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Brain injury, neuroinflammation and Alzheimer's disease

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With as many as 300,000 United States troops in Iraq and Afghanistan having suffered head injuries (Miller, 2012), traumatic brain injury (TBI) has garnered much recent attention. While the cause and severity of these injuries is variable, severe cases can lead to lifelong disability or even death. While aging is the greatest risk factor for Alzheimer's disease (AD), it is now becoming clear that a history of TBI predisposes the individual to AD later in life (Sivanandam and Thakur, 2012). In this review article, we begin by defining hallmark pathological features of AD and the various forms of TBI. Putative mechanisms underlying the risk relationship between these two neurological disorders are then critically considered. Such mechanisms include precipitation and 'spreading' of cerebral amyloid pathology and the role of neuroinflammation. The combined problems of TBI and AD represent significant burdens to public health. A thorough, mechanistic understanding of the precise relationship between TBI and AD is of utmost importance in order to illuminate new therapeutic targets. Mechanistic investigations and the development of preclinical therapeutics are reliant upon a clearer understanding of these human diseases and accurate modeling of pathological hallmarks in animal systems.

Keywords: traumatic brain injury, Alzheimer disease, neuroinflammation, chronic traumatic encephalopathy, tauopathy, amyloid-beta peptides, neuronal loss, transgenic rat model

INTRODUCTION TO TRAUMATIC BRAIN INJURY

It is estimated that as many as 300,000 U.S. troops in Iraq and Afghanistan have suffered head injuries (Miller, 2012). In the general population, roughly 1.7 million brain injuries are reported, leading to more than 52,000 deaths (Faul et al., 2010). The cause and severity of these injuries is variable, but severe cases can lead to lifelong disability or even death. It is estimated that as many as 5.3 million people have traumatic brain injury (TBI)-associated disabilities. Moreover, TBI-associated direct and indirect costs are approximated to be more than 75 billion dollars a year (Coronado et al., 2012). Beyond the effects of acute injury, troubling new findings indicate that even minor brain injury can predispose to neurodegeneration and dementia in later life. While aging is generally accepted to be the greatest risk factor for Alzheimer's disease (AD), it is now widely recognized that a history of TBI is a key risk factor for the disease (Sivanandam and Thakur, 2012). For example, incidence of AD is significantly increased in individuals who have a documented history of TBI (Sivanandam and Thakur, 2012).

ALZHEIMER'S DISEASE: SEVERITY OF THE PROBLEM

Largely due to population-wide increases in life-span, AD is rapidly becoming the public health crisis of our time. There are currently over three million Americans afflicted with the disease, a figure that is projected to increase to nearly nine million Americans and over 100 million world-wide by 2050 (Brookmeyer et al., 2007). Unfortunately, AD prevalence will continue to rise in parallel with the aging of the world's populations unless something is done (Brookmeyer et al., 2007). Because of the long prodromal phase leading to clinical manifestation of AD, TBI early in life would not impact AD diagnosis until decades later. At that point, the full impact of TBI-induced AD on soldiers and their families would place an unprecedented burden on the United States public health system.

AD is a devastating, mind-robbing neurodegenerative disease that is defined at autopsy by β-amyloid plaques [chiefly comprised of amyloid-β (Aβ) peptides], neurofibrillary tangles (NFTs), and widespread loss of cortical neurons (Selkoe, 2001). Although these features are pathognomonic of AD, Alois Alzheimer himself originally identified a third pathology—inflammation of the brain's glial supporting cells (Alzheimer et al., 1995). While one interpretation is that all forms of neuroinflammation are deleterious for the aging brain, we have hypothesized that re-balancing inflammatory signals as opposed to shutting them off completely might limit AD progression (Town et al., 2005; Weitz and Town, 2012). In that vein, it has been shown that genetic or pharmacologic blockade of a key pathway responsible for suppressing inflammation, the transforming growth factor-beta

(TGF-β)-Smad 2/3 signaling cascade, reduces AD-like pathology. Specifically, peripheral blockade of the TGF-β-Smad 2/3 signaling pathway leads to brain penetration of peripheral macrophages and amelioration of the defining pathology of AD—β-amyloid plaques—in the Tg2576 transgenic mouse model of cerebral amyloidosis (Town et al., 2008; Rezai-Zadeh et al., 2009; Town, 2009; Gate et al., 2010). These results have importance, because there is currently no treatment or cure available for AD.

