

## Research Article

### Inflammasome Regulation and Inflammasome Inhibitors

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### Introduction

Interleukin-1 $\beta$  (IL-1 $\beta$ ) is an inflammatory cytokine that contributes to homeostasis in the human body through its diverse physiological functions. IL-1 $\beta$  also has pathological significance and plays an important role in a broad spectrum of diseases, including cancer and inflammatory diseases. IL-1 $\beta$  is initially produced as an inactive precursor in the process of “priming” by activation of the transcription factor NF- $\kappa$ B. The

cleavage of pro-IL-1 $\beta$ , called “processing”, is required for the activation of IL-1 $\beta$ . The inflammasome, a large molecular weight multi-protein complex, plays an important role in “processing”. In this article, we focus on the functions of inflammasomes involved in the activation of IL-1 $\beta$  and consider inflammasome-associated diseases and IL-1 $\beta$  inhibitors.

### 1. IL-1 $\beta$ and its activation

IL-1 $\beta$  has diverse functions and plays important roles in the adaptation of cells and in cellular and tissue repair following damage by various physical, chemical, and biological factors.<sup>1)</sup> On the other hand, inappropriate activation of IL-1 $\beta$  leads to the onset and/or progression of diseases. For example, IL-1 $\beta$ , mostly derived from macrophages, is implicated in the progression of atherosclerosis.<sup>2)</sup> In a tumor microenvironment, IL-1 $\beta$  can induce the recruitment of tumor-associated macrophages (TAMs) and tumor immunosuppressive myeloid-derived suppressor cells (MDSCs), which promote tumor development in breast cancer.<sup>3)</sup>

The release of IL-1 $\beta$  is regulated by two steps. IL-1 $\beta$  is first synthesized as biologically inactive pro-IL-1 $\beta$  (Step 1), then is activated by inflammasomes

as the second step and subsequently released into the external milieu<sup>4)</sup> (**Fig. 1**). In Step 1, IL-1 $\beta$  is produced as a 269-AA precursor protein by NF- $\kappa$ B, then is processed by caspase-1, also known as IL-1 $\beta$ -converting enzyme (ICE), to release the mature IL-1 $\beta$ . Step 2 is called “processing”. The IL-1 $\beta$  precursor is also processed by other serine proteases such as elastase, chymases, granzyme A, cathepsin G, and proteinase-3, then binds to IL-1 receptors.<sup>5,6)</sup> Caspase-1 activation involves inflammasome activation machinery. Briefly, upon the recognition of pathogens or cellular damage by upstream pattern-recognition receptors, pro-caspase-1 binds to an adapter protein ASC (apoptosis-associated speck-like protein containing a caspase-recruitment domain (CARD)) via a caspase-recruitment domain: CARD, to initiate enforced-proximity activation of caspase-1 in the inflammasome (**Fig. 1**).<sup>7,8)</sup>

