NLRP3炎症小体的负向调控机制

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摘要 NLRP3炎症小体是由NOD样受体(NOD-like receptor, NLR) NLRP3、接头蛋白ASC和胱冬肽酶-1(Caspase-1)所形成的多聚蛋白复合体, 能够感受来自病原微生物的病原相关分子模式(pathogen-associated molecular patterns, PAMPs)和胞内自身危险信号-危险相关分子模式(danger-associated molecular patterns, DAMPs), 促进细胞因子IL-1 β 和IL-18的成熟和分泌、引起细胞焦亡, 从而在多种生理、病理过程中发挥重要作用. NLRP3炎症小体是目前研究最深入的炎症小体, 其表达水平和活化强度与多种疾病的发生、发展密切相关, 如感染性疾病、痛风、II型糖尿病、动脉粥样硬化、阿尔兹海默症及癌症等. 因此, 阐明NLRP3炎症小体活化的调控机制, 对于揭示这些疾病发生、发展的机理, 寻找免疫调节治疗的新途径具有重要意义. 本文详细介绍了NLRP3炎症小体的负向调控机制.

关键词 NLRP3, 炎症小体, 固有免疫, 免疫调节, 炎症

炎症小体(inflammasome)是由炎性蛋白传感器分子、凋亡相关斑点样蛋白(apoptosis-associated speck-like protein, ASC)和胱冬肽酶-1(Caspase-1)组成的多聚蛋白复合体, 能够识别来自病原微生物的病原相关分子模式(pathogen-associated molecular patterns, PAMPs)和内源性的危险信号-危险相关分子模式(danger-associated molecular patterns, DAMPs). 多种蛋白传感器分子, 如NLRP3, AIM2, NLRP1等可形成炎症小体, 通过识别不同的PAMPs和DAMPs, 在炎症等多种生理、病理过程中发挥重要作用. 本文主要介绍NLRP3炎症小体及其负向调控机制.

1 NLRP3炎症小体

NLRP3是NOD样受体(NOD-like receptor, NLR)家族中的重要成员. NLR属于胞浆型模式识别受体(pattern recognition receptor, PRR), 其结构由三部分组成: C端富含亮氨酸重复结构域(leucine-rich repeat, LRR); 中间的核苷酸结合寡聚化结构域(nucleotide-binding oligomerization domain, NOD; 又称NACHT结构域)和/或NACHT相关结构域(NACHT-associated domain, NAD); N端效应结构域由两部分组成: 胱天蛋白酶招募结构域(caspase-activating and recruitment domain, CARD)或热蛋白结构域(pyrin domain, PYD), 作用是

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将NLR与下游接头蛋白、效应分子连接起来^[1]。依据N端效应区的不同, NLR家族分为NLRA, NLRB, NLRC, NLRP和NLRX 5个亚族^[2]。其中, NLRP1, NLRP3, NLRP6, NLRP12和NLRC4等多个成员可分别形成炎症小体, NLRP3是目前研究最深入的炎症小体^[1,3,4]。

NLRP3通过PYD结构域与ASC相互作用, 然后ASC通过其CARD结构域募集并激活pro-Caspase-1, 这种相互作用形成了大的细胞溶质蛋白复合物NLRP3炎症小体^[5]。被招募的pro-Caspase-1通过自切割、水解成三个独立的结构, 即CARD结构域和两个具有酶活性的片段(即p10和p20)。活化片段p10与p20形成异四聚体, 即为Caspase-1的活性形式。活性形式的Caspase-1对在胞质中以自抑制形式存在的Gasdermin D (GSDMD)进行切割, 使GSDMD释放活性N端蛋白, N端蛋白结合细胞膜并在细胞膜上寡聚形成孔道状结构, 可使细胞内容物释放, 并引起细胞焦亡^[6,7]。激活形式的Caspase-1对细胞因子前体pro-IL-1 β 与pro-IL-18进行切割, 产生成熟的IL-1 β 和IL-18, 继而分泌到胞外, 发挥多种生物学功能^[8]。

