细胞焦亡与代谢性疾病的研究进展

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摘要 细胞焦亡是一种与炎性应答有关的细胞程序性死亡方式, 与高血脂、高血糖、痛风和动脉粥样硬化等多种代谢性疾病密切相关。通过caspase-1依赖或非依赖的机制调节的细胞焦亡都参与代谢性疾病的发展。在caspase-1依赖的细胞焦亡中, 多种代谢性疾病有关的危险信号激活Nod样受体蛋白3炎症小体, 导致细胞焦亡、白介素-1β水平增加, 进而激活局部及全身炎症反应, 是代谢性疾病发生发展的重要原因之一。革兰氏阴性菌释放的脂多糖能直接激活caspase-4/5/11, 导致caspase-1非依赖的细胞焦亡。抑制细胞炎症小体–焦亡通路未来可能成为改善代谢性疾病的有效治疗策略之一, 然而, 由于细胞焦亡调节代谢稳态的机制仍不清楚, 因此还需要进一步研究。

关键词 细胞焦亡; 代谢性疾病; NLRP3炎症小体; 治疗

Research Progress of Pyroptosis and Metabolic Diseases

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Abstract Pyroptosis is a form of programmed cell death associated with inflammatory responses, which is closely related to various metabolic diseases including hyperlipidemia, hyperglycemia, gout, and atherosclerosis. Of note, caspase-1-dependent and caspase-1-independent pyroptosis are involved in the development of metabolic diseases. In caspase-1-dependent pyroptosis, metabolic diseases-triggered danger signals activate Nod-like receptor 3 inflammasome. The inflammasome initiates the pyroptosis and increases serum interleukin-1β levels, and subsequently triggers the local and systemic inflammatory responses, further promoting the development of metabolic disease. On the other hand, lipopolysaccharide released from Gram-negative bacteria induces the cell pyroptosis by activating caspase-4/5/11. Inhibition of the inflammasome-pyroptosis axis may be a potential strategy to improve the metabolic diseases in the future. However, given the underline mechanism through which pyroptosis regulates the metabolic homeostasis remains elusive, further studies are needed to be investigated.

Keywords pyroptosis; metabolic disease; NLRP3 inflammasome; therapy

随着现代人饮食结构的改变, 代谢性疾病发病率在全球范围飙升, 已成为威胁全球人类健康的主要因素[1]。代谢综合征包括腹型肥胖、胰岛素抵抗、血脂异常、血压升高、并发血栓前状态、促炎状态、非酒精性脂肪肝病和生殖障碍等一系列症状[2]。而代谢性疾病的发病机制复杂, 目前国内外主流的治疗手

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段仍然存在治疗靶点单一、肝肾损害和停药反弹等问题[3]。细胞焦亡作为近年新发现的细胞程序性死亡方式, 越来越受到研究人员的关注。最近的研究表明, 细胞焦亡与代谢性疾病的发生发展密切相关。因此, 考察焦亡在代谢性疾病发病进程中发挥的作用对促进代谢性疾病的诊断和治疗至关重要。本文对细胞焦亡的机制及其与代谢性疾病的关系做简要综述, 未来对特定组织器官中细胞焦亡机制的进一步研究将有助于促进对代谢性疾病的理解、诊断和治疗。

1 细胞焦亡

1.1 细胞焦亡的发现

细胞焦亡是一种与炎性应答有关的程序性细胞死亡[4], 大量研究表明细胞焦亡在代谢性疾病的发生发展中发挥重要作用。除微生物感染因素外, 心肌梗死、高血脂、高血糖等非感染因素也能引起细胞焦亡[5-6]。ZYCHLINSKY等[7]于1992年首次描述了细胞焦亡现象, 这一现象由COOKSON和BRENNAN于2001年首次命名[8]。细胞焦亡的特征为炎性caspase激活导致胞膜成孔、透化, 细胞肿胀, 最终导致细胞内容物释放, 从而激活强烈的炎症反应[9]。细胞焦亡作为机体内一种重要的先天免疫反应, 在防御病毒和细菌感染过程中发挥重要作用[10]。细胞焦亡不仅能消除利于病原体复制的细胞内环境, 而且还能释放感染因子和胞质内容物募集并激活免疫细胞, 有助于清除宿主体内的病原体[11]。然而细胞焦亡过度活化将会加重炎症反应, 在一定程度上导致组织器官的损伤[10]。

1.2 细胞焦亡的分子机制

细胞焦亡是通过依赖caspase-1或非依赖caspase-1的机制进行调节的。危险信号激活人caspases-1/4/5和鼠caspases-1/11, 当这些炎性caspase被激活时, 会进一步切割GSDMD(Gasdermin D)蛋白, 产生氨基端(N-端)切割产物GSDMD-N[12], 其定位在质膜并进一步寡聚化, 在膜上形成小孔导致质膜迅速透化[13], 这种细胞膜的功能障碍导致细胞肿胀、破裂, 细胞内容物及白介素1β(interleukin-1β, IL-1β)等促炎因子释放[12,14], 产生炎症反应。

