

## 综述

## ASC斑点在炎症扩散中的作用

徐芳, 唐媛媛, 朱寒寒, 曲梅花\*

(潍坊市第二人民医院, 潍坊 261041)

**摘要:** 凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a CARD, ASC)是一种存在于组织损伤和炎症部位的适配蛋白。ASC蛋白聚集形成ASC斑点和炎症小体的激活是细胞对病原体和细胞损伤的快速响应机制。ASC斑点形成后, 诱导相应机制在细胞膜上产生孔洞, 破坏细胞膜, 导致细胞内炎症因子、ASC斑点等从细胞内释放。具有朊病毒样扩散特性ASC斑点可引起炎症反应和炎症扩散, 是神经退行性疾病、酒精性肝损伤、新型冠状病毒肺炎等炎症性疾病的致病因素。中药单体黄精多糖、蒲公英甾醇、人参皂苷Rg1等通过抑制ASC斑点达到抑制炎症反应的作用。目前, 靶向抑制ASC斑点的纳米抗体用于炎症性疾病治疗的研究也在进行中。本文通过探讨ASC斑点在炎症扩散和相关疾病中的作用和机制, 为靶向抑制ASC斑点形成的新型抗炎药物的发现提供思路。

**关键词:** ASC斑点; 炎症; 细胞焦亡; 中药

## The role of ASC specks in the spread of inflammation

XU Fang, TANG Yuanyuan, ZHU Hanhan, QU Meihua\*

(Weifang Second People's Hospital, Weifang 261041, China)

**Abstract:** The apoptosis-associated speck-like protein containing a CARD (ASC) is an adapter protein that is widely present in areas of tissue damage and inflammation. The aggregation of ASC protein to form ASC specks and the activation of inflammasomes are rapid response mechanisms of cells to pathogens and cellular damage. After ASC specks are formed, they induce pores in the cell membrane, and lead to the release of intracellular inflammatory factors and ASC specks. ASC specks, with their prion-like spreading properties, can trigger inflammatory responses and spread inflammation, serving as pathogenic factors in inflammatory diseases such as neurodegenerative diseases, alcoholic liver injury, and coronavirus disease 2019 (COVID-19). Monomeric compounds from traditional Chinese medicine, such as polysaccharides from *Polygonatum cyrtonema* Hua, taraxasterol, and ginsenoside Rg1, inhibit ASC specks to suppress inflammatory responses. Currently, research is also being conducted on nanoantibodies targeting ASC specks for the treatment of inflammatory diseases. This review explores the role and mechanisms of ASC specks in inflammation spread and related diseases, providing insights for the discovery of novel anti-inflammatory drugs that target and inhibit the formation of ASC specks.

**Key Words:** ASC specks; inflammation; pyroptosis; traditional Chinese medicine

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第一作者: E-mail: 863433194@qq.com

\*通信作者: E-mail: qumeihua2016@163.com

凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a CARD, ASC)是由PYCARD(pyrin and caspase recruitment domain containing)基因编码的一种接头蛋白, 含有热蛋白结构域(pyrin domain, PYD)和半胱天冬酶募集结构域(caspase recruitment domain, CARD), 相对分子质量约为22 000。

ASC蛋白通过其PYD和CARD结构域分别与核酸结合寡聚结构域受体(nucleotide-binding oligomerization domain-like receptors, NLRs)、天冬氨酸蛋白水解酶1前体(pro-cysteinyI aspartate specific proteinase-1, pro-Caspase-1)相互作用, 组装形成一个直径1~2  $\mu\text{m}$ 的胞内大分子聚集体, 即ASC斑点<sup>[1,2]</sup>。ASC斑点是人体组织损伤后炎症微环境的重要成分, 是炎症小体活化的标志。ASC斑点的异常激活与炎症性疾病、自身免疫病、神经退行性疾病和癌症的发生均有密切关系。在痛风、阿尔兹海默症<sup>[3]</sup>、炎症性肠病、2型糖尿病、酒精性肝炎<sup>[4]</sup>等炎症性疾病的发生中, ASC斑点的形成可导致过度的炎症反应和组织损伤<sup>[3,4]</sup>。

