

# The Role of NLRP3 Inflammasome in Oral Squamous Cell Carcinoma

Rui Shi<sup>1,2</sup>, Xuan Zhuang<sup>3</sup>, Tong Liu<sup>4</sup>, Song-nan Yao<sup>3</sup>, Feng-shan Xue<sup>3</sup>

<sup>1</sup>Department of Oral and Maxillofacial Reconstruction, The Affiliated Hospital of Qingdao University 266600, Qingdao, 266555, People's Republic of China; <sup>2</sup>School of Stomatology of Qingdao University, Qingdao, 266555, People's Republic of China; <sup>3</sup>Cardiac Surgery Intensive Care Unit Department, the Affiliated Hospital of Qingdao University, Qingdao, 266555, People's Republic of China; <sup>4</sup>The Affiliated Tai'an City Central Hospital of Qingdao University, Taian, 271000, People's Republic of China

Correspondence: Song-nan Yao; Feng-shan Xue, Cardiac Surgery Intensive Care Unit Department of the affiliated hospital of Qingdao University 266600, Qingdao, People's Republic of China, Email yaosongnan@qdu.edu.cn; 15166616637@163.com

**Background:** Oral squamous cell carcinoma (OSCC) is the most common malignant tumor in the head and neck. More and more evidence emphasizes the importance of inflammation in the progression of OSCC. The main signaling pathway of acute and chronic inflammation consists of the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome.

**Objective:** This review focuses on the role of NLRP3 immune kinase body and giving a contribution to the development of new treatment strategies against OSCC.

**Conclusion:** The NLRP3 inflammasome plays a vital role in the pathogenesis and development of OSCC and may serve as a promising therapeutic target for autoimmune diseases.

**Keywords:** NLRP3<sub>1</sub>, oral squamous cell carcinoma<sub>2</sub>, Caspase-1<sub>3</sub>, GSDMD<sub>4</sub>, autophagy<sub>5</sub>

## Introduction

Oral squamous cell carcinoma (OSCC) is the most common type of cancer in the oral cavity, accounting for more than 90% of all oral cancers.<sup>1</sup> Although many improvements have been made in multimodality therapy including surgery, radiation, and chemotherapy, the overall survival rate of OSCC patients still ranges from 50% to 60%.<sup>2</sup> Therefore, the discovery of the molecular mechanisms regulating the occurrence and development of OSCC is of utmost importance, since it may ultimately lead to the establishment of more effective therapeutic strategies.

The innate immune response is initiated by pattern recognition receptors (PRRs).<sup>3</sup> It is the first line of defense against pathogen invasion and maintains the homeostasis. PRRs identify the presence of unique microbial components, which are the pathogens.<sup>4</sup> The endogenous stress induces the release of associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) which in turn activate the downstream inflammatory pathways to eliminate microbial infection and repair the damaged tissues.<sup>5</sup> The inflammasomes are a group of intracellular polypeptide complexes that recognize PAMP, DAMP, and activate inflammatory caspase-1. The NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome is a cytosolic multiprotein complex composed of the innate immune receptor protein NLRP3, the adapter protein ASC, and the protease caspase-1. It responds to microbial infection, endogenous danger signals, and environmental stimuli.<sup>6</sup> The assembled NLRP3 inflammasome contributes to the innate immune defense and homeostatic maintenance by activating caspase-1 to induce gasdermin-D (GSDMD)-dependent pyroptosis and the release of IL-1 $\beta$  and IL-18.<sup>7</sup> The active caspase-1 can also cleave GSDMD, whose n-terminal domain forms pores on the plasma membrane, thus triggering a dissolved, pro-inflammatory form of cell death, called scorch focal death.

NLRP3 inflammasome is crucial to trigger the immune defense against bacterial, fungal, and viral infections.<sup>8</sup> However, the relationship between NLRP3 inflammasome and OSCC needs a further detailed clarification. Therefore,

this article summarized the mechanism of inflammatory NLRP3 and its relationship with OSCC, providing a theoretical basis for the guidance in the diagnosis and treatment of OSCC.

