NLRP3 Inflammasome: A New Target in Major Depressive Disorder

Elísabet Alcocer-Gomez; Mario D. Cordero

Inflammasome has emerged recently as an unexpected sensor for metabolic danger and stress. Indeed, it has been implicated in the development of major diseases such as gout, type 2 diabetes, and obesity-induced insulin resistance and is increasingly suspected of playing a major role in other human pathologies such as cancer, asbestosis, and Alzheimer's disease. The inflammasome is a protein complex that comprises an intracellular sensor, typically a Nod-like receptor (NLR), the precursor procaspase-1, and the adaptor ASC. Inflammasome activation leads to the maturation of caspase-1 and the processing of its substrates, IL-1b, and IL-18. Of all the NLRs, NLRP3 is activated by the most diverse array of danger signals. Recently, it has been hypothesized the implication of inflammasome in depression and related comorbid systemic illnesses, however, was necessary to demonstrate the activation of NLRP3 inflammasome in depressive patients. This event was intuited because IL-1b, one of the two known cytokines activated by the inflammasome complex, has been implicated in stress, depression, and central nervous system (CNS) dysregulation. A recent paper published in CNS Neuroscience and Therapeutics by Zhang et al. have showed in first time that the NLRP3 inflammasome is involved in lipopolysaccharideinduced mice depressive-like behaviors. In parallel, the authors of the present paper have showed in first time the activation of NLRP3 inflammasome in blood mononuclear cells from depressive patients with a high correlation between IL-1b and IL-18 with Beck Depression Inventory scores of depressive patients. These are two papers demonstrating in an animal model and patients, the hypothesis of Iwata et al. These findings provide new insight into the pathogenesis of major depressive disorder. Now, we must deepen about this and study several point involved in the pathogenesis of this disease.

The Mechanism of Disease

Major depressive disorder is a severe and potentially debilitating psychiatric illness that is characterized by a significant change in mood accompanied by other symptoms such as low self-esteem, anhedonia, and disrupted sleeping, eating, and cognition. Despite the fact that it affects up to 10% of the general population worldwide, its pathogenic mechanism remains elusive. Consequently, research is now aimed at characterizing its pathophysiology at the cellular and molecular level. The first question that we must respond is concerning to the events which induce the activation of inflammasome in this disease. Psychological stress as inductor of increased IL-1b serum levels has been proposed; however, molecular mechanisms by which psychological stress could induce activation of inflammasome are unknown. Depression is a very common disease in the general population worldwide in which, together to environmental factors, it is clear that genetic factors are involved, so in addition to psychological stress, we have to look for endogenous events which induce inflammasome activation. It could be interesting to investigate the role of molecules involved in the pathophysiology of depression, which could have potential to induce NLRP3 inflammasome activation.

Supporting this hypothesis, it has been showed that cortisol correlates with increased levels of IL-1b in hypothalamic–pituitary–adrenal (HPA) axis dysregulation such as in anorexia nervosa. Because hippocampus has an important role in the pathogenesis of depression, it will be interesting to analyze the implication and impact of NLRP3 in- flammasome activation in the area of hippocampus and neurogenesis, two major changes in this disease known. In agreement with these, it has been observed that IL-1b inhibits the differentiation of hippocampal neural precursor cells.

Implications in the Treatment of Depression

The other important question is the implication of inflammasome in the treatment of depression. It has been found that antidepressant treatment reduces serum levels of IL-1b, but not TNFa, suggesting that IL-1b plays a major role in treatment response. We have described that amitriptyline, a tricyclic antidepressant, reduce NLRP3 and caspase-1 gene expression, and IL-1b and IL- 18 serum levels. Other typical treatments of depression are monoamine neurotransmitters, selective serotonin reuptake inhibitors (SSRIs), and serotonin–noradrenalin reuptake inhibitors; however, the efficacy of these treatments remains uncertain showing significant limitations related to treatment-resistant depression. So, inflammasome could be a biomarker to evaluate the effectiveness and resistant to antidepressants. According to this hypothesis, it has been shown that the resistance to SSRI may be driven by the pathologically increased IL-1b.

Genetics Implications

The major goals of personalized medicine are to predict an individual's susceptibility to developing an illness, achieve accurate diagnosis, and optimize the most efficient and favorable response to treatment. Mutations and polymorphisms in NLR-coding genes or in genetic loci encoding inflammasome-related proteins correlate with a variety of autoinflammatory diseases and propose susceptibility mechanism. In this case, several polymorphisms in the two known cytokines activated by the inflammasome complex have shown increase the susceptibility to depression in response to stressful life events. Therefore, the role of new polymorphisms in NLRP3 or other NLR-coding genes could be an interesting new way to evaluate susceptibility profile in depressive patients. Future Considerations Personalized medicine holds the hope of increasing the likelihood that patients with depression will respond to treatment and achieve remission. In agreement with this, the NLRP3 inflammasome represents a possible and interesting sensor with potential to offer a personalized biomarker that help predict response to particular treatments. Furthermore, a dose-dependent screening with several drugs in cells from patients may provide profiles of the most indicated treatments in each case. Several studies have indicated discrepancies regarding the pathological role of inflammation in MDD. These discrepancies could be the result of the presence of subgroups of patients with different levels of psychological stress. Anyway, NLRP3 inflammasome offers a new perspective in the study of depression, in particular, and psychiatric diseases in general.