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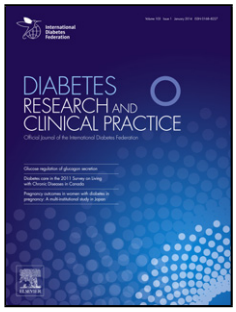

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Author: Nathalie Esser Sylvie Legrand-Poels Jacques Piette André J. Scheen Nicolas Paquot

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Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes

Nathalie Esser[1,2], Sylvie Legrand-Poels[1], Jacques Piette[1], André J. Scheen[2], Nicolas Paquot[1,2]

1. Virology and Immunology Unit, GIGA-Research, University of Liege, Liege, Belgium
2. Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, University Hospital of Liege, Liege, Belgium

Corresponding author:

Dr. Nathalie Esser

Division of Diabetes, Nutrition and Metabolic Disorders,

Department of Medicine, CHU Sart Tilman, University of Liege,

B-4000 Liege, Belgium

Tel: +3243667238; Fax: +3243667068;

Email: Nathalie.Esser@ulg.ac.be

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ABSTRACT :

It is recognized that a chronic low-grade inflammation and an activation of the immune system are involved in the pathogenesis of obesity-related insulin resistance and type 2 diabetes. Systemic inflammatory markers are risk factors for the development of type 2 diabetes and its macrovascular complications. Adipose tissue, liver, muscle and pancreas are themselves sites of inflammation in presence of obesity. An infiltration of macrophages and other immune cells is observed in these tissues associated with a cell population shift from an anti-inflammatory to a pro-inflammatory profile. These cells are crucial for the production of pro-inflammatory cytokines, which act in an autocrine and paracrine manner to interfere with insulin signaling in peripheral tissues or induce β-cell dysfunction and subsequent insulin deficiency. Particularly, the pro-inflammatory interleukin-1β is implicated in the pathogenesis of type 2 diabetes through the activation of the NLRP3 inflammasome. The objectives of this review are to expose recent data supporting the role of the immune system in the pathogenesis of insulin resistance and type 2 diabetes and to examine various mechanisms underlying this relationship. If type 2 diabetes is an inflammatory disease, anti-inflammarory therapies could have a place in prevention and treatment of type 2 diabetes.

Keywords:

Type 2 diabetes – obesity – insulin resistance – macrophages – NLRP3 inflammasome – inflammation – metabolic syndrome

INTRODUCTION

Obesity, in particular excess visceral adiposity, is associated with insulin resistance, hyperglycaemia, dyslipidaemia and hypertension, which together are termed "metabolic syndrome" [1]. These metabolic disorders increase the risk of development of type 2 diabetes mellitus (T2DM) and cardiovascular diseases and contribute to high rates of mortality and morbidity [1]. T2DM is the most prevalent metabolic disease in the world and is characterized by defects in insulin secretion and a peripheral insulin resistance in the skeletal muscle, the adipose tissue and the liver. The progression from obesity-related insulin resistance to T2DM remains poorly understood but implicates a failure of pancreatic β-cells to compensate for insulin resistance leading to chronic hyperglycaemia. A chronic low-grade inflammation and an activation of the immune system are observed in abdominal obesity and may have a role in the pathogenesis of obesity-related metabolic disorders [2-5]. This review summarizes data implicating the immune system in the pathophysiogy of insulin resistance and T2DM. We will also examine the biological, tissular and cellular inflammatory markers associated with obesity-related metabolic disorders that may predict the development of T2DM. Molecular mechanisms underlying this inflammatory activation state will be reviewed and preliminary results obtained with anti-inflammatory therapies in the prevention and treatment of T2DM will be described.

1. SYSTEMIC MARKERS OF INFLAMMATION

1.1. Inflammatory markers in obesity, metabolic syndrome and T2DM

White blood cell counts and plasma levels of coagulation factors (fibrinogen and plasminogen activator inhibitor 1 (PAI-1)), acute-phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA), pro-inflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6), and chemokines are elevated in obese and T2DM patients and shown to be reduced when these patients are engaged in a more intensive lifestyle causing weight loss [6-11]. These pro-inflammatory markers also positively correlated with insulin resistance and the features of the metabolic syndrome, in most cases, independently of the degree of obesity [6, 7, 12-14].