Caspase-1依赖的细胞焦亡始于炎症感受器和分子模式的识别[14]。炎症是修复组织损伤的先天免疫反应, 细胞感受器模式识别受体(pattern recognition receptors, PRRs)响应病原相关分子模式(pathogen-associated molecular patterns, PAMPs)和危险或损伤相关分子模式(danger/damage-associated molecular patterns, DAMPs)介导感染或无菌性炎症, 参与早期炎症的发生[15]。

Nod样受体(Nod-like receptors, NLRs)亚单位响应DAMP或PAMP装配激活, 形成的多蛋白复合物被称为炎症小体[16]。炎症小体的装配激活caspase-1, caspase-1将GSDMD蛋白切割为两个部分, GSDMD-N插入细胞膜形成开放的孔道[12,17-18], 这破坏了细胞膜的生理活性, 导致细胞肿胀、破裂。活化的caspase-1也能切割IL-1β和IL-18前体促进其成熟和分泌[19-20], 导致炎症反应的发生。许多因子能激活炎症小体引发焦亡, 研究最多的Nod样受体蛋白3(Nod-like receptor pyrin domain 3, NLRP3)多蛋白复合物密切参与焦亡过程[21]。NLRP3的激活受包括PAMPs、细菌毒素和DAMPs在内的多种因素调节, 如活性氧(reactive oxygen species, ROS)、高迁移率族蛋白B1(high mobility group B1, HMGB-1)、尿酸晶体、病毒蛋白、细胞外ATP、β淀粉样蛋白纤维和胆固醇晶体[15]。高血脂、高血糖通过危险相关分子模式激活NLRP3炎症小体。此外, 氧化应激诱导的颗粒吞噬或活病原体吞噬作用导致溶酶体破裂, 释放组织蛋白酶B促进NLRP3与斑点样蛋白(speck-like protein, ASCs)的相互作用进而引发焦亡[5]。

实验证据表明, 革兰氏阴性菌产生的脂多糖(lipopolysaccharide, LPS)是诱发细胞焦亡的重要因素[13], 参与caspase-1非依赖的细胞焦亡过程。LPS直接与caspase-4/5/11的半胱天冬酶募集结构域(caspase recruitment domain, CARD)结合, 导致caspase寡聚化, 一旦超过阈值, caspase-4/5/11便会催化切割GSDMD蛋白, 产生后续的细胞焦亡过程[22-23]。

2 细胞焦亡与糖代谢

糖代谢对体内环境稳态具有重要作用。糖代谢紊乱会导致一系列代谢性疾病, 如糖尿病、肥胖症、低血糖等[15]。多种糖代谢中间体所涉及的酶已经被证实与NLRP3的激活密切相关[24]。

糖尿病是一种以细胞功能异常、代谢异常和炎症为特征的代谢性疾病。炎症过程已经被证实在糖尿病中起关键作用, 例如慢性低度炎症与糖尿病患者的高血糖有关。一些DAMPs激活炎症小体, 导致

IL-1β升高、细胞焦亡并参与诱导低度炎症[15]。糖尿病患者的高血糖使ROS和糖基化终产物(advanced glycation end products, AGEs)水平升高, 二者是炎症小体的有效激活剂。其中ROS已经被证明能诱导NLRP3炎症小体形成, 引发细胞焦亡。QIU等[25]认为, 高血糖诱导NLRP3炎症小体激活导致的细胞焦亡可能依赖于ROS的形成。GAO等[26]研究发现, 高血糖可激活NADPH-氧化酶系统, 导致ROS生成和NLRP3炎症小体活性上调。ROS作为DAMPs激活炎症小体, 导致细胞焦亡、IL-1β水平升高, 进而导致低度炎症[15]。AGEs水平增加与ROS有关, 参与糖尿病低度炎症的维持, 这可能与炎性小体和Toll样受体的激活有关[15]。另外, 细胞焦亡增加HMGB-1水平, HMGB-1作为DAMPs可能使细胞焦亡引起的炎症反应在局部组织放大进而导致全身炎症反应。

细菌感染可能通过影响糖代谢导致细胞焦亡。沙门氏菌可通过摄取宿主细胞的葡萄糖进而破坏代谢, 降低还原型烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NADH)水平, 导致线粒体ROS产生, 进而引发caspase-1依赖的细胞焦亡。研究表明, 恢复NADH能使细胞免于焦亡[27]。革兰氏阴性细菌细胞壁的脂多糖能通过促进ROS的产生加重高糖和缺氧–复氧诱导的大鼠心肌细胞损伤, 诱导NLRP3炎症小体介导的焦亡。NLRP3炎症小体的缺失或使用抗氧化剂*N*-乙酰半胱氨酸治疗可以改善NLRP3激活后AGEs导致的胰岛细胞损害[28]。抑制炎症小体的激活或清除ROS有助于缓解高血糖和缺氧–复氧诱导的大鼠心肌细胞损伤[25]。