2 NLRP3炎症小体相关疾病

NLRP3炎症小体除在感染性疾病(如病毒感染、细菌感染等)中发挥重要作用外, 还与多种疾病的发生和进展密切相关, 如神经系统疾病、代谢性疾病、自身免疫病等。错误折叠的蛋白质聚集体和伴随某些疾病产生的异常累积的代谢物, 已被证明是NLRP3炎症小体的激活剂^[9]。在痛风和假性痛风病人的关节和关节周围组织中沉积的尿酸单钠(monosodium urate, MSU)或焦磷酸钙二水合物(calcium pyrophosphate dihydrate, CPPD)晶体可以激活NLRP3炎症小体^[10]。阿尔兹海默症(Alzheimer's disease, AD)病人的 β 淀粉样蛋白无法被正确切割为规则形式, 形成朊病毒样错误折叠寡聚体, 可以激活NLRP3炎症小体^[11]。帕金森病(Parkinson's disease, PD)病人死亡的神经元释放的 α -synuclein(α -Syn)与 β 淀粉样蛋白形态相似, 也可以激活NLRP3炎症小体^[12]。动脉粥样硬化(atherosclerosis)患者体内大量的胆固醇也是NLRP3炎症小体的激活剂^[13]; NLRP3炎症小体活化后产生的IL-18则可以促进动脉粥样硬化的发生发展; IL-18缺乏导致动脉粥样硬化斑块尺寸减小^[14]。积聚在II型糖尿病(type 2 dia-

betes, T2D)患者的胰岛中的胰岛淀粉样多肽(IAPP)可以促进IL-1 β 的表达^[15]。NLRP3炎症小体活化后释放的IL-1 β 促进胰岛素抵抗、引起 β 细胞功能损伤和细胞凋亡, 因而与II型糖尿病的发生、发展密切相关^[9]。除此之外, NLRP3炎症小体的活化异常还与结肠炎、关节炎、肥胖等密切相关^[16]。因此, NLRP3炎症小体在机体内环境稳态的维持中起到了重要作用, 其活化失衡将导致多种疾病的发生和发展。

3 NLRP3炎症小体活化机制

NLRP3炎症小体的活化需要双信号的参与, 即分为引发(priming)和激活(activation)两个阶段(图1)。第一信号即引发阶段, 由TLR或者TNF受体活化转录因子NF- κ B, 从而上调NLRP3以及IL-1 β /IL-18前体的表达。NLRP3蛋白表达被认为是NLRP3炎症小体活化的关键限速步骤^[17,18]。而在包括巨噬细胞在内的多种细胞中, 静息状态下NLRP3的表达量很低, 需要第一信号活化诱导NLRP3的转录和表达, 为激活阶段提供物质储备。近期的研究同样表明, 第一信号的活化也可以通过激活TLR-信号分子IL-1受体相关激酶(IL-1 receptor-associated kinase, IRAK-1), 发挥其激酶活性激活TRAF6, 发挥其促进NLRP3寡聚化等作用, 为NLRP3炎症小体的激活做准备^[19]。

NLRP3炎症小体活化的第二信号是由多种结构和功能不同的激活剂所激活, 如ATP、尿酸盐、胆固醇、 β 淀粉样蛋白和微生物毒素等多种物质; 尽管这些物质能有效诱导NLRP3炎症小体组装, 但它们都不直接与NLRP3结合。因此, NLRP3炎症小体的激活和组装可能通过中间产物起作用, 如通过诱导膜损伤、钾离子外流和细胞内钙离子浓度升高等^[20]。目前认为, NLRP3炎症小体的激活主要通过以下机制。(i) 溶酶体损伤。有研究发现一些NLRP3炎症小体的激活剂如二氧化硅和铝盐晶体等物质以内吞的形式进入细胞, 吞噬体与溶酶体融合, 引起溶酶体损伤和破坏, 释放内容物使NLRP3炎症小体活化。当抑制吞噬体酸化或组织蛋白酶B(Cathepsin B)后NLRP3炎症小体的活化被抑制^[21]。(ii) 胞内离子浓度变化。钾离子外流可以激活NLRP3炎症小体^[22]。最新的研究发现转运钾离子的跨膜蛋白TWIK2(two-pore domain weak inwardly rectifying K⁺ channel 2)是巨噬细胞NLRP3炎症小体激活

