

Is inflammation a major factor in all chronic diseases?

NLRP3 炎症小体: 2 型糖尿病治疗的新靶点?

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摘要 炎症之于机体是一把双刃剑, 适度的炎症反应利于机体对抗外界病原微生物的感染, 而失调的炎症反应又会使这把利剑挥向机体自身, 过度放大或持续存在的炎症反应是导致机体组织损伤和器质性病变的主要原因。事实上, 一直以来炎症就被认为与许多慢性疾病的发生发展有着千丝万缕的联系。鉴于此, *Science*于2005年提出的125个科学问题中就包括“炎症是否是所有慢性疾病发生的重要原因?”。尽管在2型糖尿病、神经退行性疾病、动脉粥样硬化、痛风及肿瘤等多种严重危害人类健康的重大疾病中都检测到有慢性炎症参与的证据, 但是长期以来慢性炎症在这些疾病当中发生的细胞和分子机制并不清楚, 相关抗炎干预靶点也并未得到确切鉴定。近年, 随着对固有免疫模式识别受体和信号转导机制的深入研究, 人们发现, 包括NLRP3在内的一些固有免疫模式识别受体通过识别上述慢性疾病当中的危险信号, 从而启动炎症反应和疾病的发生, 提示NLRP3等固有免疫模式识别受体及其信号通路可能成为包括2型糖尿病在内的相关炎症性疾病治疗的新靶点。本文将着重介绍近年有关NLRP3炎症小体活化与T2DM的关系, 以及靶向NLRP3炎症小体的T2DM治疗研究方面的进展。

关键词 NLRP3 炎症小体, 2 型糖尿病, 治疗, 靶点

“NLRP3炎症小体”作为调控炎症产生的分子开关是近年天然免疫研究领域的重中之重^[1,2]。活化的NLRP3炎症小体可使胞内IL-1 β 前体发生剪切, 分泌至胞外, 形成具有促炎功能的成熟IL-1 β ^[3,4]。研究显示, NLRP3炎症小体的持续活化参与多种严重危害人类健康的炎症性疾病的进程, 如2型糖尿病、阿尔茨海默病、动脉粥样硬化、痛风等^[1]。尤其是2型糖尿病, 在我国已呈流行之态势, 几乎每10个成年人中就有1个处于前糖尿病或已然糖尿病状态^[5,6]。

1 NLRP3炎症小体及其活化机制

作为哺乳动物22个NOD样受体家族成员中极具代表性的NLRP3受体, 是目前学界研究的最为广泛和深入的一类NOD样受体成员^[1,7]。通常认为, NLRP3受

体包含3个功能区段, 即负责识别和结合病原相关或危险相关分子模式(PAMPs/DAMPs)的富含亮氨酸重复区段(LRRs)^[8], 负责NOD样受体寡聚体形成的核苷酸结合区段(NACHT)^[9], 以及负责下游信号传递, 行使效应功能的PYD或CARD区段^[10,11]。活化的NLRP3炎症小体是一种基于NLRP3受体寡聚而形成的大分子复合物, 除包括NLRP3受体自身外, 还包括另外两个重要的组分蛋白, 即胞内接头蛋白ASC以及Caspase1前体^[12,13]。通常NLRP3炎症小体的活化需要两条信号通路依次激活, 在Toll样受体的介导下, 第一信号(通常由细菌脂多糖, 氧化型低密度脂蛋白及饱和脂肪酸等机体代谢产物提供)通过MyD88, 可NF- κ B依赖性的上调胞内NLRP3蛋白和IL-1 β 前体的表达, 以完成NLRP3炎症小体活化的准

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备过程,即启动阶段^[14,15].而机体持续产生的病原或危险相关分子模式为NLRP3炎症小体的最终活化提供了必要的第二信号途径^[16],使在启动阶段表达上调的NLRP3蛋白通过NACHT结构域发生自我寡聚,借助PYD结构域与接头蛋白ASC发生相互作用,进而通过CARD结构域招募胞内的Caspase-1前体,并使之发生剪切,释放出具有水解酶活性的成熟Caspase-1^[17,18].活化的Caspase-1将剪切底物IL-1 β 及IL-18前体转变成具有促炎功能的成熟IL-1 β 及IL-18,并释放至胞外,造成机体局部或全身性的炎症反应^[19].不同的炎症小体其复合物的组装过程或略有差异,然而使Caspase-1前体发生剪切,形成具有成熟功能的Caspase-1,并使下游底物前体发生剪切却大致相同^[20].