3 细胞焦亡与脂代谢

肥胖与低度慢性炎症相关, 慢性炎症可导致代谢综合征及其相关并发症的发生, 如胰岛素抵抗和2型糖尿病[29]。脂肪组织炎症症状增强可促使细胞因子产生, 进一步促进胰岛素抵抗的发展。许多研究证明, 肥胖症与脂肪组织中NLRP3表达升高有关。NLRP3炎症小体激活的IL-1β在肥胖诱导的胰岛素抵抗和2型糖尿病的发展中发挥重要作用。IL-1β通过减少胰岛素受体底物1(insulin receptor substrate-1, IRS-1)的酪氨酸磷酸化和下调*IRS-1*基因表达直接抑制胰岛素信号通路, 从而诱导胰岛素抵抗。在动物实验中, 相对于野生型实验动物, IL-1β缺乏组在高脂喂养条件下其脂肪组织炎症和胰岛素抵抗症状均得到改善, 葡萄糖稳态维持水平提高[30]。

游离脂肪酸(free fatty acids, FFAs)水平升高被认为是肥胖、胰岛素抵抗和2型糖尿病的重要指标, 已经被证实作为DAMPs激活NLRP3炎症小体。PAMPs和DAMPs可能造成慢性炎症, 同时也被认为能引起焦亡, 这提示, 高FFA水平可能引起细胞焦亡。

高同型半胱氨酸(homocysteine, HCY)是造成肥胖的危险因素, 已经发现肥胖患者血清半胱氨酸水平升高[31], 高水平的HCY在LPS存在和缺乏的状态下都可引起焦亡[32]。研究人员发现, 瘦素缺乏小鼠和高脂饮食肥胖小鼠脂肪垫中NLRP3炎性小体被激活, 在肥大脂肪细胞中, 依赖NLRP3的caspase-1激活可能通过焦亡诱导肥胖症脂肪细胞死亡[33]。

肠道菌群在肥胖和焦亡中也扮演着重要角色。长期食用高脂食物会导致肠道菌群失调, 以及肠道内革兰氏阴性细菌数量增加。目前已经证实, 摄入高脂肪食物会增加血液LPS的水平, 其由肠道内的革兰氏阴性菌产生[34]。HERSOUG等[34]观察到脂肪细胞死亡与来自肠道菌群的脂多糖有关。脂肪细胞内的LPS可能激活caspase-4/5/11, 进而引起细胞焦亡; 此外脂肪细胞内的LPS可能参与脂肪细胞的大小调节和冠状结构的生成, 但其机理仍待阐明。LIU等[35]证明, 核因子-κB(nuclear factor-Kappa B, NF-κB)信号通路参与脂肪细胞焦亡, 褪黑素能分别抑制GSDMD转录和NLRP3炎症小体活化, 从而减弱细胞焦亡。LPS和HCY浓度升高可引起免疫应答, 导致caspase-1激活、NLRP3炎症小体组装和细胞焦亡[36]。肥胖症患者的脂肪细胞应激诱导焦亡的确切机理目前还不清楚, LAHA等[36]提出, HCY和LPS介导的肥胖脂肪细胞焦亡可能是肠道菌群失衡导致的。

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)向非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)的进展源于肝脏和肝外驱动因子发生的众多事件。例如非酯化脂肪酸和内脏脂肪组织分泌的促炎性脂肪因子积累以及肠道细菌代谢产物能使肠道通透性增加, 进而引发肝炎和肝纤维化。在NASH患者和小鼠脂肪性肝炎中都可观察到LPS和炎性caspase(人caspase-1/4/5, 鼠caspase-1/11)升高, 这为GSDMD-N结构域的剪切和后续的焦亡提供了先决条件。因此, 细胞焦亡在NAFLD的发生发展中可能扮演重要角色。GSDMD

作为焦亡的执行蛋白调控细胞因子分泌、NF-κB激活和脂肪生成。XU等[37]证明, GSDMD-N在NASH的发病过程中扮演重要角色, GSDMD-N可自发诱导肝损伤, GSDMD的表达随NASH的严重程度增加。*GSDMD*$^{-/-}$小鼠显示出脂肪变性变少, 生脂基因表达减少, 脂解基因表达上调[38], 这为NAFLD提供了新的治疗策略。先天警报素HMGB1在肝脏损伤后对细胞焦亡活化有重要作用[39]。多种导致肝损伤的因素诱导HMGB1从细胞核移位到细胞质, 接着释放到细胞外环境。细胞外HMGB1与其受体Toll样受体4(Toll-like receptor 4, TLR4)和晚期糖基化终产物受体(receptor of advanced glycation endproducts, RAGE)结合, 激活NLRP3炎症小体和caspase-1, 最终导致肝细胞焦亡。饥饿素可抑制HMGB1, 避免肝细胞焦亡。ROYCHOWDHURY等[40]提出, 肝细胞焦亡可以直接导致肝纤维化。然而, 肝细胞特异性焦亡对NAFLD和NASH的作用仍然未知, 仍需要进一步研究肝细胞焦亡的机制。

