dementia with Lewy bodies [49] and CTE [18]. In CTE, TDP-43 immunoreactivity is commonly seen in the frontal and medial temporal cortices, brainstem, diencephalon, substantia nigra pars compacta, amygdala, hippocampus, caudate, putamen, thalamus and hypothalamus [1,18].

Accumulation of α-synuclein, the main protein component of the Lewy body aggregates seen in PD, has not been reported in CTE [22].

Studies in man and animal models have also shown that the complement system is a key component of the neuropathology of severe TBI [50]. Although studies to verify complement activation in repetitive mild TBI or in CTE are lacking, the proved neuropathological role of complement in severe TBI [50] , AD [51,52], prion disease [53], ALS [14,54] and traumatic peripheral nerve injury [9-13], makes complement a likely player also in the neuropathology of concussive injuries and CTE. Complement is a key component of innate immunity. Its activation induces chemotaxis of inflammatory cells, facilitates solubilisation and clearance of opsonised immune complexes, mediates cell lysis, and influences adaptive immunity [55,56]. Activation occurs via three distinct routes: the classical, the lectin and the alternative pathways. The classical pathway is activated by the binding of C1q to antigen-antibody complexes or directly to “danger” epitopes. The lectin pathway is triggered by binding of mannose binding lectin to certain carbohydrates on the pathogen surface, whereas the alternative pathway starts by spontaneous low-rate hydrolysis of C3 which binds to activated factor B on a surface lacking complement inhibitors. Irrespective of the initial recognition pathway, all three routes converge in the cleavage of C3 and downstream in the assembly of the membrane attack complex (MAC) a pore through the cell membrane that can result in lysis of the target cell [55, 56]. Because of the tendency of complement to drift from its target site of activation to adjacent

areas, healthy tissue is equipped with a battery of regulators which keep complement activation in check [55,56].

Deposits of the MAC component C9 have been found on injured neurons after TBI [50] and high levels of fB, C3 and sC5b-9 (soluble MAC) have been detected in the cerebrospinal fluid (CSF) of patients with severe TBI during the first 10 days after trauma [57]. Mice deficient in the C3 or C5 components subjected to traumatic brain cryoinjury showed reduced neutrophils and secondary tissue damage compared to their wildtype littermates [58]. TBI on $fB^{-/-}$ transgenic mice or mice treated with a monoclonal anti-fB antibody showed reduced post-traumatic neuronal cell death, a strong upregulation of the anti-apoptotic mediator Bcl-2 and downregulation of the pro-apoptotic Fas receptor compared to the $fB^{+/+}$ littermates, implicating the alternative complement pathway in the progression of the secondary neuronal death [59,60]. Neurological function after TBI was improved in transgenic mice with brain-targeted overexpression of complement receptor 1-related protein y (Crry), a potent inhibitor of the C3 convertase [61] or in mice treated with a recombinant Crry molecule (Crry-Ig) in which Crry is fused to the non-complement fixing mouse IgG1 Fc region [62]. Further, mice treated with C1 inhibitor, a serine protease inhibitor of the classical and lectin complement pathways, showed reduced neurobehavioural deficits and contusion volume after controlled cortical impact brain injury [63]. Involvement of the terminal complement pathway in experimental TBI has been proven because mice lacking the sole membrane bound regulator of the MAC, CD59a, display increased neuronal cell death and brain tissue destruction compared to $CD59a^{+/+}$ littermates [64]. Our group has initially shown that MAC is a key component of axonal injury, driving Wallerian degeneration after peripheral nerve trauma, and we have also recently proven that exogenous blockers of MAC assembly are neuroprotective in an experimental mouse model of severe closed head injury (unpublished observations).

