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Regulation of inflammation and T cells by glycogen synthase kinase-3: Links to mood disorders

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Abstract

Substantial evidence has implicated a role for the immune system in regulating the susceptibility to depression. Proinflammatory cytokines have been shown to be involved in promoting the induction of depressive behavior both in humans and mice, opening new avenues for therapeutic intervention. Because glycogen synthase kinase-3 (GSK3) was recently found to control the production of proinflammatory cytokines, and for many years GSK3 has been implicated in mood disorders, it has been proposed that the proinflammatory action of GSK3 may contribute to the promoting susceptibility to depressive behavior. Moreover, besides regulating cytokine production, GSK3 also promotes the differentiation of proinflammatory subtypes of Th cells, which are sufficient to induce depressive behavior in mice. Although the clear involvement of the immune system during depressive behavior still needs to be firmly demonstrated, there is growing evidence for the involvement of inflammation in the induction of depressive behavior.

I. GSK3 in mood disorders

Despite its name that suggests a role in the regulation of glycogen, glycogen synthase kinase-3 (GSK3) is an ubiquitous Ser/Thr kinase that is involved in a wide variety of cellular functions [1–3]. Besides inhibiting glycogen synthesis, GSK3 regulates proliferation, apoptosis, inflammatory responses, migration, microtubules, and a variety of other cellular processes. Among the effects of GSK3, one of its most critical actions may be to control more than 50 transcription factors, which are responsible in part for the effects of GSK3 on many different cellular functions. Many signaling pathways, but especially the PI3K/Akt pathway, converge on GSK3 to mediate phosphorylation on serine residues in the two GSK3 isoforms, serine-21 in GSK3 α and serine-9 in GSK3 β , that causes inhibition of GSK3. Besides inhibition of GSK3 by serine phosphorylation, GSK3 actions are also regulated by its cellular localization and protein-protein interactions [3]. Due to its regulation of key cellular functions, GSK3 has been implicated in a diverse variety of diseases, such as cancer, cardiovascular diseases, neurodegenerative diseases, and psychiatric diseases. Because GSK3 is inhibited by lithium, a mood stabilizer that has been used therapeutically in patients with bipolar disorder for 60 years, the role of GSK3 has been especially studied in mood disorders, the focus of this review [4].

GSK3 has a profound involvement in mood disorders. (a) Mood stabilizers and antidepressants inhibit GSK3 [5,6]. Both fast acting (ketamine) [7] and conventional

antidepressants [4], and antipsychotics [4] have been shown to promote the inhibitory serine phosphorylation of GSK3. Lithium exerts dual actions to inhibit GSK3, both by competing with Mg^{2+} binding in the active site of the enzyme, and also by promoting the inhibitory serine phosphorylation of GSK3 [8]. (b) Depression-like behaviors in rodents are reduced by pharmacological [9,10] or genetic [11–14] reduction of GSK3 activity. Lithium has been shown to reduce depressive behaviors in mice as efficiently as knocking down one allele of GSK3 β [13] and to promote the effects of the antidepressant serotonin reuptake inhibitors [15,16]. Other small molecule GSK3 inhibitors also attenuated depressive behaviors in rodents [10,11,13]. (c) Serotonergic signaling deficiency, which may occur in depression, activates GSK3 [6]. (d) GSK3 is inhibited by neurotrophins, such as brain-derived neurotrophin factor (BDNF) [17] that may be deficient in depression [18]. (e) Conversely, GSK3 knockin mice that express constitutively active GSK3 at the physiological level, because the inhibitory serines in GSK3 α/β were mutated to alanines, exhibit increased susceptibility to depressive-like and manic-like behaviors [19]. Furthermore, depression induced in mice by the learned helplessness paradigm have reduced inhibitory serine-phosphorylated GSK3 in the hippocampus and cerebral cortex. Similarly, activated GSK3 was found in the nucleus accumbens in mice after social defeat stress [20], demonstrating that active GSK3 is associated with depressive behavior. (f) Active GSK3 also promotes manic-like behaviors, measured by assessing locomotor activity [4]. Drugs inducing locomotor activity, such as amphetamine, also decrease the serine-phosphorylation of GSK3. [21]. Finally, (g) studies of human serum [22], human postmortem brain [23], and of GSK3 polymorphisms [24] further implicate dysregulated GSK3 in promoting mood disorders.