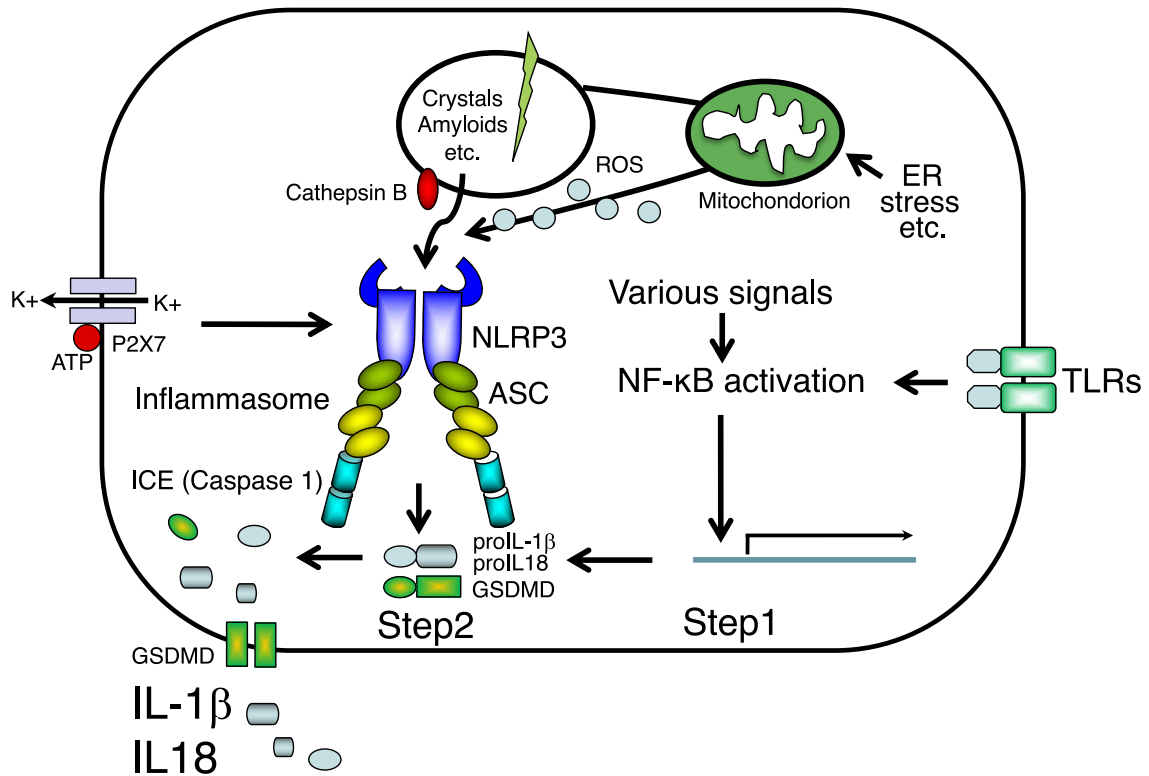


Figure 1. Schematic representation of NLRP3 inflammasome activation

## 2. Inflammasomes

The inflammasome is a large protein complex consisting of pattern recognition receptors (PRR)s, the ASC adaptor protein, and pro-caspase-1. The NLRP3 inflammasome is well-characterized and is reportedly activated by a wide range of pathogen-associated molecular patterns (PAMP)s and damage-associated molecular patterns (DAMP)s. The NLRP3 inflammasome can oligomerize by sensing changes in the intracellular environment through DAMPs and/or PAMPs: i.e., efflux of potassium, mitochondrial and phagosomal injury-induced reactive oxygen species (ROS), lysosomal damage and the release of cathepsin B, all of which induce the oligomerization of inflammasomes, leading to the processing of pro-IL-1 $\beta$  into active IL-1 $\beta$  (Step 2).<sup>9,10</sup>

Various NLRP3-activating PAMPs have been reported; i.e., bacteria- or virus-derived RNAs, DNAs, or lethal toxins, flagellin/rod proteins, muramyl dipeptide (MDP), fungus-derived  $\beta$ -glucans, hypha mannan,

zymosan, and protozoon-derived hemozoin.<sup>11</sup> NLRP3-activating DAMPs have also been reported, i.e., self-derived glucose,  $\beta$ -amyloid, hyaluronan, ATP, cholesterol crystals, monosodium urate (MSU) crystals, calcium pyrophosphate dihydrate (CPPD) crystals, environment-derived alum, asbestos, silica, alloy particles, UV radiation, and skin irritants.<sup>11</sup> The activation of caspase-1 induces pyroptosis and the cleavage of IL-1 $\beta$  precursors. Pyroptosis occurs by the cleavage of gasdermin D (GSDMD) by activated caspase-1, generating a plasma membrane pore due to the polymerization of GSDMD.<sup>12-15</sup>

Non-canonical pathways of NLRP3 inflammasome activation by inflammatory caspase-4 (human), caspase-5 (human), and caspase-11 (mouse) have also been characterized. LPS is recognized by the CARD of caspase-4 (human) or caspase-11 (mouse), resulting in activation of the NLRP3 inflammasome.

