综述

# NLRP3炎症小体在急性肺损伤中的作用和机制

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**摘要：**急性肺损伤(acute lung injury，ALI)是发病率及病死率极高的严重呼吸系统疾病，尽管呼吸支持技术取得了重要进步，但仍然缺乏有效的治疗手段。过度激活的NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor thermal protein domain associated protein 3，NLRP3)炎症小体通过诱导肺泡巨噬细胞焦亡、破坏肺泡-毛细血管屏障、促进中性粒细胞的募集并参与中性粒细胞胞外陷阱释放等机制推动ALI的进展。本文综述了NLRP3炎症小体在ALI中的作用机制及ALI中NLRP3炎症小体与调节性细胞死亡间的串扰，旨在为急性肺损伤的治疗和研究提供新的视角。

**关键词：**急性肺损伤；NLRP3炎症小体；细胞死亡

# Role and mechanism of NLRP3 inflammasome in acute lung injury

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**Abstract:** Acute lung injury (ALI) is a serious respiratory disease with high morbidity and mortality, and despite important advances in respiratory support techniques, effective treatment is still lacking. Over-activated NLRP3 (NOD-like receptor thermal protein domain associated protein 3) inflammatory vesicles contribute to the progression of ALI by inducing alveolar macrophage pyroptosis, disrupting the alveolar-capillary barrier, promoting neutrophil recruitment, and engaging in neutrophil extracellular trap release. This paper reviews the mechanisms of NLRP3 inflammasome action in ALI and the crosstalk between NLRP3 inflammasome and regulatory cell death in ALI, aiming to provide new perspectives for the treatment and study of acute lung injury.

**Key Words:** acute lung injury; NLRP3 inflammasome; cell death

急性肺损伤(acute lung injury，ALI)是发病率及病死率极高的一组综合征，是由直接或间接因素导致的急性肺换气功能下降，其更严重的形式表现为急性呼吸窘迫综合征(acute respiratory distress syndrome，ARDS)[1]。全球范围内每年约有300万ALI患者，约占重症监护病房患者的10%。在中国，ALI/ARDS的危险因素及死亡率预估与欧美国家相似，这意味着中国每年约有67万ALI患者[2]。尽管呼吸支持技术及重症医学在不断发展，但ALI的病死率仍高达40%[3]。ALI病理学主要表现为弥漫性肺泡损伤和微循环内皮屏障的破坏[4]。1967年被首次报道以来，尽管在了解ALI的流行病学、发

收稿日期：2023-10-23
基金项目：国家自然科学基金面上项目(82272212)
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病机制和病理生理学方面取得了较大的进展，但对于ALI仍然没有有效的治疗策略。目前ALI/ARDS的治疗方案大多是支持性的，包括肺保护性通气、俯卧位通气和全身性使用皮质类固醇，尚无被批准用于临床试验的药物或干预措施[5]。NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor thermal protein domain associated protein 3，NLRP3)是定位于细胞质的模式识别受体，属于NOD样受体(NOD-like receptor，NLR)家族[6]。NLRP3炎症小体对于先天免疫及机体微环境稳态至关重要，但异常激活的NLRP3炎症小体被报道与过度的炎症反应相关，在多种炎性疾病中加重疾病进展[7]。ALI是炎症级联的过程，过度激活的NLRP3炎症小体通过诱导肺泡巨噬细胞焦亡、破坏肺泡-毛细血管屏障、促进中性粒细胞的募集并参与中性粒细胞胞外陷阱释放等机制促进ALI的进展。本文就急性肺损伤中NLRP3炎症小体的作用及相关机制展开综述。