ASC蛋白在多种组织细胞及免疫细胞中均有表达, ASC在免疫细胞中的功能对于宿主防御病原体、调节免疫反应和维持组织稳态至关重要。ASC斑点是研究炎症、免疫和细胞凋亡的重要分子, 也是开发治疗炎症性疾病和自身免疫病潜在药物的靶点<sup>[5,6]</sup>。

## 1. ASC斑点概述

### 1.1 ASC斑点的形成与活化

NLRs是一类在细胞内识别病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)或损伤相关分子模式(damage-associated molecular patterns, DAMPs)的蛋白质受体家族。NLRs接受到细胞内的感染和组织损伤等危险信号时, 可以形成炎症小体, 炎症小体的激活导致Caspase-1的活化, 进而促进炎症细胞因子如IL-1 $\beta$ 和IL-18的成熟和分泌, 以及细胞焦亡(pyroptosis), 在先天免疫系统中起着关键作用。细胞内的NLRs分子包括NLRP1、NLRP3、NLRP6、NLRP12等, 其中NLRP3蛋白(也称为cryopyrin)与多种炎症性疾病有关。NLRP3蛋白由CIASI(cold induced

autoinflammatory syndrome 1)基因编码, 包含一个PYD结构域、一个中央核苷酸结合寡聚(nucleotide-binding oligomerization domain, NACHT)结构域和一个C末端富含亮氨酸的重复序列(leucine-rich repeat, LRR)。其中, NACHT结构域负责ATP结合和自身寡聚化; LRR结构域负责识别特定的配体, 如PAMPs或DAMPs; PYD结构域介导NLRP3与其他含有PYD结构域的蛋白质(如ASC)的相互作用<sup>[7]</sup>。

正常状态下NLRP3的NACHT结构域与LRR结构域结合并处于自我抑制状态, 在细胞遭受感染、损伤或代谢紊乱时, PAMPs或DAMPs刺激NLRP3蛋白构象发生变化并暴露NACHT结构域, NLRP3蛋白通过NACHT结合域发生寡聚化, NLRs与ASC通过PYD结构域同源识别联结导致大量ASC蛋白聚合, 形成ASC-ASC长螺旋纤维<sup>[8]</sup>, 这些纤维通过ASC蛋白的CRAD结构域的同型相互作用交联形成ASC斑点<sup>[1,9-11]</sup>(图1)。ASC蛋白的PYD结构域和CARD结构域对ASC斑点形成至关重要, PYD结构域的突变导致ASC蛋白无法寡聚, 不能形成ASC-ASC纤维, 而CARD结构域的失活则使ASC-PYD纤维无法有效交联, 两种突变均可导致ASC斑点无法有效组装<sup>[12]</sup>。ASC斑点形成是不可逆的, 期间所有ASC分子被募集聚合, 一个细胞仅能形成一个ASC斑点<sup>[1,13]</sup>。在ASC斑点中pro-Caspase-1通过CARD-CARD结构域相互作用结合ASC蛋白并二聚化, pro-Caspase-1自我裂解并活化成为有生物活性的Caspase-1<sup>[14]</sup>。成熟的Caspase-1从ASC斑点中释放出来, 切割白介素1 $\beta$ 前体(pro-interleukin-1 $\beta$ , pro-IL-1 $\beta$ )和白介素18前体(pro-interleukin-18, pro-IL-18), 形成成熟的炎症细胞因子IL-1 $\beta$ 和IL-18<sup>[12]</sup>, 进而激活炎症反应下游途径<sup>[15]</sup>。

ASC斑点是Caspase-1活化、释放IL-1 $\beta$ 等细胞因子的级联放大平台, ASC蛋白无法单独活化IL-1 $\beta$ , Caspase-1、IL-1 $\beta$ 的活化依赖ASC斑点的形成<sup>[12]</sup>。IL-1 $\beta$ 诱导形成多种促炎细胞因子和趋化因子, 如基质金属蛋白酶9<sup>[16]</sup>。分泌到胞外的IL-1 $\beta$ 等炎症细胞因子募集免疫细胞到炎症部位, 促进炎症反应的发生, 包括血管扩张、白细胞的迁移和炎症区域的局部渗出; 调节免疫应答, 激活巨噬细胞、淋巴细胞和其他免疫细胞, 影响免疫细胞的活性和功能, 促进抗体产生和细胞免疫的效