4 细胞焦亡对其他代谢性疾病的影响

痛风目前被认为是先天免疫系统激活介导的典型炎症疾病。痛风的发病机制是尿酸晶体在关节内的沉积, 这些晶体是炎症小体的强激活剂。炎症小体介导的IL-β释放引发痛风患者严重的炎症反应, 伴随血管舒张和中性粒细胞被迅速招募到晶体沉积部位。细胞焦亡释放IL-β等炎症因子从而放大炎症, 但此过程是否能促进痛风患者的炎症反应仍待验证[41]。尿酸钠盐晶体能快速激活小鼠巨噬细胞GSDMD的剪切, 然而RASHIDI等[42]的实验证明, *GSDMD*基因缺失不能阻止尿酸钠盐晶体诱导的细胞死亡及IL-1β释放。因此, 细胞焦亡能否作为治疗痛风的靶点仍需进一步研究。

细胞死亡和炎症在调控动脉粥样硬化中发挥重要作用。动脉粥样硬化发病伴随血液中IL-1β和IL-18的上升且与疾病严重程度相关[16], 提示炎症小体–细胞焦亡通路在动脉粥样硬化中发挥重要作用。在低密度脂蛋白受体缺失的小鼠模型中, 骨髓NLRP3、ASCs或IL-1α/β缺失能显著改善动脉粥样硬化的发病进程。胆固醇晶体在动脉血管中的沉积作为动脉粥样硬化发病的特征早已为人所知。最近的研究表明, 胆固醇结晶会破坏溶酶体并激活巨噬细胞中的NLRP3炎性小体。细胞氧化型低密度脂蛋白(oxidized low density lipoprotein, ox-LDL)和氧化型脂多糖能促进乳酸脱氢酶释放和主动脉内皮细胞焦亡[43-44]。MicroRNA-30c-5p通过抑制NLRP3炎症小体保护主动脉内皮细胞免于ox-LDL诱导的焦亡[43]。脂联素(adiponectin, APN)是一种广泛存在于血液循环中的脂细胞源性蛋白, 据报道它可以预防动脉粥样硬化。ZHANG等[44]研究发现, APN通过调控叉头框转录因子4(forkhead box transcription factor 4, FoxO4)抑制NLRP3炎症小体介导的细胞焦亡, 保护主动脉内皮细胞, 减少促炎因子的释放。

5 细胞焦亡对代谢综合征治疗进展和展望

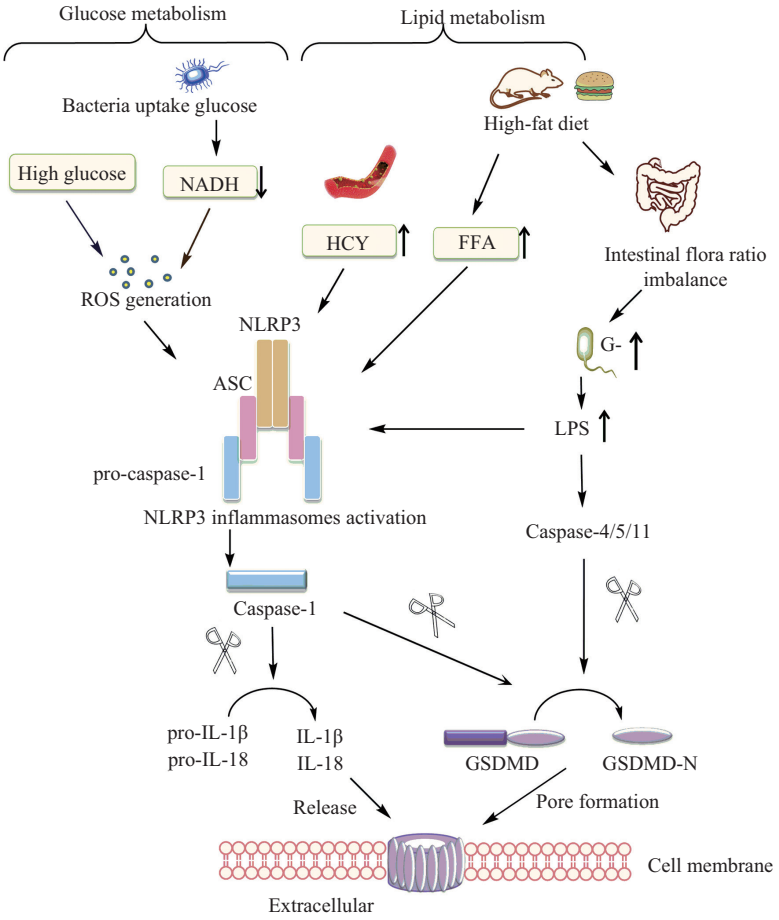
炎症小体在肥胖和胰岛素抵抗中是一种有效的治疗靶点, RINKE等[28]的研究证明, 缺乏炎症小体复合物的大鼠在高脂饮食诱导下不会出现体重增加、脂肪细胞肥大、高胰岛素血症和胰岛素抵抗等症状。本实验室的前期研究发现, 高脂饮食诱导的肥胖小鼠和经FFA处理的肝细胞发生细胞焦亡, 水溶性交联剂(genipin, GNP)对FFA诱导的肝细胞损伤和肥胖小鼠的细胞焦亡有抑制作用[45]。解偶联蛋白-2(uncoupling protein-2, UCP-2)介导了FFA诱导的细胞焦亡, *UCP-2*敲低抑制FFA介导的细胞焦亡[45]。在NLRP3功能获得性突变小鼠模型中, 去除GSDMD能缓解炎症症状[46]。