经典的NLRP3炎症小体活化机制目前有3种假说,即钾离子外流假说^[21]、线粒体活性氧假说以及溶酶体破碎假说^[22~25].细菌毒素Nigericin以及胞外ATP可使胞内钾离子大量外流,亦有研究报道胞外高钾环境可以抑制由Nigericin和ATP等诱导的NLRP3炎症小体活化,然而胞内钾离子受到何种信号调控,通过哪些蛋白的介导进而引发外流目前依然不明^[21].事实上,已有多篇文献报道ATP对经典NLRP3炎症小体的活化引起的胞内钾离子外流主要是通过P2X7通道蛋白,尽管有研究报道非选择性通道蛋白Pannexin-1的开放对NLRP3炎症小体的活化并不是必需的,然而该通道蛋白的进一步开放则促进了钾离子外流的过程^[26,27].NLRP3炎症小体在活化的过程中均可引起线粒体活性氧(mtROS)的产生增加,暗示mtROS在NLRP3炎症小体活化的过程中扮演重要的角色.然而mtROS与NLRP3炎症小体之间究竟发生了怎样的“cross-talking”进而活化之,目前机制不明^[22].越来越多的证据支持这样的观点,即线粒体活性氧产生增加可致细胞应激,如内质网应激和线粒体损伤等,而释放至胞浆中的线粒体来源的单双链DNA等核酸分子可作为活化NLRP3炎症小体的第二信号物质^[3].钙离子内流是一种与内质网应激相关的细胞生理过程.近年有研究报道,钙离子内流也可引起NLRP3炎症小体的活化^[28].溶酶体破碎释放组织蛋白酶B作为NLRP3炎症小体活化的另一条经典途径,可以解释一些颗粒性物质如 β 淀粉样多肽、疫苗佐剂PLG、二氧化硅晶体等以及一些胞内寄生的原虫如克氏锥虫等活化NLRP3炎症小体的现象,

然而有研究表明,组织蛋白酶B抑制剂虽可浓度依赖性的抑制NLRP3炎症小体的活化,但并不能完全抑制,暗示在此NLRP3炎症小体活化的过程中尚有其他未被阐明的机制参与.而释放入胞浆中的组织蛋白酶B又是如何活化NLRP3炎症小体的?是直接NLRP3炎症小体的相关组分蛋白发生相互作用进而活化之?还是通过与某些中间蛋白发生“cross-talking”后活化之?这些问题仍亟待阐明^[24].

2 NLRP3炎症小体与T2DM

2型糖尿病(T2DM)是一种与能量代谢障碍密切相关的代谢综合征,同时T2DM还是一种由体内慢性炎症引起的炎症性疾病.遗传背景和机体所处环境是引起T2DM的两大决定性因素^[29].目前T2DM在世界上很多国家和地区已呈流行之态势^[5].尤其是在我国,几乎每10个成年人中就有1个糖尿病患者,给我国经济发展和社会进步带来沉重的负担和压力^[5].现阶段对于T2DM的治疗和干预主要依赖于控制血糖的药物维持,并不能从根本上逆转T2DM的进程^[30].实际上,无论是基于胰岛素增敏而使用的格列酮类以及二甲双胍类等一线2型糖尿病治疗药物,还是近几年被美国FDA批准上市的基于肠促胰素理论开发的GLP-1类似物以及二肽基肽酶抑制剂等药物,在临床实践中均出现不同程度的毒副作用和血糖控制失败的现象,因此迫切需要从新的角度探索T2DM的发病机制和干预策略^[31,32].在之前的研究中,我们首次发现NLRP3缺失后的小鼠,可显著改善由高脂饮食诱导的胰岛素抵抗和葡萄糖不耐受,这直接明确了NLRP3炎症小体参与2型糖尿病的病变过程^[23].在此基础上,Osowski等人^[33]和Lerner等人^[34]发现代谢异常引起的内质网应激,通过PERK-eIF2 α /IRE1信号通路诱导胰腺 β 细胞中硫氧还蛋白相互作用蛋白(TXNIP)的表达,且NLRP3炎症小体活化依赖性的促进IL-1 β 的分泌,进而影响胰腺 β 细胞的存活.

