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Review

Current role of the NLRP3 inflammasome on obesity and insulin resistance: A systematic review

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ABSTRACT

NLRP3 inflammasome activation seems to be a culprit behind the chronic inflammation characteristic of obesity and insulin resistance (IR). Nutrient excess generates danger-associated molecules that activate NLRP3 inflammasome-caspase 1, leading to maturation of IL-1β and IL-18, which are proinflammatory cytokines released by immune cells infiltrating the adipose tissue (AT) from obese subjects. Although several studies have reported an association of the NLRP3 inflammasome with obesity and/or IR; contradictory results were also reported by other studies. Therefore, we conducted a systematic review to summarize results of studies that evaluated the association of the NLRP3 with obesity and IR. Nineteen studies were included in the review. These studies focused on *NLRP3* expression/polymorphism analyses in AT. Overall, human studies indicate that obesity and IR are associated with increased *NLRP3* expression in AT. Studies in obese mice corroborate this association. Moreover, high fat diet (HFD) increases *Nlrp3* expression in murine AT while calorie-restricted diet decreases its expression. Hence, *Nlrp3* blockade in mice protects against HFD-induced obesity and IR. *NLRP3* rs10754558 polymorphism is associated with risk for T2DM in Chinese Han populations. In conclusion, available studies strongly points for an association between NLRP3 inflammasome and obesity/IR.

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Abbreviations: ASC, adapter protein apoptosis-associated speck-like protein; AT, adipose tissue; BMI, body mass index; CARD, caspase recruitment domain; CASP-1, caspase-1; CI, confidence interval; DAMPs, danger associated molecular patterns; FFAs, free fatty acids; HbA1c, glycated hemoglobin; HFD, high fat diet; HOMA-IR, homeostatic model assessment-insulin resistance; IL, interleukin; IR, insulin resistance; IRS-1, insulin receptor substrate-1; KD, knockdown; KO, knockout; LFD, low fat diet; LPS, lipopolysaccharide; MeSH, medical subject headings; MHO, metabolically healthy obese; MUFA, monounsaturated fatty acid; MUO, metabolically unhealthy obese; NF-κB, nuclear factor-κB; NLRP3, NLR family pyrin domain containing-3; NLRs, nucleotide-binding oligomerization domain-like receptors; OR, odds ratio; PAMPs, pathogen associated molecular patterns; PBMCs, peripheral blood mononuclear cells; PRRs, pattern-recognition receptors; RLHs, retinoic acid-inducible gene I-like helicases; ROS, reactive oxygen species; SAT, subcutaneous adipose tissue; SFA, saturated fatty acid; SVCs, stromal vascular cells; T2DM, type 2 diabetes mellitus; TLRs, toll-like receptors; TNF, tumor necrosis factor; VAT, visceral adipose tissue; WT, wild type.

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1. Introduction

Chronic low-grade inflammation is observed in subjects with obesity and represents a mechanistic link between obesity, insulin resistance (IR) and type 2 diabetes mellitus (T2DM) [1–3]. While several studies suggest that massive expansion of adipose tissue (AT) is an important first step in driving the enhanced inflammatory state, the underlying molecular mechanisms modulating this process are still unclear [4]. A variety of immune cells, including proinflammatory macrophages (M1-like), have been shown to infiltrate the AT and affect its homeostasis by increasing the production of cytokines such as IL-1β, IL-6 and TNF [4–6].

Macrophages and other innate immune cells can induce inflammatory reactions through detection of pathogen- or danger-associated molecular patterns (PAMPs or DAMPs) using a wide range of pattern-recognition receptors (PRRs) [7–9]. Many types of PRRs have been identified so far, including toll-like receptors (TLRs), retinoic acid-inducible gene I-like helicases (RLHs) and nucleotide-binding oligomerization domain-like receptors (NLRs) [7,10,11]. The NLR family, pyrin domain-containing 3 (NLRP3) cytosolic protein is certainly the most studied NLR member [11,12]. Upon activation by PAMPs or DAMPs, NLRP3 interacts with the adapter protein apoptosis-associated speck-like protein (ASC). Then, the caspase recruitment domain (CARD) of ASC binds to the CARD domain on procaspase-1, forming the NLRP3 inflammasome [12–14]. This leads to procaspase-1 self-cleavage, generating the active caspase-1, which induces the conversion of IL-1β and IL-18 immature forms to their active forms that are secreted (Fig. 1) [12,14].

Compelling evidence suggests that activation of the NLRP3 inflammasome by DAMPs has a central role in obesity-induced inflammation, IR and T2DM [4,15–20]. The role of NLRP3 inflammasome in the pathogenesis of obesity was supported by data showing that *Nlrp3*$^{-/-}$ and *Asc*$^{-/-}$ knockout (KO) mice are protected against high fat diet (HFD)-induced obesity and IR [15,16,20,21]. Moreover, NLRP3 inflammasome/caspase-1 activation seems to be a key regulator of adipocyte differentiation and directs adipocytes toward a more insulin-resistant phenotype [17]. Consistently, caloric restriction and exercise-mediated weight loss in obese subjects with T2DM reduce *NLRP3* and *IL-1β* gene expressions in abdominal subcutaneous AT (SAT), improving insulin sensitivity [15]. However, some studies were not able to find an association between NLRP3 inflammasome and obesity or IR [22–24]. Possible explanations for the contradictory results are differences in animal models analyzed, genetic variants in the *NLRP3* gene influencing its expression, differences in *NLRP3* expression between distinct AT cells, presence of comorbidities in obese patients (such as T2DM), and presence of endogenous suppressors of the inflammasome [4].

Understanding the molecular mechanisms of chronic inflammation in AT remains a major medical challenge [25]. Thus, to further investigate the association between NLRP3 inflammasome and obesity, IR and T2DM, we performed a systematic review of the literature on the subject.

2. Materials and Methods

2.1. Search Strategy and Eligibility Criteria

This systematic review was designed and described in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [26]. To identify all studies that analyzed associations of *NLRP3* inflammasome with obesity, IR or T2DM, we performed an electronic literature search in PubMed and Embase repositories, without data restriction. The following medical subject headings (MeSH) were used for this search: ("NLRP3") AND ("Obesity" OR "Type 2 diabetes" OR "Insulin Resistance"). The search was completed on February 2017, was restricted to English, Spanish or Portuguese language papers, and included both human and animal studies. All articles identified were also searched manually to identify other important citations.

Eligibility evaluation was done by title and abstract reviews and when abstracts did not provide enough information, the full text of the paper was retrieved for evaluation. This was performed independently, in a standardized manner, by two

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