

## Editorial

# Leptin Activates NLRP3 Inflammasome-Associated with Type II Diabetes and Obesity

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## INTRODUCTION

Obesity is a major health problem worldwide and is often associated with leptin resistance and inflammation.<sup>1</sup> In this editorial, we will briefly describe the leptin system and the (NOD)-like receptor protein 3 (NLRP3) inflammasome and discuss recent discoveries related to their interaction and role in the development of metabolic disease mainly obesity and Time-division multiplexing (TDM).

## LEPTIN

Leptin is a hormone mainly secreted by adipocytes and is known for its role in long-term energy regulation, food intake, and body weight. As a hormone, its primary responsibility is to report the amount of adipose tissue in the body to the hypothalamus.<sup>2</sup> Leptin concentrations in both blood serum and plasma are elevated in direct correlation with a high body mass index (BMI) and percent body fat. A constant elevation of leptin in the body, caused by sustained over eating habits, overloads the hypothalamus and results in leptin resistance; like we observe in obese subjects.<sup>3</sup>

This resistance is a major factor in causing the chronic inflammatory diseases seen frequently in obese individuals such as asthma, diabetes, and inflammatory bowel disease. In fact, during the active stages of rheumatoid arthritis (an additional condition related to chronic inflammation), leptin levels are elevated. On the other hand, malnourished individuals with decreased leptin levels suffered more infectious diseases, but had significantly lower rates of inflammation. These results are believed to be an indication of leptin's role in activating the body's inflammatory immune responses, resulting in these chronic conditions.<sup>4</sup>

Leptin also operates similarly to pro-inflammatory cytokines known as adipocytokines.<sup>4</sup> The hormone has been reported to control energy expenditure and metabolism, and modulate the innate and adaptive immune responses. The stimulation of natural killer cells, chemotaxis of neutrophils, and secretion of tumor necrosis factor (TNF)- $\alpha$ , IL-6 and IL-12 from macrophages<sup>4,5</sup> also involves leptin. These increase leptin concentrations in adipose cells and create a cycle of constant stimulation of reactants that encourage inflammation.<sup>4</sup>

Furthermore, leptin promotes Th17 cell responses<sup>6</sup> which are a subset of effector memory T-cells that induce tissue inflammation and destruction that are markers of immune inflammatory diseases<sup>7</sup> and decrease the number of T-regulatory cells.<sup>8,9</sup> Fat stores release leptin around various lymph nodes signaling to the rest of the immune system if the body has enough energy stored to initiate an immune response which causes continuous leptin circulation in obese or individuals with type II diabetes.<sup>3</sup>

## NLRP3 INFLAMMASOMES

The nucleotide binding domain and leucine-rich repeat containing receptor (NLR) family are proteins that form inflammasomes.<sup>10,11</sup> The NLRs are classified and named in accordance with their domain structure.<sup>11</sup> The nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is mainly expressed in macrophages and has a pivotal role in development and maintenance of autoimmunity and inflammation. Research has investigated the role of leptin on NLRP3 inflammasome and found that leptin is an activator and modulator of this inflammasome.<sup>12</sup>

Activation of the NLRP3 inflammasome (Figure 1) is thought to be a two-step process.<sup>13</sup> The initial step is a priming step. When exposed to pathogen-associated molecular patterns (PAMPs) or danger associated molecular patterns (DAMPs), phosphorylation of toll-like receptors occurs and NF- $\kappa$ B is activated.<sup>14</sup> NF- $\kappa$ B causes an increase in transcription of inactivated forms of NLRP3, proIL-1 $\beta$ , and proIL-18.<sup>15</sup> A secondary stimulus causes activation of the inflammasome by oligomerizing inactive NLRP3, apoptosis-associated speck-like protein, and procaspase-1. This structure catalyzes the modification of procaspase-1 to caspase-1. This conversion contributes to the production of functional IL-1 $\beta$  and IL-18.<sup>16</sup> The activation of the inflammasome in the second step has been proposed using three different models; potassium efflux as induced by extracellular ATP, the generation of reactive oxygen species (ROS) *via* PAMP and DAMP, and crystalline structures causing lysosomal rupture and the release of its contents including cathepsin B.<sup>17</sup>

Leptin promotes IL-18 secretion by activating caspase-1. Caspase-1 in conjunction with NLRP3 inflammasomes regulates the production and secretion of IL-18 via proteolytic digestion of pro-IL-18.<sup>8,18</sup> More specifically, the IL-18 promotion via leptin is done so by enhancing reactive oxygen species (ROS) synthesis and K<sup>+</sup> efflux. This relationship activates the NLRP3 inflammasome.<sup>12</sup>