事实上,近年有不少工作从不同侧面分别向我们展示了NLRP3炎症小体与T2DM发病的内在关系.正如我们之前的研究结果所揭示的那样,胰腺组织自身可NLRP3炎症小体依赖性的产生IL-1 β ,Ehses等人^[35]发现在T2DM病人及高脂饮食诱导的T2DM模型鼠的胰腺组织中亦有大量炎性细胞浸润的现象,这无疑会进一步促进IL-1 β 的产生,加速胰腺 β 细胞的死亡.与此 β 细胞死亡过程相类似,体内长期高糖或

高脂在引起高胰岛素血症的同时,还会产生大量的胰淀素,胰淀素作为一种非可降解的 β 淀粉样多肽沉积在胰腺组织内部或周围,并作为一种危险相关分子模式为浸润其中的巨噬细胞所识别,进而活化NLRP3炎症小体,持续产生大量的IL-1 β ^[36,37]。成熟的Caspase-1是炎症小体活化后的效应分子,可将炎症因子前体剪切成具有促炎功能的成熟体。Vandanmagsar等人^[38]的研究结果显示高脂饲料诱导的2糖模型鼠的脂肪组织中Caspase-1的表达水平与对照组相比显著上升。与此结果相类似,Stienstra等人^[39]发现高脂饲料喂养Caspase-1缺陷鼠,其脂肪组织中浸润的炎性细胞数量明显减少,与对照组相比,其外周胰岛素敏感性和糖耐量均得到显著改善。此外,Vandanmagsar等人^[38]和Csak等人^[40]发现饮食诱导的脂肪肝模型鼠肝脏组织中Caspase-1的活化依赖于NLRP3炎症小体。而Wen等人^[41]则从另外一个角度阐明了脂酸诱导的NLRP3炎症小体活化是引起外周胰岛素抵抗和糖耐量受损的幕后推手。综上可知,代谢产物及代谢应激为NLRP3炎症小体的活化提供了必要的危险信号,然而这些危险信号又是如何被炎性细胞所识别进而活化NLRP3炎症小体的?精细机制目前依然不明。研究显示高糖高脂是2型糖尿病的典型病理特征,故2型糖尿病又被称为糖脂病^[42]。正如前文所述高糖高脂在引起胰腺 β 细胞胰岛素大量分泌的同时,还会伴随分泌大量的胰淀素,胰淀素沉积在胰腺组织周围,为浸润其中的炎性细胞提供NLRP3炎症小体活化的第二信号^[43]。那么第一信号是如何产生的又是如何激活的呢?事实上,高糖高脂环境自身即可作为NLRP3炎症小体活化的第一信号来源。有报道指出体内饱和脂肪酸如棕榈酸酯等可以与TLR4发生相互作用,上调IL-1 β 的转录水平,并通过抑制AMPK的激酶活性,使细胞自噬功能受损,致使线粒体清除障碍,进而导致线粒体活性氧(mtROS)产生增加,而mtROS又可作为NLRP3炎症小体活化的第二信号物质^[44,45]。总之,体内环境复杂多变,而个体自身又受到饮食、环境甚至情绪的影响,使原本提供第一信号的物质也可通过相应的信号转换激活第二信号途径,两条信号通路相互转换且相辅相成,并最终激活NLRP3炎症小体^[46]。有趣的是,体内另外一种脂肪酸即不饱和脂肪酸具有良好的抗炎效果,然而具体机制不明^[47]。我们近期阐明了不饱和脂肪酸 ω -3脂肪酸家族成员可通过G蛋白偶联受体40/120(GPR40/

120)及下游支架蛋白 β -arrestin2发挥对NLRP3炎症小体和NLRP1b炎症小体的抑制作用。此外动物实验结果证实 ω -3脂肪酸可显著改善高脂饮食诱导的T2DM模型鼠的胰岛素抵抗和葡萄糖不耐受,从而率先证明了可以靶向NLRP3炎症小体对T2DM进行干预^[48]。饱和脂肪酸和不饱和脂肪酸对炎症调节的这种截然相反的功能可能是机体在自身进化过程中的一种反馈调节方式^[49]。此外,临床调查数据显示,肥胖的2型糖尿病患者除高脂高糖症状之外,还经常伴随发生高尿酸血症^[50]。有研究指出,尿酸结晶通过上调脂肪细胞内MCP-1的表达水平,促进炎性细胞的浸润,进而影响机体脂肪组织内的炎症状态。虽然已经证实尿酸盐结晶引起的NLRP3炎症小体活化参与痛风的发生发展,然而目前尚未有直接证据显示尿酸盐结晶与肥胖诱导的炎症反应之间存在关联,尽管有研究表明降低外周循环系统中的尿酸水平可以显著改善由果糖诱导的胰岛素抵抗^[50,51]。