化学抑制焦亡对于炎症疾病患者具有很高的治疗潜力[47]。坏死性磺酰胺(necrosulfonamide)通过直接与GSDMD蛋白结合, 抑制细胞焦亡膜孔的形成, 特异性抑制炎症小体激活的下游细胞焦亡和IL-1β的释放。坏死性磺酰胺在缓解脓毒症病症中效果显著, 提示GSDMD抑制剂可能在临床上有效治疗炎性疾病。其它抑制GSDMD成孔蛋白的双硫仑(disulfiram)和Bay 11-7082抑制炎症小体介导的焦亡和IL-1β释放。双硫仑和Bay 11-7082还可直接抑制炎性caspases, 多效抑制由典型和非典型炎性小体通路触发的多种炎症过程。因此, 半胱氨酸敏感的化合物虽然缺乏特异性, 但可能对减轻炎症仍然具有吸引力[48]。多种炎症小体介导疾病小鼠模型中GSDMD的缺失能明显改善疾病的发展。干扰素调节因子2(interferon regulatory factor 2, IRF2)是干扰素调节因子家族的转录因子, 直接结合GSDMD启动子, 激活GSDMD转录和细胞焦亡发生, 干扰IRF2结合位点阻碍经典和非经典炎症小体信号通路

转导[49]。GSDMD衍生的抑制剂Ac-FLTD-CMK(*N*-acetyl-Phe-Leu-Thr-Asp-chloromethylketone)是炎性caspase-1/4/5/11的特异性抑制剂, 抑制经典和非经典炎症小体下游细胞焦亡, 减少IL-1β释放[50]。HAN等[51]的研究表明, 芥子酸(sinapic acid)抑制ASCs、NLRP3、caspase-1及IL-1β的表达。此外, 细胞自身也具有抗焦亡机制。 RÜHL等[52]发现, 钙离子通过GSDMD孔内流可以启动细胞膜修复, 这一过程通过招募转运必需体内分选复合物(endosomal sorting complexes required for transport, ESCRT)到受损的膜区域, 保护细胞免于GSDMD激活后的细胞焦亡, 可能预防成孔细胞破裂。

6 结论

细胞焦亡是一种炎症性程序性细胞死亡途径, 由人caspase-1/4/5和小鼠caspase-1/11激活。这些炎性caspases被宿主用来控制细菌、病毒、真菌或原生动物病原体[11], 近来发现焦亡与代谢性疾病发展密切相关。多种与代谢性疾病有关的危险信号如高血糖、高血脂等, 导致细胞焦亡及后续的炎症反应(图1)。焦



糖代谢紊乱如高血糖或细菌摄取葡萄糖导致的NADH水平下降引起ROS产生, 进而激活NLRP3炎症小体引起caspase-1依赖的细胞焦亡。Caspase-1分别切割IL-1β和GSDMD, 产生活性的GSDMD-N定位在细胞膜, 导致细胞肿胀破裂, 炎性因子释放到胞外, 发生细胞焦亡。高脂饮食可诱导脂代谢异常, 导致FFA水平升高、NLRP3炎症小体激活, 引起caspase-1依赖的细胞焦亡。高同型半胱氨酸水平也能激活NLRP3炎症小体, 引起caspase-1依赖的细胞焦亡。高脂饮食诱导肠道菌群失调、革兰氏阴性菌增多、血液脂多糖水平升高, 激活caspase-4/5/11引起细胞焦亡。

Disturbances in glucose metabolism, such as hyperglycemia or decreased NADH levels caused by bacterial uptake of glucose, products ROS (reactive oxygen species), which in turn activates NLRP3 inflammasome and caspase-1 dependent pyroptosis. Caspase-1 cleaves GSDMD and precursor cytokines pro-IL-1β and pro-IL-18, respectively, initiating pyroptosis and maturation of IL-1β and IL-18. The GSDMD-N forms pores on the host cell membrane, mediating the release of cytoplasmic contents. HFD (high-fat diet) induce abnormal lipid metabolism, and elevated FFA (free fatty acid) levels, subsequently activating NLRP3 inflammasome, causing caspase-1-dependent pyroptosis. HCY (high homocysteine) levels could also activate NLRP3 inflammasome and caspase-1-dependent pyroptosis. HFD induces imbalance of intestinal flora, increasing the Gram-negative bacteria, which is responsible for the blood LPS (lipopolysaccharide). The increased LPS further activates the cleavage of caspase-4/5/11 and triggers pyroptosis.

