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NLRP3炎症小体与胰岛素抵抗的研究进展

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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。在多种机制中，低度炎症对于胰岛素抵抗的发展至关重要，这是2型糖尿病的一个特征。含有NLRP3炎性小体与各种组织中胰岛素抵抗的发展有关，本文就NLRP3炎症小体在胰岛素抵抗中的作用及相关机制进行阐述。

关键词

NLRP3炎症小体，胰岛素抵抗，糖尿病

Advances in NLRP3 Inflammatory Vesicles and Insulin Resistance

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Abstract

Inflammation is a double-edged sword for the body. A moderate inflammatory response is conducive to the body's resistance to infection by external pathogenic microorganisms, while an unbalanced inflammatory response will make the sword swing towards the body itself. Over-amplified or persistent inflammatory response is the main cause of tissue damage and organic diseases. Among a variety of mechanisms, low-grade inflammation is critical for the development of insulin resistance, a feature of type 2 diabetes. The presence of NLRP3 inflammasome is associated with

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the development of insulin resistance in various tissues. In this paper, the role of NLRP3 inflammasome in insulin resistance and related mechanisms were discussed.

Keywords

NLRP3 Inflammatory Vesicles, Insulin Resistance, Diabetes Mellitus

1. 引言

2 型糖尿病(Type 2 Diabetes mellitus, T2DM)是全球最常见的代谢紊乱之一，其发展主要由两个因素共同引起：胰腺 β 细胞分泌胰岛素缺陷和胰岛素敏感组织无法对胰岛素作出反应[1]。最近，胰岛素抵抗越来越多地被认为与全身性慢性炎症有关[2]。而胰岛素抵抗(insulin resistance, IR)是 T2DM 最重要的发病机制，伴随糖尿病发生发展的全过程[3]。T2DM 的一个关键组成部分是慢性低度炎症状态，称为“转移性”。高血糖可增加循环细胞因子，导致 T2DM 慢性炎症[4]。此外，暴露于高血糖水平会损害巨噬细胞的吞噬活性，这部分解释了 T2DM 患者慢性感染发生率增加的原因[5]。NLRP3 炎症小体是迄今为止表征最好的炎性小体，可作为 IL-1β 和 IL-18 分泌的分子平台[6]。它含有衔接分子细胞凋亡相关的斑点样蛋白，含有 CARD (ASC)和 procaspase-1 [7]。

由于 NLRP3 炎症小体在响应各种危险分子模式的 IL-1β 产生中起关键作用，因此被认为是调节各种自身炎症和自身免疫性疾病的起始和发展的合理有效的靶标[8]。事实上，T2DM 与炎症小体活性增加、核苷酸结合寡聚化结构域样受体 3 (NLRP3)上调、IL-1β 和 IL-18 水平升高有关。这些事件触发中性粒细胞细胞外陷阱激活或 NETosis，这是巨噬细胞的特征性细胞死亡，可引起慢性炎症[9]。在 T2DM 患者中发现这些标志物水平较高[10]，在高血糖情况下会增强[11]。其中，NLRP3 炎症小体在炎症、胰岛素信号传导及 IR 中起核心作用，与 IR 值呈正相关[12]。下面我们就来深入地了解一下 NLRP3 小体复合物。

2. NLRP3 炎症小体复合物概述

炎症小体是由各种生理或致病刺激激活的模式识别受体形成的多态性复合物，这使它们成为先天免疫应答的重要组成部分，具有清除病原体和受损细胞的能力。炎症小体传感器根据其结构特征分为核苷酸结合结构域样受体(NLR)，黑色素瘤 2 样受体(ALRs)中不存在)和最近发现的 pyrin。这些受体具有组装炎症小体并激活半胱氨酸蛋白酶半胱天冬酶-1 的能力。除了传感器(NLR、ALR 或 pyrin)和酶组分(半胱天冬酶-1)外，大多数炎症小体还使用称为 ASC (含有半胱天冬酶活化和募集结构域的细胞凋亡相关斑点样蛋白)的衔接分子[13]。炎症小体是一种多蛋白复合物，通过促进关键细胞因子的产生和分泌来增强炎症反应。最著名的炎症小体是 NLRP3 炎症小体[14]。NLRP3 炎症小体是一种具有三个结构域的胞质蛋白：C 端的富亮氨酸重复序列(LRR)，具有 ATP 酶活性的中央核苷酸结合和寡聚化结构域 NACHT，以及 N 端的 pyrin 结构域(PYD) [15]。NLRP3 炎症小体被认为是最具特征性的，含有传感器分子 NLRP3，一种细胞凋亡相关斑点样蛋白，含有半胱天冬酶募集结构域(ASC)和半胱天冬酶原-1 [16]。对多种感染性和内源性配体有反应，并参与多种自身免疫性疾病，如肥胖[17]、糖尿病[18] [19]、关节炎[20] [21]和阿尔茨海默病[22]。尤其是糖尿病，全世界有 4.15 亿人患有糖尿病，估计有 1.93 亿人患有未确诊的糖尿病[23]。