## 1 NLRP3炎症小体

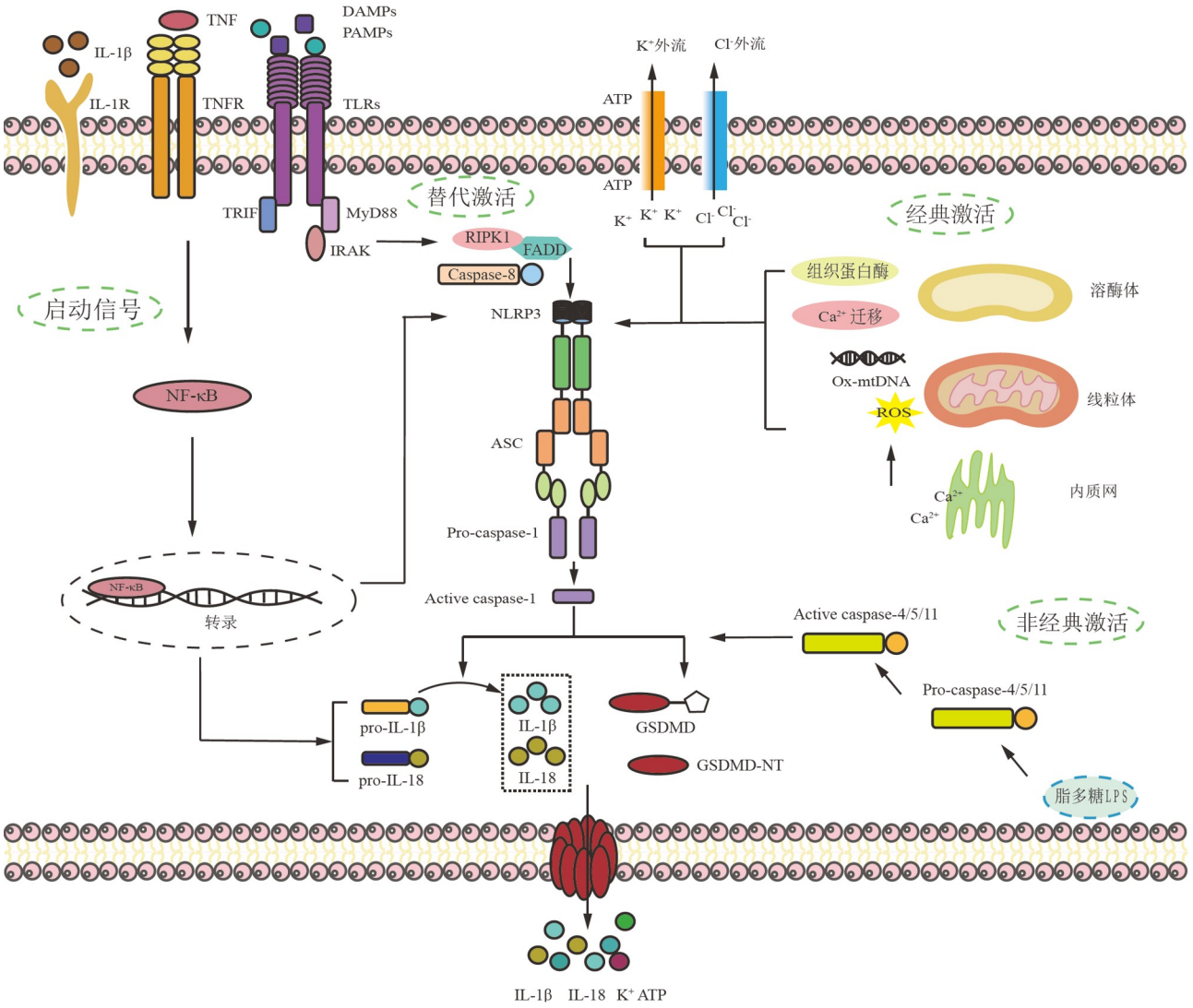
### 1.1 NLRP3炎症小体的结构与功能

NLRP3炎症小体是NLRP3蛋白、凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a CARD，ASC)和半胱天冬酶1前体(pro-cysteinylaspartate specific proteinase-1，pro-caspase-1)组成的复合体，在中性粒细胞、巨噬细胞、树突细胞、T细胞等免疫细胞的细胞质中表达[8-10]。NLRP3蛋白主要包含三部分结构域：具有腺苷三磷酸(adenosine triphosphate，ATP)催化功能的中央核苷酸结合寡聚(central nucleotide-binding and oligomerization，NACTH)结构域、C端富含亮氨酸的重复序列(leucine-rich repeat，LRR)以及N端PYD结构域(pyrin domain)[11]。NLRP3识别损伤相关分子模式(damage-associated molecular patterns，DAMPs)或病原体相关分子模式(pathogen-associated molecular patterns，PAMPs)后通过NACHT结构域自寡聚化为三聚体，随后通过PYD结构域相互作用与接头蛋白ASC结合[12]。ASC招募并促进pro-caspase-1的自我成熟，成熟的具有酶活性的异二聚体caspase-1通过切割细胞焦亡蛋白D(gasdermin D，GSDMD) N端和自抑制C端之间的连接位点，释放N端成孔片段GSDMD-NT，N端片段与质膜上的酸性磷脂结合寡聚形成孔道[13]，导致白介素(interleukin，IL)-1β和IL-18的释放[14]，同时细胞间质的液体通过该孔道渗入胞内导致细胞肿胀，造成细胞膜完整性破坏，细胞内容物如$K^+$、$Ca^{2+}$及ATP等流出而诱发细胞焦亡[15]。

### 1.2 NLRP3炎症小体的激活

NLRP3炎症小体的激活主要分为三种：经典激活方式、非经典激活方式以及替代激活方式。NLRP3炎症小体的经典激活通常需要两步(图1)，即启动信号及激活信号。启动信号通常由Toll样受体(Toll-like receptor，TLR)或细胞因子受体与对应的配体结合后触发，通过核因子κB (nuclear factor kappa B，NF-κB)信号通路上调NLRP3、pro-IL-1β及pro-IL-18的转录和翻译，为NLRP3炎症小体的组装及激活提供物质基础[16,17]。此外，启动信号还参与NLRP3炎症小体的翻译后修饰(post-translational modifications，PTM)，如泛素化及磷酸化[18,19]。激活信号是NLRP3识别PAMPs或DAMPs后通过ASC组装为NLRP3炎症小体的过程[16]。NLRP3炎症小体可由多种信号激活，如溶酶体破裂、离子通量变化($K^+$外流、$Ca^{2+}$外流及$Na^+$外流等)、活性氧(reactive oxygen species，ROS)的释放[20]及线粒体损伤时释放的脱氧核糖核酸(oxidized mitochondrial DNA，Ox-mtDNA)等，其中$K^+$外流被认为是NLRP3的主要激活信号[21]。

此外，NLRP3炎症小体还存在非经典激活方式和替代激活方式。与经典激活方式不同，非经典激活方式不需要启动信号的参与，进入细胞内的细菌脂多糖(lipopolysaccharide，LPS)直接与caspase-11/4/5结合介导GSDMD的切割，GSDMD N端成孔作用导致$K^+$的外流，进而激活NLRP3炎症小体[22-24]。替代激活方式是在人类单核细胞中观察到的一种新型NLRP3炎症小体激活方式，由NLRP3炎症小体上游TLR4-TRIF-RIPK1-FADD-CASP8信号通路激活，该激活方式并不具备NLRP3炎症小体激活的典型特征，如ASC的形成、细胞焦亡及$K^+$流出[25]，但可以快速激活IL-1β的释放。研究显示，在小鼠骨髓来源巨噬细胞中，刺激TLR4、TLR7、TLR9受体可快速激活NLRP3炎症小体，但不导致细胞焦亡及IL-1β的释




IL-1R：白介素-1受体(interleukin 1 receptor)；TNF：肿瘤坏死因子(tumor necrosis factor)；TRIF：β干扰素TIR结构域衔接蛋白(TIR domain-containing adaptor-inducing interferon-β)；MyD88：髓样分化因子88；IRAK：白介素1受体关联激酶(interleukin 1 receptor associated kinase)；RIPK1：受体相互作用激酶1(receptor-interacting protein kinase 1)；FADD：Fas相关死亡域蛋白(Fas-associated with death domain protein)

**图1 NLRP3炎症小体活化途径**

放，仅促进IL-18的释放[26]。

### 1.3 NLRP3炎症小体激活信号的调节

NLRP3炎症小体的激活信号受多种PTM的调节，其中泛素化和磷酸化是最具代表性的调节方式。

NLRP3炎症小体激活过程受泛素化及去泛素化调节。NLRP3蛋白通常在静息状态下表现为泛素化，在启动和激活时呈去泛素化[27]。多种E3泛素连接酶被报道负向调控NLRP3炎症小体激活，如膜相关环指蛋白7促进K48连接的多泛素化，导致多巴胺D1受体下游NLRP3蛋白降解[28]。此外，含有三基序的蛋白质31可直接与NLRP3炎症小体组分ASC蛋白相互作用，通过蛋白酶体途径降解NLRP3炎症小体从而负向调节NLRP3的激活[29]。环指蛋白125可启动NLRP3 LRR结构域K63连接的多泛素化以促进降解[30]。Casitas-B系淋巴瘤蛋白-b通过其泛素相关区域与NLRP3 LRR结构域K63泛素链结合，促进K48连接的多泛素化，导致NLRP3蛋白降解[30]。同样，β-转录重复包含蛋白1可通过K27连接的多泛素化促进NLRP3蛋白酶体途径降解[31]。值得注意的是，并非所有E3泛素连接酶均负向调节NLRP3激活。研究显示，E3泛素连接酶Pellino2通过催化NLRP3 K63连接的多泛素化促进