图1 细胞焦亡与糖脂代谢异常的关系

Fig.1 Relationship between pyroptosis and abnormal glucose and lipid metabolism

表1 代谢性疾病中的细胞焦亡激活剂与抑制剂

Table 1 Pyroptosis activators and inhibitors in metabolic diseases

代谢途径 Metabolic pathway	焦亡靶点 Pyroptosis targets	激动剂 Activator	抑制剂 Inhibitor
Glucose metabolism	NLRP3	ROS generation[15,26]	ROS scavenger N-acetylcysteine
		High glucose	NAPDH reduced expression of NLRP3
		Hexokinase	Dimethyl fumarate in colitis
		Enolase-impaired NADH production	Dimethyl itaconate[24]
			Sinapic acid[51]
		Excess citrate	Bay11-7082[26]
		Hypoxia-induced succinate accumulation[24]	
Lipid metabolism	NLRP3	FFA	Genipin inhibits FFA induced pyroptosis[45]
		Uncoupling protein[47]	
		HMGB1[39]	Ghrelin inhibits HMGB1[39]
		High level HCY[32]	
		HFD, lack of leptin[33]	
	GSDMD		Melatonin[35]
			Necrosulfonamide[47]
			Disulfiram, Bay11-7082
			Interferon regulatory factor[48]
	Caspase-4/5/11	LPS	Ac-FLTD-CMK[48]
			Disulfiram, Bay11-7082[48]
Atherosclerosis	NLRP3	ox-LDL	Adiponectin[44]
			miR-30c-5p[43]

NLRP3: Nod样受体蛋白3; ROS: 活性氧; HMGB1: 高迁移率族蛋白B1; GSDMD: gasdermin D; HCY: 同型半胱氨酸; HFD: 高脂饮食; ox-LDL: 氧化型低密度脂蛋白。

NLRP3: Nod-like receptor pyrin domain 3; ROS: reactive oxygen species; HMGB1: high mobility group B1; HCY: homocysteine; HFD: high-fat diet; ox-LDL: oxidized low density lipoprotein.

亡需要炎性caspases切割并激活成孔蛋白GSDMD。细胞的物理破裂导致促炎细胞因子IL-1β和内源性危险因子大量释放，意味着焦亡介导炎症发生。我们已经认识到促炎细胞因子对代谢性疾病发展的作用。例如，抑制炎症小体–细胞焦亡通路中的NLRP3炎症小体、炎性caspase、GSDMD蛋白和IL-1β等炎症因子能改善肥胖和2型糖尿病等代谢性疾病，已有研究发现炎症小体–细胞焦亡通路的抑制剂(表1)。然而，细胞焦亡过程是否在各组织器官中广泛存在？同时，组织特异性的细胞焦亡是否参与代谢性疾病发病的进程？这些问题均有待研究。这些研究将加深我们对于代谢性疾病发病机制的理解，并从细胞焦亡角度开发有效的治疗手段。

参考文献 (References)

[1] TUNCMAN G, ERBAY E, HOM X, et al. A genetic variant at the fatty acid-binding protein aP2 locus reduces the risk for hypertriglyceridemia, type 2 diabetes, and cardiovascular disease [J]. P Natl Acad Sci USA, 2006, 103(18): 6970-5.

[2] CORNIER M A, DABELEA D, HERNANDEZ T L, et al. The metabolic syndrome [J]. Endocr Rev, 2008, 29(7): 777-822.

[3] 黄丽. 生物信息学与代谢性疾病[J]. 广东化工(HUANG L. Bioinformatics and metabolic disease [J]. Guangdong Chemical Industry), 2018, 45(9): 136-9.

[4] HU Q, ZHANG T, YI L, et al. Dihydromyricetin inhibits NLRP3 inflammasome-dependent pyroptosis by activating the Nrf2 signaling pathway in vascular endothelial cells [J]. Biofactors, 2017, 44(2): 123-36.

[5] JIA C, CHEN H, ZHANG J, et al. Role of pyroptosis in cardiovascular diseases [J]. Int Immunopharmacol, 2019, 52(2): e12563.

[6] FRANTZ S, DUCHARME A, SAWYER D, et al. Targeted deletion of caspase-1 reduces early mortality and left ventricular dilatation following myocardial infarction [J]. J Mol Cell Cardiol, 2003, 35(6): 685-94.

[7] ZYCHLINSKY A, PREVOST M C, SANSONETTI P J. Shigella flexneri induces apoptosis in infected macrophages [J]. Nature, 1992, 358(6382): 167-9.