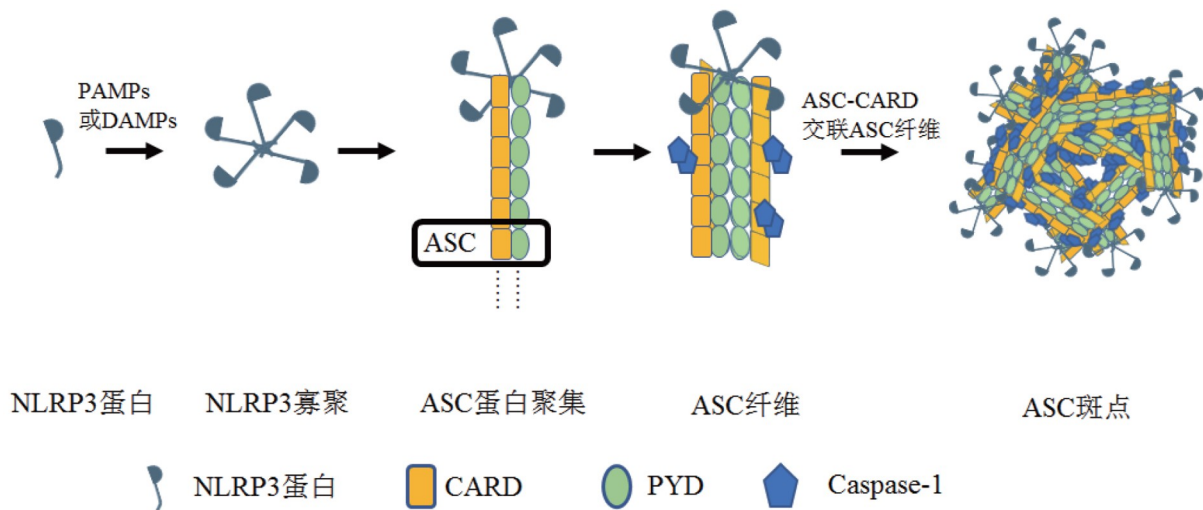


图1 ASC斑点结构

应;调节组织细胞的生存、凋亡和分化,促进组织修复和再生。但是,当ASC斑点过度活化时,可能产生细胞因子风暴。

### 1.2 细胞焦亡与ASC斑点释放

细胞焦亡是一种新型Caspase-1依赖的程序性细胞死亡,焦亡细胞失去细胞质膜的完整性并释放细胞内容物如ASC斑点和乳酸脱氢酶<sup>[17]</sup>。细胞焦亡与细胞免疫应答、炎症反应密切相关,长期的炎性小体活化导致细胞焦亡。细胞焦亡通过识别病原体相关分子或异常细胞组织释放的物质进行,包括PAMPs、DAMPs和胞质紊乱途径。PAMPs来源于微生物,包含细菌脂多糖、真菌酵母聚糖、病毒核糖核酸、尼日利亚菌素等;DAMPs是细胞受到损伤或低氧等刺激后释放的一类物质,包括细胞外腺嘌呤核苷三磷酸、活性氧、尿酸、淀粉样蛋白 $\beta$ 斑块等<sup>[18]</sup>。消皮素D (Gasdermin D, GSDMD)跨膜蛋白介导ASC斑点的释放。ASC斑点形成后,细胞中GSDMD跨膜蛋白的表达量增加,生物学活性增强<sup>[19]</sup>。活化的Caspase-1<sup>[20]</sup>切割并降解GSDMD跨膜蛋白<sup>[19,21,22]</sup>,形成GSDMD跨膜穿孔,细胞膜通透性发生改变,细胞破裂,发生细胞焦亡。ASC斑点和炎症因子IL-1 $\beta$ 等细胞内容物通过GSDMD跨膜穿孔释放到胞浆中<sup>[23-25]</sup>。另外,NK细胞释放的颗粒酶可以直接切割靶细胞中的GSDMD蛋白,促进细胞焦亡和ASC斑点释放<sup>[26]</sup>。细胞焦亡可以阻断细胞内病原体