NLRP3蛋白活化[32]。去泛素化酶对NLRP3炎症小体的激活和组装同样具有重要意义[33]。去泛素化酶通过招募E3泛素连接酶控制NLRP3炎症小体的激活，如泛素特异性蛋白酶5通过募集膜相关环指蛋白7选择性促进NLRP3蛋白K48连接的多泛素化，并通过自噬相关蛋白5自噬溶酶体途径降解NLRP3炎症小体[34]。目前，多种去泛素化酶被报道调控NLRP3炎症小体的激活，如泛素特异性蛋白酶1/7/19/22/47等[35-38]。

磷酸化可发生于NLRP3的NACHT、LRR及PYD结构域，对NLRP3炎症小体的激活和组装具有重要意义[39]。LRR结构域中Tyr861位点(小鼠为Tyr859)是第一个被定义的磷酸化位点，非受体蛋白酪氨酸磷酸酶22通过NLRP3 Tyr861位点的去磷酸化促进NLRP3炎症小体活化[40]。LRR结构域的磷酸化也可调控NLRP3炎症小体组装过程，酪蛋白激酶1A1激酶促进NLRP3在S806位点(小鼠为S804)磷酸化，通过调控NLRP3对NIMA相关激酶7的募集从而调控NLRP3的组装[33]。随着越来越多磷酸化位点及功能被发现，对NLRP3炎症小体活化的认识将进一步加深。

## 2 NLRP3炎症小体与ALI

ALI是由多种实质细胞及免疫细胞参与的病理生理过程。ALI主要病理特征包括弥漫性肺泡损伤以及微循环血管内皮屏障的破坏。同时，ALI的进程也是复杂的炎症级联反应，涉及大量的炎症细胞及细胞死亡[1,41]。异常激活的NLRP3炎症小体通过释放炎症因子、诱导细胞焦亡参与多种炎性疾病的进展[42]。在ALI期间，抑制异常激活的NLRP3炎症小体显著减少了巨噬细胞焦亡、中性粒细胞的募集、炎症因子的释放以及微循环血管内皮屏障的损伤。此外，NLRP3炎症小体被报道是多种细胞死亡方式的“桥梁”[43]。

### 2.1 ALI期间NLRP3炎症小体诱导肺泡巨噬细胞焦亡及炎症因子释放

肺泡巨噬细胞(alveolar macrophage，AM)被认为是ALI的“开关”细胞。在ALI早期，AM通过分泌促炎因子加重炎症级联反应；在ALI炎症末期，AM通过分泌抗炎因子如IL-10等促进炎症的消退以及组织修复[44]。AM焦亡程度与ALI预后密切相关[45]。ALI期间激活的NLRP3炎症小体通过促进pro-caspase-1的自我成熟诱导AM焦亡[46]。随着AM细胞质膜完整性的破坏，细胞内容物从胞内释放，如ATP，$K^+$，ROS，大分子蛋白如ASC、高迁移蛋白1(high mobility group protein 1，HMGB1)等，释放的DAMPs造成线粒体功能障碍、溶酶体损伤及内质网应激等，进而触发一系列分子事件使炎症信号进一步扩大[47]。同时，DAMPs将进一步激活NLRP3炎症小体以促进炎症因子释放，最终爆发炎症因子风暴推动ALI的进展[48]。HMGB1是经典的DAMPs，通过激活NLRP3炎症小体而加重ALI[49]。通过敲低NLRP3炎症小体中的*ASC*基因表达，减少AM焦亡可减少HMGB1的分泌[50]。使用NLRP3抑制剂或靶向敲除AM中的*NLRP3*基因以减少AM焦亡也可有效减轻ALI的损伤程度[51,52]。此外，当焦亡发生时(GSDMD-N端被切割)，部分巨噬细胞会继续“存活”且具有持续释放炎症因子及抗原递呈的能力，这种现象称为“超活化”，与细胞炎症因子风暴密切相关[53]。综上，NLRP3诱导的AM焦亡以及巨噬细胞超活化是ALI期间炎症因子风暴的机制之一。

### 2.2 NLRP3炎症小体促进中性粒细胞的募集以及NETs的释放

中性粒细胞的浸润是ALI急性渗出期的病理学标志之一[54]。急性渗出期间，聚集的中性粒细胞通过释放细胞因子、脱颗粒蛋白酶、ROS及中性粒细胞胞外陷阱(neutrophil extracellular traps，NETs)等造成组织损伤及细胞死亡[55]。NLRP3炎症小体上调趋化因子CXCL12蛋白表达从而促进中性粒细胞的募集，通过抑制NLRP3的激活可以减少ALI期间中性粒细胞的浸润[56]。积聚于肺泡的中性粒细胞通过释放NETs直接损伤内皮细胞及肺泡上皮细胞[57]。研究显示，NLRP3炎症小体激活后，通过caspase-1切割GSDMD-N端导致中性粒细胞核膜和质膜损伤，促进NETs的释放[58]。在上述研究中还观察到ASC聚集，提示NLRP3炎症小体与中性粒细胞NETs的释放间存在一种潜在机制，有待进一步研究。