## Overview of the NLRP3 Inflammasome

Inflammasome corpuscles are defined by their sensor protein (a PRR), which aggregates in response to the release of DAMPs to form a pre-caspase-1 activation platform or PAMPs.<sup>9</sup> Five PRR members form the inflammatory bodies: nucleotide-binding oligomerization domain (NOD), leucine repeat-rich protein family members NLRP1, NLRP3, NLRC4, melanoma 2 (AIM2), and pyrin that is missing in melanoma.<sup>10</sup> NLRP3 is an important PRR in the cytoplasm. It has a tripartite domain organization consisting of a carboxy-terminal leucine-rich repeat domain that possesses autoinhibitory functions and the ability of signal recognition, a central nucleotide-binding domain (NACHT) that has ATPase activity and mediates the self-oligomerization,<sup>11</sup> and an amino-terminal pyrin domain that recruits apoptosis-associated speck-like protein containing a CARD (ASC).

The role of the NLRP3 inflammasome in oral squamous cell carcinoma (OSCC) involves multiple aspects, including inflammation regulation, shaping of the tumor microenvironment, and the balance of cell proliferation and apoptosis. Its mechanism is complex and bidirectional. The NLRP3 inflammasome is activated by recognizing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs),<sup>9</sup> which promotes the maturation and release of IL-1 $\beta$  and IL-18 mediated by caspase-1. These pro-inflammatory factors can enhance the chronic inflammatory response in OSCC, thereby inducing DNA damage and promoting the malignant transformation of epithelial cells. After the activation of NLRP3, IL-1 $\beta$  can recruit immunosuppressive cells (such as regulatory T cells and M2 macrophages),<sup>10</sup> inhibit the anti-tumor immune response, and at the same time promote angiogenesis and matrix remodeling, providing support for tumor growth. In addition, common metabolic abnormalities in OSCC (such as hypoxia and reactive oxygen species accumulation) may further exacerbate inflammation and tumor invasion through the activation of NLRP3. The pyroptosis induced by the NLRP3 inflammasome plays a dual role in OSCC.<sup>5</sup> On the one hand, the cellular contents released during pyroptosis may promote local inflammation and tumor metastasis. On the other hand, excessive pyroptosis may also limit the proliferation of tumor cells. The specific effects may depend on the tumor stage and other signals in the microenvironment.