4. The tau hypothesis

Neuropathological evidence suggest that CTE begins focally at the cortical sulci and perivascularly, spreading slowly over decades to involve the cortex, medial temporal lobe, diencephalon, basal ganglia, brainstem and spinal cord [33]. A recent post-mortem study on 85 donors of the CSTE brain bank classified CTE into four stages based on topographically predictable pattern of tau pathology. Stage I is characterized by perivascular NFTs, and is clinically associated with attention and concentration disturbances. Stage II is characterized by NFTs in superficial cortical layers, in the nucleus basalis of Meynert and locus coeruleus, and is clinically associated with depression, mood swings and short-term memory loss. Stage III is characterized by cerebral atrophy, enlargement of the ventricles and pallor of the substantia nigra. In addition, tau pathology is widespread in the cortex, diencephalon, brainstem and spinal cord. Stage III is clinically associated with memory impairment, executive dysfunction (e.g. problems with planning, organizing, multi-tasking, judgment), depression and irritability. Stage IV is characterized by further brain atrophy, ventricular dilation, pallor of the substantia nigra and locus coeruleus. Tau pathology is widespread also to white matter regions and is accompanied by neuronal loss, gliosis of the cerebral cortex and hippocampal sclerosis.

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Clinically, stage IV presents with severe cognitive problems, memory loss, executive dysfunction, depression, irritability and increased violence [33].

According to the current hypothesis on the initiation and propagation of CTE pathology, the initial brain changes are caused by acceleration and deceleration forces provoked by the traumatic injury which stretch and disrupt neuronal and axonal membranes [65]. These acute cellular changes trigger a cascade of neurochemical dysfunctions, including a deregulated influx of calcium ions and efflux of potassium ions, which depolarize the axonal cell membrane. Depolarization in turn results in the release of excitatory neurotransmitters, including glutamate, which binds to its receptors to fire more action potentials, mediating the influx of more calcium ions. These events trigger an excitotoxic cascade, which depletes energy stores, impairs oxidative metabolism and results in the release of calpains, calcium-dependent proteases, which cause further tissue injury [66,67]. Mechanical shearing forces can also cause disruption of axons and dissolution of microtubules, impairing axonal transport and causing initial swelling followed by axotomy and in the end by Wallerian degeneration [66,67]. These changes are typically located in the cortical sulci, which is where tau pathology begins.

The initial trigger of tau phosphorylation, misfolding, truncation and aggregation into NFTs may be induced by caspases and calpains, released by the stretching of axons at the moment of the traumatic impact. Dissolution of microtubules, as a result of axonal injury, will also release tau, which is then phosphorylated and polymerizes into toxic filaments. The toxic gain of function of tau protein is supported by studies in which human tau overexpressed in lamprey central neurons becomes phosphorylated, accumulate in filamentous deposits and causes microtubule and synapse loss [68,69].

A recent hypothesis suggests that the predictable spreading of tau pathology from stage I to stage IV may be due to transfer of toxic tau species between neurons [70-73]. This can occur via a prion-like propagation of misprocessed tau (reviewed in [74]) and/or via the internalization of small misfolded tau species by bulk endocytosis at the somatodendritic compartment or at the axon terminals. Once exogenous tau is taken up by the neuron, it can be transported anterogradely and retrogradely, accumulating and enhancing tauopathy [75]. In addition to the trans-synaptical transfer of tau, paravenous drainage pathways may also regulate the extracellular levels of tau, Aβ and TDP-43. For example, a recent study using two-photon imaging of small fluorescent tracers showed that the CSF enters the brain parenchyma along paravascular spaces that surround penetrating arteries and that the brain interstitial fluid is cleared along these paravenous drainage pathways. In addition, fluorescent-tagged Aβ was transported along this route whereas impairment of the paravascular pathway suppressed clearance of soluble Aβ [76,77]. These findings suggest that impairment of the paravenous flow by the trauma may contribute to the accumulation of soluble proteins in neurodegenerative diseases. For example, APP may be inefficiently cleared by paravascular pathways and aberrantly cleaved to form Aβ. To date, the role of Aβ in the pathogenesis of CTE is unclear. On the other hand, there is evidence that accumulation of TDP-43 in CTE may be neurotoxic. Recent *in vivo* and *in vitro* studies suggested that overexpression of human TDP-43 and its relocation from the neuron nuclear compartment to the cytoplasm are associated with neurodegeneration and cell death [78-80].