### 2.3 调节性T细胞通过NLRP3炎症小体推动ALI的进展

调节性T细胞来源于胸腺，根据作用的不同可

以分为自然调节性T细胞(natural regulatory T cell，nTreg)及适应性调节T细胞(induced regulatory T cell，iTreg)[59]。传统观点认为，T细胞主要通过提呈抗原参与适应性免疫，但越来越多的证据显示调节性T细胞在急性炎症及组织损伤中具有重要的作用[60]。急性相ALI/ARDS患者尸检结果显示，肺间质存在大量的$CD8^+$ T细胞及$CD4^+$ T细胞，暗示调节性T细胞参与了ALI急性期的弥漫性肺泡损伤[61]。$CD8^+$ T细胞被报道参与疟疾相关肺损伤中肺泡上皮的损伤[62]。间充质干细胞通过抑制$CD8^+$ T细胞发挥治疗作用[63]。$CD4^+$ T细胞分泌富含甘油二酯激酶κ的细胞外囊泡，通过调节氧化应激和炎症促进脓毒症诱导的ALI[60]。ALI期间，$CD4^+$T细胞向辅助性T细胞17(T helper cell 17，Th17)及调节性T细胞分化，Th17细胞通过分泌促炎因子(TNF-α、IL-17、IL-1α)推动炎症进展，而调节性T细胞分化则通过分泌抗炎因子IL-10、转化生长因子-β(transforming growth factor-β，TGF-β)等在组织损伤后修复中扮演重要角色。因此，调节Th17/Treg细胞比例被认为是ALI治疗靶点之一[64]。ALI期间Th17细胞被报道通过分泌IL-17A激活NLRP3诱导细胞焦亡，加重肺损伤[65]。此外，Th17细胞分泌IL-1α也依赖于NLRP3炎症小体活化，NLRP3炎症小体通过与半胱天冬酶-8及半胱天冬酶-3蛋白发生级联，从而切割细胞焦亡蛋白E，促进IL-α的分泌[66]。这些结果表明，调节性T细胞通过激活NLRP3炎症小体促进ALI的进展。

### 2.4 ALI期间NLRP3炎症小体下游炎症因子IL-1β及IL-18加重肺组织损伤

IL-1β及IL-18是ALI期间重要的促炎因子。两者的成熟及分泌高度依赖NLRP3炎症小体的激活[67,68]。IL-1β与肺屏障功能密切相关，研究显示，IL-1β与人表皮生长因子受体及紧密连接蛋白claudins相互作用造成肺屏障功能完整性的丧失引起肺水肿[69]。IL-1β还参与肺泡内皮细胞胞旁间隙的形成，通过αVβ6/TGF-β通路直接增加肺泡Ⅱ型细胞通透性继而加重肺水肿[70]。此外，IL-1β通过下调肺泡上皮细胞中$Na^+$-$K^+$泵等离子通道表达和功能，影响肺部炎症时渗出的吸收，推动肺水肿的发生，进而导致气体交换障碍诱发低氧血症和高碳酸血症[71]。IL-1β还可与细胞表面IL-1受体结合上调黏附因子表达促进炎症细胞的募集并释放大量炎症因子，或通过下游的IL受体通路放大炎症信号[72]。IL-18是ALI/ARDS死亡率的预测因子[73]，其通过增加血管细胞黏附因子-1表达、一氧化氮合成和趋化因子产生诱导炎症反应[74]。在小鼠机械通气模型中，小鼠肺泡灌洗液中Il-18显著升高，应用Il-18中和抗体或基因敲除*Il-18*和*caspase-1*能减少肺损伤的反应[75]。高达40%的ARDS患者在治疗过程中会发生肺部二重感染，其发展将导致过高的临床病死率[76]。临床研究显示，发生肺部二重感染的ARDS患者中IL-18水平显著增加，提示IL-18可作为独立生物标志物预测ARDS严重并发症的高危患者[77]。同时，IL-18可通过上调髓系细胞触发受体1促进ALI炎症的进展[78]。综上所述，NLRP3炎症小体下游炎症因子可通过不同机制介导ALI的发生发展。

### 2.5 NLRP3炎症小体破坏肺泡-毛细血管膜屏障

微血管内皮通透性增加是ALI早期的病理标志，内皮细胞作为半透性屏障，与ALI进展及肺水肿关系密切[79]。神经酰胺是ALI中肺过度炎症反应和肺水肿的重要介质，神经酰胺导致NLRP3炎症小体激活、促炎细胞因子产生和肺微血管内皮细胞屏障功能障碍[80]。研究显示，神经酰胺通过调节硫氧还蛋白互作蛋白的表达激活NLRP3炎症小体，导致肺微血管内皮屏障功能损伤[81]。补体C3a在ALI中表达增高，C3a通过C3a受体介导肺血管内皮细胞焦亡，加重ALI，C3a受体抑制剂通过抑制NLRP3炎症小体激活及caspse-11的活化，减少ALI期间肺血管内皮细胞的焦亡，减缓ALI的进展[82]。此外，NLRP3炎症小体下游炎症因子IL-1β通过抑制VE钙黏蛋白，损害内皮细胞的完整性，加重ALI期间的内皮损伤[83]。综上，抑制NLRP3炎症小体的激活对ALI期间微血管内皮通透性具有保护作用。

## 3 ALI中NLRP3炎症小体与调节性细胞死亡的串扰

细胞死亡是细胞炎症因子风暴重要的发生机制，细胞死亡时释放的DAMPs刺激先天免疫细胞持续分泌炎症因子。此外，细胞死亡时可改变内皮细胞的通透性，使组织或器官暴露于细菌性的

PAMPs，导致炎症信号扩大[84]。炎症级联反应导致ALI病程进展，涉及多种细胞死亡类型[85]。传统的细胞死亡可分为两类，即调节性细胞死亡(regulated cell death，RCD)及意外性细胞死亡(accidental cell death，ACD)[86]。细胞焦亡、凋亡及程序性坏死是目前研究比较明确的RCD。研究显示，NLRP3炎症小体与多种RCD存在串扰(crosstalk)[87]，讨论NLRP3炎症小体与不同细胞死亡间的串扰旨在为ALI的研究及治疗提供新的策略。

### 3.1 NLRP3炎症小体调控细胞凋亡

细胞凋亡通常由于细胞内稳态的破坏而激活，主要受抗凋亡蛋白B细胞淋巴瘤2(B-cell lymphoma 2，BCL2)及促凋亡蛋白BCL2相关X/BCL2拮抗剂杀伤因子(BCL-associated X/BCL2 antagonist killer，BAX/BAK)的调控[88]。凋亡功能障碍可加重ALI的组织损伤[89]。在PM2.5诱导的小鼠ALI模型中，*NLRP3*缺陷小鼠肺部BCL12蛋白表达显著上调，BAX/BAK表达减少[90]。此外，caspase-8是外源性凋亡的启动酶，可通过死亡受体诱导外源性凋亡[90,91]。在*caspase-1*缺陷小鼠中，NLRP3炎症小体通过募集并激活caspase-8，激活小鼠巨噬细胞的凋亡[92]。另外，也有研究显示，caspase-1在激活的条件下可通过切割caspase-3/7介导外源性凋亡[93]。这些证据表明，ALI期间NLRP3炎症小体与细胞凋亡间存在串扰，并通过与凋亡信号的串扰推动ALI的进展。

