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15d-Prostaglandin J2 inhibits noncanonical inflammasome response to ameliorate endotoxin shock.

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Accumulating evidence has shown that release of inflammatory cytokine Interleukin (IL)-1 α/β is regulated by Nod-like receptor-dependent (canonical) and -independent (non-canonical) inflammasome. Caspase-11, the key component of non-canonical inflammasome, senses bacterial lipopolysaccharides (LPS) in the cytosol to induce proteolytic cleavage of IL-1 α/β and Gasdermin D. Subsequently, processed mature IL-1a/b is released through the pore on the plasma membrane that is generated by fragmented active Gasdermin D. Although excessive non-canonical inflammasome activation often causes various inflammatory diseases such as endotoxin shock, non-canonical inflammasome inhibitor has not been well identified yet. In this study, we performed screening of 201 bioactive lipids to identify 15d-prostaglandin J2 (PGJ2) as the novel non-canonical inflammasome inhibitor. Mass spectrometry analysis of 15d-PGJ2 binding proteins revealed the target of 15d-PGJ2 that is involved in caspase-11 activation. Furthermore, we found that sequential regulation of 15d-PGJ2 production by Toll-like receptor 4 and non-canonical inflammasome upon LPS stimulation. Finally, we provided *in vivo* evidence that PGJ2 treatment ameliorates septic shock in mice. These findings suggested that 15d-PGJ2 is the negative feedback inhibitor of the non-canonical inflammasome. Therefore, 15d-PGJ2 could be an effective medication for the treatment of inflammatory diseases such as endotoxin shock.