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The inflammasome: Pathways linking psychological stress, depression, and systemic illnesses

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ABSTRACT

Stress is a common occurrence in everyday life and repeated or traumatic stress can be a precipitating factor for illnesses of the central nervous system, as well as peripheral organ systems. For example, severe or long-term psychological stress can not only induce depression, a leading illness worldwide, but can also cause psychosomatic diseases such as asthma and rheumatoid arthritis. Related key questions include how psychological stress influences both brain and peripheral systems, and what detection mechanisms underlie these effects? A clue is provided by the discovery of the pathways underlying the responses to host "danger" substances that cause systemic diseases, but can also contribute to depression. The inflammasome is a protein complex that can detect diverse danger signals and produce the accompanying immune-inflammatory reactions. Interestingly, the inflammasome can detect not only pathogen-associated molecules, but also cell damage-associated molecules such as ATP. Here, we propose a new inflammasome hypothesis of depression and related comorbid systemic illnesses. According to this hypothesis, the inflammasome is a central mediator by which psychological and physical stressors can contribute to the development of depression, and as well as a bridge to systemic diseases. This hypothesis includes an explanation for how psychological stress can influence systemic diseases, and conversely how systemic diseases can lead to psychiatric illnesses. The evidence suggests that the inflammasome may be a new target for the development of treatments for depression, as well as psychosomatic and somato-psycho diseases.

1. Introduction

Major depressive disorder (MDD) is characterized by depressed mood, low self-esteem, anhedonia, and disrupted sleeping, eating, and cognition, and has now been recognized to have an overall impact on global illness that is projected to be second only to ischemic heart disease in social and economical burden by 2020 (Greden, 2001; Murray and Lopez, 1997). In the United States, about 14 million people, or about 10% of the population, suffer from depression at any point in time (Kessler et al., 2003). Because approximately one third of MDD patients do not respond to traditional pharmacological medications such as monoamine reuptake inhibitors, there is a major unmet need for the development of novel, more efficacious therapeutic agents.

Although it is clear that genetic factors are involved [heritability estimates from twin studies are reported to be 37%–38% (Kendler et al., 2006; Sullivan et al., 2000)], environmental factors such as stress are strongly implicated in the pathology of depression (Kessler, 1997). Levels of stress have increased with growing social and economic demands in recent decades, resulting in a rapid rise in the prevalence of depression (Kessler et al., 2003). Here, we discuss evidence that psychological, as well as physical stressors can activate immune and inflammation processes and lead to increased cytokine levels, contributing to structural and functional alterations of neurons and the development of MDD.

A role for inflammation and related cytokines in MDD was first suggested in the 1980's and since then evidence has accumulated in support of this hypothesis (Ader and Cohen, 1993; Maes, 1995; Maier et al., 1994; Tecoma and Huey, 1985). There have been several excellent reviews of this work, but the current paper examines a novel aspect of the immune-inflammation process in the response to stress and depression: that interkeukin-1β (IL-1β) and its regulator, "the Nod-like receptor (NLR) family, pyrin domain-containing 3 (NLRP3) inflammasome", are a bridge between psychological stress and depression. Related to this hypothesis is the possibility that the inflammasome provides a bidirectional pathway between depression and comorbid systemic illnesses, suggesting novel strategies for treating depression.

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2. Comorbidity of mood disorders and systemic/peripheral diseases

Psychosocial stress and systemic disease can both affect the onset of depression. For example, the comorbidity of depression in patients with diabetes, cancer, or cardiac disease is 17%–29%, much higher than that of the general population (10.3%) (% comorbidity of depression with specific systemic illnesses is shown in Table 1) (Evans et al., 2005). Moreover, chronic inflammation is implicated in the pathology of these diseases, and the possible mechanisms by which the NLRP3 inflammasome may serve as a key mediator is being elucidated (Table 1). There is also evidence from clinical procedures that inflammation can cause depression. For example, interferon (IFN) a cytokine that strongly activates the immune system (e.g., natural killer cells and macrophages), is used as a treatment for certain types of cancer and viral infections and causes a high prevalence of dose-dependent depressive symptoms (~50%) (Raison et al., 2006). Immune reactivity and inflammation has thus been implicated as a common factor underlying depressive effects of IFN.

Further support for this hypothesis is provided by studies demonstrating that serum levels of pro-inflammatory cytokines such as IL-1β, IL-6 and TNFα are elevated in depressed patients (Dowlati et al., 2010; Howren et al., 2009). It is well known that these cytokines can induce somatic symptoms, referred to as sickness behavior, including fatigue and loss of appetite (Schiepers et al., 2005), which overlap with common symptoms of major depression. Further, cytokines can affect mood, causing dysphoria and anxiety (Schiepers et al., 2005). Here, we explore the possibility that repeated psychological stress can induce a chronic immune reaction and elevation of cytokines and discuss how this could contribute to depression and comorbid immune/inflammation illnesses.