3 靶向NLRP3炎症小体的T2DM治疗研究

发现并鉴定靶向NLRP3炎症小体的天然来源或人工合成的小分子化合物,一方面有助于丰富NLRP3炎症小体的活化机制,另一方面更可为相关炎性疾病的治疗提供新的治疗靶点和干预方案。尽管T2DM是一种与NLRP3炎症小体密切相关的疾病,然而目前关于靶向NLRP3炎症小体的T2DM治疗研究尚处于起步阶段。目前较有希望的靶向IL-1 β 和Caspase-1的T2DM治疗药物主要有3种:(1) IL-1受体拮抗剂Anakinra;(2) IL-1 β 中和抗体;(3) Caspase-1抑制剂。Larsen等人^[52]的研究结果提示,Anakinra可以有效控制2型糖尿病患者的血糖水平,然而患者的胰岛素敏感性却并未见显著改善。此外,Anakinra在体内的半衰期过短,每日需皮下注射给药,这大大限制了其临床应用。比起Anakinra,IL-1 β 中和抗体可以显著改善胰岛素敏感性,其在体内的半衰期也得以延长,遗憾的是目前尚未见其在临床方面的应用报道^[53]。Stienstra等人^[39]发现Caspase-1抑制剂可显著改善2糖模型鼠的胰岛素抵抗和葡萄糖不耐受,然而目前还没开发出可应用于临床的Caspase-1抑制剂类药物。值得一提的是,传统2型糖尿病治疗药物格列本脲对NLRP3炎症小体的活化具有较强的抑制作用,其对2型糖尿病的治疗作用主要是通过促进尚未完全丧失功能的胰腺 β 细胞分泌胰岛素,然而并不能排除

其同时对NLRP3炎症小体的抑制作用参与改善了2型糖尿病的治疗效果^[37,54].

有理由相信抑制NLRP3炎症小体活化的天然来源或人工合成的小分子化合物对T2DM的治疗具有潜在的应用前景,如我们前期报道的 ω -3脂肪酸家族成员以及对神经炎症具有较好抑制作用的神经递质多巴胺类等^[48,55].高通量筛选平台为我们发现此类小分子化合物提供了强有力的技术支持,一批可特异性抑制NLRP3炎症小体活化的小分子化合物目前正在走入我们的视野,如2015年相继报道的人工合成小分子化合物MCC950以及体内代谢中间产物 β -羟基丁酸对NLRP3炎症小体的活化均具有较强和较特异的抑制作用.尽管研究者并未向我们展示以上两种化合物对T2DM具有治疗作用,但可以期待的是相关研究正在开展^[56,57].除以上两种最近报道的小分子化合物外,Zhao等人^[58]研究发现,小分子化合物Bay11-7082可通过抑制NLRP3炎症小体的活化及NF-KB信号通路,进而改善小鼠狼疮性肾炎的症状.而He等人^[59]进一步研究发现,Bay11-7082可直接与NLRP3蛋白发生结合,通过抑制其ATP酶活性进而抑制NLRP3炎症小体的活化.Isoliquiritigenin(异甘草素)是近年发现的另外一类通过抑制ASC聚合进而抑制NLRP3炎症小体活化的小分子化合物,可显著改善由高脂饮食诱导的代谢紊乱综合征^[60].事实上,让我们更加期待的是能够鉴定出一种可以直接靶向NLRP3蛋白本身的小分子物质,通过阻断NLRP3炎

症小体复合物的形成,进而根本上抑制NLRP3炎症小体的活化,理论上说此类小分子物质对NLRP3炎症小体的活化将具有更加特异和更加显著的抑制效果,同时对于与NLRP3炎症小体相关的炎症性疾病的治疗也将更加广谱.