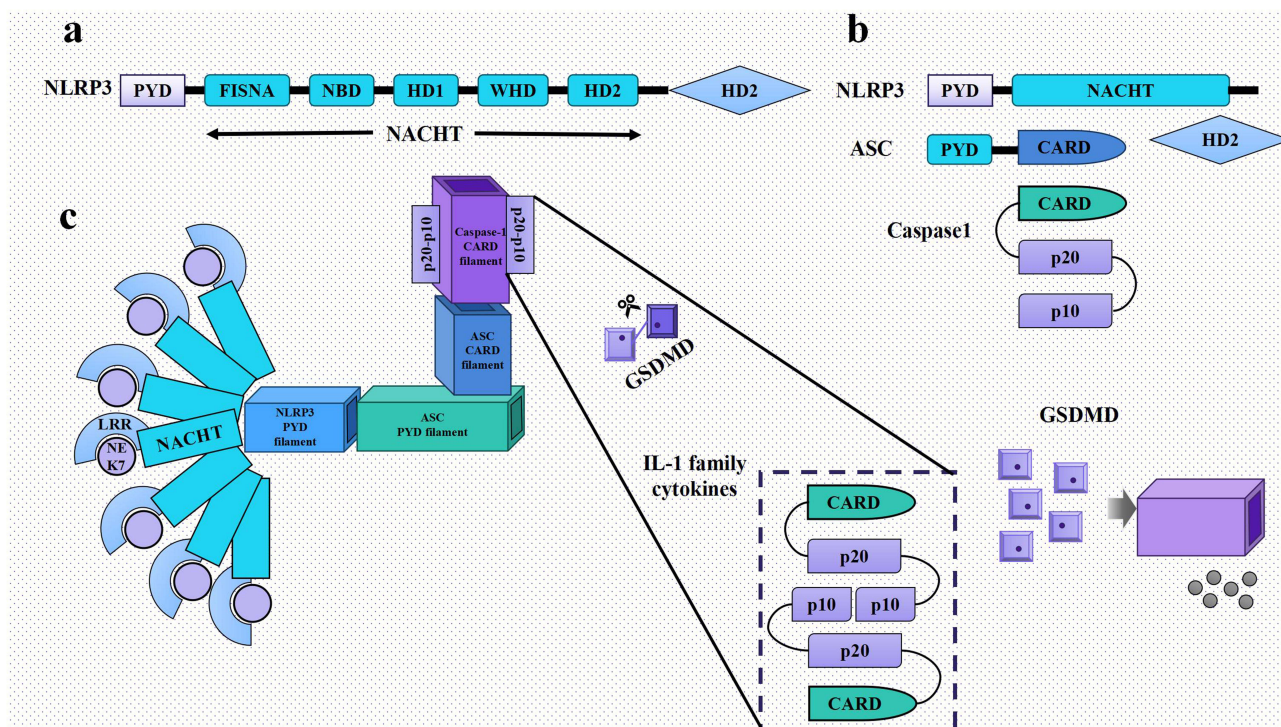
## Activation of the NLRP3 Inflammasome

NLRP3 can be activated by a variety of agonists, including PAMPs, such as viral RNA, microbial toxins, and bacterial surface components, and DAMPs, such as uric acid crystals, ATP, and aluminum adjuvants. The mechanism of the activation of the NLRP3 inflammasome is very complex. So far, studies showed that NLRP3 can be activated *in vivo* through three different signaling pathways: canonical pathways, non-canonical pathways, and alternative pathways (Figure 1).

### Canonical Pathway

At present, it is generally believed that the activation of a canonical NLRP3 pathway requires two steps: the priming step and the activation step.<sup>12</sup> The priming step involves ligands (such as LPS, pam3csk4, IL-1 TNF- $\alpha$ , and muramyl dipeptide) toll-like receptors (TLRs, such as TLR2 and TLR4) cytokine receptors (such as IL-1 receptor and TNF- $\alpha$  receptor), pattern recognition receptors (such as NOD1 and NOD2), which induce the activation of the transcription factor NF- $\kappa$ B and promote the NLRP3 and pro-IL-1 $\beta$ .<sup>13</sup> The priming step increases the expression of pro-IL-1 $\beta$  and pro-IL-18, which are substrates of caspase-1. The inflammasome components such as NLRP3, absent in AIM2, ASC and caspase-1 are also upregulated by NF- $\kappa$ B.<sup>14</sup> The priming step also regulates NLRP3 de-ubiquitylation, which is a prerequisite for its activation.

The activation step consists of NLRP3 occurs through oligomerization of the NACHT domain, and then ASC is recruited to generate the activation of caspase-1.<sup>15</sup> These three proteins are assembled into a poly protein called NLRP3 inflammasome. The activated caspase-1 converts IL-1 $\beta$  and IL-18 into their active forms, consequently inducing inflammation and also cleaves GSDMD, thus triggering a specific form of cell death called pyroptosis.



**Figure 1** NLRP3 domains. The NLRP3 inflammasome, depicting interaction of NLRP3 with ASC through their PYDs, and interaction of ASC with caspase-1 through their CARDs. A molecular model of the NLRP3 inflammasome pathway. The central adenosine triphosphatase (ATPase) domain, called NACHT, contains NBD, helical domain 1 (HD1), winged helical domain (WHD) and helical domain 2 (HD2); the C-terminal LRR domain (a), stepwise from upstream to downstream. The NLRP3 PYD filament recruits ASC by nucleating the ASC PYD filament. The CARD of ASC also clusters and forms a filament. The ASC CARD filament recruits caspase-1 by nucleating the caspase-1 CARD filament (b). The caspase-1 caspase domain (p20/p10) dimerizes and autoprocesses, resulting in its activation. The active caspase-1 then cleaves pro-cytokines in the IL-1 family to generate mature cytokines. Caspase-1 also cleaves GSDMD to generate an active GSDMD N-terminal fragment for membrane pore formation that facilitates cytokine release and pyroptosis (c).

## Non-Canonical Pathway

The non-canonical pathway of cell charring is a unique immune response to gram-negative bacteria. LPS of gram-negative bacteria can directly bind caspase-4, caspase-5, and caspase-11 to induce cell charring,<sup>16</sup> while caspase-1 is not required in this process. Pannexin-1 (Panx-1) is a membrane semi channel protein that can participate in the non-canonical pathway of cell scorch death by opening the channels of the cells.<sup>17</sup> First, LPS enters the cytoplasm through transfection, then caspase-4, caspase-5, and caspase-11 are activated. Caspase-5 and caspase-11 cleave GSDMD to form an N-terminal p30 structure, and membrane pores to destroy cell function, thus triggering cell scorch.<sup>18</sup> They can also trigger the opening of the gap junction protein Panx-1 channel, promote K<sup>+</sup> efflux, and induce the activation of NLRP3 inflammasome and IL-1 $\beta$ . ATP is released by the Panx-1 channel, promoting K<sup>+</sup> efflux and stimulating the assembly of the inflammatory bodies by activating the purinergic receptor P2X light gated ion channel (P2X7), finally causing cell pyroptosis.<sup>19</sup> Caspase-1 is not required in the non-canonical charring pathway, process, but its activation is required and the release of IL-1 $\beta$  is mediated. At present, the study on the non-canonical pathway of cell scorch death is not complete, and the relationship with the canonical pathway of cell scorch death needs further study.

