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Mini-Review 小型综述

病原体与宿主炎症小体相互作用

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摘要：炎症小体(Inflammasome)是细胞质中多种蛋白组装成的复合物，炎症小体的激活能活化半胱天冬酶-1 (caspase-1)，进而引起系列促炎细胞因子的成熟与分泌和诱导细胞焦亡。当病原体感染时，炎症小体的激活在宿主天然免疫应答中起重要作用。大量研究表明，多数情况下炎症小体对宿主起保护作用，仅少数情况下保护作用不明显或表现出有利于病原体生存的一面。在长期进化中，病原体也发展出逃避宿主炎症小体作用的策略。病原体可直接抑制炎症小体的激活或减弱炎症小体的作用。本文从病原体感染宿主中炎症小体的作用及病原体对宿主炎性症小体的逃避机制两方面对二者相互作用的最新研究进展进行综述。

关键词：病原体，炎症小体，天然免疫，逃避策略

天然免疫应答是机体抵抗病原体感染的第一道防线，它通过胚系编码的模式识别受体(pattern recognition receptors，PRRs)识别病原相关分子模式(pathogen-associated molecular patterns，PAMPs)或者损伤相关分子模式(damage-associated molecular patterns，DAMPs)。生物体内有多种 PRRs，分布于不同的细胞空间，参与宿主信号通路的激活，最终诱导机体产生免疫应答[1–2]。炎症小体(Inflammasome) 是胞浆内的多蛋白复合体，在机体天然免疫应答中起重要作用。经典的炎症小体由模式识别受体(PRRs)、凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing CARD，ASC)和半胱天冬酶 1 前体(pro-caspase-1)组成。参与组装炎症小体的 PRRs 主要是 NLRs 家族或 AIM2 样受体(AIM2-like receptors，ALRs)家族。根据识别病原体 PRRs 的不同组装为不同的炎症小体，目前研究报道最多的是 NLRP3、NLRC4、NLRP1 和

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AIM2 炎症小体，NLRP2、NLRP6、NLRP7、NLRP12 及 IFI16 等炎症小体也有报道[3–4]。另外，近年来有研究报道了 caspase-11 的非经典的炎性小体激活途径，caspase-11 能引起细胞焦亡(Pyroptosis)，在天然免疫中同样发挥着重要的作用[5]。

病原体感染和各种内外源性刺激可引起炎症小体的组装和激活，中间接头分子 ASC 通过其 PYD 和 CARD 结构域的同源蛋白相互作用分别招募炎症小体受体分子和 pro-caspase-1 组装成炎症小体。ASC 分子聚集成的 ASC 斑点是 pro-caspase-1 活化为 caspase-1 的平台。活化的 caspase-1 可诱导细胞焦亡，并对 IL-1β 和 IL-18 的成熟分泌起关键作用[6]。不同病原体感染宿主后诱导炎症小体激活的机制不同，关于不同类型炎症小体的结构组成、激活方式及相应配体的研究进展已经有综述进行了总结[4,6–10]。本文将结合作者相关研究工作，侧重于阐述病原体与宿主炎症小体之间的相互作用关系，从宿主炎症小体在抵抗各种病原体感染时的作用、病原体对宿主炎症小体的逃避策略两方面进行综合阐述。

1 病原体感染宿主中炎症小体的作用

病原体感染诱导宿主天然免疫应答中炎症小体的激活起了重要作用，炎症小体各组分敲除小鼠的构建为炎症小体各组分在宿主抗感染中的作用及病原体感染宿主的致病机理研究提供了基础。Caspase-1 是经典的炎症小体的核心组成蛋白，炎症小体的激活使 caspase-1 由前体形式自我切割为成熟的 caspase-1 并发挥重要作用。ASC 作为重要接头分子参与了大多数炎症小体的组成并发挥重要作用，我们曾研究并报道了在单核细胞增生性李斯特菌(*Listeria monocytogenes*)、肺炎链球菌(*Streptococcus pneumoniae*)等感染宿主中，NLRP3 和 AIM2 都通过 ASC 募集 caspase-1 组装炎症小体[11–12]。炎症小体激活的调控机制很多是通过对 ASC 分子的修饰来实现，如我们前期报道的 Syk 和 JNK 介导的 ASC 的磷酸化和 ASC 斑点的形成，ASC 的泛素化等[13–14]。