图1 NLRP3炎症小体活化机制

所必需的钾外排通道, 可以与P2X7受体共同调控NLRP3炎症小体的激活^[23]。钙离子内流同样可以激活NLRP3炎症小体, C/EPB同源蛋白(C/EPB homologous protein, CHOP)可以调节内质网释放Ca²⁺^[24], 除此之外, G蛋白偶联受体(G protein-coupled receptor, GPCR), 如钙感受器(CaSR)和GPCR6A、瞬时受体电位受体(transient receptor potential receptor, TRPV) TRPV2或TRPM7都可以提高胞内Ca²⁺浓度^[25]。(iii) 线粒体损伤。线粒体损伤后释放的内容物在NLRP3炎症小体激活中发挥重要作用。线粒体活性氧(mitochondria reactive oxygen species, mtROS)可以使离子通道TRPM2打开, 大量钙离子内流使细胞内钙离子浓度升高^[26]; 而且抑制了线粒体呼吸和mtROS产生以及线粒体耗竭后, NLRP3炎症小体的活化被抑制^[27]。受损的线粒体产生的mtDNA(mitochondria DNA)被氧化之后可以直接结合NLRP3并激活NLRP3炎症小体^[28,29]。巨噬细胞在受到NLRP3刺激剂的刺激后, 位于线粒体膜上的线粒体脂质心磷脂由内向外转位, 这可能是为从内质网转运

至线粒体的NLRP3提供了一个停靠位点^[30]。由此可见, 线粒体是NLRP3炎症小体激活过程中重要的细胞器。

在NLRP3炎症小体活化启动的早期, NLRP3发生了由去泛素化酶BRCC3介导的去泛素化^[31]; 而LUBAC (linear ubiquitin assembly complex)介导的ASC线性泛素化是NLRP3炎症小体组装和活化必需的^[32]。研究表明, 受NLRP3激活剂如尼日利亚菌素(Nigericin)和ATP刺激后, 参与有丝分裂的丝氨酸-苏氨酸激酶NEK7(NIMA-related kinase 7)与NLRP3的富含亮氨酸的重复结构域相互作用并与NLRP3形成高分子量复合物, 促进ASC和Caspase-1寡聚化, 激活后续信号通路^[33]。

4 NLRP3炎症小体负向调控机制

NLRP3炎症小体的活化是一把“双刃剑”, 其过度激活或抑制都会对机体造成损害。生理条件下, 机体存在NLRP3炎症小体活化的正向或负向调控, 使之维持适度的活化水平。病理条件下, NLRP3炎症小体活

化失衡将导致疾病的发生, 如感染性疾病、痛风、II型糖尿病、动脉粥样硬化、阿尔兹海默症及癌症等. 因此, 深入揭示NLRP3炎症小体活化的负向调控机制, 对于阐明这些疾病发生、发展的机理和寻找免疫调节治疗的新途径具有重要意义.

嵌合抗原受体T细胞免疫疗法(chimeric antigen receptor T-cell immunotherapy, CAR-T)是目前最具前景的肿瘤免疫治疗方法之一. 然而, CAR-T导致的细胞因子释放综合征(cytokine release syndrome, CRS)和神经毒性是其最为严重的副作用. 最近研究发现在小鼠(*Mus musculus*)模型中, 巨噬细胞大量产生的IL-1 β 在CAR-T导致的CRS和神经毒性等副作用中, 发挥关键作用^[34,35]. 因此, 阐明NLRP3炎症小体的负向调控机制对IL-1 β 分泌进行精准抑制、对于防止细胞因子的过度释放及其导致的CAR-T副作用的预防和控制, 具有潜在的应用价值.

目前研究发现, 多种机制可抑制NLRP3炎症小体活性, 如调控NLRP3表达水平、抑制NLRP3炎症小体组装和效应等(图2). 以下对NLRP3炎症小体活化的负向调控机制进行综述.

4.1 NLRP3表达调控

NLRP3蛋白表达是NLRP3炎症小体组装和活化的关键限速步骤, 调控其表达水平是NLRP3炎症小体活化调控的重要方式. 多种机制可调控NLRP3表达, 如转录水平、蛋白质翻译后修饰等.

(1) NLRP3转录调控. NF- κ B是控制NLRP3表达的关键转录因子. 在NLRP3基因启动子区有两个NF- κ B的结合位点, 其对于NLRP3基因转录是必需的^[36,37]. 本课题组发现, 在NLRP3基因启动子区有核受体AhR(aryl hydrocarbon receptor, 芳香烃受体, 一种配体依赖的转录因子)的结合序列XRE(xenobiotic response element). 经配体活化后, AhR可转位入核, 与NLRP3基因启动子区的XRE结合, 屏蔽了NF- κ B结合位点, 抑制了NLRP3转录, 进而影响了NLRP3炎症小体的活化^[38]. 另外, 泛素修饰酶A20可以通过抑制NF- κ B依赖的NLRP3, pro-IL-1 β 和pro-IL-18的转录, 抑制NLRP3炎症小体的活化^[39].