4 总结及展望

由肥胖诱导的慢性炎症是导致机体胰岛素抵抗的罪魁祸首,故而学界普遍认为肥胖是引起2型糖尿病的最主要的危险因素之一.在此过程中,基于NLRP3炎症小体活化分泌产生的IL-1 β 导致的胰腺 β 细胞损伤以及机体炎症状态的调节失衡为T2DM的病理进程提供了重要的促进力量.营养过剩可导致代谢紊乱,由后者引起的代谢应激可以相关分子模式的形式活化NLRP3炎症小体,进而产生大量具有促炎功能的成熟IL-1 β .阻断IL-1 β 信号,改善2型糖尿病患者的炎症状态,可显著改善对2型糖尿病的治疗效果.在此研究背景下,聚焦“靶向NLRP3炎症小体活化”的2型糖尿病治疗方案不仅具有重要的理论意义,更具有迫切的现实需要;不仅可为临床提供全新的治疗方案和干预策略,还可为新型2型糖尿病治疗药物的设计和开发提供崭新的视角.尽管目前有关NLRP3炎症小体活化的更加精细的分子机理尚有待阐明,同时靶向NLRP3炎症小体的2型糖尿病治疗研究也充满了大量未知的挑战,但我们相信与挑战伴随产生的往往是机遇.

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NLRP3 inflammasome: A novel target for T2DM treatment?

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Inflammation is a double-edged sword for the organism. A proper inflammation response is necessary and beneficial to us in resisting pathogen infection, however, an excessive and continuous inflammation response does harm to the health. In fact, studies over the past decade have strongly linked host inflammatory reaction to the etiology of some chronic diseases. Therefore, “Is inflammation a major cause in all chronic diseases” as one of the 125 scientific questions was proposed by the journal of *Science* in 2005. Although recent studies have provided direct evidence indicating a key role of chronic inflammation in the initiation and progression of some chronic diseases (such as type 2 diabetes, neurodegenerative diseases, atherosclerosis, gout and cancer), the cellular and molecular mechanisms are not very clear, and the exact therapeutic targets have not been characterized yet. In the recent years, with the in-depth study of the innate immune pattern recognition receptors (PRR) and the mechanism of signal transduction, people found that NLRP3 receptor as well as other PRRs could arouse inflammation reaction and subsequently disease by recognition of the danger signals, which indicated that the PRRs and the related signal pathways may be novel therapeutic targets for the type 2 diabetes and other chronic diseases. Here we summarize the molecular mechanisms of NLRP3 inflammasome activation in response to metabolic danger associated molecular patterns (DAMPs) and discuss the potential therapeutic treatment for type 2 diabetes by targeting to the NLRP3 inflammasome.

NLRP3, one of the most-extensively studied NLR sub-family members, has an evolutionarily conserved arrangement of nucleotide binding domain (NBD) for the complex assemble and followed by a leucine rich region (LRR) for the recognition of pattern-associated molecular pattern (PAMP) and damage-associated molecular pattern (DAMP). Two signal pathways are required for the activation of NLRP3 inflammasome. Signal one is provided by the agents of indicated TLRs which aim at inducing *nlrp3*/IL-1 β transcription and subsequent production of pro-IL-1 β usually provided by glucose, palmitate, uric acid, or LPS. In order to facilitate processing of pro-IL-1 β /18 into their mature forms, signal two is essential to facilitate inflammasome activation and caspase-1-dependent cleavage of pro-IL-1 β /18. In addition, NLRP3-dependent activation of caspase-1 also can be triggered by palmitate, ceramide, glucose, uric acid, reactive oxygen species (ROS), and amyloid. Promotion of this cascade occurs in a variety of tissues, including the pancreas, liver, and adipose tissue and may subsequently contribute to tissue dysfunction and the development of insulin resistance.

Inhibition of the IL-1R signaling or IL-1 β production by the NLRP3-dependent activation of caspase-1 may ward off loss of pancreatic β cell function, yet may also prevent the development of insulin resistance in liver, muscle, and adipose tissue. Although clinical evidence is currently lacking, inhibition of the IL-1R signaling or IL-1 β production may avert the development of insulin resistance, which represents an attractive therapeutic target to limit pathological complications associated with obesity, insulin resistance, and type 2 diabetes.

NLRP3 inflammasome, type 2 diabetes, treatment, target

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