大量研究结果表明，大多数病原体感染野生型和炎症小体组分缺失小鼠的模型中，*ASC*$^{-/-}$和 *Caspase1*$^{-/-}$小鼠体内重要器官含菌量增加以及存活率降低，表明炎症小体在宿主抗病原体感染中起重要的保护作用。但是，结核分枝杆菌(*Mycobacterium tuberculosis*)[15–16]等部分病原体感染宿主中炎症小体的保护作用不明显，甚至在大肠埃希菌(*Escherichia coli*)、鼠疫耶尔森菌(*Yersinia pestis*)和脑心肌炎病毒(Encephalomyocarditis Virus)感染中，炎症小体组分敲除小鼠的存活率高于野生型小鼠[17–19]。

起初的炎症小体激活相关研究均视 caspase-1 为唯一的炎症小体效应蛋白酶，但 Kayagaki 等研究发现 caspase-11 可在非经典炎症小体中激活，诱导细胞焦亡并特异性促进 IL-1α 的释放[5]。用 caspase-11$^{-/-}$小鼠的感染模型研究发现，泰国伯克霍尔德菌(*Burkholderia thailandensis*)感染会引起 caspase-11 的激活，保护野生型小鼠免受致死性泰国伯克霍尔德菌的感染[20]。另外，鼠伤寒沙门氏菌(*Salmonella Typhimurium*)的 *sifA* 突变株感染宿主模型中，caspase-11 的激活增强了体内鼠伤寒沙门氏菌的清除[20]。表 1 总结了目前已经研究报道的各种病原体感染宿主时炎症小体的作用。

表 1. 炎症小体对宿主病原体感染的保护作用——病原体在 ***Caspase1***$^{-/-}$和 ***ASC***$^{-/-}$小鼠中的菌落形成和存活

Table 1. The role of inflammasomes in host defense against pathogens infection——The CFUs and survival of pathogens in *Caspase1*$^{-/-}$ and *ASC*$^{-/-}$ mice

Pathogens	*Caspase1*$^{-/-}$		*ASC*$^{-/-}$		References
	CFU	Survival	CFU	Survival	
Anaplasma phagocytophilum	+	ND	+	ND	[21]
Aeromonas veronii	+	ND	+	ND	[22]
Bacillus anthracis	ND	−	ND	ND	[23]
Burkholderia cepacia	ND	=	ND	ND	[24]
Burkholderia pseudomallei	+	−	=	−	[25]
Burkholderia thailandensis	ND	−	ND	=	[20]
Chromobacterium violaceum	+	−	ND	−	[24]
Chlamydia muridarum	ND	ND	=/+	ND	[26]
Chlamydia pneumoniae	+	−	ND	ND	[27]
Chlamydia trachomatis	=	ND	ND	ND	[28]
Citrobacter rodentium	+	ND	ND	ND	[29]
Escherichia coli (O21:H+)	=	+	ND	ND	[17]
Francisella tularensis	+	−	+	−	[30–31]
Francisella philomiragia	ND	=	ND	ND	[24]
Klebsiella pneumoniae	ND	ND	=	−	[32]
Legionella pneumophila	+	ND	=	ND	[33–37]
Listeria monocytogenes	=/+	−	=	ND	[38–39]
Mycobacterium tuberculosis	=/+	=/−	=	=/−	[15–16]
Salmonella Typhimurium	+/−	−	=/+	=/−	[40–43]
Shigella flexneri	+	−	ND	ND	[44]
Staphylococcus aureus	=	−	=	−	[45]
Streptococcus Agalactiae	+	−	+	−	[46]
Streptococcus pneumoniae	ND	ND	+	−	[11,47]
Vibrio vulnificus	ND	−	ND	−	[48]
Yersinia pestis	=	+	ND	ND	[19]
Yersinia pseudotuberculosis	+	ND	+	ND	[49]
Aspergillus fumigatus	ND	−	ND	−	[50]
Candida albicans	+	−	+	−	[51]
Paracoccidioides brasiliensis	+	−	=/+	−	[52]
Encephalomyocarditis Virus	ND	+	ND	ND	[18]
Vesicular Stomatitis Virus	ND	−	ND	ND	[18]
West Nile virus	ND	−	+	−	[53–54]
Plasmodium berghei	ND	=	ND	=	[55–56]
Toxoplasma gondii	ND	−	ND	−	[57]
Trypanosoma cruzi	ND	−	ND	−	[58]

ND: not detected; +: increased; −: decreased; =: no significant differences.