5. Inflammatory changes

In brain donors and experimental animal models, TBI has been associated with increased reactivity of microglia [81,82]. Microglia are the resident macrophages of the brain. Similar to their peripheral equivalent, they are able of phagocytosis, antigen presentation and secretion of inflammatory mediators [83]. They continuously survey the local environment to detect and alert neighbouring cells of non-physiological changes but, despite their very dynamic phenotype, microglia are constantly suppressed in the normal brain [84]. In rodents, primates and humans, microglial hyper-reactivity persists for months to years after TBI, indicative of chronic neuroinflammation [85-89]. This phenotype is remarkably similar to the chronic microglial reactive state of the AD [90] or ageing brain [91].

6. The microglia priming hypothesis

The hypothesis of microglia priming proposes that in the ageing or neurodegenerating brain, microglial cells are chronically sensitized to respond more vigorously to a subsequent injurious event (reviewed in [92,93]). This is profoundly discordant with the behavior of peripheral macrophages, despite their common monocytic lineage origin with microglia. In fact, in the periphery, an initial challenge (e.g. lipopolysaccharide, LPS) conditions macrophages to produce a suppressed response upon restimulation with a second challenge [94].

The notion of microglia priming was initially proposed by Perry in 2007 [95] and later by van Gool [96] based on clinical observations, which reported a deleterious effect of systemic infections on the clinical outcome of elderly people or individuals with neurodegenerative diseases. For example, when elderly patients become delirious during infections, treatment of the infection may go well but the patients emerge with dementia. Similar observations have been made after postoperative delirium in elderly hip fracture patients free from preexisting dementia [97,98]. Other studies have shown that new episodes of cognitive decline in AD cases were concomitant to systemic inflammatory events [99,100]. Systemic infections have also been linked to worse outcome in multiple sclerosis patients [101]. Likewise, lung inflammation is associated with worse neurological outcome in patients with severe brain trauma [102]. According to the priming model, microglia are the cells responsible for the increased susceptibility of the brain to peripheral events.

In prion disease models, microglial priming is evident even in the preclinical stage and LPS challenge exacerbates neuronal death, induces acute cognitive impairment and accelerates disease progression [103-105]. In AD models, repeated LPS challenges exacerbate tau pathology [106], amyloid deposition [107] and inflammation [108]. In the superoxide dismutase (SOD) mouse model of familial ALS, chronic LPS administration exaggerates motor neuron degeneration, precipitates disease progression and elevates production of pro-inflammatory cytokines [109]. In animal models of mild TBI, sepsis worsen post-traumatic mortality and weight loss, motor deficit and cognitive impairments, and further exacerbates neuronal cell death concomitant with over-activation of microglial cells in the peri-lesional area [110]. These

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studies all suggest that microglia priming places subjects at risk for exacerbated neuropathology from an early stage of disease.

Despite the likelihood that microglia priming is an important event in neurodegeneration, its triggers are just starting to be uncovered.

6.1. Transition from resting to primed state

In the normal brain, microglia are dynamic but suppressed by the concerted action of regulatory proteins [84]. We propose that in the aged or traumatized or neurodegenerating brain, microglia become primed due to the abrogation of this suppression or due to the stimulation by pathological proteins.