TRAUMATIC BRAIN INJURY AND ALZHEIMER'S DISEASE RISK

The term "TBI" encompasses a wide variety of traumas. In fact, any form of brain injury is broadly classified as a TBI. Nevertheless, brain traumas can grossly be divided into two categories: (1) closed head injuries (where a rapid deceleration or blow to the head causes brain damage) or (2) penetrating head injuries (caused by a foreign object piercing the skull). Closed head injuries can come in the form of skull fractures, brain contusions caused by brain-skull impact, hematomas, and diffuse axonal injuries brought on by shearing forces. Notably, closed head injuries associated with concussions from contact sports and shockwave blasts from improvised explosive devices have garnered much recent attention. TBIs may range from mild to severe, with about 75% of injuries coming in the form of concussions or other mild TBIs (Hyder et al., 2007).

Pathological analyses of human TBI tissue have led to variable conclusions as compared with animal model studies. This is likely attributable to both the heterogeneity of the injury itself and methods of tissue collection. Nonetheless, several broad patterns of results have emerged. One of the most notable findings concerns the association between AD pathological features and TBI. For example, by examining cortical regions from TBI patients with survival times ranging from 4 h to several years, increased expression of the amyloid precursor protein (APP; which gives rise to the Aβ peptides that comprise senile plaques) has been demonstrated in the acute response to brain injury (Roberts et al., 1994; Graham et al., 1996). Another study reported that APP could be used as a general marker for axonal injury in human post-mortem material (Gentleman et al., 1993). More recently, Aβ deposits have been observed in roughly a third of TBI patients and as early as 2 h after injury (Ikonomovic et al., 2004). Overall, the conclusions were that Aβ plaques developed rapidly after injury, while NFTs formed during the chronic phase of disease (Ikonomovic et al., 2004). Follow-up studies have documented that severe TBI can induce Aβ42 (widely regarded as the more pathogenic species of the peptide), potentially leading to increased risk of AD later in life (DeKosky et al., 2007).

A very recent study examined survivors of a single TBI 1–47 years after the trauma, and reported that NFTs and Aβ pathology were present in approximately one-third of these patients. Such findings demonstrate the long-term consequences of a single TBI event (Johnson et al., 2012). On the other hand, more chronic, mild TBIs are associated with a distinct pathology, termed chronic traumatic encephalopathy (CTE) (McKee et al., 2010). Notably in CTE, NFTs are typically found with gliosis, but β-amyloid deposits are less obvious as compared with AD (Costanza et al., 2011). Unfortunately, CTE has become increasingly recognized in war veterans, boxers, and athletes in other impact sports (McKee et al., 2010; Costanza et al., 2011; Gavett et al., 2011; Stern et al., 2011; Goldstein et al., 2012; Miller, 2012; Shively et al., 2012; McKee et al., 2013). These troubling findings are no doubt cause for concern.

MECHANISMS TO ACCOUNT FOR THE RISK RELATIONSHIP BETWEEN TRAUMATIC BRAIN INJURY AND ALZHEIMER'S DISEASE

As mentioned above, TBI is a strong epigenetic risk factor for development of AD later in life. Strikingly, several defining AD pathological hallmarks have been observed following TBI in patient brains and in numerous TBI animal models. In addition to neuronal and synaptic loss (Kotapka et al., 1992; Smith et al., 1997; Maxwell et al., 2010), AD-characteristic lesions include accumulation of Aβ peptides, hyper-phosphorylated tau protein (the principle component of NFTs), and persistent microgliosis. A key question that arises from these observations is: what are the mechanism(s) responsible for development of AD in patients with a clinical history of TBI?

Aβ PATHOLOGY AND SPREADING

Aβ deposits and widespread axonal Aβ accumulation have been found in patients' brains shortly after TBI (Roberts et al., 1991, 1994; Graham et al., 1995; Smith et al., 2003a; Ikonomovic et al., 2004; Uryu et al., 2007) and are still present many years after a single severe head trauma or repetitive mild TBIs (Tokuda et al., 1991; Johnson et al., 2012). Remarkably, following TBI, the major type of soluble and deposited Aβ peptide found in patients' brains is Aβ42, well-known for its neurotoxicity and high propensity to aggregate (Gentleman et al., 1997; DeKosky et al., 2007). Several studies have described dramatic APP accumulation in swollen axons after TBI, which would provide an abundant source of substrate for Aβ production (Gentleman et al., 1993; Sherriff et al., 1994; Gorrie et al., 2002). Axonal swelling observed after TBI has been ascribed to cytoskeletal alteration and interruption of protein transport (Maxwell et al., 2003).