[8] COOKSON B T, BRENNAN M A. Pro-inflammatory programmed cell death [J]. Trends Microbiol, 2001, 9(3): 113-4.

[9] JORGENSEN I, MIAO E. Pyroptotic cell death defends against intracellular pathogens [J]. Immunol Rev, 2015, 265(1): 130-42.

[10] ORNING P, LIEN E, FITZGERALD K. Gasdermins and their

role in immunity and inflammation [J]. J Exp Med, 2019, 216(11): 2453-65.

[11] MAN S M, KARKI R, KANNEGANTI T D. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases [J]. Immunol Rev, 2017, 277(1): 61-75.

[12] LIU X, ZHANG Z, RUAN J, et al. Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores [J]. Nature, 2016, 535(7610): 153-8.

[13] GALLUZZI L, VITALE I, AARONSON S A, et al. Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018 [J]. Cell Death Differ, 2018, 25(3): 486-541.

[14] MA Y, JIANG J, GAO Y, et al. Research progress of the relationship between pyroptosis and disease [J]. Am J Transl Res, 2018, 10(7): 221-3.

[15] CAROLINE M, ANJOS V, NOGUEIRA-MACHADO J. Inflammasome as a new therapeutic target for diabetic complications [J]. Recent Pat Endocr Metab Immune Drug Discov, 2016, 10(1): 56-62.

[16] HENAO-MEJIA J, ELINAV E, THAISS C A, et al. Inflammasomes and metabolic disease [J]. Annu Rev Physiol, 2014, 76: 57-78.

[17] SBORGI L, R HL S, MULVIHILL E, et al. GSDMD membrane pore formation constitutes the mechanism of pyroptotic cell death [J]. EMBO J, 2016, 35(16): 1766-78.

[18] CHEN X, HE W, HU L, et al. Pyroptosis is driven by non-selective gasdermin-D pore and its morphology is different from MLKL channel-mediated necroptosis [J]. Cell Res, 2016, 26(9): 1007-20.

[19] HE W, WAN H, HU L, et al. Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion [J]. Cell Res, 2015, 25(12): 1285-98.

[20] CONTI B, PARK L C, CALINGASAN N Y, et al. Cultures of astrocytes and microglia express interleukin 18 [J]. Molecular Brain Research, 1999, 67(1): 46-52.

[21] SHI J, GAO W, SHAO F. Pyroptosis: gasdermin-mediated programmed necrotic cell death [J]. Trends Biochem Sci, 2017, 42(4): 245-54.

[22] SHI J J, ZHAO Y, WANG Y P, et al. Inflammatory caspases are innate immune receptors for intracellular LPS [J]. Nature, 2014, 514(7521): 187-92.

[23] QIU S, LIU J, XING F. 'Hints' in the killer protein gasdermin D: unveiling the secrets of gasdermins driving cell death [J]. Cell Death Differ, 2017, 24(4): 588-96.

[24] HUGHES M M, O'NEILL L A J. Metabolic regulation of NLRP3 [J]. Immunol Rev, 2018, 281(1): 88-98.

[25] QIU Z, LEI S, ZHAO B, et al. NLRP3 inflammasome activation-mediated pyroptosis aggravates myocardial ischemia/reperfusion injury in diabetic rats [J]. Oxid Med Cell Longev, 2017, 2017(15): 1-17.

[26] GAO P, HE F F, TANG H, et al. NADPH oxidase-induced NALP3 inflammasome activation is driven by thioredoxin-interacting protein which contributes to podocyte injury in hyperglycemia [J]. J Diabetes Res, 2015, 2015: 504761.

[27] SANMAN L E, QIAN Y, EISELE N A, et al. Disruption of glycolytic flux is a signal for inflammasome signaling and pyroptotic cell death [J]. Elife, 2016, 5: e13663.

[28] RINKE S, VAN DIEPEN J A, TACK C J, et al. Inflammasome is a central player in the induction of obesity and insulin resistance [J]. P Natl Acad Sci USA, 2011, 108(37): 15324-9.

[29] PAWELZIK S C, AVIGNON A, IDBORG H, et al. Urinary prostaglandin D2 and E2 metabolites associate with abdominal obesity, glucose metabolism, and triglycerides in obese subjects [J]. Prostaglandins Other Lipid Mediat, 2019, 145: 106361.

[30] RHEINHEIMER J, DE SOUZA B M, CARDOSO N S, et al. Current role of the NLRP3 inflammasome on obesity and insulin resistance: A systematic review [J]. Metabolism, 2017, 74: 1-9.

[31] MENTESE A, ALVER A, SUMER A, et al. Effects of homocysteine on adipocyte differentiation and CD36 gene expression in 3T3-L1 adipocytes [J]. J Cell Commun Signal, 2016, 10(1): 55-60.

[32] XI H, ZHANG Y, XU Y, et al. Caspase-1 inflammasome activation mediates homocysteine-induced pyrop-apoptosis in endothelial cells [J]. Circ Res, 2016, 118(10): 1525-39.