Suppressing mechanisms include the interaction between neuronally derived proteins such as the glycoprotein CD200 or fractalkine, and their receptors on microglial cells. For example, deletion of CD200 in mice, results in exacerbated microglial activation in several models of inflammation [111,112] whereas enhancing CD200 signaling, by intracerebral injection of the CD200 fusion protein, rescues the overactivated microglial phenotype in aged mice challenged with LPS [113]. *In vitro*, treatment of fractalkine ligand, CX_3CL, to LPS-stimulated microglia attenuates production of inflammatory mediators including IL-1β, IL-6, TNF-α and inducible nitric oxide synthase (iNOS) [114-116]. *In vivo*, fractalkine receptor deficient mice challenged with LPS show amplified microglial expression of IL-1β and prolonged depressive-like behavior compared to wildtype or heterozygote mice [117] whereas inhibition of IL-1β associated inflammatory enzymes blocked the depressive behavior and restored microglia homeostasis [118]. More recent studies proposed that the brain specific microRNA-124 (miR-124) is a potential suppressor of microglial function [119]. Overexpression of miR-124 in bone marrow-derived macrophages resulted in lower levels of TNF-α and iNOS, and a higher level of the anti-inflammatory cytokine TGF-β1, reflecting a quiescent phenotype. On the other hand, knock down of miR-124 attenuated the downregulation of MHC class II and CD45 in microglia and macrophages, again pointing towards a role for miR-124 in maintaining the quiescent phenotype. Ponomarev *et. al.* [119] proposed that the inhibiting activity of miR-124 on microglial function is mediated via C/EBP-α and its downstream effector PU.1. Both transcription factors are involved in differentiation of myeloid and monocytic lineage cells and are downregulated in miR-124 transfected cells.

Microglia priming may also be induced by stimulation with pathological proteins, including protein aggregates such as Aβ and NFTs formed after TBI. For example, *in vitro* studies have shown that exposure to Aβ primes microglia to produce an exaggerated respiratory burst during phagocytosis [120]. In addition, our group has recently shown that deposition of activated complement proteins, known to opsonize damaged axons after trauma [9,11], can also regulate the microglial phenotype [8,121]. In mice, deletion of the major regulator of the C3 convertase, Crry, induces deposition of active C3 in tissue and induces microglia priming, likely by binding to complement receptor 3 (CD11b/CD14) on microglia. Crry deficient mice – with primed microglia – showed exaggerated microglia expression of pro-inflammatory molecules following LPS challenge. Furthermore, we identified evidence of microglia priming in the normal appearing white matter of brain donors with progressive multiple sclerosis and

showed that, in an experimental model of multiple sclerosis, microglia priming is responsible for earlier disease onset and more severe clinical course compared to unprimed mice [8,121].

After recurrent mild TBI, deposition of active complement proteins, including C3, may occur in response to diffuse axonal injury, provoked by accelerating and decelerating forces. Disrupted axonal membranes expose epitopes, which are recognized as "danger" and are targeted by complement proteins. C3 activation products may then bind to CR3 on microglia and induce priming. Other sensors of endogenous tissue damage are toll-like receptors (TLRs) which, in concert with complement proteins [122], recognize as "danger" conserved molecular patterns, whether it is exogenous pathogens or endogenous tissue damage that are detected [123]. TLR2 and 4 are expressed by microglia [124,125] and have been shown to drive inflammation in response to the alarmin high mobility group box-1 protein (HMGB1) [126], a danger-associated molecular pattern (DAMP) molecule which is released by injured cells in a C3-dependent manner [127] within 30 minutes to 6 hours after severe trauma [128]. Although the TLR signaling is predicted to initiate an acute pro-inflammatory response [129], ligation of TLRs may be involved in priming of microglia or in mild (recurrent) trauma.

6.2. Transition from primed to active state

Exposure of primed microglia to an injurious stimulus – i.e. infections, surgery or vaccination – can lead to microglia overactivation, which trigger or accelerate dementia.

