Regulation by glycogen synthase kinase-3 of inflammation and T cells in CNS diseases

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Elevated markers of neuroinflammation have been found to be associated with many psychiatric and neurodegenerative diseases, such as mood disorders, Alzheimer's disease, and multiple sclerosis (MS). Since neuroinflammation is thought to contribute to the pathophysiology of these diseases and to impair responses to therapeutic interventions and recovery, it is important to identify mechanisms that regulate neuroinflammation and potential targets for controlling neuroinflammation. Recent findings have demonstrated that glycogen synthase kinase-3 (GSK3) is an important regulator of both the innate and adaptive immune systems' contributions to inflammation. Studies of the innate immune system have shown that inhibitors of GSK3 profoundly alter the repertoire of cytokines that are produced both by peripheral and central cells, reducing pro-inflammatory cytokines, and increasing anti-inflammatory cytokines. Furthermore, inhibitors of GSK3 promote tolerance to inflammatory stimuli, reducing inflammatory cytokine production upon repeated exposure. Studies of the adaptive immune system have shown that GSK3 regulates the production of cytokines by T cells and the differentiation of T cells to subtypes, particularly Th17 cells. Regulation of transcription factors by GSK3 appears to play a prominent role in its regulation of immune responses, including of NF-κB, cyclic AMP response element binding protein, and signal transducer and activator of transcription-3. *In vivo* studies have shown that GSK3 inhibitors ameliorate clinical symptoms of both peripheral and central inflammatory diseases, particularly experimental autoimmune encephalomyelitis, the animal model of MS. Therefore, the development and application of GSK3 inhibitors may provide a new therapeutic strategy to reduce neuroinflammation associated with many central nervous system diseases.

Keywords: glycogen synthase kinase-3, GSK3, inflammation, cytokines, EAE, multiple sclerosis, mood disorders, neurodegenerative diseases

INTRODUCTION

The immune system responds to infection or damage to attempt to restore homeostasis. Immune system responses are classified as adaptive or innate based on the activation timing and antigen presentation. Innate immune cells provide the first line of defense against pathogens, acting as sentinels to detect signs of distress. Upon the first signs of distress, activated sentinel cells of the innate immune system release soluble mediators of inflammation, such as cytokines and chemokines, to clear the pathogen. On the other hand, adaptive immunity is a slower response dependent on T cells and B cells reacting with antigen-presenting cells. Together, the innate and adaptive immune systems contribute to the process of inflammation, and dysregulation of either system can contribute to a variety of pathological conditions. Importantly, immune cell activation is usually rapidly reversed by anti-inflammatory and immunosuppressive functions in order to avoid damaging the host. Although the immune responses are mainly thought to be triggered in the periphery, there are also organ specialized immune cells, which exhibit unique immune function.

There is growing recognition that inflammatory signaling molecules have profound influences on many functions of the central nervous system (CNS). These effects include actions of both the innate and adaptive immune systems, as well as glia within the CNS (Raison et al., 2006; Dantzer et al., 2008; Miller et al., 2009; Miller, 2010). While it is important to remember that many of these neuroimmune actions are beneficial, as well as necessary, for a healthy CNS, research has been particularly focused on detrimental effects of neuroinflammation in association with psychiatric and neurodegenerative diseases. This has raised awareness that much remains to be learned about signaling mechanisms that regulate neuroinflammation, and that targeting regulators of neuroinflammation may prove to be a useful therapeutic strategy capable of affecting a diverse array of CNS disorders. Recent evidence is reviewed here demonstrating that glycogen synthase kinase-3 (GSK3) is an important regulator of both innate and adaptive immune system mediators that can profoundly affect the CNS.

NEUROINFLAMMATION

In contrast to other organs, the brain does not display a classical immune response but is capable of mounting its own inflammatory responses. The blood brain barrier serves to separate the brain's local inflammatory responses from systemic inflammation by limiting, but not entirely preventing, the penetration of