## Alternative Pathway

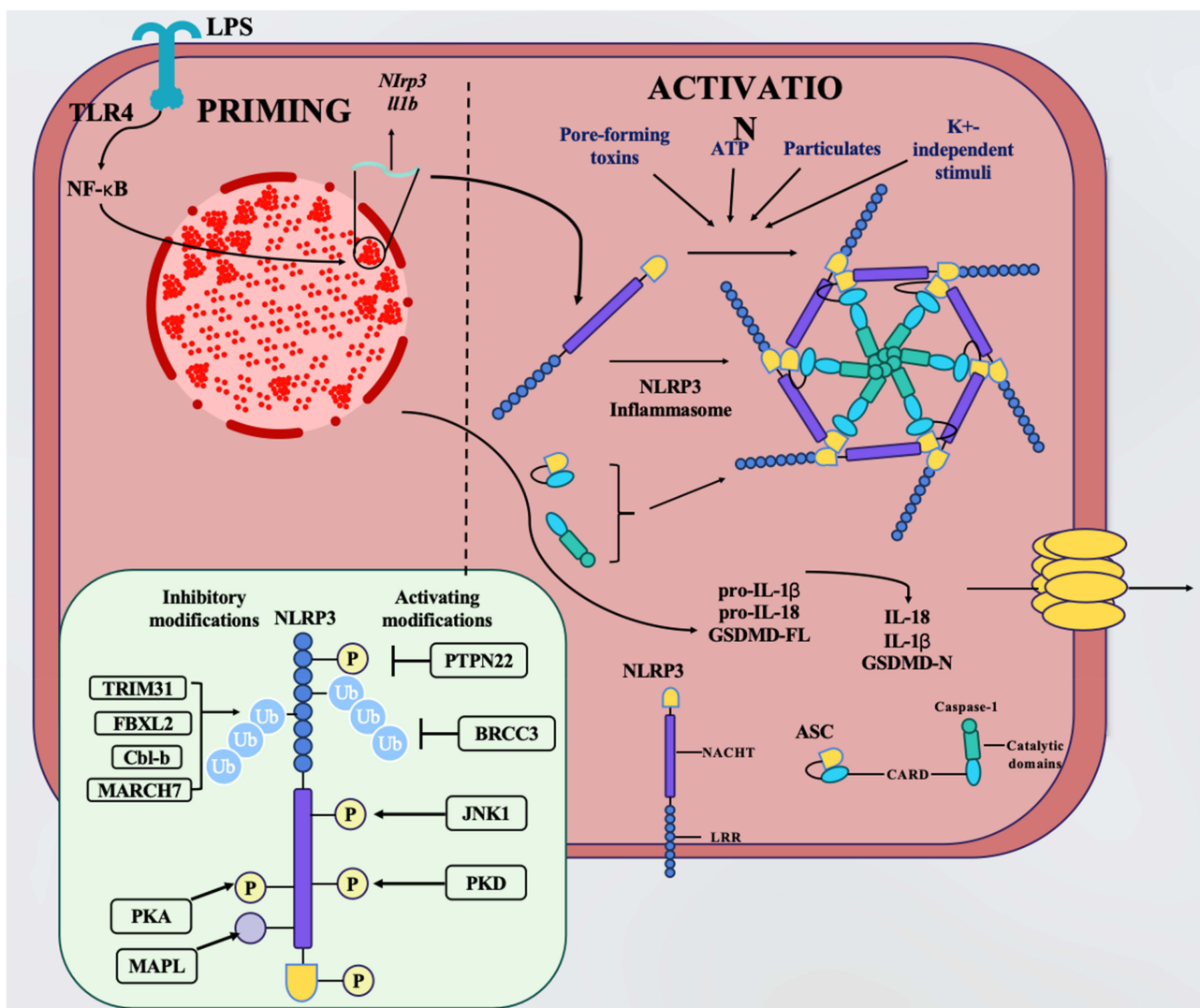
TLR ligands in the alternative pathways are insufficient to activate caspase-1 or induce the maturation of human and pig monocytes and IL-1 $\beta$  secretion.<sup>20</sup> The substitute NLRP3 inflammasome is activated through the TLR4-TRIF RIPK1-FADD-CASP8 signaling pathway upstream of NLRP3, but this new intralayer lacks any typical and atypical activation in NLRP3, including ASC spot formation, focal death induction or K<sup>+</sup> efflux. Recent studies showed that apolipoprotein C3 also activates caspase-8 dependent alternative NLRP3 endosomes in human monocytes.<sup>21</sup> In addition, this apolipoprotein interacts with Tlr2 and Tlr4 to induce them to form heterodimers, thereby promoting the activation of Ca<sup>2+</sup> through the