In an attempt to clarify mechanisms of plaque appearance after brain trauma, several non-transgenic rodent and rabbit models have been utilized. While these animal models have proved useful to characterize axonal Aβ accumulation after TBI, wild-type rodents and rabbits did not manifest cerebral β-amyloid plaques. This is likely owed to the fact that these TBI animal models have relatively low abundance of brain endogenous Aβ species that do not reach a critical threshold for aggregation (Lewen et al., 1995; Pierce et al., 1996; Bramlett et al., 1997; Hoshino et al., 1998; Iwata et al., 2002; Stone et al., 2002; Hamberger et al., 2003; Abrahamson et al., 2006). Another strategy has been to rely on transgenic mice that develop age-dependent Aβ plaque deposition. Unlike their wild-type counterparts, these animal models have contributed to our understanding of mechanisms of Aβ deposition after TBI. Like their non-transgenic counterparts, these transgenic mice manifest axonal Aβ post-TBI. However, and unlike wild-type animals, these transgenics demonstrate enhanced accumulation of β-amyloid plaques after TBI (Smith et al., 1998, 1999; Hartman et al., 2002; Uryu et al., 2002; Abrahamson et al., 2009). Moreover, studies in various animal models indicate that expression of amyloidogenic

β- and γ-secretases and their substrate—APP—is increased after TBI, suggesting that Aβ peptides are generated *de novo* following brain trauma (Cribbs et al., 1996; Blasko et al., 2004; Chen et al., 2004; Nadler et al., 2008; Loane et al., 2009; Tran et al., 2011a; Yu et al., 2012). Thus, long-lasting elevation of Aβ following TBI is likely to result in Aβ pathology, up to and including senile plaque formation.

An important related concept is the idea of Aβ pathology "spreading." Interestingly, studies from Mathias Jücker's laboratory and others have shown that intracerebral infusion of brain extracts containing aggregated Aβ can initiate Aβ deposition in brains of APP transgenic mice (Kane et al., 2000; Walker et al., 2002; Meyer-Luehmann et al., 2006; Eisele et al., 2009). Furthermore, it has been shown that Aβ seeds can migrate between axonally interconnected areas, suggesting that Aβ peptides can spread from the site of injection to other brain regions (Walker et al., 2002; Eisele et al., 2009). These results provide a potential mechanism for TBI-induced amyloid pathology spreading from the site of the TBI to other brain areas classically associated with AD-type pathological lesions but not directly subjected to the TBI.

TBI has also been shown to induce tauopathy. In that regard, it is important to note that a similar process has been described for spreading of NFTs by axonal transport after injection of abnormally folded tau filaments into a mouse model of cerebral amyloidosis (Clavaguera et al., 2009). Such findings suggest the possibility of abnormal tau protein seeds that spread following TBI. These results are summarized in **Table 1**.

NEUROINFLAMMATION

In patients' brains as well as in experimental animal models, TBI has been associated with microglial activation (Carbonell and Grady, 1999; Koshinaga et al., 2000; Davalos et al., 2005; Morganti-Kossmann et al., 2007; Ojo et al., 2013). The early phase of microglial activation in response to brain injury is accompanied by increased levels of interleukin-10 and TGF-β, which are generally regarded as anti-inflammatory cytokines that are capable of mediating neural protection and regeneration (Knoblach and Faden, 1998; Csuka et al., 1999; Tyor et al., 2002). Anti-inflammatory microglia with phagocytic properties have the potential to clear Aβ species and β-amyloid plaques; remarkably, Aβ-containing microglia have been found in association with plaques after TBI (Chen et al., 2009). Such findings suggest that microglia play a principle role in remodeling cerebral amyloid following brain injury (Giunta et al., 2008).

Depending on their activation state, microglia can be deleterious or beneficial in the context of cerebral amyloid deposition (Town et al., 2005; Weitz and Town, 2012). However, in rodents, primates and humans, microglial activation persists for months or even years after TBI, indicative of chronic neuroinflammation (Smith et al., 1997; Csuka et al., 2000; Gentleman et al., 2004; Nagamoto-Combs et al., 2007; Nagamoto-Combs and Combs, 2010; Ramlackhansingh et al., 2011; Shitaka et al., 2011). Chronic cerebral inflammation is typically associated with increased abundance of proinflammatory cytokines such as IL-1β, TNF-α and IL-6 and an array of chemokines (Stover et al., 2000; Morganti-Kossmann et al., 2001; Rothwell, 2003; Dietrich et al., 2004; Israelsson et al., 2008). This phenotype is remarkably similar to the low-level pro-inflammatory, chronic microglial activation state that occurs in AD and ultimately fails to restrict amyloid deposition. Additionally, it has been extensively reported that aging microglia undergo structural deterioration and cellular senescence, which likely predicts poor Aβ clearance aptitude (Flanary and Streit, 2004; Fiala et al., 2005; Hickman et al., 2008; Njie et al., 2012). Furthermore, TBI is classically followed by oxidative stress and hypoxia, which are known to stimulate microglia and astrocytes and induce release of IL-1β, TNF-α, interferon-γ and IL-6 (Luth et al., 2001). These pro-inflammatory cytokines can stimulate γ-secretase activity and enhance APP levels and amyloidogenic APP processing, potentially exacerbating Aβ pathology (Tamagno et al., 2003; Blasko et al., 2004; Liao et al., 2004; Rogers et al., 2008; Agostinho et al., 2010). In addition, increased expression of presenilin-1 and nicastrin in TBI-activated microglia has been described in mice, reinforcing the probable implication of microglia in post-injury Aβ pathology (Liao et al., 2004; Nadler et al., 2008). Altogether, these mechanisms could perpetrate a chronic vicious cycle involving inefficient activation of microglia, cerebral Aβ accumulation and spreading, and development of AD-type pathology. In summary then, the early inflammatory response after TBI may negatively impact AD pathology later on.