## 3. Inflammasome activation and diseases

### 3-1. Autoinflammatory diseases

Variation in the *CIAS1* gene encoding NLRP3 (also called cryopyrin) of only a single amino acid can constitutively activate the NLRP3 inflammasome, leading to cryopyrin-associated periodic syndrome (CAPS). CAPS was first identified after the discovery

of MLRP3 and is an autoinflammatory disease with various manifestations but with the same causative gene. Examples include familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), neonatal-onset multisystemic inflammatory disease

(NOMID)/chronic infantile neurological, cutaneous, and arthritis syndrome (CINCA). Secretion of IL-1 $\beta$  is increased without stimulation or by small amounts of DAMPs or PAMPs.<sup>16-21)</sup>

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease and is an inherited autosomal recessive disorder characterized by activation

### 3-2. Metabolic syndrome

The NLRP3 inflammasome is also involved in low-grade subclinical inflammation induced by chronic exposure to high concentrations of free fatty acids and glucose, which reportedly cause increased  $\beta$ -cell apoptosis and insulin resistance in type 2 diabetic patients.<sup>25-27)</sup> *In vivo* experiments showed that islet amyloid polypeptide oligomers are co-produced with insulin and activate the NLRP3 inflammasome.<sup>28,29)</sup> High concentrations of glucose activate intracellular NF- $\kappa$ B, leading to the production of IL-1 $\beta$  precursors.<sup>25)</sup> Amyloid- $\beta$  can induce IL-1 $\beta$  via NLRP3 inflammasomes in a process involving the

### 3-3. Chronic inflammation and malignant tumors

Chronic inflammation increases the risk of malignant tumor.<sup>34)</sup> High expression of IL-1 $\beta$  is associated with human breast cancer tumor progression and prognosis.<sup>35)</sup> The expression of IL-1 $\beta$  and of its receptors in human breast carcinoma tissues leads

## 4. IL-18 and inflammasome activation

IL-18 is an IL-1 family cytokine and can be processed by caspase-1. The pathogenesis of IL-1-related diseases suggests the involvement of IL-18.<sup>37)</sup> IL-18 was originally identified as an interferon (IFN)- $\gamma$ -inducing factor.<sup>38)</sup> IL-18 is the factor most structurally related to IL-1 $\beta$ . IL-18 is synthesized

of the pyrin inflammasome due to mutations in the *MEFV* gene encoding the mutant pyrin.<sup>22)</sup> Other autoinflammatory diseases characterized by increased IL-1 $\beta$  secretion include NLRP12 autoinflammatory syndrome and high IgD syndrome (HIDS)/mevalonate kinase deficiency (MKD).<sup>23,24)</sup>

phagocytosis of amyloid- $\beta$  and subsequent lysosomal damage and release of cathepsin B in glial cells in patients with Alzheimer's disease (FAD).<sup>30)</sup> We have shown that direct interaction of amyloid peptides with NLRP3 in a cell-free system using a wheat germ cell-free synthetic system can promote the formation of NLRP3 inflammasomes.<sup>31)</sup> Several crystals also activate the NLRP3 inflammasome. For example, cholesterol crystals cause atherosclerosis, and sodium urate crystals cause gout.<sup>32)</sup> The above diseases activate inflammasomes and thus they can be referred to as inflammasomopathies.<sup>33)</sup>

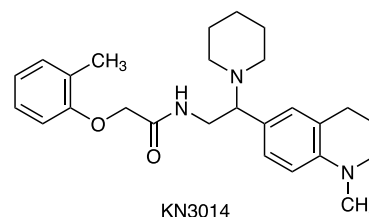
to the activation of malignant cells, contributing to angiogenesis, tumor growth, and tumor invasion in the cancer microenvironment.<sup>36)</sup> Thus, inflammasome activation could be an important therapeutic target for malignant tumors.