TLR SCIMP Lyn Syk TRPM2 axis, NADPH oxidase and caspase-8. Although caspase-8 is the key upstream molecule that activates the NLRP3 endoplasm, its exact mechanism is still unclear.<sup>22</sup> Therefore, the detailed mechanism of the interaction between NLRP3 and caspase-8 may be the next step to open a new door to alternative pathways (Figure 2).

## Inflammation in OSCC Tumor Microenvironment

Inflammatory signals are involved in many types of cancer, contributing to the induction of epithelial to mesenchymal transformation, epigenetic regulation, cell plasticity, generation of tumor stem cells, and tumor intratumoral heterogeneity.<sup>23,24</sup> The tumor microenvironment changes constantly during tumorigenesis due to the mutations of malignant cells. Inflammation increases the risk of cancer and the immune escape of cancer cells by releasing cytokines, growth factors, chemokines and angiogenic factors, as well as by generating genomic instability.<sup>25</sup>

Macrophages and fibroblasts are the most abundant cells in the tumor microenvironment.<sup>26</sup> Macrophages are the main cells expressing the NLRP3 inflammasome. The NLRP3 inflammasome is activated through mechanisms such as the



**Figure 2** The canonical pathway of NLRP3-inflammasome activation. Priming stimuli such as LPS drive NF-κB-dependent expression of NLRP3 and pro IL-1β, as well as NLRP3 licensing. Numerous PTMs have been described that promote either activation or inhibition of. Following the priming step, a broad spectrum of PAMP or DAMP stimuli triggers NLRP3 activation. Active NLRP3 oligomerizes and forms an inflammasome complex by nucleating the adaptor protein ASC to form a speck leading to the recruitment and activation of the inflammasome effector protein caspase-1. Caspase-1 processes pro-IL-1β and pro-IL-18 into their active forms. Caspase-1 also cleaves gasdermin D (GSDMD), which forms pores in the membrane that may serve as the conduit for IL-1β release, as well as leading to pyroptotic cell death.

recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) by pattern recognition receptors, as well as changes in ion currents and the generation of reactive oxygen species (ROS).

Once activated, the NLRP3 inflammasome prompts macrophages to release mature inflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ) and interleukin-18 (IL-18), triggering an inflammatory response. It can also induce pyroptosis of macrophages and regulate their polarization. In diseases, these two interact with each other and play a crucial role in the pathogenesis and development of infectious diseases, autoimmune diseases, metabolic diseases, etc. The energy metabolites secreted by fibroblasts are an important component of the tumor microenvironment, providing energy for tumor progression.<sup>27</sup> MicroRNAs (miRNAs) are the most sensitive biomarkers and therapeutic targets in oral squamous cell carcinoma (OSCC) within cancer-associated fibroblasts (CAFs) and tumors. When miR-138 is overexpressed, tumor invasiveness is inhibited, and the migration of OSCC cells and CAFs is reduced.<sup>28</sup> A study by Sun et al found that compared with normal fibroblasts,<sup>29</sup> miR-382-5p is overexpressed in CAFs, and its overexpression is associated with the migration of OSCC cells and invasive macrophages towards many chemotactic factor-controlled tissues.

Monocyte chemoattractant protein-1 (MCP-1, also called CCL2) is the most important in tumor progression. Tumor associated macrophages secrete cytokines, chemokines, and enzymes that stimulate cell growth, differentiation, tumor progression and angiogenesis.<sup>30</sup> Cytokines in the tumor microenvironment are produced by a variety of cell types and play their autocrine and paracrine role locally or the system directly interacts with their special membrane receptors. IL-1 family plays many roles in tumor immunity. IL-1 consists of seven ligands with proinflammatory activity (IL-1 $\alpha$ , IL-1 $\beta$ , IL-18, IL-33, IL-36 $\alpha$ , IL-36 $\beta$ , and IL-36 $\gamma$ )<sup>31</sup> and anti-inflammatory cytokines (IL-37 and IL-38), with a key role in host defense response and in the inflammatory response leading to the development of OSCC.