### 3.2 NLRP3炎症小体与细胞程序性坏死

NLRP3炎症小体与细胞程序性坏死存在协同效应。程序性坏死是由RIPK1、RIPK3及混合谱系激酶样(mixed lineage kinase domain-like，MLKL)激酶介导的细胞程序性死亡，表现为细胞能量转换缺失，细胞膜完整性破坏及细胞内容物的流出[94]。RIPK1作为程序性坏死的效应酶介导NLRP3的替代激活途径[25]。RIPK3可通过caspase-8激活NLRP3炎症小体[95]。此外，研究显示，caspase-8缺失情况下RIPK3亦可独立激活NLRP3炎症小体[96]。这表明RIPK3对NLRP3炎症小体的活化具有重要作用。MLKL激活后导致细胞破裂使得$K^+$外流，$K^+$是NLRP3炎症小体重要的激活信号，通过提高胞外$K^+$浓度抑制$K^+$外流后，激活的MLKL仍可激活NLRP3炎症小体，提示MLKL通过细胞内源性途径激活NLRP3炎症小体[97,98]。RIPK3/MLKL形成的程序性死亡复合物也可通过损伤线粒体以激活mROS/AKT信号通路，诱导NLRP3激活[99]。这些证据表明，程序性坏死与NLRP3炎症小体间存在协同效应，在ALI期间通过死亡信号通路的串扰扩大炎症信号，放大急性炎症造成的损伤。

### 3.3 NLRP3与泛凋亡

泛凋亡是近期报道的一种新型细胞调节性死亡[100]。泛凋亡的进展依赖于泛凋亡小体的形成，NLRP3炎症小体是泛凋亡小体的关键组分之一[101]。研究显示，miR-29a-3p通过抑制泛凋亡小体可显著减少ALI期间的炎症因子释放及细胞死亡[102]。在小鼠ALI模型中，松果菊多酚通过抑制一氧化氮的产生减少NLRP3依赖的泛凋亡，显著减少肺损伤[87]。这些证据表明，NLRP3炎症小体具有调控多种细胞死亡的潜力，随着NLRP3抑制剂的开发有望为ALI提供全新的治疗方式。

## 4 小结

异常激活的NLRP3炎症小体参与多种炎性疾病的进展。ALI期间异常激活的NLRP3炎症小体通过介导肺泡巨噬细胞焦亡、促进中性粒细胞的募集以及NETs的释放，影响促炎因子的成熟及分泌，破坏肺泡-毛细血管膜屏障等多种途径，参与急性肺损伤的病理生理过程。此外，NLRP3炎症小体与多种RCD存在串扰，ALI期间NLRP3炎症小体通过与细胞焦亡、凋亡及程序性坏死调节性死亡的死亡信号串扰扩大炎症信号并加重组织损伤。越来越多的证据表明，NLRP3炎症小体在ALI发病机制中发挥重要作用。近年来，以NLRP3炎症小体为靶点的抑制剂持续开发，持续探究NLRP3炎症小体参与ALI发生发展的相关机制，将为ALI的治疗提供新思路和新方向。

## 参考文献

[1] Zhao L, Su F, Zhang N, et al. The impact of the new acute respiratory distress syndrome (ARDS) criteria on Berlin criteria ARDS patients: a multicenter cohort study. BMC Med, 2023, 21(1): 456

[2] Lian J, Lin J, Zakaria N, et al. Acute lung injury: disease modelling and the therapeutic potential of stem cells.