除此之外, 目前许多研究表明长链非编码RNA(long non-coding RNA, lncRNA)也可以调控NLRP3的

图2 NLRP3炎症小体的负向调控机制

转录. LncRNA XLOC_000647可以通过抑制NLRP3启动子的活性来降低NLRP3的表达^[40].

(2) NLRP3转录后调控. micro RNA(miRNA)是一类由内源基因编码的长度约为20~40个核苷酸的非编码单链小RNA分子, 在基因转录后表达调控中发挥重要作用. miR-223和EB病毒(epstein-barr virus, EBV)诱导产生的miR-BART15均可以特异性地靶向NLRP3 mRNA的3'-UTR(untranslated region), 实现对NLRP3的mRNA水平的负向调控, 导致NLRP3蛋白水平下降, 从而影响NLRP3激活的阈值^[41,42]. 本课题组与贾继辉课题组^[43]合作, 发现miR-22也可以特异性靶向NLRP3 mRNA, 抑制NLRP3表达和NLRP3炎症小体活化; miR-22可通过这一机制在维持胃环境稳态中发挥关键作用, 并可作为干预胃癌的潜在靶点. 除miRNA在NLRP3的转录后调控中发挥重要作用外, RNA结合蛋白TTP(tristetraprolin)可以靶向NLRP3的3'-UTR中的富含AU的元件并抑制NLRP3表达^[44].

(3) NLRP3蛋白降解. 泛素蛋白酶体途径和自噬溶酶体途径是细胞内重要的蛋白质质控系统, 均参与NLRP3蛋白的降解过程. 通过上述两条途径降解的蛋白质, 均需发生泛素化修饰. 因此, 泛素化修饰在调控NLRP3蛋白表达中发挥重要作用.

泛素化修饰涉及泛素活化酶(E1)、泛素转运酶或泛素偶联酶(E2)和泛素-靶蛋白连接酶(E3)的一系列反应, 将高度保守的泛素连接到蛋白质的赖氨酸残基(Lys, K)侧链上. 其中, E3泛素连接酶决定泛素靶分子的特异性, 在泛素途径中具有重要的作用. 本课题组研究发现, E3泛素连接酶TRIM31可以直接结合NLRP3, 促进NLRP3发生K48位偶联的多聚泛素化, 进而促进NLRP3的蛋白酶体降解, 从而抑制NLRP3炎症小体的活性^[45].

神经递质多巴胺可以通过巨噬细胞中的多巴胺D1受体发出信号激活环状单磷酸腺苷(circle adenosine monophosphate, cAMP), 其结合NLRP3并通过E3泛素连接酶MARCH7介导的泛素化促进其通过自噬溶酶体途径降解^[46]. 另外, 其他E3泛素连接酶, 如ARIH2, SCF^{FBXL2}也促进NLRP3泛素化修饰, 并抑制NLRP3炎症小体的活化^[47,48]. 虽然多个实验室均报道了NLRP3可发生泛素化修饰, 但是其具体的发生泛素化的氨基酸位点至今尚不明确.

4.2 NLRP3炎症小体组装和效应调控

线粒体损伤以及随后的线粒体内容物(mtROS和mtDNA)的释放或暴露, 对于NLRP3炎症小体的组装是至关重要的. 因此, 控制线粒体信号的释放或者清除受损的线粒体可以调节NLRP3炎症小体的活化. 自噬是回收胞质大分子结构和细胞器的基本分解代谢过程. 自噬可以参与炎症小体或pro-IL-1 β 分子的去泛素化; 同时自噬可以移除受损的线粒体, 这表明自噬可以阻止mtROS和mtDNA释放到细胞质中, 从而限制NLRP3炎症小体的组装. NLRP3炎症小体活化后, 自噬受体p62(也称为SQSTM1)在线粒体附近形成聚集; 同时引发受损线粒体发生Parkin连接酶依赖的泛素化, 将p62与多聚泛素链结合, p62通过其LC3相互作用结构域与自噬体对接蛋白LC3相互作用, 最终损伤的线粒体被p62包裹到新形成的自噬体中^[49~52]. 除了自噬机制以外, 磷酸酶SHP2(Src homology 2 domain-containing tyrosine phosphatase-2)通过移位到线粒体与腺嘌呤核苷酸转移酶1(adenine nucleotide translocase 1, ANT1: 一种控制线粒体通透性转换的中心分子)相互作用并使之去磷酸化, 来维持线粒体膜电位, 防止mtROS和mtDNA释放, 从而抑制NLRP3炎症小体活化^[52]. 还有研究发现, 一氧化碳(CO)抑制了脂多糖(lipopolysaccharide, LPS)和ATP诱导的mtROS产生、线粒体膜电位的降低以及mtDNA向细胞质中转运, 从而抑制NLRP3炎症小体的活化^[53].