的复制,将病原体暴露于机体免疫系统,防御感染进一步扩大<sup>[27]</sup>。

### 1.3 细胞外ASC斑点与炎症扩散

慢性炎症性疾病患者的血液中存在细胞外ASC斑点,是炎症相关的血液生物标志物,可通过血液循环加重炎症反应<sup>[28]</sup>。炎症可以通过ASC斑点跨细胞传播(图2)。细胞产生ASC斑点后无法通过其自噬清除机制进行降解,一般情况下,ASC斑点通过胞吐或细胞焦亡裂解进入细胞外环境,形成含有NLRP3和ASC的寡聚复合物,即细胞外ASC斑点<sup>[8,29]</sup>。细胞外ASC斑点非常稳定,在细胞外环境保持生物活性,可以抵抗蛋白酶水解。ASC斑点具有类似朊病毒的特性,能够“感染”旁细胞并聚集可溶性ASC蛋白形成新的ASC-ASC纤维,为新的ASC斑点的形成提供了模板<sup>[8]</sup>。细胞外ASC斑点既可以激活细胞外Caspase-1,也可以被吞噬细胞内化后形成新的ASC斑点<sup>[30]</sup>,继而激活Caspase-1,或被吞噬细胞和非吞噬细胞的邻近细胞内化后激活Caspase-1<sup>[8,28,31]</sup>,进而激活和触发细胞的炎症级联反应<sup>[17]</sup>。研究显示,腹腔或皮下注射外源性ASC斑点可诱导小鼠急性炎症发生<sup>[8]</sup>。细胞外ASC斑点还可以诱导中性粒细胞聚集、脱颗粒和释放炎症介质,扩大炎症区域;细胞外ASC斑点也可以进入循环系统,经循环系统播散至其他组织部位,导致炎症区域扩大并持续发生<sup>[8,17,28,31]</sup>。细胞外ASC斑点最终被细胞中的溶酶体降解。ASC