1.2. Inflammatory markers for development of T2DM in obese patients

Subclinical chronic inflammation seems to be an independent risk factor for the development of T2DM. Indeed, high levels of many inflammatory factors at baseline in diverse human populations are correlated with incident T2DM, regardless of the initial degree of insulin resistance and obesity. Prospective studies have identified white blood cell count [12, 15], pro-inflammatory cytokines [16], chemokines [17], and other several indirect markers of inflammation such as fibrinogen, sialic acid and PAI-1 [15, 18] as predictors of T2DM. In contrast to all these inflammatory biomarkers, CRP measurement is less expensive, standardized and widely available. Particularly a highly sensitive measurement of CRP has been developed to detect this protein with greater accuracy at lower levels. A number of prospective studies have shown that high sensitivity-CRP (hs-CRP) levels predict development of T2DM in different non-diabetic populations regardless the degree of adiposity, fat distribution and insulin resistance. All these studies were included in a recent review and meta-analysis which provided further evidence that elevated CRP levels are significantly associated with increased risk of T2DM (relative risk [RR] 1.26 [95% confidence interval or CI 1.16-1.37]) [19]. This meta-analysis also detected a significant dose-response association between IL-6 (its inducer) and T2DM risk (RR 1.31 [95% CI 1.17-1.46]) [19].

1.3. Inflammatory markers for cardiovascular disease in T2DM patients

Since hs-CRP plasma levels have been associated with cardiovascular diseases and death in the general population [20] and in patients with metabolic syndrome [21], an important question is the possible association of inflammatory markers with these risks in T2DM patients. The Hoorn population-based study was the first to show that CRP is a predictor of mortality in T2DM individuals over a 5- to 7-year period [22]. Other observational studies in T2DM populations then showed that markers of inflammation and coagulation, and in particular CRP, are independent predictors of coronary heart disease [23, 24] and mortality [25]. However, the association between CRP and cardiovascular risk seems to be much weaker in T2DM patients than in the general population [24, 26] and needs to be more extensively studied. Interest has also been focused on cardiovascular risk prediction by pro-inflammatory cytokines plasma levels. For instance, in the ADVANCE trial, IL-6 plasma levels significantly improved the prediction of macrovascular events and death in T2DM patients [27].

2. TISSUE INFLAMMATION IN OBESITY AND T2DM

A number of experimental and clinical data have clearly established that adipose tissue, liver, muscle and pancreas are sites of inflammation in presence of obesity and T2DM. An infiltration of macrophages into these tissues is seen in animal models of obesity and diabetes as well as in obese human individuals with metabolic syndrome or T2DM. These cells are crucial for the production of pro-inflammatory cytokines [4], including TNFα, IL-6 and IL-1β. They act in an autocrine and paracrine manner to promote insulin resistance by interfering with insulin signaling in peripheral tissues through activation of the c-JUN N-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB) pathways [2]. These pathways are activated in multiple tissues in obesity and T2DM and have a central role in promoting tissue inflammation.

2.1. Inflammation in insulin-sensitive tissues

2.1.1 Adipose tissue

Hotamisligil and colleagues were the first to show an increased expression and production of TNFα in adipose tissue of obese individuals and its direct role in obesity-induced insulin resistance [28]. Accumulating data then confirmed a specific up-regulation of genes encoding inflammatory factors and an over-production of many cytokines and chemokines in enlarged adipose tissue [5]. Furthermore, improvement in insulin sensitivity induced by weight loss was accompanied by a decrease in the expression of pro-inflammatory genes [28, 29]. So adipose tissue inflammation was considered as a crucial event leading to metabolic syndrome, T2DM and atherosclerotic cardiovascular diseases.