peripheral inflammatory mediators and immune cells (Lampson, 1987; Fuchs and Bullard, 1988). This unique protection from systemic inflammation likely developed to protect neurons, since they are long-lived cells with limited capacity to recover from noxious insults. However, although for many years the immune privileged status of the CNS was misinterpreted to mean exclusion of immune cells, it is now evident that "immunosurveillance is an integral part of the functioning brain" (Schwartz and Shechter, 2010). In the CNS, microglia are the sentinel cells that constantly survey the environment and become activated to produce an inflammatory response to infection or damage (Kim and De Vellis, 2005). In conjunction with microglia responses, astrocytes are also well-established to contribute to neuroinflammatory responses (Lieberman et al., 1989; Hamby and Sofroniew, 2010). Acutely or chronically, these glial responses could be beneficial or detrimental because they allow microglia to migrate to afflicted sites where they produce cytokines and growth factors that can contribute to the recovery, or be deleterious, for affected neurons, and may contribute to many diseases of the nervous system (Matyszak, 1998; Correale and Villa, 2004; Campbell, 2005; Cartier et al., 2005; Hauwel et al., 2005; Kim and De Vellis, 2005; Imitola et al., 2006; Kielian, 2006; Schwartz et al., 2006). Thus, it is crucial to identify mechanisms that induce and regulate neuroinflammation. The prevalence of markers of inflammation associated with psychiatric and neurodegenerative diseases suggest there is prolonged activation and impaired down-regulation of neuroinflammation in these conditions, including influences by the peripheral immune system. Thus, it remains difficult to dissociate distinct contributions of the peripheral and CNS inflammatory systems, making it challenging to identify therapeutic targets to control neuroinflammation.

GSK3 PROMOTES NEUROINFLAMMATION

Inflammatory responses were first found to be promoted by GSK3 following stimulation of several types of toll-like receptors (TLR) in monocytes and peripheral blood mononuclear cells (Martin et al., 2005). This demonstrated that GSK3 is necessary for full stimulation of the production of several pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-α (TNFα), and inhibitors of GSK3 greatly reduced the production of pro-inflammatory cytokines. Remarkably, *in vivo* administration of GSK3 inhibitors provided protection from endotoxin shock sufficiently enough to allow the survival of most mice from an otherwise lethal (LD_{100}) dose of lipopolysaccharide (LPS; Martin et al., 2005). This study showed for the first time the powerful ability of GSK3 inhibitors to shift the balance of the inflammatory response from pro-inflammatory to anti-inflammatory, and revealed the therapeutic potential for these drugs in inflammatory conditions (Martin et al., 2005). These findings raised the novel possibility that inhibitors of GSK3 may prove to be beneficial in conditions involving inflammation (Jope et al., 2007).

The pro-inflammatory action of GSK3 and anti-inflammatory actions of its inhibitors have been demonstrated with a variety of inflammatory molecules and extended to several cell types (Gao et al., 2008; Wang et al., 2009a,b, 2011a; Gurrieri et al., 2010; Kao et al., 2010; Klamer et al., 2010; Baarsma et al., 2011; for

review Beurel et al., 2010), including cells in the CNS that contribute to neuroinflammation. In LPS-stimulated microglia, GSK3 promotes the production of cytokines and other inflammatory molecules, such as IL-1β, TNFα, IL-6, IL-8, RANTES, CXCL-10, and nitric oxide (NO; Luna-Medina et al., 2005; Hashioka et al., 2007; Beurel and Jope, 2009b; Cheng et al., 2009; Huang et al., 2009; Yuskaitis and Jope, 2009). As in the periphery, NF-κB is thought to be a critical transcription factor targeted by GSK3 for promoting neuroinflammation (Yuskaitis and Jope, 2009; Wang et al., 2010), as discussed below. In addition to microglia, GSK3 also promotes cytokine production by astrocytes (Park et al., 2006; Beurel and Jope, 2010), in particular IL-6, and promotes the IL-6/signal transducer and activator of transcription-3 (STAT3)-dependent activation of glial fibrillary acidic protein (GFAP), which is a critical marker of astrogliosis (Beurel and Jope, 2008, 2009b). Tolerance is a mechanism whereby cells dampen their response to two consecutive identical stimuli, and the promotion of IL-6 production by GSK3 was shown to also involve GSK3 counteracting LPS-induced tolerance for IL-6 production in astrocytes (Beurel and Jope, 2010).

Besides regulating cytokine production in glia, GSK3 also promotes migration and activation of glial cells (Beurel and Jope, 2008; Yuskaitis and Jope, 2009). Inhibition of GSK3 promotes microglial survival during oxygen–glucose deprivation (Chong et al., 2007) and treatment with erythropoietin both inhibited GSK3 and supported microglia survival (Li et al., 2006), actions that may contribute to minimizing permanent CNS damage.