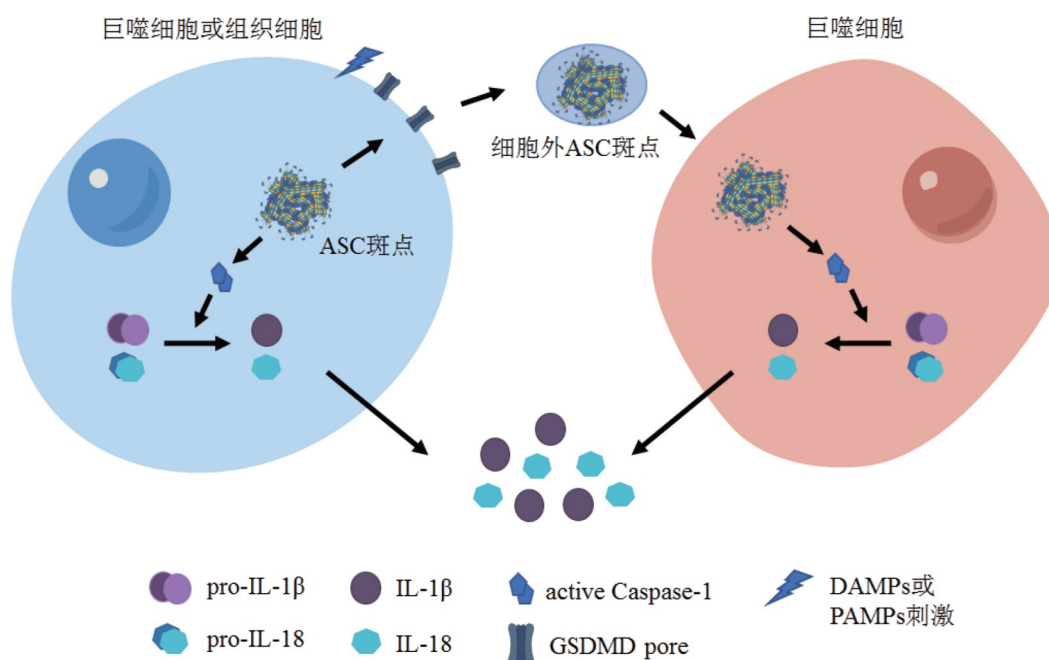


图2 ASC斑点在炎症扩散中的示意图

斑点降解失败或溶酶体受到损伤时,细胞可持续产生并分泌过量的炎症细胞因子,导致过度的炎症反应。

细胞外ASC斑点作为细胞间通讯的新型介质,在固有免疫和适应性免疫的进展中发挥重要作用。细胞外ASC斑点可诱导免疫细胞产生针对ASC斑点的抗体,催化细胞因子的成熟,促进建立适应性免疫<sup>[3]</sup>。ASC斑点的自身抗体能够增强巨噬细胞摄取ASC斑点并促进IL-1 $\beta$ 的释放<sup>[8]</sup>。ASC斑点产物之一IL-18可以激活淋巴细胞,促进T淋巴细胞和B淋巴细胞的增殖<sup>[32]</sup>,增强NK细胞的活性,刺激细胞因子干扰素 $\gamma$ 、肿瘤坏死因子 $\alpha$ 、IL-1和IL-2的活化和释放。另一种ASC斑点产物IL-1 $\beta$ 刺激T细胞的增殖,增加CD103<sup>+</sup>CD69<sup>+</sup>组织常驻记忆T细胞和树突状细胞的数量<sup>[33]</sup>。

ASC斑点的形成和释放可以通过经典的蛋白免疫印迹技术、共聚焦显微镜和电子显微镜技术、高通量图像和流式细胞术技术等方法进行研究和可视化<sup>[34]</sup>。成像流式细胞术可评估外周血或单核细胞中ASC斑点形成水平,酶联免疫吸附实验技术可检测评估血液或体液中ASC斑点水平<sup>[31,35]</sup>。多反应监测质谱测定可用于准确定量人类生物标本中ASC蛋白水平,用于辅助诊断慢性肾病炎症水

平<sup>[36]</sup>。肺支气管肺泡灌洗液中ASC单体和聚合物的数量、性质是肺ASC斑点活性的标志,肺支气管肺泡灌洗液中ASC单体和聚合物浓度可以反映肺微环境的炎症状态和肺功能丧失程度<sup>[37]</sup>。

## 2. ASC斑点在炎症扩散相关疾病中的作用

ASC斑点广泛存在于损伤和炎症部位,与多种炎症、免疫、代谢紊乱等疾病有关,由损伤和炎症部位细胞产生并经细胞焦亡释放进入循环系统,过度活化的炎性小体引起细胞因子过量分泌,严重时引发全身炎症反应<sup>[3,38-41]</sup>。

### 2.1 ASC斑点与神经退行性疾病

阿尔兹海默症(Alzheimer's disease, AD)是一种进行性发展的神经系统退行性疾病,起病隐匿。ASC斑点是AD中神经炎症的驱动因素,其朊病毒样扩散性质使AD患者的神经炎症不断加重<sup>[3]</sup>。AD患者脑组织中存在 $\beta$ 淀粉样蛋白(amyloid  $\beta$  protein, A $\beta$ )<sup>[41]</sup>,A $\beta$ 作为DAMPs,激活中枢神经系统中神经胶质细胞内NLRP3,通过级联反应形成ASC斑点,导致神经组织炎症反应和神经胶质的细胞焦亡<sup>[42]</sup>。焦亡的神经胶质细胞释放的ASC斑点和炎症细胞因子可进一步促进和放大神经炎症反应。研究显示,AD病人大脑神经胶质细胞内和细

胞外均能检测出ASC斑点, 释放到细胞外的ASC斑点迅速和A $\beta$ 结合<sup>[43]</sup>, 参与A $\beta$ 沉积, 在A $\beta$ 聚集和扩散过程中均发挥作用<sup>[44]</sup>。帕金森病小鼠大脑组织中细胞内外的ASC斑点数量均明显增多, 导致反应性神经胶质细胞增生和 $\alpha$ -突触核蛋白病理性增多, 明显加快了多巴胺能神经元变性和运动缺陷<sup>[45]</sup>。