More recently, adipose tissue has been associated with a marked accumulation of immune cells in its stromovascular fraction during obesity [4] (Figure 1). Particularly, obesity induces an infiltration of macrophages in adipose tissue of both mice and humans [30, 31]. Although it was shown that enlarged adipocytes themselves produce pro-inflammatory cytokines and chemokines [32], adipose tissue macrophages seem to be crucial for the production of adipose tissue-derived pro-inflammatory cytokines. Indeed, their recruitment correlates with the degree of obesity and is linked to systemic inflammation, insulin resistance [30] and metabolic syndrome [33]. Moreover, weight loss induced by surgery [29] or diet and exercise [10] results in a reduction in the number of adipose tissue macrophages in parallel to the decreased expression of pro-inflammatory markers in both adipose tissue and plasma of obese individuals.

Macrophages can be classified into two distinct subtypes: the "classically activated macrophages" phenotype, termed M1, which secrete pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and the "alternatively activated macrophages" phenotype, termed M2 which produce anti-inflammatory cytokines such as IL-10 [4]. While well-established in mice [34, 35], the existence of distinct M1 and M2 subsets of adipose tissue macrophages has not been confirmed in human, where macrophages have rather been described as being a mix between M1 and M2 phenotypes [36]. In addition to adipose tissue macrophages infiltration, obesity causes a phenotypic switch from the M2 to M1 phenotype, correlating with insulin resistance both in mice and humans [34-36]. Direct and paracrine signals issued from M1 macrophages can impair insulin signaling and adipogenesis in adipocytes whereas M2 macrophages seem to protect against obesity-induced insulin resistance [4].

Although macrophages are the most abundant leukocyte population in expanding adipose tissue, the adaptive immune system may also contribute to obesity-induced inflammation. Infiltrating lymphocytes precede macrophage populations in obese adipose tissue concomitant with early insulin resistance and may play a role in adipose tissue inflammation by modifying the number and the activation state of adipose tissue macrophages [37-40]. In mouse models of obesity, an increased numbers of cytotoxic CD8+ effector cells is suspected to initiate the recruitment and activation of adipose tissue macrophages and promote pro-inflammatory cascades associated with insulin resistance [38, 40]. Obesity also induces modification in the balance between pro-inflammatory (T helper 1 and T helper 17 lymphocytes) and anti-inflammatory (T helper 2 and regulatory T lymphocytes) CD4+ cells subsets, leading to secretion of cytokines from newly recruited adipose tissue macrophages [39-41]. Of particular interest, the number of anti-inflammatory regulatory T lymphocytes decreases with obesity in adipose tissue of both mice and humans [37, 39, 40] and even more in obese patients with metabolic syndrome [33]. The regulatory T lymphocytes express high amount of the anti-inflammatory cytokine IL-10 which inhibit macrophage migration and induce the differentiation of M2 macrophages [35, 37]. A boost in the number of these cells in obese mice can improve insulin sensitivity and reduce macrophage infiltration in adipose tissue [37]. These data suggest that regulatory T cells may repress adipose tissue inflammation and play a role in providing protection against insulin resistance-induced inflammation linked to obesity [33, 37]. The number of many other immune cells is also modified in adipose tissue during obesity and could regulate inflammation and insulin resistance[4] (Figure 1).

Overall, these data reveal a complex interplay between cells of innate and adaptive immunity and the balance among these immune cells appears to be important for the homeostasis and

control of adipose tissue inflammation in obesity and T2DM. However, the molecular events that initiate immune cell recruitment and activation are not fully understood.