Altogether, it is now well accepted that GSK3 is active in mouse models of both depression and mania, although this seems to be regulated by different pathways in the two conditions. The activation of GSK3 associated with depression may be dependent on neuronal circuitry related to deficiencies in the serotonergic or neurotrophin pathways, whereas the activation of GSK3 associated with manic-like behavior seems to be mediated by the action of GSK3 in the dopaminergic pathway [4]. A variety of actions of GSK3 have been associated with its regulation of mood, including regulation of apoptosis, neurogenesis and inflammation. This review focuses on the inflammatory effects of GSK3 that may be related to mood disorders.

II. GSK3 promotes inflammation

Inflammation evolved to inform the immune system of the invasion of pathogens and to promote their clearance. Schematically, the immune system is defined by two arms, the innate and the adaptive immune systems. The innate immune system is mediated mainly by macrophages and dendritic cells, or antigen presenting cells. These cells act as the first line of defense against pathogens. After phagocytosis and presentation at their surface of pathogen peptides that can later be recognized by the MHC, the innate immune system prepares the foundation for the activation of the adaptive immune system to ensure that pathogens are adequately cleared. Simultaneously, the innate immune system also produces pro-inflammatory cytokines and chemokines to help recruit the adaptive immune system. The adaptive immune system, which is a slower responder to insults than the innate immune system, includes T and B cells that act as the second line of defense to clear pathogens that

were not cleared by the innate system, and also to induce memory of the pathogen to provide a faster response in case of a second exposure to the same pathogen. The adaptive immune system response is delayed because it requires the activation/differentiation of the cells, which involves epigenetic modifications. The adaptive immune response also requires and produces cytokines, and only certain subpopulations of T cells have specific mechanisms to clear the pathogen, as CD8 T cells for example can become lytic and help destroy pathogens by secreting perforin. The antibodies produced by B cells are also critical in the clearance of certain pathogens, with the help of the complement system. Finally, the T helper (Th) cells, which coordinate the dialogue between the innate and adaptive immune systems, develop the capacity of memory to allow the distinction between the self and the non-self, and are also critical cytokine producers. Th cells have received a lot of attention in the autoimmune field because they are thought to mediate autoimmune diseases, and it has been proposed that some psychiatric diseases may involve aspects of autoimmune diseases.

1. GSK3 regulates the innate immune system

GSK3 was first discovered to promote the production of pro-inflammatory cytokines and to inhibit anti-inflammatory cytokine production in monocytes in response to TLR activation [25]. These findings showed that GSK3 shifts the balance towards proinflammatory responses, and that inhibiting GSK3 favors anti-inflammatory responses in response to TLR activation [26]. These actions on cytokine production have been confirmed in several different cell types, including macrophages, dendritic cells, and brain immune cells, including microglia and astrocytes. Therefore, besides inhibiting peripheral immune responses, GSK3 inhibitors also reduce neuroinflammation [26]. GSK3 is thought to promote phosphorylation of NF- κ B and STAT3, which are key regulators of the production of proinflammatory cytokines, while inhibiting CREB and AP-1, which are responsible for increased expression of the anti-inflammatory cytokine IL-10 [26]. The mTOR pathway has also been shown to reduce inflammatory cytokine production by inhibiting GSK3 [27]. As a consequence of the inhibition of inflammatory cytokine production by GSK3 inhibitors, treatment with GSK3 inhibitors protect 70% of mice from an otherwise lethal septic shock, and also provide protection from a variety of other inflammatory diseases (for review [26]).

2. GSK3 regulates the adaptive immune system

Th cells are a subpopulation of CD4⁺ T cells, which differentiate depending on the microenvironment's content of cytokines. Thus, CD4⁺ T cells differentiate towards Th1 cells upon stimulation with IL-12, and Th1 cells characteristically secrete IFN γ . CD4⁺ T cells differentiate to Th2 cells upon stimulation with IL-4, and Th2 cells secrete IL-4 and IL-10. CD4⁺ T cells differentiate to Th17 cells upon stimulation with IL-6 and TGF β , and Th17 cells received their name because they secrete IL-17. And CD4⁺ T cells differentiate to Tregs upon exposure to TGF β , and Tregs are characterized by their expression of Foxp3 (for review [28]).