## 5. Inflammasome inhibitors

### 5-1. KN3014

KN3014: *N*-(2-(1-Methyl-1,2,3,4-tetrahydroquinolin-6-yl)-2-(piperidin-1-yl)ethyl)-2-(*o*-tolylloxy)acetamide (C<sub>26</sub>H<sub>35</sub>N<sub>3</sub>O<sub>2</sub>) has a molecular weight of 422 and contains a piperidine ring. KN3014 was selected from compounds that directly inhibit the interaction between the PYD domains of NLRP3 and ASC by protein-protein interaction inhibition screening of wheat germ cell-free synthesized proteins. The interaction between the PYD domains of AIM2 and ASC was also inhibited, suggesting that the compound has affinity for the PYD domain of ASC.<sup>43)</sup> KN3014 at a concentration of 50  $\mu$ M completely

inhibits the secretion of IL-1 $\beta$  by autoinflammation from peripheral blood mononuclear cells derived from patients with Muckle-Wells syndrome and does not inhibit the production of TNF $\alpha$ , indicating that it does not act in the Step 1 priming of IL-1 $\beta$  activation.<sup>43)</sup>

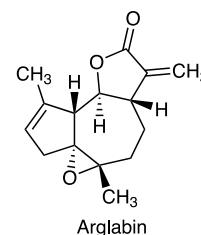


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## 5-2. Arglabin

Arglabin is a sesquiterpene- $\gamma$ -lactone extracted from the herb *Artemisia glabella*. Mouse peritoneal macrophages were pretreated with LPS (10 ng/mL) for 2 hours, incubated in the presence or absence of arglabin (50 nmol/L) for 1 hour, then cholesterol crystals (1 mg/mL) were added to all of the samples. After 6 hours of incubation, the expression of NLRP3, an IL-1 $\beta$  precursor, as well as caspase-1 precursor, and active caspase-1 in

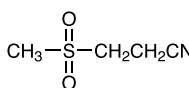
all of the cell lysates were analyzed. There was no change in the amount of IL-1 $\beta$  precursor, and activation of active caspase-1 from caspase-1 precursor was inhibited, indicating that this inhibitor specifically inhibits Step 2.<sup>44)</sup>



## 5-3. Dapansutrile (OLT1177)

Dapansutrile is an orally available sulfonyl compound that inhibits the release of IL-1 $\beta$  and IL-18, but not of TNF $\alpha$ . Dapansutrile thus inhibits Step 2 without affecting Step 1 in the presence of LPS (1  $\mu$ g/mL) for 4 hours and inhibits IL-1 $\beta$  release after stimulation with 10  $\mu$ M nigericin or 5 mM ATP. There

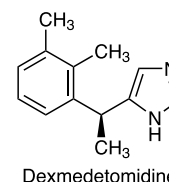
was no significant difference in the mRNA levels of the *nlrp3*, *asc*, *caspase-1*, *il1 $\beta$* , and *il18* genes, suggesting it does not affect priming (Step 1) in the formation of the NLRP3 inflammasome.<sup>45)</sup>



## 5-4. Dexmedetomidine

Dexmedetomidine is an  $\alpha_2$ -adrenergic receptor agonist effective in reducing IL-1 $\beta$  in lung parenchyma and in alveolar lavage fluid due to hyperoxic conditions in the lungs. Culturing RAW 264.7 mouse macrophage cells in a medium containing 100 ng/mL LPS for 1 hour, then with 1 nM dexmedetomidine and 5 mM ATP for 1 hour, inhibited IL-1 $\beta$  release into the

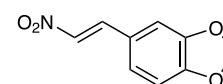
culture medium and suppressed the expression of NLRP3, pro-IL-1 $\beta$ , and caspase-1 precursor. These results suggest that the inhibition of IL-1 $\beta$  release is not due to direct inhibition of the inflammasome but rather to the inhibition of priming (Step 1).<sup>46)</sup>



## 5-5. 3,4-Methylenedioxy- $\beta$ -nitrostyrene (MNS)

3,4-Methylenedioxy- $\beta$ -nitrostyrene (MNS) is a  $\beta$ -nitrostyrene derivative exhibiting tyrosine kinase inhibitory activity. Mouse bone marrow-derived macrophages primed with LPS (100 ng/mL) for 4 hours, treated with MNS in the range of 0.5-10  $\mu$ M for 15 minutes, and incubated with ATP (5 mM) for 30 minutes, inhibited IL-1 $\beta$  release into the culture supernatant in