Recently, inhibition of GSK3 was suggested to promote stabilization of the brain blood barrier (Ramirez et al., 2010). This was based on findings in cultured brain microvascular endothelial cells that GSK3 inhibition reduced the production of several inflammatory molecules and monocyte adhesion to and migration across cytokine-stimulated cells. Furthermore, *in vivo* inhibition of GSK3 reduced leukocyte adhesion to brain endothelium under inflammatory conditions.

PRO-INFLAMMATORY MECHANISMS OF GSK3
GSK3 CAN PROMOTE PRO-INFLAMMATORY CYTOKINE PRODUCTION THROUGH NF-κB ACTIVATION

Regulation of the inflammatory transcription factor NF-κB was found to be key for the pro-inflammatory actions of GSK3 (Martin et al., 2005; Gong et al., 2008a,b; Yuskaitis and Jope, 2009; Wang et al., 2010). Inhibitors of GSK3 reduced TLR-induced production of inflammatory cytokines by inhibiting the transcriptional activation of NF-κB (Martin et al., 2005). This supported previous reports that GSK3 is necessary for the full transcriptional activity of NF-κB (Hoeflich et al., 2000), and that GSK3 supported NF-κB transcriptional activity in a promoter-specific manner (Steinbrecher et al., 2005). This selective action of GSK3β on NF-κB-induced inflammatory gene expression may facilitate the therapeutic anti-inflammatory uses of GSK3 inhibitors since it indicates that inhibition of GSK3 will not interfere with all the actions of NF-κB. The role of GSK3 in the regulation of NF-κB in inflammation was further expanded by the demonstration of a role for GSK3 in the desensitization of LPS-induced inflammatory signaling by TNFα (Park et al., 2011).

GSK3 BLOCKS ANTI-INFLAMMATORY CYTOKINES

Conversely to inflammatory signaling, GSK3 reduces the production of the anti-inflammatory cytokine IL-10, and inhibitors of GSK3 increased anti-inflammatory cytokine production (Martin et al., 2005; Hu et al., 2006; Antoniv and Ivashkiv, 2011; Ren et al., 2011). Inhibition of IL-10 production by GSK3 was reported to involve a competition for limiting amounts of CBP/p300, with GSK3-promoted activation of NF-κB depleting the amount of CBP/p300 available for cyclic AMP response element binding protein (CREB)-induced IL-10 production (Martin et al., 2005; Hu et al., 2006; Hofmann et al., 2010). It was also proposed that the down-regulation of IL-10 production by GSK3 contributes to the synergistic inflammatory signaling induced by co-treatment with interferons and TLR ligands (Hu et al., 2006; Lin et al., 2008). Furthermore, the production of IL-10 by IFNβ, thought to be important for the anti-inflammatory therapeutic properties of IFNβ in multiple sclerosis (MS) patients, was shown to be dependent on inhibition of GSK3 (Wang et al., 2011a).

TGFβ1 also has anti-inflammatory properties. Although the mechanism whereby TGFβ1 suppresses inflammation remains unclear, it has been proposed that TGFβ1 can antagonize the production of certain pro-inflammatory cytokines in response to inflammatory stimuli by inhibition of GSK3 to promote β-catenin signaling (Dai et al., 2011). Additionally, it is also thought that because TGFβ is required for the induction of regulatory T cells (Tregs), which produce IL-10, the anti-inflammatory action of TGFβ is mediated through its induction of Tregs *in vivo* where Tregs counteract the action of the pro-inflammatory effector CD4$^+$ T cells and of the pro-inflammatory cytokines (Campbell and Koch, 2011). Recently, it was shown that inhibition of GSK3 increases the anti-inflammatory properties of Tregs by increasing β-catenin levels in response to TGFβ (Graham et al., 2010). GSK3 was also shown to regulate activation of Smad transcription factors (Fuentealba et al., 2007; Sapkota et al., 2007; Guo et al., 2008; Liang et al., 2008; Heldin et al., 2009), indicating a direct effect of GSK3 on the TGFβ-induced signaling pathway.

Therefore, it appears that NF-κB activation is a key pro-inflammatory pathway promoted by GSK3, whereas CREB and β-catenin are inhibited by GSK3 to maintain low levels of anti-inflammatory molecules.