女性绝经期内源性雌激素的消耗会激活炎症反应, 雌性生殖器官产生含ASC斑点的细胞外囊泡并扩散到大脑中, 导致中枢神经损伤和大脑炎症。围绝经期妇女的大脑更容易患神经退行性疾病脑卒中, 又称中风<sup>[46]</sup>。ASC斑点是中风后炎症相关先天免疫反应的重要物质, 是脑卒中潜在的生物标志物。原发性脑卒中后, 受损细胞启动NLRP3, 产生并释放ASC斑点, 扩大梗死面积。He等<sup>[47]</sup>研究发现, 实验小鼠第二次中风的脑损伤比第一次中风严重得多, 细胞外ASC斑点以NLRP3依赖的方式介导复发性卒中, 并加重缺血性脑卒中的预后。

创伤性脑损伤(trumatic brain injury, TBI)由头部或身体受到重击或震动造成, 可能导致长期并发症或死亡。在脑和脊髓损伤后, 细胞产生含ASC斑点的细胞外囊泡, 细胞外囊泡释放ASC斑点<sup>[38]</sup>, 引起显著的生理损伤。20%~25%的TBI患者会发展为急性肺损伤, 细胞外囊泡介导的ASC斑点是TBI诱导的肺损伤炎症的致病因素之一, 细胞外囊泡介导的神经-呼吸ASC斑点轴引发了TBI诱导的肺损伤<sup>[48]</sup>。目前, 机械通气是唯一治疗创伤性肺损伤的干预措施。细胞外囊泡摄取阻断剂低分子肝素和抗ASC单克隆抗体, 可以阻断ASC斑点激活<sup>[49]</sup>, 有潜力治疗TBI和TBI诱导的肺损伤。此外, ASC斑点有望用作TBI和TBI诱导的肺损伤严重程度或发展程度的生物标志物<sup>[50]</sup>。

## 2.2 ASC斑点与酒精性肝损伤

酒精刺激肝细胞和巨噬细胞产生尿酸、腺嘌呤核苷三磷酸、线粒体活性氧等DAMPs, 导致肝细胞和巨噬细胞产生ASC斑点。ASC斑点是酒精性肝损伤的驱动因素, 诱导肝细胞和巨噬细胞释放促炎因子IL-1 $\beta$ 、IL-18等, 免疫细胞被募集至炎症区域, 导致肝细胞焦亡和纤维化<sup>[51]</sup>。Petrasek等<sup>[52]</sup>研究发现, NLRP3、Caspase-1或ASC蛋白的基因敲除小鼠可减轻酒精性肝脂肪变性和损伤, 预防酒

精性肝炎和纤维化。酒精性肝炎患者和酗酒小鼠的肝脏和血液中细胞内外ASC斑点持续存在, 并可以触发其他细胞产生新的ASC斑点, 扩大肝脏炎症区域, 加重酒精性肝损伤<sup>[4,39]</sup>。

## 2.3 ASC斑点与新型冠状病毒肺炎(corona virus disease 2019, COVID-19)

中性粒细胞是体内最多的白细胞, ASC斑点促其释放中性粒细胞胞外诱捕网(neutrophil extracellular traps, NETs)<sup>[53]</sup>。NETs具有极大的破坏性, 会水解细胞外基质蛋白, 激活固有免疫, 引起过度炎症反应, 诱导中性粒细胞死亡和巨噬细胞焦亡, 干扰血液氧合, 导致组织器官损伤和血栓形成。

COVID-19呼吸衰竭患者的中性粒细胞中存在大量ASC斑点, ASC斑点刺激NETs的释放和中性粒细胞的死亡, 使免疫细胞过度激活, 导致严重的COVID-19<sup>[53]</sup>。此外, COVID-19病毒感染会激活单核细胞、中性粒细胞和巨噬细胞中的ASC斑点, 导致细胞因子风暴。抑制免疫细胞ASC斑点形成、活化从而减轻NETs的释放和细胞因子风暴是治疗COVID-19的一种方法。 $\alpha$ -亚麻酸可以降低ASC斑点水平, 抑制NETs诱导的巨噬细胞的凋亡, 减轻肺损伤<sup>[54]</sup>。