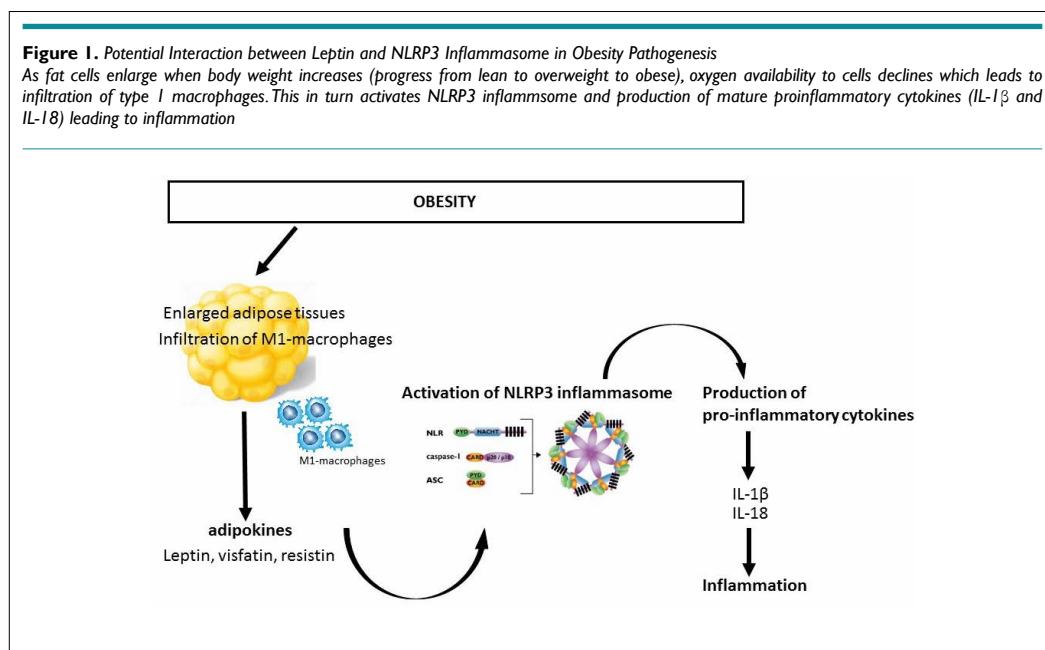
The role of NLRP3 inflammasome in metabolic syndrome and type II diabetes can be split into two subcategories which include mediated roles by sensing endogenous inflammasome activators and indirect roles by inflammasome associated alteration by manipulation of the gut microbiota.<sup>19</sup> There are multi-

ple mechanisms that have been investigated that could potentially activate the NLRP3 inflammasome in high fat induced diets; one of which includes a pancreatic hormone that is co-secreted with insulin and triggers IL-1 $\beta$  secretion by isolate macrophages.<sup>20</sup>

## OBESITY AND TYPE II DIABETES

Improvements Inflammation is a player in the pathogenesis of obesity. The chronic overfeeding associated with obesity causes macrophage saturation in the adipose tissue and results in pro-inflammatory cytokine production.<sup>21</sup> This endogenous signaling triggers the intracellular innate immune NLRP3 sensor, results in caspase-1 activation and the production of IL-1 $\beta$  and IL-18.<sup>21</sup> These cytokines are directly related to the development of insulin resistance that we observe in type II diabetes.<sup>16,22</sup> Specifically, IL-1 $\beta$  inhibits adipocyte differentiation<sup>23,24</sup> while the absence of IL-18 induces obesity and insulin resistance.<sup>25,26</sup> Conversely, the absence of the NLRP3 inflammasome has been shown inhibit the development of obesity-induced insulin resistance<sup>27</sup>, which would suggest that the inflammasome is a contributor.

Different immune cells, including proinflammatory macrophages, have been shown to penetrate the adipose tissue (AT) and affect its homeostasis by increasing the production of cytokines such as IL-1 $\beta$ , IL-6 and TNF. Macrophages and other innate immune cells can promote inflammatory reactions through detection of pathogen- or danger-associated molecular patterns (PAMPs or DAMPs) using a variety of pattern-recognition receptors (PRRs). One type of PRRs identified are nucleotide-binding oligomerization domain-like receptors (NLRs), specifically looking at NLRP3.<sup>28</sup>



When PAMPs or DAMPs are activated the 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.<sup>28</sup> This causes procaspase-1 self-cleavage, creating the active caspase-1, which leads to the conversion of IL-1 $\beta$  and IL-18 immature forms to their active forms that are secreted. NLRP3 inflammasome-activated IL-1 $\beta$  has a vital role in the development of obesity-induced insulin resistance (IR) and type 2 diabetes mellitus (T2DM).

Research involving the relationship between obesity and NLRP3 are working towards finding therapies to decrease obesity along with decreasing the expression of NLRP3. Research has found decreased NLRP3 and IL-1 $\beta$  expressions in subcutaneous adipose tissue (SAT) from T2DM patients after a year of calorie restriction and exercise-mediated weight loss. Scientists have also found that there is a relationship between nutrient excess and inflammation from the initiation of the NLRP3 inflammasome by dietary free fatty acids (FFAs) which are DAMPs. In mice research, scientists have found that high fat diets (HFDs) increase NLRP3 expression in AT, but found that calorie-restricted diets will often decrease the expression of this gene.<sup>28</sup> Further research will be needed to find a solution for the human model, but in mice models, the ablation of NLRP3 protected the mice against HFD-induced obesity and IR as well as decreasing the blood glucose and insulin levels.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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