COOPERATION OF GSK3 WITH mTOR TO REGULATE CYTOKINE PRODUCTION

A number of inflammatory signaling pathways converge on GSK3 to regulate cytokine production, reinforcing the concept that GSK3 has a central role in the regulation of cytokine production and other inflammatory outcomes. GSK3 promotes the activation of myeloid dendritic cells (DC) and their secretion of cytokines (Ono et al., 2007; Rodionova et al., 2007; Hoarau et al., 2008; Larabee et al., 2011; Liu et al., 2011; Wang et al., 2011b). During DC generation, inhibition of the mammalian target of rapamycin (mTOR) confers resistance to maturation, whereas inhibition of mTOR prior to TLR activation enhanced pro-inflammatory cytokine production. GSK3 activity was shown to be inhibited by the mTOR pathway and modulated the capacity of DCs to produce pro-inflammatory cytokines (Turnquist et al., 2010; Brown et al., 2011; Wang et al., 2011b). The production of cytokines by DCs also

influences the differentiation of T helper (Th) cells (Ono et al., 2007) that are highly dependent on cytokines to differentiate toward different lineages (O'Shea and Paul, 2010).

GSK3 INFLUENCES IMMUNE CELL FATE

Glycogen synthase kinase-3 also regulates other transcription factors involved in inflammation besides NF-κB and CREB, particularly STATs. This allows GSK3 to control the amplitude and the duration of inflammatory responses. Thus, it was shown that GSK3 participates in the synergistic action of IFNγ on LPS-induced signaling in part by modulating the downstream signaling induced by IFNγ, the JAK/STAT pathway. Although GSK3 was not involved in the short term activation of IFNγ-induced STAT1 (Beurel and Jope, 2008), inhibitors of GSK3 blocked IFNγ-induced STAT1 activation at longer times in macrophages through SHP2 derepression (Tsai et al., 2009). Furthermore, a differential role of GSK3 in regulating the activation of different STAT subtypes was uncovered, as GSK3 was found to promote STAT3 and STAT5 activation, while GSK3 did not affect STAT6 activation (Beurel and Jope, 2008). This regulation of STAT3 activation by GSK3 may be particularly relevant for the signaling induced by IL-6, as well as for the production of IL-6 in response to both LPS and the combination LPS and IFNγ (Beurel and Jope, 2009a,b).

Although GSK3 has been mainly thought of as a regulator of cytokine production, an unexpected role of GSK3 was found to be in the regulation of the differentiation of Th subsets. Cytokines are key determinants for Th differentiation toward a particular lineage and STAT3 is a crucial instigator of the differentiation toward Th17 cells (O'Shea and Paul, 2010). Thus, it was found that GSK3 is required for Th17 cell production, perhaps due to both promoting IL-6 production and STAT3 activation (Harrington et al., 2005), although other processes likely also contribute to this action of GSK3 on Th17 cells (Beurel et al., 2011). This recent discovery that GSK3 promotes Th17 cell differentiation provides a new step in the understanding of the GSK3-dependent regulatory mechanisms of the immune system. Th17 cells are critical for the pathogenicity of many autoimmune diseases (Langrish et al., 2005; Ivanov et al., 2006; Komiyama et al., 2006), so the finding that inhibition of GSK3 blocked Th17 cell differentiation provides a new avenue of therapeutic intervention that may contribute to controlling Th17-driven diseases.

SURVIVAL ADVANTAGES OF BLOCKING GSK3 ACTIVITY

Glycogen synthase kinase-3 has long been known to promote cell death mediated by the intrinsic apoptotic pathway, whereas it protects from extrinsic apoptosis (Beurel and Jope, 2006; Sun et al., 2008). Several apoptosis-regulating properties of GSK3 have been identified in the immune system. Thus, for example, during the clonal expansion of activated T cells, there is induction of the activated T cell death (ACTD; Kondrack et al., 2003), which is thought to be due to a loss of access to survival signals. ACTD is thought to be critical to prevent autoimmune responses, but need to be tightly regulated because complete elimination of responding T cells would confer increased susceptibility to infections. GSK3 was shown to be required for ACTD and inhibition of GSK3 promotes survival of T cells (Sengupta et al., 2007). GSK3 was also found to be critical to induce apoptosis of DC (Hoarau et al., 2008).