2 病原体逃避宿主炎症小体识别的策略

在长期的进化过程中，宿主炎症小体的作用对病原体产生了选择压力，促使其发展出能够抑制或者弱化宿主炎症小体作用的自我保护机制[59–60]。目前已经研究报道的病原体逃避宿主炎症小体的策略主要是以下两个方面：一是弱化炎症小体的作用；二是抑制炎性小体的激活。

2.1 病原体限制或弱化炎症小体的作用

病原体感染宿主过程中，主要通过对炎症小体识别的配体表达量的下调或者对配体结构的改变来限制或弱化炎症小体的作用。土拉弗朗西斯菌(*Francisella tularensis*)可以通过修改 LPS 中类脂 A 的结构，逃避宿主炎症小体的识别[61]。鼠伤寒沙门氏菌和单核细胞增生性李斯特菌(*Listeria monocytogenes*)通过抑制鞭毛的表达来逃避炎症小体的识别[38,62–63]。另外，在耶尔森菌属(*Yersinia*)感染模型中，经典和非经典炎症小体的激活需要 T3SS 成孔蛋白(Yop B 和 Yop D)，耶尔森菌的 Yop K 蛋白能够对这两种蛋白进行抑制，通过降低这两种成孔蛋白进入靶细胞的水平来限制炎症小体的作用[49]。除上述方式外，病原菌还可通过分泌小分子和代谢产物逃避宿主炎症小体的识别。如沙门氏菌通过控制 TCA 循环的代谢产物柠檬酸盐和顺乌头酸酶，避免 NLRP3 炎症小体的激活[64]。

2.2 病原体抑制炎性小体的激活

一些胞内病原菌通过抑制 caspase-1 的活化，从而减少促炎细胞因子的产生及细胞死亡，使其能够在宿主体内长期存活。主要有以下几种途径：首先，病原菌的 T3SS 分泌系统的效应蛋白能有效抑制炎症小体激活。如耶尔森菌属的 T3SS 分泌系统效应蛋白 YopM 可以通过其 YLTD 基序直接抑制 caspase-1 的募集及加工成熟，效应蛋白 YopE 和 YopT 也可通过调节 caspase-1 的寡聚化而阻止其激活[65–66]。铜绿假单胞菌(*Pseudomonas aeruginosa*)的 T3SS 效应蛋白 ExoU 通过其磷酸酶活性抑制 caspase-1 活化[67]。其次，病原菌可通过激活 Rho GTP 酶调控肌动蛋白聚合抑制炎症小体的激活。如铜绿假单胞菌 Rho GTPase 激活 ExoS 蛋白，ExoS 和 caspase-1 相互作用进而抑制 caspase-1 活化和 IL-1β 的分泌[68]。鼠伤寒沙门氏菌分泌效应蛋白 SopE，它是一个 Rho GTP 酶鸟苷酸交换因子，能够促进肌动蛋白骨架重排，以依赖酶活性的方式调控炎症小体的激活[69–70]。此外，还有一些病原菌直接以炎症小体的受体分子为靶点，进化出自身特有的逃避机制。如结核分枝杆菌(*Mycobacterium tuberculosis*)利用其 ESX 分泌系统分泌效应蛋白，调控 AIM2 炎症小体的激活[71]。Higa 等发现副溶血弧菌(*Vibrio parahaemolyticus*)的效应蛋白 VopQ 和 VopS 能够抑制 NLRP3 炎症小体的激活[72]。金黄色葡萄球菌(*Staphylococcus aureus*)通过修饰细胞壁来阻止溶酶体的破裂，间接减少 NLRP3 炎症小体的激活[73]。除抑制经典的炎症小体激活之外，弗氏志贺菌(*Shigella flexneri*)分泌的 OspC3 效应蛋白，可以直接结合到 caspase-4 的 p19 亚基上，抑制非经典炎症小体的激活[74]。