Peripheral infections are a widely recognized trigger of cognitive decline and delirium in elderly and AD patients. For example, AD patients who experienced systemic infections, showed concomitant precipitating cognitive decline. The periods of infection were associated with elevated levels of TNF-α. Notably, subjects with low TNF-α levels did not show cognitive decline over the 6-month investigated period [100]. Another study showed that cognitive impairment in AD patients was concomitant to a systemic inflammatory event and was preceded by raised levels of IL-1β [99]. Surgery can also activate the peripheral immune system and trigger an exaggerated inflammatory response in the brain [130]. Postoperative cognitive dysfunction (POCD) is the decline of cognitive performance observed after surgery, with possible long-term effects, such as changes in personality and social integration [131]. POCD has an estimated prevalence of 15-25% in patients over the age of 60, with age as main risk factor [130]. In experimental surgery, aged mice produce significantly higher levels of IL-1β compared to wildtype mice, supporting a role for surgery as a trigger for activation on a brain primed by aging [130]. Vaccination may also be a potential trigger for the transition from primed to active microglial state [132]. This would be especially relevant in view of research into developing vaccinations for AD [133-135]. Drug addictions, such as those reported for some cases of CTE who died from drug overdose, can also regulate the activation of microglia. For example in mice, microglial activation is an early step in methamphetamine-induced neurotoxicity[136]. The use of steroids could also regulate microglial function, but to our knowledge there are no studies which have tested this hypothesis.

An essential question is how the communication between the periphery and the brain occurs. It is well known that peripheral inflammation can activate CNS centers by a number of routes, including the circumventricular organs, vagal afferents, and the brain endothelium (see [137]

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for review). Blood-borne cytokines are thought to diffuse into the brain through fenestrated capillaries and stimulate parenchymal astrocytes to release secondary mediators within the brain such nitric oxide and prostaglandins [138]. Circulating cytokines could also induce the production of pro-inflammatory cytokine by macrophage-like cells in the circumventricular organs and choroid plexus, acting directly or indirectly on neurons which project to the brain parenchyma [139]. Another route of transmission of the peripheral immune message to the brain is via neural afferent pathways. This has been functionally demonstrated by vagal nerve resection experiments that abrogated LPS-induced inflammation and sickness behavior in rodents [140,141]. TLRs, expressed by many immune cells and also by endothelial cells [142], are the obvious responders to systemic infections especially to LPS via the TLR4 and its co-receptors MD2 and CD14 [143]. Therefore they are likely involved in mediating inflammation from the periphery to the brain. For a comprehensive review on TLR signaling see [144].

Overactivation of microglia can ultimately precipitate neuropathology and the clinical outcome of elderly or patients with ongoing neurodegeneration [99,100,145-147]. For example, microglial pro-inflammatory cytokines can stimulate γ-secretase activity and enhance APP levels and amyloidogenic APP processing, potentially exacerbating Aβ pathology [146,147]. Another example comes from studies on the triple transgenic mouse model of AD in which overexpression of IL-1β increases tau phosphorylation [145]. The hypothesis of microglia priming in recurrent mild brain trauma is shown in Figure 1.

7. Therapeutical targets

Currently there is no treatment or therapy to stop or reverse the neurodegenerative sequelae triggered by repetitive concussions or CTE. It is apparent that knowledge of the regulatory pathways that control tau or Aβ pathology, as well as the mechanisms that regulate microglia priming will help to identify new therapeutic targets and guide in the development of novel strategies to treat patients at risk. Therapies could be timed and targeted to intervene early after brain trauma to prevent accumulation of protein aggregates and priming of microglia, for example by administering therapies as prophylactic cover before a sporting match or a military operation. Alternatively, therapies could be targeted to reduce the impact of peripheral insults on primed cells, by monitoring traumatized patients for years post-trauma and administering therapies as prompt interventions for example during systemic infections.