[33] GIORDANO A, MURANO I, MONDINI E, et al. Obese adipocytes show ultrastructural features of stressed cells and die of pyroptosis [J]. J Lipid Res, 2013, 54(9): 2423-36.

[34] HERSOUG L G, M LLER P, LOFT S. Role of microbiota-derived lipopolysaccharide in adipose tissue inflammation, adipocyte size and pyroptosis during obesity [J]. Nutr Res Rev, 2018, 31(2): 153-63.

[35] LIU Z, GAN L, XU Y, et al. Melatonin alleviates inflammasome-induced pyroptosis through inhibiting NF-κB/GSDMD signal in mice adipose tissue [J]. J Pineal Res, 2017, 63(1): e12414.

[36] LAHA A, MAJUMDER A, SINGH M, et al. Connecting homocysteine and obesity through pyroptosis, gut microbiome, epigenetics, peroxisome proliferator-activated receptor γ, and zinc finger protein 407 [J]. Can J Physiol Pharmacol, 2018, 96(10): 971-6.

[37] XU B, JIANG M, CHU Y, et al. Gasdermin D plays a key role as a pyroptosis executor of non-alcoholic steatohepatitis in humans and mice [J]. J Hepatol, 2018, 68(4): 773-82.

[38] BEIER J I, BANALES J M. Pyroptosis: an inflammatory link between NAFLD and NASH with potential therapeutic implications [J]. J Hepatol, 2018, 68(4): 643-5.

[39] EZQUERRO S, MOCHA F, FR HBECK G, et al. Ghrelin reduces TNF-α–iduced human hepatocyte apoptosis, autophagy, and pyroptosis: role in obesity-associated NAFLD [J]. J Clin Endocr Metab, 2018, 104(1): 21-37.

[40] ROYCHOWDHURY S, SELVAKUMAR P C, CRESCI G A. The role of the gut microbiome in nonalcoholic fatty liver disease [J]. Med Sci, 2018, 6(2): 47-61.

[41] SO A K, MARTINON F. Inflammation in gout: mechanisms and therapeutic targets [J]. Nat Rev Rheumatol, 2017, 13(11): 639-47.

[42] RASHIDI M, SIMPSON D, HEMPEL A, et al. The pyroptotic cell death effector gasdermin D is activated by gout-associated uric acid crystals but is dispensable for cell death and IL-1β release [J]. J Immunol, 2019, 203(3): 736-48.

[43] LI P, ZHONG X, LI J, et al. MicroRNA-30c-5p inhibits NLRP3 inflammasome-mediated endothelial cell pyroptosis through

FOXO3 down-regulation in atherosclerosis [J]. Biochem Biophys Res Commun, 2018, 503(4): 2833-40.

[44] ZHANG L, YUAN M, ZHANG L, et al. Adiponectin alleviates NLRP3-inflammasome-mediated pyroptosis of aortic endothelial cells by inhibiting FoxO4 in arteriosclerosis [J]. Biochem Biophys Res Commun, 2019, 514(1): 266-72.

[45] RATHKEY J K, ZHAO J, LIU Z, et al. Chemical disruption of the pyroptotic pore-forming protein gasdermin D inhibits inflammatory cell death and sepsis [J]. Sci Immunol, 2018, 3(26): 27-38.

[46] HAN Y, QIU H, PEI X, et al. Low-dose sinapic acid abates the pyroptosis of macrophages by downregulation of lncRNA-MALAT1 in rats with diabetic atherosclerosis [J]. J Cardiovasc Pharmacol, 2018, 71(2): 104-12.

[47] ZHONG H, LIU M, JI Y, et al. Genipin reverses HFD-induced liver damage and inhibits UCP2-mediated pyroptosis in mice [J]. Cell Physiol Biochem, 2018, 49(5): 1885-97.

[48] HU J J, LIU X, XIA S, et al. FDA-approved disulfiram inhibits pyroptosis by blocking gasdermin D pore formation [J]. Nat Immunol, 2020, doi: 10.1038/s41590-020-0669-6.

[49] XU B, JIANG M, CHU Y, et al. Gasdermin D plays a key role as a pyroptosis executor of non-alcoholic steatohepatitis in humans and mice [J]. J Hepatol, 2018, 68(4): 773-82.

[50] KAYAGAKI N, LEE B L, STOWE I B, et al. IRF2 transcriptionally induces GSDMD expression for pyroptosis [J]. Sci Signal, 2019, 12(582): eaax4917.

[51] JIE Y, ZHONGHUA L, CHUANPING W, et al. Mechanism of gasdermin D recognition by inflammatory caspases and their inhibition by a gasdermin D-derived peptide inhibitor [J]. P Natl Acad Sci USA, 2018, 115(26): 6792-7.

[52] RÜHL S, SHKARINA K, DEMARCO B, et al. ESCRT-dependent membrane repair negatively regulates pyroptosis downstream of GSDMD activation [J]. Science, 2018, 362(6417): 956-60.