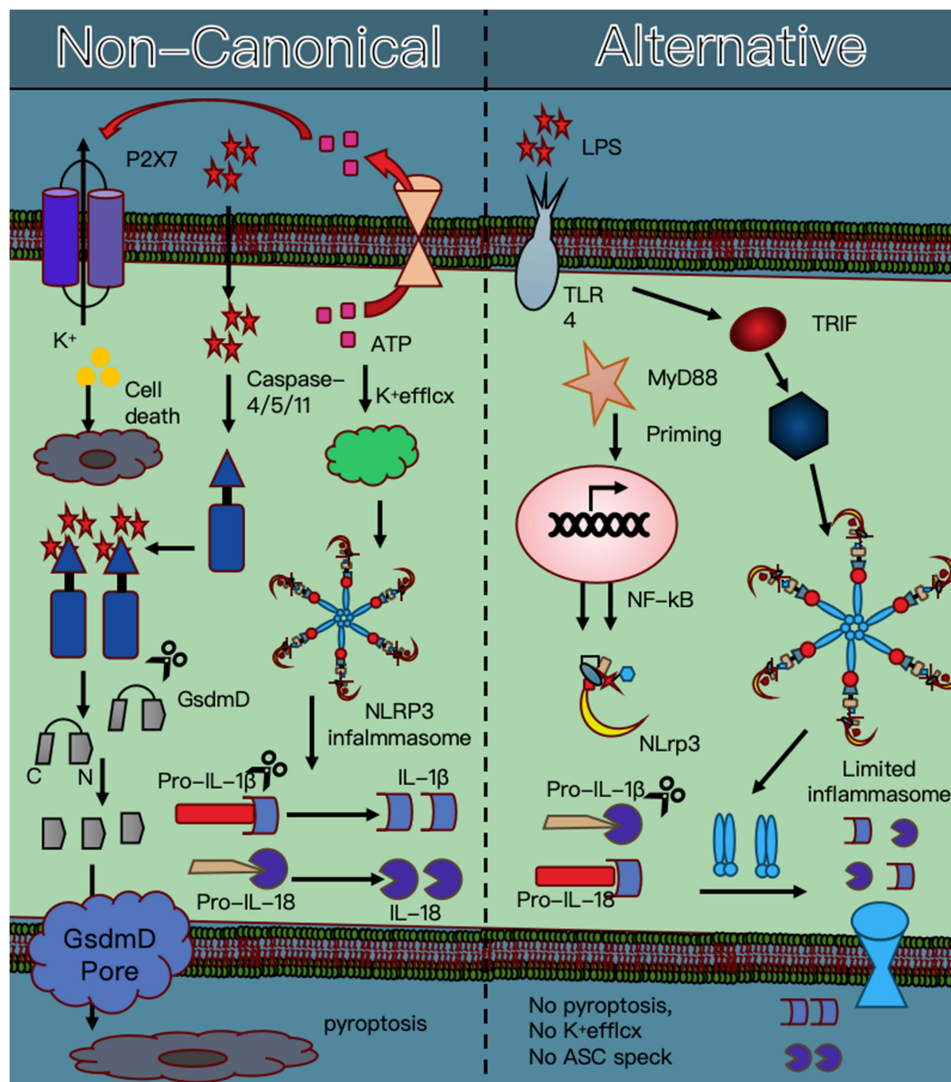
Some studies showed that the increased levels of several cytokines in the tumor, such as IL-6 and IL-8, are associated with metastasis and poor prognosis in patients with head and neck cancer associated with lymph node metastasis, including OSCC.<sup>32</sup> A study by Yadav et al showed that the treatment with recombinant IL-6 induces the epithelial to mesenchymal transition in CAL27 related to OSCC through the JAK/STAT3/Snail signaling pathway. Lee et al found that IL-1 $\beta$  secreted by infiltrating immune cells and OSCC cells at the tumor site may provide an inflammatory microenvironment that promotes angiogenesis and epithelial to mesenchymal transition, and releases carcinogenic cytokines, including IL-6 and IL-8 by inducing cancer cells.<sup>33</sup> In a word, inflammasomes regulate the expression of OSCC through different regulatory pathways, and an in-depth mechanism research can provide some guidance for the clinical treatment of OSCC (Figure 3).