3. Innate immune response mechanisms

Host survival requires defense mechanisms against external danger substances, including the ability to discriminate "nonself" from "self" and to eliminate or neutralize danger molecules. The mechanisms by which the immune system detects diverse danger signals were only recently elucidated with the discovery of Toll-like receptors (TLRs). TLRs are pattern recognition receptors (PRRs) on the cell-surface of immune cells, characterized by extracellular leucine-rich repeats (LRRs) and an intracellular Toll/IL-1 receptor (TIR) domain (Fig 1). TLRs recognize invariant molecular structures called pathogen-associated molecular patterns (PAMPs) (Schroder and Tschopp, 2010; Tschopp et al., 2003). As a result, there is release of pro-inflammatory "alarm" cytokines, including IL-1β, one of the most potent endogenous pyrogens, as well as tumor necrosis factor-alpha (TNFα) and IL-6 (Tschopp et al., 2003).

Induction of TNFα and IL-6 in response to TLR occurs via activation of gene transcription (Hoshino et al., 1999; Tamandl et al., 2003). The formation of IL-1β also requires TLR4 induction of gene transcription, but requires an additional step, the processing of pro-IL-1β to the mature, active form of IL-1β, which is then released (Bryant and Fitzgerald, 2009) (Fig 1). The processing and release of pro-IL-1β occurs via NLRP3, part of a multiprotein complex referred to as the "inflammasome" (Martinon et al., 2002). A key activator of inflammasome is the ATP purinergic type 2X7 (P2X7)

Table 1
Systemic/Peripheral diseases comorbid with depression and the role of IL-1β and the NLRP3 inflammasome.

Physical diseases associated with NLRP3 inflammasome	Stimulator	Pathology/Implication of NLRP3 on physical disease	Prevelence of Depression	References
Metabolic Disorders				
Type II Diabetes Mellitus	Hyperglycemia Fatty acids	β cell death, Insulin resistance	26%	Zhou et al. (2010),Mason et al. (2012) Evans et al.(2005)
Obesity	Fatty acids	Decrease insulin sensitivity	20%-30%	Wen et al. (2011), Vandanmagsar et al. (2011), Evans et al.(2005)
Cardiovascular disease	Cholesterol crystals	Inflammation / polymorphism in the NLRP3 locus and concordance with fibrinogen gene variants	17%-27%	Duewell et al. (2010), Mason et al. (2012), Evans et al.(2005)
Autoimmuno Diseases				
Rheumatoid Arthritis	?	Chronic inflammation of the synovium / Increased expression of NLRP3	13%-20%	Kastbom et al. (2008), Mason et al. (2012), Sheehy et al. (2006)
Systemic lupus erythematosus (SLE)	U1-snRNP	Inflammatory response causes cell death and organ failure	22.5%-42%	Bachen et al. (2009), Shin et al. (2012), Nery et al. (2007)
Alzheimer's disease	Amyloid β	Nlrp3$^{-/-}$ microglia demonstrated a significant reduction in the proinflammatory mediators when treated with amyloid-β	30%-50%	Mitroulis et al. (2010), Mason et al. (2012), Evans et al. (2005), Halle et al. (2008)
Multiple Sclerosis (MS)	?	Nlrp3 found to play a role in the progression of disease in an experimental autoimmune encephalomyelitis model	25%-50%	Gris et al. (2010), Mason et al. (2012), Fischer et al. (2012)
Infection / Environmental Disease				
HIV	HIV	Activation of immune system against the virus	5%-30%	Pontillo et al. (2012), Evans et al. (2005)
Asthma	Allergen?	A substaital reduction in inflammation and leukocyte recruitment to the lung in Nlrp3$^{-/-}$ and IL-1R$^{-/-}$ mice compared to WT mice	18%	Besnard et al. (2011), Mason et al. (2012)
Chronic obstructive pulmonary disorders	Inflammation (uric acid ?)	Chronic bronchitis and emphysema	10%-42%	Eisner et al. (2005) Gasse et al. (2009), Mason et al. (2012)
Healthy Subject				
General population			10.3% (12-month)	Caferella et al. (2012)
			17.1% (Lifetime)	Kessler et al. (1994), Evans et al. (2005)

Listed are the systemic diseases associated with NLRP3, as well as the different types of danger substances that lead to IL-1β release (or activate caspase-1). The prevalence of depression in populations with these different diseases is much higher (up to 30% or even higher) than that of the general population, which is 10.3%.
(Bachen et al., 2009; Besnard et al., 2011; Cafarella et al., 2012; Duewell et al., 2010; Eisner et al., 2005; Evans et al., 2005; Fischer et al., 2012; Gasse et al., 2009; Gris et al., 2010; Halle et al., 2008; Kastbom et al., 2008; Kessler et al., 1994; Mason et al., 2012; Mitroulis et al., 2010; Nery et al., 2007; Pontillo et al., 2012; Sheehy et al., 2006; Shin et al., 2012; Vandanmagsar et al., 2011; Wen et al., 2011; Zhou et al., 2010).

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