## 3. ASC斑点与相关药物

部分中药可以抑制炎症反应中ASC斑点形成, 减少IL-1 $\beta$ 和IL-18的产生, 发挥免疫调节和抑制炎症的作用<sup>[14]</sup>。抑郁症发病与ASC斑点有关, 黄精多糖是一种植物多糖, Shen等<sup>[5]</sup>发现, 黄精多糖通过抑制抑郁症模型小鼠中NLRP3/ASC/Caspase-1炎性小体信号通路, 阻碍ASC斑点的形成和活化, 发挥抗氧化、抗炎、抗抑郁作用, 减轻抑郁症小鼠的神经炎症。蒲公英有效成分蒲公英甾醇能显著抑制尼日利亚菌素和细胞外腺嘌呤核苷三磷酸诱导的小鼠原代巨噬细胞炎症模型中ASC斑点的形成, 下调活化的Caspase-1水平, 阻碍成熟IL-1 $\beta$ 释放和GSDMD裂解, 抑制细胞焦亡<sup>[55]</sup>。人参皂苷Rg1通过抑制内质网应激、减少ASC斑点形成的方式改善高脂饮食小鼠的非酒精性脂肪肝<sup>[56]</sup>。雷公藤甲素通过调控NLRP3-ASC相互作用减轻小鼠异丙肾上腺素诱导的心脏纤维化<sup>[6]</sup>。芥子甙通过抑制巨噬细

胞LPS诱导的ASC斑点和炎症介质的活化发挥抗炎和免疫调节作用<sup>[57]</sup>。次生草药代谢物小豆蔻素通过抑制小鼠骨髓源性巨噬细胞和人外周血单核细胞的NLRP3激活<sup>[58]</sup>，阻止ASC寡聚化，提高了小鼠脂多糖诱导的脓毒性休克的存活率。

Bertheloot等<sup>[59]</sup>发现，ASC纳米抗体可缓解小鼠尿酸钠结晶盐诱导的膝关节痛风及甲基化牛血清白蛋白诱导的膝关节炎症反应。ASC纳米抗体靶向分解焦亡细胞释放的ASC斑点，阻断ASC斑点朊病毒样传播，抑制IL-1 $\beta$ 成熟，减轻过度的炎症反应，并且不影响细胞焦亡前IL-1 $\beta$ 的生成，保证宿主的正常免疫防御功能。远红外线作为一种物理方法，能抑制脂多糖诱导的单核巨噬细胞中ASC斑点形成和IL-1 $\beta$ 分泌，刺激ASC泛素化，促进ASC斑点在单核巨噬细胞中自噬降解，减轻大鼠深二度皮肤烧伤引起的炎症细胞浸润并改善预后<sup>[60]</sup>。

## 4 总结与展望

ASC斑点在炎症疾病进展中发挥了重要作用，ASC斑点在炎症水平诊断和疾病预后中具有一定的临床价值。中药通过抑制ASC斑点，改善多种疾病的病理状态，发挥多种炎症性疾病的防治作用，包括抑郁症、心血管疾病、酒精性肝损伤、肺损伤等。一些中药提取物和中药单体通过调节ASC斑点信号转导机制改善炎症，有治疗免疫炎症的作用，但其在实际临床应用中有待进一步研究。针对ASC斑点的实际临床应用药物较少，亟待研发更有效果的药物。在中药的基础上，生物医药、化学、物理多学科交叉，结合更多的新技术、新方法，从中药单体、中药提取物、中药复方、西药等多层面探究ASC斑点治疗的新思路。未来ASC斑点相关药物研发会越来越多，期待实际临床应用ASC斑点成为治疗炎症疾病的重要途径。

ASC斑点在炎症疾病中的作用较为复杂，ASC斑点在炎症扩散中的现有机制不完善。研究ASC斑点的形成、致病和调控机制可以为许多疾病的治疗提供新的靶标和思路，靶向ASC斑点药物的研发为炎症疾病的治疗提供了新的方向。

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