3. NLRP3 炎症小体的激活

由于 NLRP3 炎症小体可以被多种激动剂激活，包括 PAMPs，如病毒 RNA、微生物毒素和细菌表面成分，以及 DAMPs，如尿酸晶体、ATP、铝佐剂和 β 淀粉样蛋白肽，其激活机制极其复杂。迄今为止，研究表明 NLRP3 炎症小体可以通过三种不同的信号通路激活：规范 NLRP3 炎症小体激活，非规范 NLRP3 炎症小体激活和替代 NLRP3 炎症小体激活，也称为一步 NLRP3 炎症小体激活[24] [25]。

3.1. NLRP3 炎症小体的启动

目前，人们普遍认为规范 NLRP3 炎症小体激活需要两个步骤：启动步骤和激活步骤。在启动步骤中，Toll 样受体(TLR，如 TLR3 和 TLR4)、细胞因子受体(如 IL-1 受体和 TNF-α 受体)或 NLR (如 NOD2 和 NOD4)的配体(如 LPS、pam1csk1、IL-2、TNF-α 和 MDP)可诱导转录因子 NF-κB 的活化，促进 NLRP3 和 IL-1β 前体的表达[26] [27] [28] [29]。除了在转录调控中的作用外，最近的研究表明，启动步骤还可以调节 NLRP3 的翻译后修饰(PTM)，例如磷酸化或泛素化。JAMM 域包含锌 $^{2+}$金属蛋白酶 BRCC3 (人类 BRCC36)是一种去泛素化酶，可在启动步骤中诱导 NLRP3 的去泛素化，促进 NLRP3 炎症小体的活化[30]。另据报道，在启动步骤中，c-Jun N 端激酶(JNK1)介导的 NLRP3 S194 磷酸化对于 NLRP3 炎症小体组装和激活有重要的作用[31]。这些研究表明，启动步骤对于通过转录调节和 PTM 激活 NLRP3 炎症小体至关重要。

3.2. NLRP3 炎症小体的激活途径

3.2.1. 规范 NLRP3 炎症小体激活

激活步骤涉及 NLRP3 炎症小体激动剂的识别以及炎症小体组装和激活。与只能识别一种或几种结构相似的刺激的 PRR 相比，据报道 NLRP3 被多种不相关的 PAMP 和 DAMP 激活，但没有证据表明 NLRP3 直接与这些效应子结合[32]。迄今为止，多种分子和细胞事件，包括离子通量(如 K 外排，Cl^-外排、钠流入和钙 $^{2+}$动员)、线粒体功能障碍、NLRP3 刺激诱导的活性氧(ROS)和线粒体 DNA (mtDNA)的释放、溶酶体破坏和反式高尔基体分解被认为是炎症小体组装和激活的上游信号[33]-[39]。尽管 NLRP3 激动剂可以通过上述信号通路激活炎症小体，但这些信号通路均不适用于所有 NLRP3 激动剂，并且没有一致的 NLRP3 激活通路。因此，NLRP3 感知这些刺激的确切机制以及炎症小体组装和激活的机制仍有待进一步阐明[40]。

3.2.2. 非规范 NLRP3 炎症小体激活

非经典激活途径主要由革兰阴性细菌产生的 LPS 激活，caspase-11 的 CARD 结构域可以直接与 LPS 的脂质 A 部分结合[41]。活化的 CASP11 或 CASP1 切割加斯皮素 D (GSDMD)，然后在质膜中形成孔，导致细胞裂解(焦亡)。GSDMD 孔还促进成熟形式的 IL-18β 的释放[42]。这种非规范的炎症小体代表额外的防御层，与已经进化为绕过细胞表面 TLR4 的病原体有关[43]。除革兰氏阴性菌外，自编码氧化磷脂 1-棕榈酰基-2-花生四烯酰-sn-甘油-3-磷酸胆碱(oxPAPC)已被证明可直接与鼠半胱天冬酶-11 和直系同源人半胱天冬酶-4 结合，并激活树突状细胞(DC)中的非规范 NLRP3 炎症小体[44]。最近的一项研究表明，oxPAPC 通过与巨噬细胞中的半胱天冬酶-3 和 LPS 竞争性结合而不是 DC 来抑制非规范 NLRP11 炎症小体，从而保护微生物免受脓毒性休克[45]。oxPAPC 对不同细胞中非规范 NLRP3 炎症小体活化的矛盾影响需要进一步研究[40]。