Subcutaneous versus visceral adipose tissues

Abdominal obesity is the key component of the metabolic syndrome, with a predominance of intra-abdominal visceral fat accumulation, indirectly measured by waist circumference in clinical practice. So, besides total adiposity, the pathogenic role of adipose tissue seems to be determined by its specific anatomic location. Indeed, although both subcutaneous and visceral adipose tissues are associated with metabolic risk profile, high visceral adipose tissue is more strongly correlated with metabolic syndrome than its subcutaneous counterpart[42]. Furthermore, it is associated with ectopic lipid accumulation in the liver and skeletal muscle, which participates to local insulin resistance and contributes to associated metabolic complications [43]. Subcutaneous and visceral adipose tissues differ by phenotypic, physiological and functional characteristics [43]. Specific differences in inflammatory profile have also been reported, with more macrophages [29, 31, 33], T lymphocytes [31, 33], and inflammatory molecules in the visceral vs the subcutaneous tissues of obese individuals [29, 33]. Moreover, a lower number of anti-inflammatory regulatory T lymphocytes was recently found in the visceral adipose tissue of obese individuals with metabolic syndrome [33]. This less favourable inflammatory profile of visceral adipose tissue is in line with the belief this tissue has a more important role in the development of obesity-related insulin resistance.

2.1.2 Liver

Nonalcoholic fatty liver disease (NAFLD) often accompanies abdominal obesity, and its prevalence increases in parallel to that of T2DM. NAFLD includes a large spectrum of lesions, from simple benign steatosis to steatohepatitis (nonalcoholic steatohepatitis or NASH), which can lead to cirrhosis and hepatocarcinoma [44]. Inflammation clearly plays a pivotal role in the progression of this disease process. NAFLD and subsequent hepatic insulin resistance in obesity are associated with increased expression and overproduction of inflammatory mediators, including TNFα, IL-6 and IL-1β [45]. Unlike adipose tissue, the liver is densely populated with resident macrophages, the Kupffer cells, which account for over 10% of total liver cells. The number of Kupffer cells does not increase with obesity, but their activation state changes [45, 46]. Although Kupffer cells have been less studied than adipose tissue macrophages in the context of insulin resistance, they clearly contribute to the

production of inflammatory mediators that promote insulin resistance in liver [46]. Interestingly, as earlier described for adipose tissue macrophages, alternative M2 activation phenotype of Kupffer cells appears to ameliorate insulin resistance and to delay the progression to NASH in mice [46]. These data suggest that steatosis might induce a sub-acute inflammatory response in liver, similar to that observed in the adipose tissue inflammation following adipocyte lipid accumulation. Alternatively, pro-inflammatory mediators in the portal circulation, potentially produced by abdominal fat, might also initiate hepatic inflammation.

2.1.3 Muscle

The muscle is another major site of insulin resistance in obesity and T2DM. Recent reports have shown an infiltration of macrophages within skeletal muscles of obese mice, particularly in the inter-muscular adipose depots [30]. Just as adipose tissue, these skeletal muscle macrophages exhibit a pro-inflammatory M1 phenotype [47] accompanied with an increased expression of inflammatory factors in muscle cells [30, 47] contributing locally to insulin resistance. Moreover, the gene expression of phenotype markers of pro- and anti-inflammatory macrophages in human skeletal muscle seems to correlate with insulin sensitivity [48]. However, the content of macrophages in skeletal muscle in obesity is by far lower than in adipose tissue or liver, and further research is needed to determine if skeletal muscle is mainly a target of inflammation-induced insulin resistance or if local inflammatory cascades may also play a role in insulin resistance.

2.2. INFLAMMATION IN PANCREAS AND INSULIN DEFICIENCY

The progression from obesity-related insulin resistance to T2DM implicates a failure of pancreatic β cells to compensate for insulin resistance, leading to chronic hyperglycaemia. An inflammation was also demonstrated in pancreatic islets of T2DM patients as shown by the presence of amyloid deposits, fibrosis, increased β cell death and infiltration of macrophages along with increased levels of pro-inflammatory cytokines and chemokines [3]. Moreover this increase of immune cells in pancreatic islets is described before the onset of T2DM. Particularly the expression and local release of the pro-inflammatory cytokine IL-1β are increased in pancreatic islet of T2DM individuals [49]. This cytokine seems to be a master regulator of islet inflammation in T2DM by increasing local expression of pro-inflammatory cytokines and chemokines [50] leading to immune cell recruitment in islets. This local

inflammation can reduce insulin secretion and trigger β-cell apoptosis leading to decrease islet mass, all critical events in the progression of T2DM.