Because GSK3 is a critical inducer of proinflammatory cytokines, and because cytokines are required for CD4⁺ T cells to differentiate, GSK3 has also been shown to regulate the differentiation of subsets of Th cells. GSK3 promotes the production of Th1 and Th17 cells, and does not affect Th2 cell differentiation, but its role in the regulation of Tregs is not

established, as some researchers found that GSK3 inhibition promotes Treg production [29], while others did not find an effect [30,31]. In addition to regulating the production of cytokines that influence Th cell differentiation, GSK3 also intrinsically controls the differentiation of Th1 and Th17 cells by regulating some of the key transcription factors responsible for the differentiation of Th1 and Th17 cells [30–32]. Thus, GSK3 promotes STAT1 activation in Th1 cells, but did not affect STAT4 activation, and GSK3 inhibitors reduced Tbet expression during Th1 differentiation. GSK3 promotes STAT3 activation in Th17 cells without affecting the master regulator transcription factor of Th17 cells, ROR γ T. This suggests that GSK3 acts early in the differentiation of Th1 and Th17 cells. GSK3 expression is also increased in CD4⁺ T cells during differentiation of Th1 and Th17 cells, although the mechanism whereby GSK3 expression increases remains unknown. Although the actions of GSK3 in Th1 and Th17 cell differentiation are mediated by cytokines and STATs, it is unlikely that this is the only mechanism whereby GSK3 controls Th17 differentiation. There seems to be a selectivity regarding the isoform of GSK3 involved in the regulation of Th17 cells. Thus, GSK3 β seems to promote Th17 cells induced by IL-6 and TGF β [30,31], whereas GSK3 α suppressed Th17 differentiation induced by IL-1, an action attributed to the inhibition by GSK3 α of Akt and mTOR activation by IL-1 [32]. It has also been proposed that regulation of β -catenin by GSK3 in response to TGF β was an important action of GSK3 in the regulation of Tregs [29]. GSK3 also affects survival of T cells. For example, activated T cell death (ACTD) requires GSK3 activity, and inhibition of GSK3 promotes survival of T cells [33].

Altogether, although most of the actions of GSK3 that have been described concern the regulation of cytokine production by the innate immune system, it appears that GSK3 is also implicated in the regulation of CD4⁺ T cell differentiation independently of its action on cytokine production by the innate immune system. Indeed, mice lacking GSK3 β only in T cells are resistant to induction of experimental autoimmune encephalomyelitis (EAE), the mouse model of multiple sclerosis, whereas mice lacking GSK3 α in T cells develop EAE similar to their littermate controls [30]. Because EAE is highly dependent on Th1 and Th17 cells pathogenicity, this finding showed that the intrinsic regulation by GSK3 of Th cell differentiation is a critical action of GSK3 in T cells.

III. Mood disorders and inflammation

With a lifetime incidence of ~20% in the United States, mood disorders (depression and bipolar disorder) are prevalent diseases [34,35]. Currently there are significant inadequacies in available treatments. Many patients fail to improve after antidepressant treatment, or terminate their treatment prematurely. Alterations of the immune system, especially increased markers of inflammation, have been found to be associated with mood disorders in many studies. Thus, susceptibility to depression appears to be increased by inflammation, and therapeutic responses to antidepressants are impaired by inflammation. In the serum of some patients with major depression or bipolar disorder, there is an elevation of the proinflammatory cytokines IL-6, IL-1 β and TNF α . Moreover, administration of lipopolysaccharide [36] or interferon- α [37] promotes depressive symptoms in humans. Administration of anti-inflammatory drugs, such as cyclo-oxygenase inhibitors or etanercept, improve mood in patients with inflammatory diseases. In rodents, it has been

shown that these behaviors could be recapitulated, using either LPS to induce “sickness behavior”, or administration of cytokines [38]. Furthermore, psychological stress is sufficient to increase proinflammatory cytokine production and to induce depressive behavior [39]. Therefore, there is accumulating evidence that inflammatory cytokines are closely associated with depression in patients and with depressive-like behavior in rodents. Miller’s group recently reported the results of a clinical trial in which administration of an anti-TNF antibody in depressed patients ameliorated depression in a subset of patients that had elevated inflammatory markers, suggesting that all depressed patients were not equivalent in terms of disease and that a classification of depressed patients according to their inflammatory status may be useful. However, neither the source (central or peripheral) nor the exact cytokine to target to prevent depressive behavior has been identified yet. Nevertheless, it is thought that the innate immune system plays a critical role in the induction of depressive behavior. It has been proposed that GSK3 could promote depressive behavior by promoting the production of pro-inflammatory cytokines, but currently there is no report of the direct involvement of GSK3 in cytokine-induced depressive behavior. It has been reported that in response to LPS, GSK3 knockin mice exhibit increased sickness behavior in the tail suspension test, and this was associated with increased IL-6 production [19], but further investigations are required to determine if promotion of inflammation by GSK3 contributes to the detrimental role of GSK3 in mood disorders.