ANIMAL MODELS: PRESENT AND FUTURE

The development of clinically-relevant animal models is critically important to enable future study at the intersection of TBI and AD research. Animal models of AD fail to exhibit some of the key pathological earmarks of the human syndrome, even after significant brain injury (Uryu et al., 2002; Tran et al., 2011a,b). For example, one of the principle symptoms lacking in transgenic mouse models constructed with mutations that cause early-onset familial AD is fulminant neuronal loss (Duyckaerts et al., 2008). For while most transgenic mouse models display amyloid deposition, and some exhibit tau pathology, almost all do not have appreciable neuronal death (Duyckaerts et al., 2008). For instance, the principle readouts after TBI in a widely-used mouse model of AD, the 3× Tg-AD mouse, consist primarily of hyperphosphorylated tau and β-amyloid plaques, because the model does not allow insight into the widespread cortical neuronal loss observed in the human disease (Tran et al., 2011a).

By contrast, we have recently published a novel rat transgenic model of AD, line TgF344-AD. This transgenic line expresses mutant human APP and presenilin-1, which are each independent genetic causes of early-onset familial AD. Notably, this rat displays the full spectrum of human AD hallmarks, including cerebral amyloidosis, tauopathy, gliosis, and most importantly, large-scale apoptotic loss of neurons in cortical and hippocampal regions. Moreover, these animals display significant age-dependent cognitive disturbance (Cohen et al., 2013). The precise reason(s) for the differences between this new transgenic rat model and analogous mouse models are unclear. Rats are four-to-five million years closer to humans on the evolutionary tree than mice. In addition, rats, like humans and unlike mice, have all six tau isoforms. Therefore, rats have a physiology

Table 1 | Alzheimer's disease-type lesions induced by various TBIs in humans and in animal models.

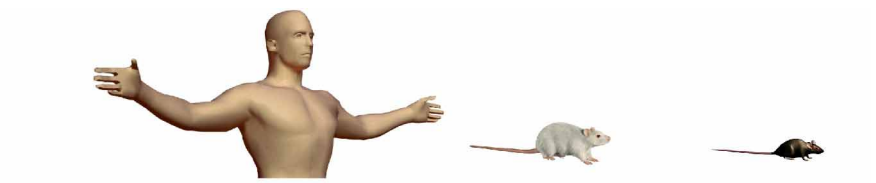
AD-like lesions induced by TBI	Species	Type of injury involved	References
Amyloidogenic APP processing and Aβ accumulation	Mouse	Focal	Cribbs et al., 1996
		CCI	Hartman et al., 2002; Abrahamson et al., 2006, 2009; Loane et al., 2009; Tran et al., 2011a; Yu et al., 2012
		Closed head	Nadler et al., 2008
	Rat	Mild compression contusion	Lewen et al., 1995
		Lateral fluid-percussion	Pierce et al., 1996; Bramlett et al., 1997; Hoshino et al., 1998; Iwata et al., 2002
		Cortical electro-coagulation	Luth et al., 2001
		Traumatic axonal	Stone et al., 2002
		CCI	Blasko et al., 2004
	Rabbit	Rotational acceleration	Hamberger et al., 2003
	Pig	Rotational acceleration	Smith et al., 1999; Chen et al., 2004
	Human	Single severe head	Roberts et al., 1991, 1994; Gentleman et al., 1993, 1997; Graham et al., 1995; Ikonomovic et al., 2004; DeKosky et al., 2007; Uryu et al., 2007; Johnson et al., 2012
		Dementia pugilistica	Tokuda et al., 1991; Schmidt et al., 2001
Tauopathy	Mouse	Repetitive mild	Yoshiyama et al., 2005; Ojo et al., 2013
		Blast and/or concussive	Goldstein et al., 2012
		CCI	Tran et al., 2011a
	Rat	Lateral fluid percussion	Hoshino et al., 1998
	Pig	Rotational acceleration	Smith et al., 1999
	Human	Repetitive mild trauma/Dementia pugilistica Severe closed head Single acute brain Blast and/or concussive	Tokuda et al., 1991; McKenzie et al., 1996; Geddes et al., 1999 Zemlan et al., 1999 Smith et al., 2003b; Johnson et al., 2012 Goldstein et al., 2012
Neuroinflammation	Mouse	Repetitive mild	Shitaka et al., 2011; Ojo et al., 2013
		Fluid percussion	Carbonell and Grady, 1999
		CCI	Israelsson et al., 2008
		Laser-induced focal ablation	Davalos et al., 2005
	Rat	CCI	Smith et al., 1997; Koshinaga et al., 2000
	Monkey	Surgical lesion	Nagamoto-Combs et al., 2007
	Human	Various	Gentleman et al., 2004; Morganti-Kossmann et al., 2007; Ramlackhansingh et al., 2011; Johnson et al., 2013