## NLRP3 and OSCC

Chronic inflammation can lead to the disappearance of cell growth inhibition, autonomous angiogenesis, and the inhibition of apoptosis, leading to the transformation of cells from a benign to a malignant form, also enhancing metastasis.<sup>34</sup> Cytokines secreted by immune cells during tumor metastasis increase, leading to epithelial cells transformation into mesenchymal cells.<sup>35</sup> Therefore, the molecular mechanism between tumor and inflammation is the key to understand the treatment to prevent tumors and infection.

Han et al demonstrate the relationship between NLRP3 and the proliferation ability of OSCC cells and found that NLRP3 knockdown significantly reduces cell viability and affects the colony formation of OSCC cells. This result reveals that the inhibition of NLRP3 expression in turn inhibits the proliferation of OSCC. An OSCC xenotransplantation model was established in nude mice by the subcutaneous implantation of hnlrp3 transfected cells (shNLRP3) into the back of mice. The tumor volume was calculated, and the tumor weight was recorded. The results showed that NLRP3 silencing significantly reduced the tumor size and weight.<sup>36</sup> Therefore, *in vitro* and *in vivo* experiments proved that NLRP3 silencing impairs the function of NLRP3, thereby inhibiting the growth of OSCC *in vivo*.

IL-6 is a key factor in inducing the inflammatory response. Li et al evaluated the development of OSCC in relation to NLRP3 to further determine the function of IL-6 and the associated protein pathways. Their immunoblotting results showed that IL-6 treatment significantly increased the levels of pJAK2, pSTAT3, Sox4, and NLRP3 proteins, as well as ASC, pro-IL-1 $\beta$ , and IL-1 $\beta$  proteins associated with NLRP3 activation.<sup>37</sup> The expressions of pro-IL-18, IL-18, and NLRP3 in OSCC cells also increased with the increase in the concentration of IL-6. These results confirmed that IL-6 may activate the expression of NLRP3 and thereby promote the proliferation of OSCC cells. Meanwhile, through the



**Figure 3** The activation mechanism of non-canonical and alternative NLRP3-inflammasome pathway. Activation of non-canonical NLRP3 inflammatory bodies (left) is induced by transfection or internalization of infection into the cytoplasm. Caspase-11/4/5 induces cell charring through the cleavage of GSDMD. This process also activates pannexin-1 through caspase-11, releases ATP and induces  $K^+$  efflux, which drives the assembly of NLRP3 inflammatory bodies and the release of IL-1 $\beta$ . Alternative NLRP3 inflammatory bodies (right) are activated in response to LPS in human monocytes, requiring receptor interacting serine/threonine protein kinase 1 (RIPK1), FADD and caspase-8 to activate. This pathway is  $K^+$  independent and does not induce cell death.

JAK2/STAT3/Sox4/NLRP3 pathway, the authors found that Sox4 silencing was associated with a significant decrease in the levels of IL-6-mediated IL-1 $\beta$  and IL-18 in tumors, which was confirmed by IHC and ELISA.<sup>37</sup> Therefore, they demonstrated that inhibiting Sox4 can also significantly suppress the expression of NLRP3, thus affecting the tumor growth and inflammatory response in tumor-bearing mice induced by IL-6. The above experiments confirmed that the abnormal and excessive activation of NLRP3 significantly promotes the inflammatory response induced by IL-6,<sup>37</sup> thereby facilitating the occurrence and progression of OSCC.

## Therapeutic Potential of Inflammasome in OSCC

NLRP3 inflammasome is involved in a variety of inflammatory related diseases, including cancer, representing an attractive potential target for the development of a new treatment drug.<sup>38</sup> Several molecules and drugs can regulate the activity of NLRP3 inflammasome. Many scientists indirectly affect the function of the effectors of NLRP3 inflammasome by targeting other molecules. Up to now, the current treatment of diseases related to NLRP3 inflammasome involves  $\beta$  antibody or recombinant IL-1 receptor antagonists targeting IL-1 $\beta$  or IL-1 $\beta$ .<sup>39</sup> This review summarizes the function of

various small molecule inhibitors of NLRP3 inflammasome to lay a foundation for a better development of the mechanism of action of NLRP3 inhibitors potentially working against OSCC.