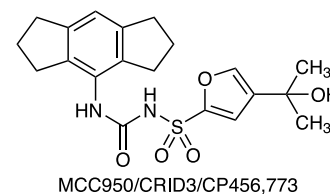
a dose-dependent manner. MNS inhibits only Step 2 because it does not affect TNF $\alpha$  production, an indicator of Step 1. MNS targets NLRP3 directly and inhibits oligomerization of the NLRP3 inflammasome (Step 2) by suppressing ATPase activity.<sup>47)</sup>



## 5-6. MCC950/CRID3/CP456,773

MCC950 was selected from the compounds from which diallyl sulfonylurea, a diabetes drug, was identified. MCC950 inhibits IL-1 $\beta$  precursor processing (Step 2).<sup>48,49)</sup> Initial studies showed that the priming of mouse bone marrow-derived macrophages with 10 ng/mL LPS or human peripheral blood monocyte-derived macrophages with 1  $\mu$ g/mL LPS for 3 hours, followed by 5 mM ATP for 30 minutes or 10  $\mu$ M nigericin for 1 hour, suppressed the release of IL-1 $\beta$

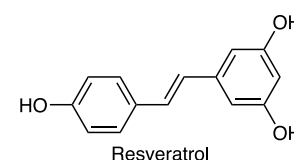
in a dose-dependent manner within the range of 0.01-10  $\mu$ M MCC950. MCC950 did not affect TNF $\alpha$  production, suggesting that MCC950 inhibits NLRP3 inflammasome oligomerization (Step 2) by affecting the ATP binding site of NLRP3.<sup>50,51)</sup>



## 5-7. Resveratrol

Resveratrol is a polyphenol found in grape peels.<sup>52)</sup> Pretreatment of mesenchymal stem cells (MSCs) with 200  $\mu$ M resveratrol for 1 hour before irradiation reduced the expression of NLRP3 and IL-1 $\beta$  induced by 4 Gy of

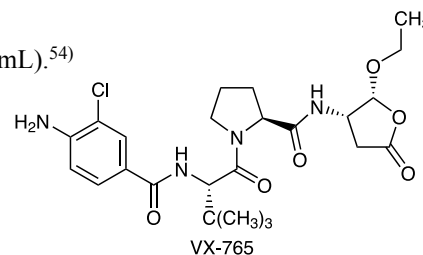
radiation, suggesting that inflammasome inhibition occurs at Step 1.<sup>53)</sup>



### 5-8. VX-765

VX-765 is an orally ingestible pro-drug that is metabolized to VRT-043198, a competitive inhibitor of caspase-1. IL-1 $\beta$  release from PBMCs (isolated from FCAS patients) was inhibited following incubation with

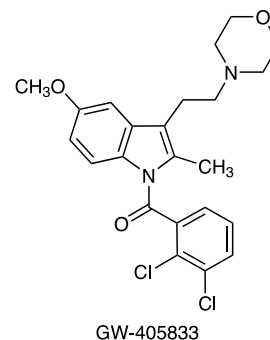
LPS (0.01-10 ng/mL).<sup>54)</sup>



### 5-9. GW-405833

GW-405833 is an agonist of the cannabinoid (CB) receptor 2 (CB2) for tetrahydrocannabinol, the main component of cannabis.<sup>55)</sup> GW-405833 affects the P2X7

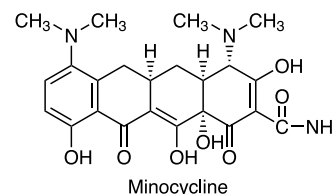
ATP receptor and inhibits activation of the NLRP3 inflammasome.<sup>56)</sup>



### 5-10. Minocycline

Minocycline is a tetracycline antibiotic. Minocycline inhibits the production of IL-1 $\beta$  and IL-18 from the BV2 mouse microglia cell line in a dose-dependent manner, as determined using the ischemia-reperfusion model. The production of TNF $\alpha$  and IL-6 was also suppressed, suggesting that the suppression of IL-1 $\beta$  production