(Continued)

Table 1 | Continued

AD-like lesions induced by TBI	Species	Type of injury involved	References
Neuronal loss/apoptosis	Mouse	CCI	Lewen et al., 2001; Yatsiv et al., 2005; Tehranian et al., 2006
		Weight-drop	Hutchison et al., 2001
	Rat	Fluid percussion injury	Cortez et al., 1989; Dietrich et al., 1994; Rink et al., 1995; Sinson et al., 1997; Yakovlev et al., 1997; Conti et al., 1998; Pierce et al., 1998; O'Dell et al., 2000; Raghupathi et al., 2002
		CCI	Sutton et al., 1993; Clark et al., 1997, 2001
		Weight-drop	Pravdenkova et al., 1996
	Human	Various	Mantyla, 1981; Bigler et al., 1992; Clark et al., 2000; Ng et al., 2000; Liou et al., 2003; Hausmann et al., 2004; Nathoo et al., 2004

AD, Alzheimer's disease; CCI, controlled cortical impact.



	Man	AD Rat	AD Mouse
Lifespan	> 70 years	2-3 years	2-3 years
Tau isoforms	6	6	3
Tauopathy	+	+	-
Cerebral Amyloidosis	+	+	+
Neuronal Death	+	+	-
Potential for TBI/CTE Investigation	limited to post mortem	high	limited by lack of neuronal death

FIGURE 1 | Modeling the risk relationship between traumatic brain injury and Alzheimer's disease. Presence (+) or absence (–) of various pathological features is indicated. AD, Alzheimer's disease; TBI, Traumatic Brain Injury; CTE, Chronic Traumatic Encephalopathy.

that is more similar to the human and may be more permissive to neurodegenerative disease. For these reasons, it will be highly informative to test whether TBI precipitates earlier neuronal loss and tauopathy in this line of rats. Moreover, the behavioral correlates of neuronal damage and loss can be carefully related in a way that more closely approximates human trauma and associated cognitive decline. Specifically, if TBI leads to neuronal loss in the long term, these rats might be used to determine if therapeutic intervention(s) could be introduced to attenuate or prevent neurodegeneration and cognitive impairment (**Figure 1**).

CONCLUSIONS AND FUTURE DIRECTIONS

The correlation between brain injury and neurodegenerative disease is now well-established (Szczygielski et al., 2005; Shively et al., 2012). The combined problems of TBI and AD will become

increasingly significant burdens to society. Both diseases will require early identification in the form of imaging or biomarkers to allow for therapeutic intervention at the earliest possible stages. Unfortunately, a treatment or therapy does not currently exist for either disease. A thorough, mechanistic understanding of the precise relationship between TBI and AD is of utmost importance in order to illuminate new therapeutic targets. However, as we have highlighted, key questions remain regarding the precise mechanisms linking the many forms of brain injury with precipitation of AD-type neurodegeneration.

These mechanistic investigations and the development of pre-clinical therapeutics will rely critically on a clearer understanding of both human pathologies. A key limiting factor is the large gap in our knowledge of the link between post-mortem observations in humans after TBI with animal model systems. Part of the uncertainty can be attributed to limitations inherent to experimental models of TBI. Therefore, it is expected that more precise modeling of pathological hallmarks in animal models will allow us to fill the knowledge gap. Specifically, it will be critical to develop models that accurately mimic the forces impacting the human brain under a variety of circumstances (Morales et al., 2005; Blennow et al., 2012).

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