一些病毒也进化出抑制炎症小体激活的机制。部分病毒含有的 CARD 或 pyrin 蛋白作为内源性负调控子，通过 Pyrin-Pyrin 或者 CARD-CARD 之间的相互作用抑制炎症小体的激活[87]。如黏液瘤病毒(Myxoma virus)编码只含 pyrin 结构域的蛋白 M013，能够和 NLRP3 相互作用，抑制其结合到 ASC 上，从而抑制炎症小体的激活[88–89]。卡波济氏肉瘤相关疱疹病毒(The Kaposi’s sarcoma-associated

herpes virus)的 Orf63 蛋白含有的 NBD-LRR 结构域，能够对 NLRP1 和 NLRP3 进行干扰[90]，这类通过同源结构域干扰进而抑制炎症小体激活的病毒还有纤维瘤病毒(Shope fibroma virus)和麻疹病毒(Measles virus)[91–92]。此外，痘病毒(Poxvirus)、猪瘟病毒(Swine fever virus)、杆状病毒(Baculoviruses)等也能够通过分泌一些效应蛋白，通过直接或者竞争性抑制 caspases 调控炎症小体的激活[93–99]。

迄今为止，研究发现病原体可通过不同的逃避机制逃避宿主炎症小体的识别，弱化炎症小体的作用或直接抑制宿主炎症小体的激活，同一种病原体可以发展出多种逃避宿主炎症小体的机制，从而使其能够在宿主体内长期存活。表 2 和表 3 分别总结了目前研究报道的细菌和病毒逃避宿主炎症小体作用的机制。

表 2. 病原菌逃避宿主炎性小体作用的机制

Table 2. The evasion mechanisms of bacteria against host inflammasomes

Bacteria	Evasion mechanisms	References
Francisella tularensis	*mviN* or *ripA* genes prevent the AIM2 inflammasome activation; Evade caspase-11 by modifying their lipid A and this modifications enable TLR4 evasion	[61,75–76]
Legionella pneumophila	T4SS effector SdhA are involved in maintenance of vacuole stability to prevent activation of caspase-11; SdhA functions to prevent bacterial DNA release into macrophage cytosol; Downregulates the expression of the ASC and the NLRC4;	[20,77–78]
Listeria monocytogenes	Represses flagellin, which contributes indirectly to the reduction in sensing by the NLRC4 inflammasome	[79]
Mycobacterium tuberculosis	*zmp1* gene encoding a putative Zn^{2+} metalloprotease inhibits caspase-1 activation; Inhibits AIM2 inflammasome activation by ESX1 secretion system;	[71,80–81]
Pseudomonas aeruginosa	T3SS effector ExoU inhibits caspase-1and NLRC4 inflammasome; ExoS effector interferes with inflammasome-mediated IL-1β production and indirectly affects caspase-1 activation	[67–68]
Salmonella Typhimurium	Downregulates the expression of flagellin and SPI-1 T3SS during systemic infections; Bacteria resides in the vacuole and evade caspase-11; T3SS effector SifA is involved in maintenance of vacuole stability to prevent activation of caspase-11; TCA enzyme inhibits NLRP3 inflammasome activation	[20,35,64,82–83]
Shigella flexneri	OspC3 interacts with the p19 subunit of caspase-4 and inhibits caspase-4 activation by preventing heterodimerization of p19 subunit and p10 subunit	[74]
Staphylococcus aureus	Modifies cell wall to prevent degradation by lysosomes in infected host cells, contributes indirectly to the reduction in sensing by the NLRP3 inflammasome	[73]
Yersinia pestis	YopM inhibits recruitment of caspase-1 to ASC speck by binding to caspase-1 via a YLTD motif in the LRR domain that acts as a pseudo-substrate for caspase-1; YopK limits the ability of the inflammasome by modulating translocation of a T3SS-dependent substrate; Generates tetra-acylated LPS during infection, evades both TLR4 and non-canonical inflammasome activation by modifying the structure of their LPS	[49,65,80,84–85]
Yersinia pseudotuberculosis	YopM effector injected into the host cells via T3SS, directly bind to caspase-1 and prevent its activation;	[49,65]
Yersinia enterocolitica	Yop effectors indirectly trigger the disruption of the actin cytoskeleton and the inhibition of phagocytosis; YopE and YopT directly inhibit caspase-1 activation and IL-1β release;	[66,86]
Vibrio parahaemolyticus	VopQ and VopS selectively inhibit NLRC4 inflammasome activation	[72]