MCC950 is the most fully studied and effective inhibitor of NLRP3 inflammasome, with high specificity, and no inhibitory effect on NLRP1, AIM2, and NLRC4 inflammasome. It mainly reduces IL-1 by inhibiting ASC oligomerization in human and mouse macrophages  $\beta$ . The research on other tumors is fully developed, but only few studies focus on the role of MCC950 on OSCC. Lei et al found that MCC950 used to block the activation of NLRP3 immune kinase significantly reduces IL-1 $\beta$  in OSCC mice. The number of bone marrow derived suppressor cells, regulatory T cells and tumor associated macrophages is induced and reduced. The experimental results showed that NLRP3 enzyme/IL-1 $\beta$  pathway activation provides an inflammatory microenvironment that promotes the progression of head and neck squamous cell carcinoma.<sup>40</sup> Thus, MCC950 can effectively inhibit the activation of NLRP3 through this pathway, thereby inhibiting its progress.

Oridonin is a bioactive diterpenoid purified from *Rabdosia rubescens*, which is a plant with proved cancer inhibitory effects in many tumors. Its mechanisms of action include the inhibition of proliferation, cell cycle arrest and induction of autophagy. Previous studies showed that oridonin regulates a series of signal transcriptions and inhibits apoptosis through regulatory pathways. It significantly up-regulated Bax protein and down-regulated Bcl-2 in OSCC cells.<sup>40</sup> The increase of Bax/Bcl-2 ratio is accompanied by the cleavage of caspase 9 and the downstream caspase 3 and PARP, indicating that the activation of this protein involved in the apoptosis of OSCC cells is induced by oridonin. Yang et al found that oridonin is effective against OSCC by inhibiting its proliferation, as well as inducing G2/M phase arrest and apoptosis of OSCC cells. Oridonin exerts its anti-cancer ability at least partially by inhibiting the PI3K/AKT signaling pathway. These findings suggest that oridonin may be an anticancer drug effective in the treatment of OSCC.

BAY 11-7082 is a sulfonic acid derivative and a strong inhibitor of NLRP3 inflammasome by inhibiting the ATPase activity of NLRP3, which is necessary for its activation. Scuderi et al evaluated the beneficial role of BAY-117082 in vitro and in vivo by xenotransplantation models of oral cancer. This compound significantly reduces the expression of NLRP3, ASC and caspase-1. NLRP3 promotes the maturation of pro-IL-1 $\beta$  and pro-IL-18 into their bioactive forms IL-1 $\beta$  IL-18, the latter inducing inflammation and cell necrosis. The expression of IL-18 is significantly reduced, indicating that BAY-117082 indeed inhibits cell inflammation and necrosis. In addition, BAY-117082 treatment reduces CD4, CD8 and CD30 in a dose-dependent manner compared with the control group.<sup>40</sup> Therefore, BAY-117082 can be considered as an effective therapeutic strategy to reduce or offset the progress of OSCC and regulate NLRP3 inflammasome and apoptosis. However, further research is needed for a better understanding of the role of the pathways regulating these effects in oral carcinogenesis.

DDP is a first-line clinical treatment for OSCC that induce focal death of OSCC,<sup>41</sup> with a mechanism depending on the GSDME/caspase-3 pathway. Low GSDME expression is found in many tumor cells compared to normal cells, due to the abnormal methylation of high GSDME. Therefore, the use of DNA methyltransferase inhibitors, such as decitabine, in combination with DDP induces the expression of GSDME and effectively promotes cell death. When GSDME is overexpressed, the inhibition of caspase-3 by the specific inhibitor Z-DEVD-FMK inhibits the activation of GSDME and the scorch death of OSCC cells, suggesting the involvement of caspase-3 through GSDME.

## Summary and Perspective

Although NLRP3 inflammasome has specific key functions in the immune system, its role in cancer is still complex and elusive. Therefore, additional studies should be performed to solve the following problems to further understand these effects: the factors driving NLRP3 inflammasome activation in tumors. Potential crosstalk pathways and molecular interactions that affect the regulation of NLRP3 inflammasome; the effect of NLRP3 inflammasome on the regulation of immune cells, anti-tumor immunity, and immunotherapeutic efficiency. Targeting some of its downstream pathways in NLRP3 inflammatory tumors, alone or in combination with chemotherapy or other immunotherapeutic methods, may have a potential effect against cancer. Overall, NLRP3 inflammasome plays a crucial role in the progression of OSCC and has clinical research value.

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## Disclosure

The authors declare no conflict of interest.

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