Since the initiating events of CTE include accumulation of hyperphosphorylated tau and in some cases of Aβ, targeting the formation or processing of these protein aggregates would seem to be a promising strategy for treatment. However, AD research is still controversial on the pathological role of tau and APP/Aβ metabolism. Specifically, it is still unclear whether it triggers chronic neurodegeneration or it is simply the epiphenomenon of underlying pathogenic responses to neuronal damage. Over the past decade, our group has collected evidence which support a protective role for complement inhibitors in axonal damage [8-10,13]. We demonstrated that both genetic and pharmacological inhibition of MAC formation protects the peripheral nerve from early axon loss after traumatic injury [9,10,148], and stimulates post-

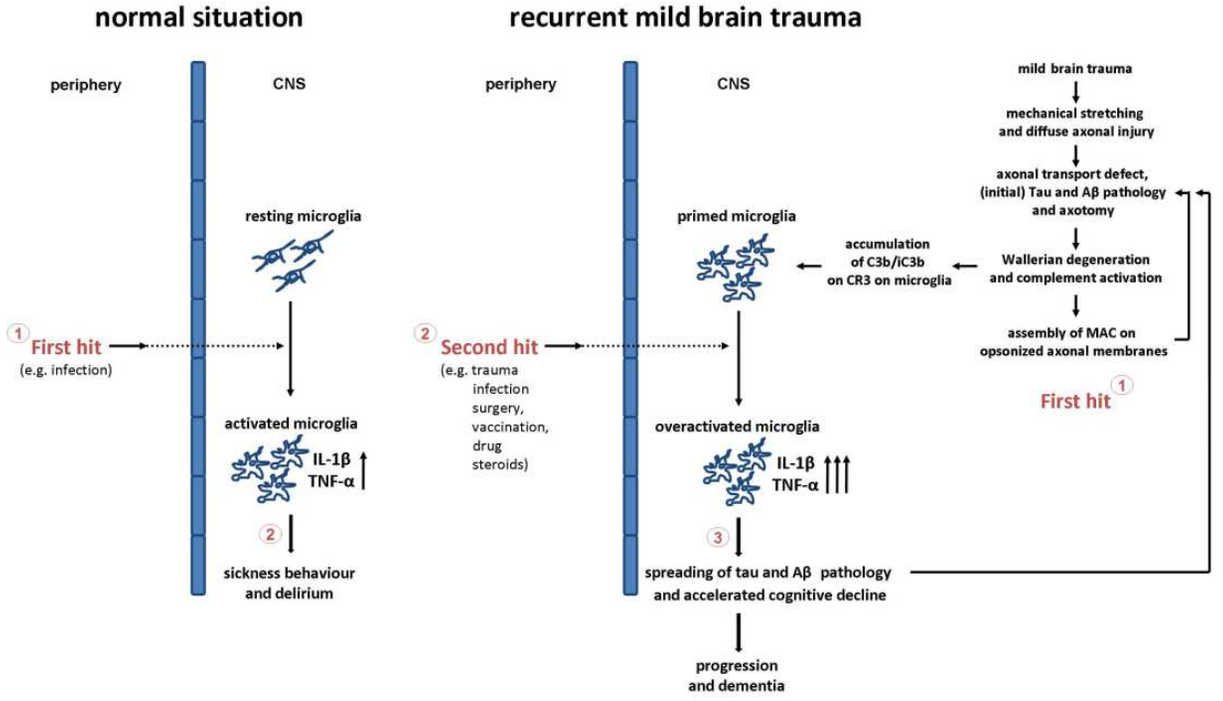

Figure 1. Hypothesis of microglia priming in recurrent mild brain trauma. In the normal situation, a peripheral event, such as an infection, is the first hit to the brain, activating resting microglia to produce inflammatory mediators affecting neuronal function and producing sickness behavior or delirium. In the context of recurrent mild brain injury, mild TBI provokes mechanical accelerating and decelerating forces, which cause axonal stretching and damage fragile axons, producing diffuse axonal injury. Diffuse axonal injury is characterized by disrupted axonal transport and microtubule disassembly, which culminate in the accumulation of tau and APP deposits, forming in some cases Aβ plaques around damaged axons. Impaired axonal transport also results in the formation of axonal swelling and axotomy, triggering Wallerian degeneration. Degenerating axons activate complement, which accumulates on targeted damaged membranes. MAC amplifies tissue injury whereas activated C3 products, C3b/iC3b, bind to their receptor CR3 on microglia. These injury-provoked cellular and neurochemical changes are the first hit which initiates diffuse axonal pathology and triggers priming of microglia for over-activation in response to a second hit. Under these circumstances, a peripheral injurious event, such a subsequent brain trauma, an infection, surgery, vaccination, use of recreational drugs or steroids, is the second hit to the brain that over-activates primed microglia to produce an elevated amount of inflammatory mediators. Pro-inflammatory molecules facilitate spreading of tau and Aβ pathology, driving neuropathology, accelerating cognitive decline and ultimately determining dementia.