The impact of the adaptive immune system, especially T cells, is not well-understood in the etiology of mood disorders. Altered stress-induced proliferation and function of T cells isolated from depressed patients have been reported, which could result from increased Fas-mediated apoptosis, reduced T cell response to glucocorticoids, or increased cytokine levels responsible for modulating T cell subtype production and responses (for review [40]). Because cytokines, especially IL-6, are elevated in a significant number of depressed patients, and it is difficult to identify an individual cytokine responsible for promoting depressive behavior, pinpointing downstream events of cytokines may help to understand the role of inflammation in depression. Because Th17 cells are highly dependent on the production of IL-6, and IL-6 is elevated in depressed patients, Th17 cells were examined and shown to promote depressive behavior in mice [41]. GSK3 promotes the production of Th17 cells, as lithium blocked Th17 cells induced during depressive behavior, whereas in contrast GSK3 knockin mice, have elevated Th17 cells, which correlates with GSK3 knockin mice being more susceptible to depression. These findings suggest that one way GSK3 may promote depressive behavior is by promoting the production of Th17 cells, as well as promoting inflammation.

Altogether, there is accumulating evidence converging on the role of GSK3 in promoting inflammation and suggesting that this may impact depressive behavior (Figure 1). However further investigations are required to decipher the role of GSK3 in depression. Nevertheless, inflammation appears as a potential new therapeutic strategy to reduce depressive behavior. The question remaining will be to determine if this will be sufficient to be therapeutic for depressive behavior, and for this the source of the insult causing alterations in cytokines and T cells needs to be identified.