Altogether, GSK3 promotes pro-inflammatory cytokine production by regulating a network of transcription factors. GSK3 also receives signals in order to finely tune this cytokine production. But GSK3 also, intrinsically to immune cells, affects their maturation, differentiation, and survival rendering GSK3 an attractive target for therapeutic interventions.

INFLAMMATION IN PSYCHIATRIC DISEASES

The mood disorders depression and bipolar disorder are prevalent diseases with a high lifetime incidence of ∼20% in the US (Greden, 2001; Belmaker and Agam, 2008), but current treatments are often inadequate, as many patients do not respond or prematurely terminate treatment (Krishnan and Nestler, 2008). Much evidence has shown that mood disorders are associated with alterations of the immune system, especially increased markers of inflammation. For example, extensive evidence has demonstrated that inflammation promotes susceptibility to depression and impairs responses to antidepressants. Elevated serum levels of inflammatory cytokines, such as the cytokines IL-6 and TNFα, have been reported in patients with major depression or bipolar disorder (Anisman and Merali, 2003; O'Brien et al., 2004a, 2006, 2007; Schiepers et al., 2005; Raison et al., 2006; Dantzer et al., 2008; Miller et al., 2009; Miller, 2010). A significant portion of people develop depression following the therapeutic bolstering of immunity by interferon-α administration (Reichenberg et al., 2001; Wright et al., 2005; Prather et al., 2009). Depressive symptoms thought to be due to cytokines also occur after a mild activation of the innate immune system (Raison et al., 2006; Dantzer et al., 2008; Miller et al., 2009). Antidepressants are less effective in patients with activated inflammation, and antidepressant responses are improved in some patients by co-treatment with anti-inflammatory drugs (O'Brien et al., 2007; Roumestan et al., 2007; Dantzer et al., 2008; Miller et al., 2009; Rivest, 2009). Administration of drugs that inhibit the actions of cytokines or their signaling pathways, such as cyclooxygenase inhibitors and etanercept, improve mood in patients with inflammatory diseases (Mendlewicz et al., 2006; Muller et al., 2006; Tyring et al., 2006). These links demonstrating inflammation increases susceptibility to mood disorders have been recapitulated in rodents. For example, administration of individual inflammatory cytokines, or of LPS to induce inflammation, causes depression-like behaviors in rodents that are reversed by antidepressant administration (Dantzer and Kelley, 2007). Increased cytokine levels or administration of cytokines in rodents or humans have been reported to induce behavioral changes with characteristics similar to mood disorders (Licinio and Wong, 1999; Hayley et al., 2005; Simen et al., 2006). Importantly, psychological stress in both humans and rodents is sufficient to activate the production of inflammatory cytokines and to induce depressive symptoms (Anisman and Merali, 2003; O'Brien et al., 2006; Gabbay et al., 2009). Thus, there is much evidence that inflammation can precipitate depression and impair therapeutic responses. While it remains to be determined if inflammatory cytokines contribute to the onset or represent an outcome of mood disorders, it has been suggested that reducing inflammation may contribute to therapeutic interventions based on the depressive effects that cytokines can produce and on evidence that classical antidepressants are anti-inflammatory (Reynolds et al., 2005; Schiepers et al., 2005).

While many investigators have focused on actions of the innate immune system in depression, the impact of the adaptive immune system, especially T cells, remains poorly understood even though the innate and adaptive immune systems are highly integrated. Examinations of the effects of stress and depression on T cell responses demonstrated altered proliferation of peripheral blood mononuclear cells in response to stimulation with T cell mitogens in samples from patients with depression (Bartrop et al., 1977; Kronfol et al., 1983; Schleifer et al., 1983, 1984; Stein et al., 1991). T cell alterations also were indicated by *in vivo* measurements of T cell-mediated immune function in depressed patients (Hickie et al., 1993; Sephton et al., 2009). Studies of mechanisms implicated increased Fas-mediated T cell apoptosis (Eilat et al., 1999; Ivanova et al., 2007; Szuster-Ciesielska et al., 2008), reduced T cell responses to glucocorticoids that are elevated in major depression (Pariante and Miller, 2001), or increased cytokine levels that modulate T cell subtype production and responses (Cope et al., 1994, 1997; Lee et al., 2008). These and additional reports (Miller, 2010) of altered T cells in depression led to demonstrations that T cells mediate the negative impact of depression on health outcomes in depressed patients with infectious diseases or cancer.