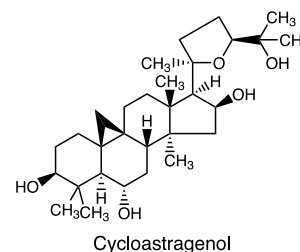
occurs at priming (Step 1) rather than inhibition of the inflammasome.<sup>57)</sup>



### 5-11. Cycloastragenol

Cycloastragenol is an aglycon derived from the hydrolysis of astragaloside IV. Cycloastragenol suppresses ER stress-induced ROS production from cells

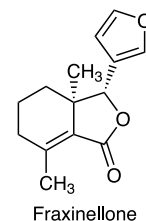
stimulated by palmitate in a dose-dependent manner.<sup>58)</sup>



### 5-12. Fraxinellone

Fraxinellone inhibits NF- $\kappa$ B in the macrophage cell line RAW264.7.<sup>59)</sup> Fraxinellone (10-30  $\mu$ M) inhibits LPS (500 ng/mL)-induced IL-1 $\beta$  production from THP-1-derived macrophages in a dose-dependent manner and inhibits Step 1 IL-6 and TNF production. Caspase-1

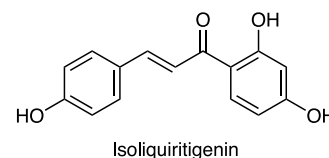
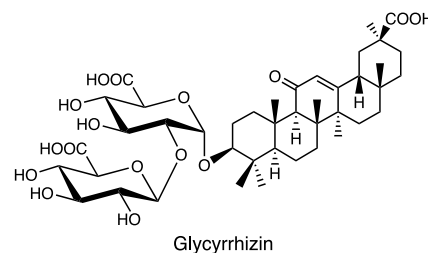
cleavage was also inhibited but the expression levels of the inflammasome components NLRP3, ASC, and caspase-1 were unaffected, suggesting a direct action on inflammasomes.<sup>60)</sup>



### 5-13. Glycyrrhizin and Isoliquiritigenin

Glycyrrhizin and isoliquiritigenin are the main active ingredients of Chinese herbal medicines such as Kanzo-to and Shakuyaku-kanzo-to. Glycyrrhizin and isoliquiritigenin inhibit pro-IL-1 $\beta$  production in mouse bone marrow-derived macrophages when incubated with LPS (1  $\mu$ g/mL) and isoliquiritigenin (1-10  $\mu$ M) or glycyrrhizin (0.1-1 mM) for 3 hours. When pre-incubated with LPS (200 ng/mL) for 3 hours and with glycyrrhizin or isoliquiritigenin and ATP, proIL-1 $\beta$  is not

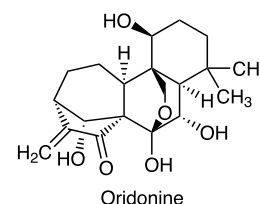
processed to IL-1 $\beta$ , suggesting that both active ingredients may affect Steps 1 and 2.<sup>61)</sup>



### 5-14. Oridonine

Oridonine is a component of the herb yama-hakka, found in Chinese herbal medicines such as Kami-shoyo-san and Bofu-tsusho-san. Oridonine inhibits caspase-1 cleavage, IL-1 $\beta$  release, and pyroptosis in mouse bone marrow-derived macrophages incubated with LPS (50 ng/mL) for 3 hours, followed by nigericin and 0.5-2

$\mu$ M oridonine for 30 minutes. Oridonine binds to the NOD domain of NLRP3 and inhibits the NLRP3 inflammasome by blocking the binding of NLRP3 to NEK7.<sup>62)</sup>



## In summary

We reviewed inflammasome activation, related diseases, and inflammasome inhibitors. The regulation of inflammasome activation is more complicated than described here and the pathophysiologies of the resulting disease are even more complicated.

The greater the types of inhibitors available for study, the greater the number of clinical application studies possible. We hope that this paper will help the development of therapeutic agents for inflammasome research and related diseases.

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