NLRP3炎症小体需要各个组分通过其结构域之间的相互作用来完成组装. 某些特异性调节蛋白可以作用于这些结构域, 通过竞争性结合来抑制NLRP3炎症小体组装和活化. 例如, Caspase 12^[54]和COPs(CARD-only proteins)^[55~57]等可以通过CARD结构域间的相互作用抑制ASC与Caspase-1的结合, 从而抑制Caspase-1的活性来调控炎症小体; 而POPs(PYD-only proteins), 包括POP1(也称为PYDC1和ASC2)和POP2(也称为PYDC2), 则通过干扰炎症小体中的PYD结构域间的相互作用, 影响NLRP3与ASC结合, 实现对NLRP3炎症小体的负向调节^[58~60]. T细胞来源的IFN- γ 可以通过激活诱导型硝酸氧化合酶(iNOS)下调NLRP3的活性, iNOS可以促进一氧化氮(NO)的增加, 而NO可以诱导NLRP3亚硝基化抑制NLRP3炎症小体的组装, 并由此抑制NLRP3炎症小体的活性^[61]. IFN- β 同样也

可以通过诱导NO来负调节NLRP3炎症小体^[62]. LRRFIP2(leucine-rich repeat Fli-I-interacting protein 2)可以在NLRP3炎症小体激活时通过其N末端与NLRP3结合来募集Caspase-1的抑制剂Flightless-I, LRRFIP2增强了Flightless-I和Caspase-1之间的相互作用, 促进了Flightless-I抑制Caspase-1对pro-IL-1 β 和pro-IL-18的切割作用, 从而抑制NLRP3炎症小体的活性^[63]. 除此之外, 某些病毒同样可以调控NLRP3炎症小体. 例如, 麻疹病毒(measles, MV)编码的一种非结构V蛋白可以通过其C-末端结构域与NLRP3相互作用, 从而抑制NLRP3炎症小体介导的IL-1 β 分泌, 以拮抗宿主的固有免疫反应^[64].

5 NLRP3炎症小体抑制剂

NLRP3炎症小体过度活化导致多种疾病的发生、发展, 抑制其过度活化, 将有助于相关疾病的防治. 因此, 多个实验室研发了多种特异性靶向NLRP3炎症小体的小分子抑制剂, 并对它们在不同疾病小鼠模型中的作用进行了深入研究.

二芳基磺酰脲的衍生物MCC950通过阻断NLRP3诱导的ASC的寡聚化, 抑制NLRP3炎症小体, 且可以减轻小鼠脑脊髓炎(experimental autoimmune encephalomyelitis, EAE)的严重程度^[65]. MCC950还可以通过抑制NLRP3炎症小体活性, 缓解多种疾病, 如粥样硬化损伤、狼疮肾炎、非酒精性脂肪肝(nonalcoholic steatohepatitis, NASH)、阿尔兹海默症、心肌梗死和脑出血后的大脑损伤等^[66-71]. 另一种小分子抑制剂CY-09, 可通过与NLRP3的NACHT结构域的ATP结合基序结合, 抑制NLRP3的ATP酶活性, 从而特异性地阻断NLRP3炎症小体的组装与活化, 并且对于小鼠低温相关的自身炎症综合征(cryopyrin-associated auto-inflammatory syndrome, cAPS)和II型糖尿病模型有显著的治疗效果^[72]. IKK β 的抑制剂BAY 11-7082也可以抑制NLRP3的ATP酶活性, 从而抑制NLRP3炎症小体的组装与活化^[73]. MNS(3,4-methylenedioxy- β -nitrostyrene)可以通过抑制NLRP3 ATP酶活性阻断NLRP3炎症小体的组装^[74]. 曲尼司特(tranilast, TR)是一种抗过敏的临床药物, 它可以直接结合NLRP3的NACHT结构域并通过阻断NLRP3的寡聚化来抑制NLRP3炎症小体的组装, 体内实验表明, 它对痛风性关节炎、低温相关的自身炎

