NLRP3 inflammasome: common nexus between depression and cardiovascular diseases

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Several NLRP3 inflammasome inhibitors are being developed and studied, and various processes can inhibit its activation (FIG. 1). In the coming years, therefore, we could see similar pharmacological treatments for depression and CVD.

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We read with great interest the Review by Carney and Freedland (Depression and coronary heart disease. *Nat. Rev. Cardiol.* <http://dx.doi.org/10.1038/nrcardio.2016.181>; 2016)¹, in which the mechanisms linking depression and coronary heart disease are discussed. Specifically, this Review provides an update on biological and behavioural mechanisms, as well as potential interventions to decrease the risk of cardiac events in patients with depression. However, we note the omission of discussion of the NLRP3 inflammasome complex from this Review.

The inflammasome has emerged as an unexpected sensor of metabolic danger and stress. Indeed, the inflammasome has been implicated in the development of major diseases such as gout, type 2 diabetes mellitus, and obesity-induced insulin resistance, and other human pathologies such as cancer, asbestosis, and Alzheimer disease². 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-1 β and IL-18 (REF. 3). Of all the NLRs, NLRP3 is activated by the most diverse array of danger signals.

The NLRP3 inflammasome has been widely studied in cardiovascular diseases (CVDs). NLRP3 regulation of wound healing in CVD has been discussed⁴. Furthermore, the NLRP3 inflammasome in the pathogenesis of atherosclerosis has also been studied^{5,6}. Indeed, several studies have proposed that inflammasome activation in cardiovascular tissues produces a variety of injurious actions, independent of the typical inflammation, suggesting noncanonical effects of inflammasome activation⁷.

Our group has shown the participation of the NLRP3 inflammasome in the pathophysiology of depression in both animal models and patients, as well as the effect of NLRP3 inhibition^{8,9}. The role of the inflammasome in depression and mood disorders has been widely reviewed¹⁰. The NLRP3 inflammasome is particularly activated after exposure

to damage-associated molecular patterns (known as DAMPs), such as extracellular ATP, excess glucose, ceramides, amyloids, urate, and cholesterol crystals, several of which increase CVD risk¹¹ and are also involved in mood disorders¹⁰. Accordingly, our preliminary studies demonstrate that high fat diets or high sucrose diets induce NLRP3-mediated cardiac damage accompanied by depressive symptoms (E.A.-G. and M.D.C., unpublished data), showing a similar NLRP3-dependent pathophysiological pattern in both diseases (FIG. 1). Furthermore, important processes that modulate inflammasome activation, such as autophagy and mitophagy¹², are altered in CVD and depression^{13,14}.

Finally, stress is an important physiological process in depression and several systemic diseases, including CVD^{9,15}. Molecular mechanisms of stress have been associated with several of the NLRP3 inflammasome pathways, including DAMPs. Psychological stress (an important depressive modulator) can activate the NLRP3 inflammasome, leading to the release of IL-1 β , which can contribute to the pathophysiology of systemic diseases, such as diabetes mellitus and CVDs.

Figure 1 | Inducers of the NLRP3 inflammasome related to depression and cardiovascular disease, and inhibitory strategies. Several damage-associated molecular patterns (known as DAMPs), such as ATP release, increased levels of cholesterol or glucose, increased levels of IL-1 β , reactive oxygen species (ROS), and stress exposure, have been shown to induce NLRP3 inflammasome activation. Given that these potential NLRP3 inflammasome inducers have been associated with the pathophysiology of both depression and cardiovascular diseases, the use of the various NLRP3 inhibitors might be beneficial in both diseases.

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Competing interests statement

The authors declare no competing interests.