Substantial evidence indicates that dysregulated GSK3 contributes to mood disorders (Li and Jope, 2010): brain GSK3 is abnormally active in postmortem human prefrontal cortex from depressed subjects (Karege et al., 2007), GSK3 is activated in mouse brain in the learned helplessness model of depression (Polter et al., 2010), antidepressants inhibit GSK3 (Li et al., 2004), reducing GSK3 activity ameliorates depression-like behaviors in rodents (Gould et al., 2003; Kaidanovich-Beilin et al., 2004; O'Brien et al., 2004b; Beaulieu et al., 2008), and abnormally active GSK3 in GSK3 knockin mice increases susceptibility to depression-like behaviors (Polter et al., 2010). Since inflammation is a candidate cause of increased susceptibility to depression, it is notable that GSK3 strongly promotes inflammation in the periphery (Martin et al., 2005) and CNS (Beurel and Jope, 2009b, 2010; Yuskaitis and Jope, 2009), which is reduced by GSK3 inhibitors. GSK3 knockin mice showed also a mild exacerbation of their depressive-like behavior in response to LPS administration compared to wild-type mice (Polter et al., 2010). Therefore, part of the therapeutic effects of the mood stabilizer lithium, as well as of antidepressants that inhibit GSK3, may come from their anti-inflammatory effects following inhibition of GSK3. However, further investigations are needed to definitively test if promotion of inflammation by GSK3 contributes to mood disorders.

INFLAMMATION IN NEURODEGENERATIVE DISEASES

Inflammatory markers, particularly increased levels of inflammatory cytokines and activated microglia and astrocytes, have been reported in many neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis, as well as MS, which is generally considered an autoimmune disease (Amor et al., 2010; Glass et al., 2010; Philips and Robberecht, 2011). This may be due to impaired mechanisms of inflammation resolution or persistent stimulation of inflammatory responses, such as may be caused by the generation of "danger" signals from degenerating neurons that activate damage-associated molecular patterns (DAMPs). Activation of the

inflammatory system has beneficial effects, such as phagocytosis of dead cells and production of factors bolstering neuronal function and neurogenesis. However, it is generally thought that long-term inflammation associated with neurodegenerative diseases exacerbates the diseases by releasing signaling molecules that impair neuronal function and survival, increasing the impairments associated with the primary disease lesion.

ALZHEIMER'S DISEASE

Alzheimer's disease is a severe, progressive neurodegenerative disease with a growing prevalence and only modestly effective therapies are available. There are two classical neuropathological features of AD: intraneuronal filamentous aggregates of hyper-phosphorylated tau and other proteins called neurofibrillary tangles, and extracellular deposits of aggregated amyloid-β (Aβ) peptides called amyloid plaques. The levels of many cytokines, such as IL-1β, IL-6, and TNFα, and chemokines are upregulated in AD, as previously reviewed (Akiyama et al., 2000; Block and Hong, 2005; Sastre et al., 2006). This inflammation and increased cytokine production is also exhibited by transgenic mouse models of AD (Benzing et al., 1999; Matsuoka et al., 2001). Activation of astrocytes and microglia and the ensuing production of inflammatory molecules has been reported to be stimulated by degenerating neurons, neurofibrillary tangles, and Aβ and other cleavage products of amyloid precursor protein, and activated astrocytes and microglia are found surrounding amyloid plaques in AD brain (Bach et al., 2001; Combs et al., 2001; Ho et al., 2005). Inflammation may contribute to the increased risk for AD following traumatic brain injury or diabetes, both of which can cause increased inflammation, as well as to the prevalent co-morbidity of depression with AD, since much evidence links inflammation with depression as discussed above. Many investigations have reported evidence that hyperactive GSK3 in AD contributes to both of its neuropathological hallmarks by phosphorylating tau and promoting Aβ production (Jope and Johnson, 2004; Lesort and Jope, 2010) and to neuronal death (Beurel and Jope, 2006; Mines et al., 2011). These many links between AD and GSK3 have led to a substantial effort to develop GSK3 inhibitors for treating AD (Hooper et al., 2008; Martinez and Perez, 2008; Muyllaert et al., 2008; Hernandez et al., 2010). GSK3 inhibitors reduce inflammatory mediators implicated in AD, such as NO (Yuskaitis and Jope, 2009) and inflammatory cytokines (Beurel et al., 2010). Considering the evidence for inflammation contributing to AD pathology and that GSK3 promotes inflammation, interventions with GSK3 inhibitors may also be beneficial by reducing the inflammation that is thought to exacerbate neurodegenerative processes in AD.