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References

1. Cohen P, Frame S. The renaissance of gsk3. *Nat Rev Mol Cell Biol.* 2001; 2:769–776. [PubMed: 11584304]
2. Doble BW, Woodgett JR. Gsk-3: Tricks of the trade for a multi-tasking kinase. *J Cell Sci.* 2003; 116:1175–1186. [PubMed: 12615961]
3. Jope RS, Johnson GV. The glamour and gloom of glycogen synthase kinase-3. *Trends Biochem Sci.* 2004; 29:95–102. [PubMed: 15102436]
4. Jope RS. Glycogen synthase kinase-3 in the etiology and treatment of mood disorders. *Front Mol Neurosci.* 2011; 4:16. [PubMed: 21886606]
5. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci U S A.* 1996; 93:8455–8459. [PubMed: 8710892]
6. Li X, Zhu W, Roh MS, Friedman AB, Rosborough K, Jope RS. In vivo regulation of glycogen synthase kinase-3beta (gsk3beta) by serotonergic activity in mouse brain. *Neuropsychopharmacology.* 2004; 29:1426–1431. [PubMed: 15039769]
7. Beurel E, Song L, Jope RS. Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. *Mol Psychiatry.* 2011 in press.
8. McManus EJ, Sakamoto K, Armit LJ, Ronaldson L, Shpiro N, Marquez R, Alessi DR. Role that phosphorylation of gsk3 plays in insulin and wnt signalling defined by knockin analysis. *Embo J.* 2005; 24:1571–1583. [PubMed: 15791206]
9. Gould TD, Gray NA, Manji HK. Effects of a glycogen synthase kinase-3 inhibitor, lithium, in adenomatous polyposis coli mutant mice. *Pharmacol Res.* 2003; 48:49–53. [PubMed: 12770514]
10. Kaidanovich-Beilin O, Milman A, Weizman A, Pick CG, Eldar-Finkelman H. Rapid antidepressive-like activity of specific glycogen synthase kinase-3 inhibitor and its effect on beta-catenin in mouse hippocampus. *Biol Psychiatry.* 2004; 55:781–784. [PubMed: 15050857]
11. Beaulieu JM, Zhang X, Rodriguiz RM, Sotnikova TD, Cools MJ, Wetsel WC, Gainetdinov RR, Caron MG. Role of gsk3 beta in behavioral abnormalities induced by serotonin deficiency. *Proc Natl Acad Sci U S A.* 2008; 105:1333–1338. [PubMed: 18212115]
12. Kaidanovich-Beilin O, Lipina TV, Takao K, van Eede M, Hattori S, Laliberte C, Khan M, Okamoto K, Chambers JW, Fletcher PJ, MacAulay K, Doble BW, Henkelman M, Miyakawa T, Roder J, Woodgett JR. Abnormalities in brain structure and behavior in gsk-3alpha mutant mice. *Mol Brain.* 2009; 2:35. [PubMed: 19925672]
13. O'Brien WT, Harper AD, Jove F, Woodgett JR, Maretto S, Piccolo S, Klein PS. Glycogen synthase kinase-3beta haploinsufficiency mimics the behavioral and molecular effects of lithium. *J Neurosci.* 2004; 24:6791–6798. [PubMed: 15282284]
14. Omata N, Chiu CT, Moya PR, Leng Y, Wang Z, Hunsberger JG, Leeds P, Chuang DM. Lentivirally mediated gsk-3beta silencing in the hippocampal dentate gyrus induces antidepressant-like effects in stressed mice. *Int J Neuropsychopharmacol.* 2011; 14:711–717. [PubMed: 20604988]
15. Faria MS, Teixeira NA. Reversal of learned helplessness by chronic lithium treatment at a prophylactic level. *Braz J Med Biol Res.* 1993; 26:1201–1212. [PubMed: 8136720]
16. Nixon MK, Hascoet M, Bourin M, Colombel MC. Additive effects of lithium and antidepressants in the forced swimming test: Further evidence for involvement of the serotonergic system. *Psychopharmacology (Berl).* 1994; 115:59–64. [PubMed: 7862913]
17. Mai L, Jope RS, Li X. Bdnf-mediated signal transduction is modulated by gsk3beta and mood stabilizing agents. *J Neurochem.* 2002; 82:75–83. [PubMed: 12091467]
18. Warner-Schmidt JL, Duman RS. Vegf as a potential target for therapeutic intervention in depression. *Curr Opin Pharmacol.* 2008; 8:14–19. [PubMed: 18061540]