traumatic axonal regeneration and functional recovery [149]. In addition, blockade of C3 activation in a mouse model of microglia priming reversed priming and suppressed experimental autoimmune encephalitis (EAE)-induced inflammation [8]. Studies from other groups have also shown that inhibition of C3 activation via the alternative pathway is protective in the experimental mouse model of closed head injury [60,62]. The complement system plays a vital role because it is the first line of defence against pathogens; it generates chemoattractants for inflammatory cells, facilitates solubilisation and clearance of opsonised immune complexes, mediates cell lysis, and influences adaptive immunity [150,151]. Therefore, the stage at which the complement system should be inhibited to block its detrimental effects but maintain its protective functions, is of considerable importance. The problem of systemic inhibition of complement might be overcome by targeting the agent to a specific site or choosing an agent, which allows certain physiological functions of complement while inhibiting others. For

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example, specific blockers of the CR3 receptors on microglia could be useful in modulating microglia priming whereas targeting the terminal complement pathway could be an attractive proposition because it maintains function of the initial steps of the complement cascade, including opsonisation, but it blocks the detrimental effect of the MAC on neuronal membranes. The therapeutic effects of complement inhibitors remain to be tested in experimental models of CTE but it is of high relevance since the recent advent of complement drugs into the clinic makes complement therapy a real option for patients.

Ultimately, prevention is the logical option. To this end, the World Medical Association (WMA) has recommended guidelines to make sport safer. For example, changing the boxing rules to reduce the number of fighting rounds and to introduce the mandatory use of thickly-padded head gear and gloves to diminish the impact from a punch may lower the risk of CTE in boxers (WMA, 2005). However, in sports where repeated blows to the head are unavoidable, appropriate assessment and management of the concussive injury may be critical for preventing long-term consequences. Therefore, a number of recommendations were developed following the 1st (Vienna 2001), 2nd (Prague 2004), 3rd (Zurich 2008) and 4th (Zurich 2012) international consensus conference on concussion in sport [152]. These include removal of an injured athlete from the field and strict monitoring over the first few hours following concussion, whereas returning to the field should follow a stepwise protocol from no activity to light aerobic exercise to full practice and playing.

8. Conclusions and future directions

Although public awareness and media attention on the long-term effects of repetitive brain trauma - especially in professional athletes - have increased in recent years, knowledge of the neurobiology and pathogenesis of this condition is still limited and treatment is not available. However, as the number of professional athletes increases and sports get more competitive, the expectation is that the number of sports-related CTE cases may increase in the future. This prediction together with the potential of CTE to impact a broad population from athletes to veterans to victims of abuse, make CTE an important public health issue. Therefore research should invest in this area. It is clear that accurate clinical diagnostic criteria for CTE alone or mixed disease and prospective longitudinal studies, terminating in autopsy, would be essential to identify patients, develop biomarkers, further our knowledge on the temporal evolution and mechanisms of the disease. It would be also important to determine whether severity of the trauma, number of exposures, age at first exposure, gender, age and race may play a role in the development of CTE.

Functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (voxel-based morphometry) seem a promising tool to monitor brain damage [153]. For example, studies carried out at baseline and repeated immediately after concussion and later until symptom resolution, have shown that fMRI is sensitive enough to detect abnormal activation patterns in varsity hockey and football athletes who have suffered a concussion. Therefore, fMRI could provide an objective way to measure the severity of a concussion and subsequent recovery [153].