PARKINSON'S DISEASE

Like many other neurodegenerative diseases, substantial evidence indicates that neuroinflammation contributes to PD, and its models in rodents. For example, activated inflammatory processes in the substantia nigra have been implicated in the loss of dopaminergic neurons in PD patients and in animal models of PD (Esposito et al., 2007; Hald et al., 2007; Mcgeer and Mcgeer, 2008; Barnum and Tansey, 2010), and some (Gagne and Power, 2010), but not all (Wahner et al., 2007; Driver et al., 2011), studies have indicated that non-steroidal anti-inflammatory drug

use reduces the risk of PD. However, the innate immune system may not be acting alone in promoting PD. Evidence has been reported of activated T cells in the substantia nigra in rodent PD models (Kurkowska-Jastrzebska et al., 1999) and post-mortem PD brains (Brochard et al., 2009), and elimination of T cells attenuated dopaminergic neuron loss in rodent PD models (Brochard et al., 2009). As in AD, there is evidence both that GSK3 contributes to neuronal degenerative processes in PD (King et al., 2001; Chen et al., 2004) and that neurotoxic mechanisms, such as α-synuclein in PD, activate GSK3 (Duka et al., 2009; Yuan et al., 2010). Thus, inhibition of GSK3 may protect susceptible neurons from degeneration and reduce the inflammation that appears to promote neurodegenerative processes in PD.

MULTIPLE SCLEROSIS

Multiple sclerosis appears to result from aberrant innate and adaptive immune system actions in the CNS, likely initiated by an autoimmune response that causes inflammation, demyelination, and neuronal degeneration (Weiner, 2008). Thus, in contrast to the other neurodegenerative diseases that appear to initiate with neuronal insults, MS is initiated by aberrant actions of the adaptive immune system. Studies of MS patients and of the animal model of MS (experimental autoimmune encephalomyelitis, EAE) have implicated the Th17 and Th1 subsets of Th cells as key mediators of the disease (Langrish et al., 2005; Ivanov et al., 2006; Tzartos et al., 2008). This first wave of adaptive immune system activity and inflammation seems to be followed by a second wave of neuroinflammation, and both are thought to contribute to the death of oligodendrocytes. Thus, inflammation with activation of microglia and astrocytes are well-established components of MS and targeting the response of these cells has been explored (Kang et al., 2010).

The crucial inflammatory component of MS suggests that inhibitors of GSK3 may provide some amelioration of the disease. Indeed, in EAE, administration of lithium to inhibit GSK3 effectively prevents the disease and almost completely terminates ongoing disease (De Sarno et al., 2008; Beurel et al., 2011). Notably, inhibitors of GSK3 also prevent production of Th17 cells that are critical for the disease (Beurel et al., 2011), suggesting that GSK3 inhibitors provide at least two actions that may contribute to alleviation of MS.

CONCLUSION

Glycogen synthase kinase-3 is now well-established to contribute to inflammatory processes in the periphery, and growing evidence indicates that GSK3 also promotes neuroinflammation. This action appears to be largely the result of GSK3 promoting the activities of transcription factors that mediate inflammatory responses, particularly NF-κB and STAT3. Furthermore, although both paralogs of GSK3, GSK3α and GSK3β, share many common actions, there is increasing evidence that they can also have non-redundant functions (Hoeflich et al., 2000; Liang and Chuang, 2006; Force and Woodgett, 2009). Most of the studies on inflammation focused on GSK3β, mainly because more tools have been developed for studying GSK3β. However, there is a differential role of GSK3α and GSK3β in the regulation of IL-6 production (Beurel and

Jope, 2008). Therefore, identifying differential role for GSK3α and GSK3β may be a promising avenue for future studies. Importantly, GSK3 has been implicated in pathological processes of psychiatric and neurodegenerative diseases that also exhibit increased inflammatory activation, such as mood disorders, AD, PD, and MS. Thus, GSK3 may provide a feasible therapeutic target to control inflammation along with ameliorating other pathological processes in several diseases of the CNS.

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