Adv Exp Med Biol, 2020, 1298: 149-166
[3] Madotto F, Pham T, Bellani G, et al. Resolved versus confirmed ARDS after 24 h: insights from the LUNG SAFE study. Intensive Care Med, 2018, 44(5): 564-577
[4] Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. Nat Rev Dis Primers, 2019, 5(1): 18
[5] Banavasi H, Nguyen P, Osman H, et al. Management of ARDS—what works and what does not. Am J Med Sci, 2021, 362(1): 13-23
[6] Hochheiser IV, Pilsl M, Hagelueken G, et al. Structure of the NLRP3 decamer bound to the cytokine release inhibitor CRID3. Nature, 2022, 604(7904): 184-189
[7] Coll RC, Schroder K, Pelegrín P. NLRP3 and pyroptosis blockers for treating inflammatory diseases. Trends Pharmacol Sci, 2022, 43(8): 653-668
[8] Chen M, Ye X, He X, et al. The signaling pathways regulating NLRP3 inflammasome activation. Inflammation, 2021, 44(4): 1229-1245
[9] Wang H, Lin X, Huang G, et al. Atranorin inhibits NLRP3 inflammasome activation by targeting ASC and protects NLRP3 inflammasome-driven diseases. Acta Pharmacol Sin, 2023, 44(8): 1687-1700
[10] Johnson JL, Ramadass M, Haimovich A, et al. Increased neutrophil secretion induced by NLRP3 mutation links the inflammasome to azurophilic granule exocytosis. Front Cell Infect Microbiol, 2017, 7: 507
[11] Ortega MA, De Leon-Oliva D, García-Montero C, et al. Reframing the link between metabolism and NLRP3 inflammasome: therapeutic opportunities. Front Immunol, 2023, 14: 1232629
[12] Vande Walle L, Lamkanfi M. Drugging the NLRP3 inflammasome: from signalling mechanisms to therapeutic targets. Nat Rev Drug Discov, 2024, 23(1): 43-66
[13] Swanson KV, Junkins RD, Kurkjian CJ, et al. A noncanonical function of cGAMP in inflammasome priming and activation. J Exp Med, 2017, 214(12): 3611-3626
[14] Xie Q, Shen WW, Zhong J, et al. Lipopolysaccharide/adenosine triphosphate induces IL-1β and IL-18 secretion through the NLRP3 inflammasome in RAW264.7 murine macrophage cells. Int J Mol Med, 2014, 34(1): 341-349
[15] Yu P, Zhang X, Liu N, et al. Pyroptosis: mechanisms and diseases. Sig Transduct Target Ther, 2021, 6(1): 128
[16] Shim DW, Cho HJ, Hwang I, et al. Intracellular $NAD^+$ depletion confers a priming signal for NLRP3 inflammasome activation. Front Immunol, 2021, 12: 765477
[17] Wu Y, Huang D, Wang X, et al. Suppression of NLRP3 inflammasome by Platycodin D via the TLR4/MyD88/NF-κB pathway contributes to attenuation of lipopolysaccharide induced acute lung injury in rats. Int Immunopharmacol, 2021, 96: 107621
[18] Song N, Liu ZS, Xue W, et al. NLRP3 phosphorylation is an essential priming event for inflammasome activation. Mol Cell, 2017, 68(1): 185-197.e6
[19] Ren G, Zhang X, Xiao Y, et al. ABRO1 promotes NLRP3 inflammasome activation through regulation of NLRP3 deubiquitination. EMBO J, 2019, 38(6): e100376
[20] Ma Y, Wang Z, Wu X, et al. 5-Methoxytryptophan ameliorates endotoxin-induced acute lung injury *in vivo* and *in vitro* by inhibiting NLRP3 inflammasome-mediated pyroptosis through the Nrf2/HO-1 signaling pathway. Inflamm Res, 2023, 72(8): 1633-1647
[21] Paik S, Kim JK, Silwal P, et al. An update on the regulatory mechanisms of NLRP3 inflammasome activation. Cell Mol Immunol, 2021, 18(5): 1141-1160
[22] Devant P, Dong Y, Mintseris J, et al. Structural insights into cytokine cleavage by inflammatory caspase-4. Nature, 2023, 624(7991): 451-459
[23] Liu C, Shen Y, Huang L, et al. TLR2/caspase-5/Panx1 pathway mediates necrosis-induced NLRP3 inflammasome activation in macrophages during acute kidney injury. Cell Death Discov, 2022, 8(1): 232
[24] Enosi Tuipulotu D, Feng S, Pandey A, et al. Immunity against *Moraxella catarrhalis* requires guanylate‐binding proteins and caspase-11-NLRP3 inflammasomes. EMBO J, 2023, 42(6): e112558
[25] Gaidt MM, Ebert TS, Chauhan D, et al. Human monocytes engage an alternative inflammasome pathway. Immunity, 2016, 44(4): 833-846
[26] Lin KM, Hu W, Troutman TD, et al. IRAK-1 bypasses priming and directly links TLRs to rapid NLRP3 inflammasome activation. Proc Natl Acad Sci USA, 2014, 111(2): 775-780
[27] Hwang I, Lee E, Jeon SA, et al. Histone deacetylase 6 negatively regulates NLRP3 inflammasome activation. Biochem Biophys Res Commun, 2015, 467(4): 973-978
[28] Yan Y, Jiang W, Liu L, et al. Dopamine controls systemic inflammation through inhibition of NLRP3 inflammasome. Cell, 2015, 160(1-2): 62-73
[29] Song H, Liu B, Huai W, et al. The E3 ubiquitin ligase TRIM31 attenuates NLRP3 inflammasome activation by promoting proteasomal degradation of NLRP3. Nat Commun, 2016, 7(1): 13727
[30] Tang J, Tu S, Lin G, et al. Sequential ubiquitination of NLRP3 by RNF125 and Cbl-b limits inflammasome activation and endotoxemia. J Exp Med, 2020, 217(4): e20182091
[31] Wang D, Zhang Y, Xu X, et al. YAP promotes the

activation of NLRP3 inflammasome via blocking K27-linked polyubiquitination of NLRP3. Nat Commun, 2021, 12(1): 2674

[32] Humphries F, Bergin R, Jackson R, et al. The E3 ubiquitin ligase Pellino2 mediates priming of the NLRP3 inflammasome. Nat Commun, 2018, 9(1): 1560

[33] Niu T, De Rosny C, Chautard S, et al. NLRP3 phosphorylation in its LRR domain critically regulates inflammasome assembly. Nat Commun, 2021, 12(1): 5862

[34] Cai B, Zhao J, Zhang Y, et al. USP5 attenuates NLRP3 inflammasome activation by promoting autophagic degradation of NLRP3. Autophagy, 2022, 18(5): 990-1004

[35] Liu T, Wang L, Liang P, et al. USP19 suppresses inflammation and promotes M2-like macrophage polarization by manipulating NLRP3 function via autophagy. Cell Mol Immunol, 2021, 18(10): 2431-2442

[36] Di Q, Zhao X, Tang H, et al. USP22 suppresses the NLRP3 inflammasome by degrading NLRP3 via ATG5-dependent autophagy. Autophagy, 2023, 19(3): 873-885

[37] Palazón-riquelme P, Worboys JD, Green J, et al. USP7 and USP47 deubiquitinases regulate NLRP3 inflammasome activation. EMBO Rep, 2018, 19(10): e44766

[38] Song H, Zhao C, Yu Z, et al. UAF1 deubiquitinase complexes facilitate NLRP3 inflammasome activation by promoting NLRP3 expression. Nat Commun, 2020, 11(1): 6042

[39] He Y, Hara H, Núñez G. Mechanism and regulation of NLRP3 inflammasome activation. Trends Biochem Sci, 2016, 41(12): 1012-1021

[40] Spalinger MR, Kasper S, Gottier C, et al. NLRP3 tyrosine phosphorylation is controlled by protein tyrosine phosphatase PTPN22. J Clin Invest, 2016, 126(5): 1783-1800

[41] Wei T, Zhang C, Song Y. Molecular mechanisms and roles of pyroptosis in acute lung injury. Chin Med J (Engl), 2022, 135(20): 2417-2426

[42] Mangan MSJ, Olhava EJ, Roush WR, et al. Targeting the NLRP3 inflammasome in inflammatory diseases. Nat Rev Drug Discov, 2018, 17(8): 588-606

[43] Malireddi RKS, Kesavardhana S, Kanneganti TD. ZBP1 and TAK1: master regulators of NLRP3 inflammasome/pyroptosis, apoptosis, and necroptosis (PAN-optosis). Front Cell Infect Microbiol, 2019, 9: 406