In the future, it would also be important to learn from advances made in other fields of neurodegeneration research, based on the consideration that CTE and other neurodegenerative disorders share many neuropathological and neurocognitive traits. For example, CTE patients could be screened for genes associated with AD, or FTLD or ALS. Epidemiological data have already implicated the apolipoprotein E epsilon 4 (APOE ε4) allele, important genetic risk factor for AD, in the development of AD after TBI [154,155] and carriers of the APOE ε4 allele were found to be at increased risk of Aβ accumulation following brain injury [156]. However, large epidemiological studies on the influence of the APOE ε4 allele on the risk of CTE are still missing. Other candidate genes which may turn out to be risk factors for CTE, and therefore predict poor outcome after trauma, may include TARDBP, encoding for TDP-43 involved in FTLD and ALS [157]; the GRN gene, encoding granulin and associated with FTLD [158]; the MAPT gene, encoding for tau and mutated in some cases of FTLD [158].

In addition, the future development of experimental animal models which best mimic the neuropathology seen in man after repeated mild brain injury or CTE, would be crucial to identify the mechanisms of trauma-induced neurodegeneration and test neuroprotective therapies. Currently available animal models of CTE involve the triple transgenic AD mouse because it develops hyperphosphorylated tau and Aβ plaques. However it lacks the widespread neuronal loss which is observed in the human disease [159,160], making experimental observation difficult to translate into the clinic. A recently published transgenic rat model of AD, line TgF344-AD, may represent a better model to study CTE in rodents [161]. This transgenic rat expresses mutant human APP and presenilin-1, each independently associated with early onset familial AD. This AD model expresses all hallmarks of human AD, including Aβ plaques, hyperphosphorylated tau, gliosis and loss of cortical and hippocampal neurons, including age-dependent cognitive deficit [161]. Therefore, these rats may be a good model to monitor Aβ and tau pathology as well as neuronal loss and cognitive impairment after repetitive mild TBI, and also test therapies to stop or reverse post-traumatic neurological deficit. Insights into the mechanisms and treatment options for repeated mild brain injury or CTE, will assist policy makers (e.g. sports league officials or military commanders) to draw accurate guidelines for the prevention and the treatment of brain trauma whether in the playingfield or in the battlefield.

Abbreviations

Aβ β-amyloid

AD Alzheimer's disease

ALS amyotrophic lateral sclerosis

APOEε4 Apolipoprotein E epsilon 4

APP amyloid precursor protein

C1q complement 1q

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C3 complement 3

C5 complement 5

C9 complement 9

CR3 complement receptor 3

CNS central nervous system

Crry complement receptor 1-related protein y

CSF cerebrospinal fluids

CSTE center for the study of traumatic encephalopathy

CTE chronic traumatic encephalopathy

EAE experimental autoimmune encephalomyelitis

fB complement factor B

fMRI functional magnetic resonance imaging

FTLD frontotemporal lobar dementia

FTLD frontotemporal lobar dementia with ubiquitin-positive inclusions

GTs glial tangles

HMGB1 high mobility group box-1

IL-1β interleukin 1 beta

IL-6 interleukin 6

iNOS inducible nitric oxide synthase

LPS lipopolysaccharide

MAC membrane attack complex

miR-124 microRNA-124

NFTs neurofibrillary tangles

NFL national football league

NTs neuropil threads

PD Parkinson's disease

POCD postoperative cognitive dysfunction

sC5b-9 soluble complement 5b-9, MAC

SOD superoxide dismutase

TBI traumatic brain injury

TDP-43 transactivation responsive region deoxyribonucleic acid-binding protein 43

TGF-β1 tumor growth factor beta 1

TLRs toll-like receptors

TNF-α tumor necrosis factor alpha

WMA world medical association

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