症综合征和II型糖尿病等NLRP3炎症小体相关人类疾病的小鼠模型具有显著的预防或治疗作用^[75]. 此外, 丙烯酸衍生物INF39作为一种无毒、不可逆的NLRP3炎症小体抑制剂, 能够减少巨噬细胞释放IL-1 β ; 而且体内研究证实, 口服给药后能够减轻2,4-二硝基苯磺酸(2,4-dinitrobenzenesulfonic acid, DNBS)诱导的大鼠(*Rattus norvegicus*)结肠炎^[76]. 冬凌草甲素(oridonin)是中草药冬凌草的主要成分, 具备抗炎效果, 它可以通过与NLRP3第279位的半胱氨酸结合阻断NLRP3与Nek7的相互作用, 从而阻断NLRP3炎症小体的组装和激活, 对于小鼠腹膜炎(peritonitis)、痛风性关节炎(gouty arthritis)和II型糖尿病模型具有预防和治疗的效果^[77].

酮类代谢产物 β -hydroxybutyrate(BHB)通过阻止钾离子流出, 减少ASC寡聚和微粒的形成来减弱Caspase-1的激活和IL-1 β 的释放, BHB或酮源饮食可以减弱Muckle-Wells综合征、家族性低温自身炎症综合征和尿酸盐晶体诱导的腹膜炎的小鼠模型体内Caspase-1的激活和IL-1 β 的分泌^[78]. 氟芬那酸(flufenamic acid)和甲芬那酸(mefenamic acid)则通过抑制氯离子外流抑制NLRP3炎症小体活化, 且在阿尔兹海默症小鼠模型中具有一定的治疗效果^[79]. 南蛇藤醇(celastrol)则可以通过促进自噬减少ROS的产生来抑制NLRP3炎症小体的激活, 并抑制LPS诱导的全身性炎症和DSS诱导的结肠炎^[80].

6 总结与展望

NLRP3炎症小体作为目前研究最为深入的一种炎症小体, 其活化和调控机制仍远未阐明. 例如, 钾离子外流和胞内钙离子浓度升高、线粒体损伤和溶酶体损伤具体通过什么机制激活炎症小体? 这些都需要进一步深入探究, 以更好地揭示NLRP3炎症小体的活化机制和研发靶向NLRP3炎症小体的相关疾病治疗策略. 对于NLRP3炎症小体的负向调控机制, 也有待于进一步丰富. 例如, 是否有其他的蛋白质翻译后修饰可以调控NLRP3的表达和NLRP3炎症小体的活化? JNK1介导的NLRP3磷酸化对于NLRP3去泛素化和后续的组装非常重要^[82], 那么是否有相应磷酸酶能够通过去磷酸化修饰, 发挥抑制NLRP3炎症小体的作用? 靶向相关激酶和泛素化修饰过程的小分子化合物, 是否能够特异性的抑制NLRP3炎症小体活化? 等等. 深入揭示NLRP3炎症小

体负向调控的分子机制, 对于阐明NLRP3炎症小体相关疾病发生、发展的机理, 寻找免疫调节治疗的新途径具有重要意义. 在此基础上, 在靶向NLRP3炎症小

体活化和调控的不同环节, 进行相关小分子化合物筛选和药物研发, 将对NLRP3炎症小体活化失衡导致的多种疾病的防控提供更多、更理想的选择.

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Negative regulatory mechanisms of NLRP3 inflammasome

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NLRP3 inflammasome is a multi-protein platform which comprises NOD like receptor NLRP3, adaptor ASC and caspase-1. NLRP3 inflammasome recognizes pathogen-associated molecular patterns (PAMPs) from pathogen microbes and endogenous danger-associated molecular patterns (DAMPs) and then promotes the maturation and secretion of IL-1 β and IL-18 and induces pyroptosis. NLRP3 inflammasome plays crucial roles in many types of diseases, such as infectious diseases, gout, type 2 diabetes, atherosclerosis, Alzheimer's disease and cancer. Thus, investigation of the regulatory mechanisms of NLRP3 inflammasome activation has important scientific significance and application value in elucidating the mechanism of the immune responses as well as developing novel ways of immunomodulatory therapy. Here we provide a review on the negative regulatory mechanisms of NLRP3 inflammasome.

NLRP3, inflammasome, innate immunity, immune regulation, inflammation

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