[44] Ye C, Li H, Bao M, et al. Alveolar macrophage-derived exosomes modulate severity and outcome of acute lung injury. Aging (Albany NY), 2020, 12(7): 6120-6128

[45] Liu B, Li Y, Xiang J, et al. Significance of pyroptosis in immunoregulation and prognosis of patients with acute Respiratory distress syndrome: evidence from RNA-seq of alveolar macrophages. J Inflamm Res, 2023, Volume 16: 3547-3562

[46] Ding H, Yang J, Chen L, et al. Memantine alleviates acute lung injury via inhibiting macrophage pyroptosis. Shock, 2021, 56(6): 1040-1048

[47] Murao A, Aziz M, Wang H, et al. Release mechanisms of major DAMPs. Apoptosis, 2021, 26(3-4): 152-162

[48] Ratajczak MZ, Kucia M. SARS-CoV-2 infection and overactivation of Nlrp3 inflammasome as a trigger of cytokine “storm” and risk factor for damage of hematopoietic stem cells. Leukemia, 2020, 34(7): 1726-1729

[49] Qu L, Chen C, Chen YY, et al. High-mobility group box 1 (HMGB1) and autophagy in acute lung injury (ALI): a review. Med Sci Monit, 2019, 25: 1828-1837

[50] Hou L, Yang Z, Wang Z, et al. NLRP3/ASC-mediated alveolar macrophage pyroptosis enhances HMGB1 secretion in acute lung injury induced by cardiopulmonary bypass. Lab Invest, 2018, 98(8): 1052-1064

[51] Jiang R, Xu J, Zhang Y, et al. Ligustrazine alleviate acute lung injury through suppressing pyroptosis and apoptosis of alveolar macrophages. Front Pharmacol, 2021, 12: 680512

[52] Liu B, Wang Z, He R, et al. Buformin alleviates sepsis-induced acute lung injury via inhibiting NLRP3-mediated pyroptosis through an AMPK-dependent pathway. Clin Sci, 2022, 136(4): 273-289

[53] Liu X, Xia S, Zhang Z, et al. Channelling inflammation: gasdermins in physiology and disease. Nat Rev Drug Discov, 2021, 20(5): 384-405

[54] Park I, Kim M, Choe K, et al. Neutrophils disturb pulmonary microcirculation in sepsis-induced acute lung injury. Eur Respir J, 2019, 53(3): 1800786

[55] Potey PM, Rossi AG, Lucas CD, et al. Neutrophils in the initiation and resolution of acute pulmonary inflammation: Understanding biological function and therapeutic potential. J Pathol, 2019, 247(5): 672-685

[56] Peng Y, Wu Q, Tang H, et al. NLRP3 regulated CXCL12 expression in acute neutrophilic lung injury. J Inflamm Res, 2020, 13: 377-386

[57] Scozzi D, Liao F, Krupnick AS, et al. The role of neutrophil extracellular traps in acute lung injury. Front Immunol, 2022, 13: 953195

[58] Münzer P, Negro R, Fukui S, et al. NLRP3 inflammasome assembly in neutrophils is supported by PAD4 and promotes NETosis under sterile conditions. Front Immunol, 2021, 12: 683803

[59] Zhang H, Xia N, Tang T, et al. Cholesterol suppresses human iTreg differentiation and nTreg function through

mitochondria-related mechanisms. J Transl Med, 2023, 21(1): 224

[60] Tu G, Zhang Y, Ma J, et al. Extracellular vesicles derived from $CD4^+$ T cells carry DGKK to promote sepsis-induced lung injury by regulating oxidative stress and inflammation. Cell Mol Biol Lett, 2023, 28(1): 24

[61] Ohya M, Tateishi A, Matsumoto Y, et al. Bystander $CD8^+$ T cells may be involved in the acute phase of diffuse alveolar damage. Virchows Arch, 2023, 482(3): 605-613

[62] Claser C, Nguee SYT, Balachander A, et al. Lung endothelial cell antigen cross-presentation to $CD8^+$T cells drives malaria-associated lung injury. Nat Commun, 2019, 10(1): 4241

[63] Zhu J, Feng B, Xu Y, et al. Mesenchymal stem cells alleviate LPS-induced acute lung injury by inhibiting the proinflammatory function of $Ly6C^+$ $CD8^+$ T cells. Cell Death Dis, 2020, 11(10): 829

[64] Guan T, Zhou X, Zhou W, et al. Regulatory T cell and macrophage crosstalk in acute lung injury: future perspectives. Cell Death Discov, 2023, 9(1): 9

[65] Zhou KL, He YR, Liu YJ, et al. IL-17A/p38 signaling pathway induces alveolar epithelial cell pyroptosis and hyperpermeability in sepsis-induced acute lung injury by activating NLRP3 inflammasome. Adv Biol, 2023, 7 (12): e2300220

[66] Chao YY, Puhach A, Frieser D, et al. Human TH17 cells engage gasdermin E pores to release IL-1α on NLRP3 inflammasome activation. Nat Immunol, 2023, 24(2): 295-308

[67] Weber A, Wasiliew P, Kracht M. Interleukin-1β (IL-1β) processing pathway. Sci Signal, 2010, 3(105): cm2

[68] Li LH, Chen TL, Chiu HW, et al. Critical role for the NLRP3 inflammasome in mediating IL-1β production in shigella sonnei-infected macrophages. Front Immunol, 2020, 11: 1115

[69] Ma X, Yu X, Zhou Q. The IL1β-HER2-CLDN18/CLDN4 axis mediates lung barrier damage in ARDS. Aging (Albany NY), 2020, 12(4): 3249-3265

[70] Yu J, Ni L, Zhang X, et al. Surfactant protein d dampens lung injury by suppressing NLRP3 inflammasome activation and NF-κB signaling in acute pancreatitis. Shock, 2019, 51(5): 557-568

[71] Peteranderl C, Sznajder JI, Herold S, et al. Inflammatory responses regulating alveolar ion transport during pulmonary infections. Front Immunol, 2017, 8: 446

[72] Boraschi D, Italiani P, Weil S, et al. The family of the interleukin-1 receptors. Immunol Rev, 2018, 281(1): 197-232

[73] Makabe H, Kojika M, Takahashi G, et al. Interleukin-18 levels reflect the long-term prognosis of acute lung injury and acute respiratory distress syndrome. J Anesth, 2012, 26(5): 658-663