表 3. 病毒对宿主炎性小体的逃避机制

Table 3. The evasion mechanisms of viruses against host inflammasomes

Viruses	Evasion mechanisms	References
African swine fever virus	A224L protein interacts with the proteolytic fragment of caspase-3 and inhibits caspase-3 activity	[96]
Amsacta moorei entomopoxvirus	P33 acts as a substrate inhibitor of effector caspases; AMV-IAP inhibits caspase-3 activation	[94–95]
Baculoviruses	p35 and p49 proteins can inhibit caspases	[93,97–99]
Cowpox virus	CrmA inhibits the activity of caspase-1，-4，-5，-8，-9，-10	[100–101]
Ectromelia virus	SPI-2 inhibits the activity of caspase-1and caspase-8	[102]
Influenza A virus	NS1 protein inhibits caspase-1 activation	[103]
Molluscum contagiosum virus	MC159 proteins indirectly inhibit caspase-8	[104]
Myxoma virus	SERP2 inhibits caspase-1, caspase-8 and caspase-10; M013 interacts with the ASC-1 and inhibits caspase-1 activation; Inhibits NF-kB signaling to interfere inflammasome activation	[88,105]
Shope fibroma virus	gp013L directly associates with ASC and inhibits PYD-mediated signal transduction	[91]
Spodoptera littoralis nucleopolyhedrovirus	P49 inhibits insect and human effector caspases	[106]
The Kaposi's sarcoma-associated herpes virus	Orf63 interacts with NBD to inhibit NLRs oligomerization	[90]
γ-herpesviruses	E8 protein interacts with the caspase-8 prodomain	[104]

3 展望

近年来，大量的研究已经证明，宿主炎症小体在天然免疫应答及炎性疾病的发生中起着至关重要的作用。在长期进化中，由于选择压力的存在，病原体也产生了各种逃避炎症小体的机制。尽管现在已有大量关于炎症小体的研究，绝大多数对宿主是起到保护作用的，但在少数病原体感染过程中，炎症小体反而会减少宿主的存活，导致这种差异的原因以及病原体与炎症小体之间互作的具体机制尚不清楚，了解这些机制对疾病的预防和控制有着重要意义。未来，可能还会发现更多的病原菌以及逃避机制。此外，线粒体与炎症小体的激活以及炎性信号通路息息相关，胞内菌在与宿主细胞相互作用中进化出一些机制阻止细胞死亡以利于其自身的生存，如下调炎性信号的表达或抑制激活细胞死亡信号的蛋白复合物的组装等。未来关于线粒体对炎症小体的激活以及调控方式的研究能使我们进一步了解炎性小体。最近 Shi 和 Kayagaki 等几乎同时发现，Gasdermin D 是炎性半胱天冬酶的一个基质，Gasdermin D 可以被 caspase-1 和 caspase-11 切割引起细胞焦亡[107–108]。这些新发现拓宽了我们对炎症小体及其组成蛋白功能的认识，对炎症小体的研究也有越来越广的方向。

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Progress in research on interactions between pathogens and inflammasomes

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Abstract: Inflammasomes are multi-protein complexes located in the cytosol and activate caspase-1. Subsequently, inflammasomes induce maturation and secretion of series of pro-inflammatory cytokines and pyroptosis. Inflammasome activation plays a critical role in host innate immune responses against infectious pathogens. Inflammasomes can protect host against most pathogens. However, the protection role of inflammasome seems sometimes less obvious, or it shows detrimental to the host and facilitates the pathogens. Pathogens evolved evasion strategies against inflammasomes under selective pressure, and could weaken or inactivate the functions of inflammasomes. In this review, we summarize the progress in research on the active role of inflammasomes in host immune response against pathogens and the inflammasome-evasion strategies of pathogens.

Keywords: pathogens, inflammasome, innate immune, evasion strategies

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