19. Polter A, Beurel E, Yang S, Garner R, Song L, Miller CA, Sweatt JD, McMahon L, Bartolucci AA, Li X, Jope RS. Deficiency in the inhibitory serine-phosphorylation of glycogen synthase kinase-3 increases sensitivity to mood disturbances. *Neuropsychopharmacology*. 2010; 35:1761–1774. [PubMed: 20357757]
20. Wilkinson MB, Dias C, Magida J, Mazei-Robison M, Lobo M, Kennedy P, Dietz D, Covington H 3rd, Russo S, Neve R, Ghose S, Tamminga C, Nestler EJ. A novel role of the wnt-dishevelled-gsk3beta signaling cascade in the mouse nucleus accumbens in a social defeat model of depression. *J Neurosci*. 2011; 31:9084–9092. [PubMed: 21697359]
21. Beaulieu JM, Sotnikova TD, Yao WD, Kockeritz L, Woodgett JR, Gainetdinov RR, Caron MG. Lithium antagonizes dopamine-dependent behaviors mediated by an akt/glycogen synthase kinase 3 signaling cascade. *Proc Natl Acad Sci U S A*. 2004; 101:5099–5104. [PubMed: 15044694]
22. Li X, Friedman AB, Zhu W, Wang L, Boswell S, May RS, Davis LL, Jope RS. Lithium regulates glycogen synthase kinase-3beta in human peripheral blood mononuclear cells: Implication in the treatment of bipolar disorder. *Biol Psychiatry*. 2007; 61:216–222. [PubMed: 16806104]
23. Karege F, Perroud N, Burkhardt S, Schwald M, Ballmann E, La Harpe R, Malafosse A. Alteration in kinase activity but not in protein levels of protein kinase b and glycogen synthase kinase-3beta in ventral prefrontal cortex of depressed suicide victims. *Biol Psychiatry*. 2007; 61:240–245. [PubMed: 16876135]
24. Adli M, Hollinde DL, Stamm T, Wiethoff K, Tsafridi M, Kirchheiner J, Heinz A, Bauer M. Response to lithium augmentation in depression is associated with the glycogen synthase kinase 3-beta -50t/c single nucleotide polymorphism. *Biol Psychiatry*. 2007; 62:1295–1302. [PubMed: 17628506]
25. Martin M, Rehani K, Jope RS, Michalek SM. Toll-like receptor-mediated cytokine production is differentially regulated by glycogen synthase kinase 3. *Nat Immunol*. 2005; 6:777–784. [PubMed: 16007092]
26. Beurel E, Michalek SM, Jope RS. Innate and adaptive immune responses regulated by glycogen synthase kinase-3 (gsk3). *Trends Immunol*. 2010; 31:24–31. [PubMed: 19836308]
27. Wang H, Brown J, Gu Z, Garcia CA, Liang R, Alard P, Beurel E, Jope RS, Greenway T, Martin M. Convergence of the mammalian target of rapamycin complex 1- and glycogen synthase kinase 3-beta-signaling pathways regulates the innate inflammatory response. *J Immunol*. 2011; 186:5217–5226. [PubMed: 21422248]
28. O'Shea JJ, Paul WE. Mechanisms underlying lineage commitment and plasticity of helper cd4+ t cells. *Science*. 2010; 327:1098–1102. [PubMed: 20185720]
29. Graham JA, Fray M, de Haseth S, Lee KM, Lian MM, Chase CM, Madsen JC, Markmann J, Benichou G, Colvin RB, Cosimi AB, Deng S, Kim J, Alessandrini A. Suppressive regulatory t cell activity is potentiated by glycogen synthase kinase 3{beta} inhibition. *J Biol Chem*. 2010; 285:32852–32859. [PubMed: 20729209]
30. Beurel E, Kaidanovich-Beilin O, Yeh WI, Song L, Palomo V, Michalek SM, Woodgett JR, Harrington LE, Eldar-Finkelman H, Martinez A, Jope RS. Regulation of th1 cells and experimental autoimmune encephalomyelitis by glycogen synthase kinase-3. *J Immunol*. 2013; 190:5000–5011. [PubMed: 23606540]
31. Beurel E, Yeh WI, Michalek SM, Harrington LE, Jope RS. Glycogen synthase kinase-3 is an early determinant in the differentiation of pathogenic th17 cells. *J Immunol*. 2011; 186:1391–1398. [PubMed: 21191064]
32. Gulen MF, Bulek K, Xiao H, Yu M, Gao J, Sun L, Beurel E, Kaidanovich-Beilin O, Fox PL, DiCorleto PE, Wang JA, Qin J, Wald DN, Woodgett JR, Jope RS, Carman J, Dongre A, Li X. Inactivation of the enzyme gsk3alpha by the kinase ikk promotes akt-mtor signaling pathway that mediates interleukin-1-induced th17 cell maintenance. *Immunity*. 2012; 37:800–812. [PubMed: 23142783]
33. Sengupta S, Jayaraman P, Chilton PM, Casella CR, Mitchell TC. Unrestrained glycogen synthase kinase-3 beta activity leads to activated t cell death and can be inhibited by natural adjuvant. *J Immunol*. 2007; 178:6083–6091. [PubMed: 17475833]
34. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med*. 2008; 358:55–68. [PubMed: 18172175]

35. Greden JF. The burden of recurrent depression: Causes, consequences, and future prospects. *J Clin Psychiatry*. 2001; 62 (Suppl 22):5–9. [PubMed: 11599650]
36. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. 2009; 65:732–741. [PubMed: 19150053]
37. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, Pollmacher T. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry*. 2001; 58:445–452. [PubMed: 11343523]
38. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun*. 2007; 21:153–160. [PubMed: 17088043]
39. Anisman H, Merali Z. Cytokines, stress and depressive illness: Brain-immune interactions. *Ann Med*. 2003; 35:2–11. [PubMed: 12693607]
40. Miller AH. Depression and immunity: A role for t cells? *Brain Behav Immun*. 2010; 24:1–8. [PubMed: 19818725]
41. Beurel E, Harrington LE, Jope RS. Inflammatory t helper 17 cells promote depression-like behavior in mice. *Biol Psychiatry*. 2013; 73:622–630. [PubMed: 23174342]

Figure 1.
Potential interactions between GSK3, inflammation and depression