[74] Kaplanski G. Interleukin-18: biological properties and role in disease pathogenesis. Immunol Rev, 2018, 281 (1): 138-153

[75] Dolinay T, Kim YS, Howrylak J, et al. Inflammasome-regulated cytokines are critical mediators of acute lung injury. Am J Respir Crit Care Med, 2012, 185(11): 1225-1234

[76] Ayzac L, Girard R, Baboi L, et al. Ventilator-associated pneumonia in ARDS patients: the impact of prone positioning. A secondary analysis of the PROSEVA trial. Intensive Care Med, 2016, 42(5): 871-878

[77] Peukert K, Sauer A, Seeliger B, et al. Increased alveolar epithelial damage markers and inflammasome-regulated cytokines are associated with pulmonary superinfection in ARDS. J Clin Med, 2023, 12(11): 3649

[78] Zhong WJ, Duan JX, Liu T, et al. Activation of NLRP3 inflammasome up-regulates TREM-1 expression in murine macrophages via HMGB1 and IL-18. Int Immunopharmacol, 2020, 89: 107045

[79] dos Santos CC, Amatullah H, Vaswani CM, et al. Mesenchymal stromal (stem) cell therapy modulates miR-193b-5p expression to attenuate sepsis-induced acute lung injury. Eur Respir J, 2022, 59(1): 2004216

[80] Simmons S, Erfinanda L, Bartz C, et al. Novel mechanisms regulating endothelial barrier function in the pulmonary microcirculation. J Physiol, 2019, 597(4): 997-1021

[81] Ouyang H, Wang Y, Wu J, et al. Mechanisms of pulmonary microvascular endothelial cells barrier dysfunction induced by LPS: the roles of ceramides and the Txnip/NLRP3 inflammasome. Microvascular Res, 2023, 147: 104491

[82] Feng Q, Zhang YS, Zhuang Y, et al. Inhibition of the C3a receptor attenuates sepsis-induced acute lung injury by suppressing pyroptosis of the pulmonary vascular endothelial cells. Free Radical Biol Med, 2022, 184: 208-217

[83] Xiong S, Hong Z, Huang LS, et al. IL-1β suppression of VE-cadherin transcription underlies sepsis-induced inflammatory lung injury. J Clin Invest, 2020, 130(7): 3684-3698

[84] Napodano C, Carnazzo V, Basile V, et al. NLRP3 inflammasome involvement in heart, liver, and lung diseases—a lesson from cytokine storm syndrome. Int J Mol Sci, 2023, 24(23): 16556

[85] Deshpande R, Zou C. Pseudomonas aeruginosa induced cell death in acute lung injury and acute respiratory

distress syndrome. Int J Mol Sci, 2020, 21(15): 5356

[86] Galluzzi L, Vitale I, Aaronson SA, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ, 2018, 25(3): 486-541

[87] Guo J, Luo Y, Zuo J, et al. Echinacea polyphenols inhibit NLRP3-dependent pyroptosis, apoptosis, and necroptosis via suppressing NO production during lipopolysaccharide-induced acute lung injury. J Agric Food Chem, 2023, 71(19): 7289-7298

[88] Chen KW, Demarco B, Heilig R, et al. Extrinsic and intrinsic apoptosis activate pannexin-1 to drive NLRP3 inflammasome assembly. EMBO J, 2019, 38(10): e101638

[89] Z'graggen BR, Tornic J, Müller-Edenborn B, et al. Acute lung injury: apoptosis in effector and target cells of the upper and lower airway compartment. Clin Exp Immunol, 2010, 161(2): 324-331

[90] Xiong R, Jiang W, Li N, et al. PM2.5-induced lung injury is attenuated in macrophage-specific NLRP3 deficient mice. Ecotoxicol Environ Saf, 2021, 221: 112433

[91] Tummers B, Mari L, Guy CS, et al. Caspase-8-dependent inflammatory responses are controlled by its adaptor, FADD, and necroptosis. Immunity, 2020, 52(6): 994-1006.e8

[92] Chung H, Vilaysane A, Lau A, et al. NLRP3 regulates a non-canonical platform for caspase-8 activation during epithelial cell apoptosis. Cell Death Differ, 2016, 23(8): 1331-1346

[93] Taabazuing CY, Okondo MC, Bachovchin DA. Pyroptosis and apoptosis pathways engage in bidirectional crosstalk in monocytes and macrophages. Cell Chem Biol, 2017, 24(4): 507-514.e4

[94] Minagawa S, Yoshida M, Araya J, et al. Regulated necrosis in pulmonary disease. a focus on necroptosis and ferroptosis. Am J Respir Cell Mol Biol, 2020, 62(5): 554-562

[95] Moriwaki K, Bertin J, Gough PJ, et al. A RIPK3-caspase 8 complex mediates atypical Pro-IL-1β processing. J Immunol, 2015, 194(4): 1938-1944

[96] Lawlor KE, Khan N, Mildenhall A, et al. RIPK3 promotes cell death and NLRP3 inflammasome activation in the absence of MLKL. Nat Commun, 2015, 6(1): 6282

[97] Conos SA, Chen KW, De Nardo D, et al. Active MLKL triggers the NLRP3 inflammasome in a cell-intrinsic manner. Proc Natl Acad Sci USA, 2017, 114(6): E961-E969

[98] Liu Y, Xing LH, Li FX, et al. Mixed lineage kinase-like protein protects against Clostridium perfringens infection by enhancing NLRP3 inflammasome-extracellular traps axis. iScience, 2022, 25(10): 105121

[99] Huang HR, Cho SJ, Harris RM, et al. RIPK3 activates MLKL-mediated necroptosis and inflammasome signaling during *Streptococcus* infection. Am J Respir Cell Mol Biol, 2021, 64(5): 579-591

[100] Pandian N, Kanneganti TD. PANoptosis: a unique innate immune inflammatory cell death modality. J Immunol, 2022, 209(9): 1625-1633

[101] Christgen S, Zheng M, Kesavardhana S, et al. Identification of the PANoptosome: a molecular platform triggering pyroptosis, apoptosis, and necroptosis (PANoptosis). Front Cell Infect Microbiol, 2020, 10: 237

[102] Cui Y, Wang X, Lin F, et al. MiR-29a-3p improves acute lung injury by reducing alveolar epithelial cell PANoptosis. Aging Dis, 2022, 13(3): 899-909