3.2.3. 替代 NLRP3 炎症小体激活

在该途径中，仅 TLR 配体不足以激活半胱天冬酶-1 或诱导人与猪单核细胞中 IL-1β 的成熟和分泌[46] [47]。此外，替代 NLRP3 炎症小体通过 TLR4-TRIF-RIPK1-FADD-CASP8 信号通路激活，该通路位于

NLRP3 的上游。尽管替代 NLRP3 炎症小体激活也需要 NLRP3-ASC-半胱天冬酶-1 信号传导，但这种新型炎症小体缺乏规范和非规范 NLRP3 炎症小体激活的任何特征，包括 ASC 斑点形成，焦亡诱导或 K 外排。最近的研究表明，载脂蛋白 C3 (ApoC3)也激活人单核细胞中半胱天冬酶-8 依赖性的替代 NLRP3 炎症小体[48] [49]。尽管半胱天冬酶-8 是激活替代 NLRP3 炎症小体的关键上游分子，但确切的机制仍然未知。

4. NLRP3 炎症小体与胰岛素抵抗

对于 90%~95%的患者，T2DM 是由进行性胰岛素分泌不足引起的，导致胰岛素抵抗和相对胰岛素分泌缺乏[50]。NLRP3 炎性小体与各种组织中胰岛素抵抗的发展有关[51]。NLRP3 介导的炎症发作后，细胞分泌大量促炎细胞因子，从而加剧胰岛素抵抗并加速疾病的进展。NLRP3 炎症小体诱导的 IL-1β 产生在肥胖和糖尿病的发展中起重要作用。IL-1β 通过减少胰岛素受体底物-1 (IRS-1)的酪氨酸磷酸化和负调节胰岛素受体底物-1 (IRS-1)基因表达，直接抑制胰岛素信号通路[14]。尽管许多体细胞类型表达胰岛素受体，但胰岛素在葡萄糖稳态中的作用以胰岛素对骨骼肌、肝脏和白色脂肪细胞的直接影响为典型。这些组织在代谢稳态中扮演着不同的角色，需要组织特异性的胰岛素信号转导途径[52]。胰岛素通过激活磷酸化-去磷酸化途径的复杂级联来促进葡萄糖摄取到肌肉纤维中。在骨骼肌中，胰岛素与 InsR 结合，导致关键酪氨酸残基磷酸化[53]。InsR 的磷酸化导致胰岛素受体底物(IRS)-85 迁移到质膜，在那里它被磷酸化。IRS-3 的磷酸化导致磷脂酰肌醇(PI)-3 激酶(PI-110K)的 p3 调节亚基活化及其 p4 催化亚基的活化，从而促进磷脂酰肌醇-5,15,3 三磷酸的增加[54]。另外，IKK/NF-κB 途径可能通过 IKK 介导的胰岛素受体底物 1 (IRS-1)或胰岛素受体(IR)的丝氨酸磷酸化增加引起胰岛素抵抗，导致胰岛素诱导的酪氨酸磷酸化受损并随后抑制下游胰岛素信号传导，抑制胰岛素信号级联中 GLUT4 等分子的表达，以及诱导分子(如诱导性 NOS)的表达，这可能促进 IRS-1 丝氨酸磷酸化并诱导 IRS-1 酪氨酸残基的硝化，导致胰岛素信号传导受损[55]。而 PKC 对肌肉胰岛素敏感性影响的研究主要集中在常规 PKC (cPKCα，-βI，-βII 和-γ)和新型 PKC (nPKCδ，-ε，-η 和-θ)，它们都依赖于 DAG 进行完全激活。PKCθ 和 PKCε 的双重抑制或共沉默可减弱肌细胞对棕榈酸活化巨噬细胞的条件培养基的胰岛素抵抗和炎症反应[56]。JNK 是 MAPK 家族的成员，JNKs 可能通过诱导 IRS 的丝氨酸和苏氨酸磷酸化直接引起胰岛素抵抗，从而破坏 IRS 与 IR 的相互作用以损害下游胰岛素信号传导[57]。胰岛素通过不同的机制调节血糖水平，这些机制控制葡萄糖摄取、糖异生和糖原解的速率。胰岛素信号对正常的心血管、神经和肾脏功能至关重要[58]。

5. 结语

在本综述中，我们总结了目前对 NLRP3 炎症小体在细胞质中激活的机制的理解。我们还描述了 NLRP3 炎症小体复合物激活或抑制炎性小体组装的结合伴侣。我们对调节 NLRP3 炎症小体信号传导的机制以及这些机制如何影响炎症反应提供了进一步的见解，重点研究了激活和调节过度 NLRP3 炎症小体激活的分子机制。最重要的是，我们讨论了目前的证据，表明 NLRP3 炎症小体扰乱葡萄糖稳态，并一定程度上参与了胰岛素抵抗。

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