3. SENSORS AND MEDIATORS OF INFLAMMATION IN OBESITY AND T2DM

Although subclinical inflammation is important in the pathogenesis of T2DM, the events initiating this inflammatory process remain unclear and could involve different but synergic mechanisms leading to the activation of NF-κB and JNK pathways, cytokines and chemokines release and recruitment of immune cells.

3.1. IL-1β and NLRP3 inflammasome

IL-1β, one of the major pro-inflammatory cytokine produced by macrophages, has been shown to be a key contributor to the pathogenesis of T2DM. IL-1β signaling occurs through the IL-1 receptor-I and leads to the activation of NF-κB pathways and the generation of other inflammatory mediators, such as TNFα and IL-1β itself, thus initiating a self-amplifying cytokine network [50]. The control of IL-1β production is tightly regulated and depends on two signals. First, a pro-inflammatory signal stimulates the transcription of *IL1B* with subsequent storage of inactive pro-IL-1β into the cell. A second signal then induces the production of active, mature IL-1β by cleavage of its inactive precursor by caspase-1, which is activated in a large cytoplasmic multiprotein complex called the inflammasome [51]. Inflammasomes are central components of the innate immune response and recognize microbial products (pathogen-associated molecular patterns (PAMPs)) or endogenous molecules (danger-associated molecular pattern (DAMPs)) by innate pattern recognition receptors (PRRs). Structurally, inflammasomes are usually formed through the interaction between a PRR, mainly a member of the nucleotide-binding oligomerization domain like receptor (NLR) family, the adaptor protein apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) and the pro-caspase-1 [51]. Among several NLRs that form inflammasome platforms, there are compelling evidences for a major role of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome in the progression from obesity to T2DM (Figure 2). NLRP3 inflammasome activation and subsequent IL-1β production have been first described in pancreatic β-cells and islet-infiltrating macrophages. They contribute to islet inflammation induced by chronic exposure to high levels of free fatty acids and glucose, leading to increased apoptosis and impaired insulin secretion of β-cells [49, 52, 53].

Moreover, islet amyloid polypeptide (IAPP), a protein that forms amyloid deposits in the pancreas, seems to contribute to IL-1β production in islets through activation of the NLRP3 inflammasome [54].

Accumulating evidences also give to NLRP3 inflammasome a central role in obesity-induced insulin resistance [33, 55, 56]. The expression of NLRP3 inflammasome components, the activity of caspase-1 and the levels of IL-1β are increased in adipose tissue, mainly in macrophages, of obese mice and humans and directly correlate with insulin resistance, features of the metabolic syndrome and severity of T2DM [33, 56]. The deleterious effects of visceral adipose tissue might be also related to an up-regulated expression and activation of NLRP3 inflammasome compared to subcutaneous adipose tissue in overweight and obese patients [33, 57]. The NLRP3 inflammasome seems to act as a sensor of metabolic danger signals that accumulate during obesity, including high levels of glucose [52], saturated free fatty acids [58, 59], lipid intermediates such as ceramides [56] and uric acid [51], and its activation results in IL-1β production and induction of numerous cytokines and chemokines. Moreover its inhibition has shown to have pleiotropic effects combining improved insulin signaling in adipose tissue, liver and skeletal muscle, and increased insulin secretion in the pancreas [55, 56].

We have recently strengthened the involvement of NLRP3 inflammasome in obesity-related metabolic disorders by studying several features related to NLRP3 inflammasome activation in a unique subgroup of obese individuals who not display the typical metabolic disorders associated with obesity despite their excessive fatness, and are at lower risk of developing T2DM and cardiovascular diseases. This phenotype is referred in the literature as "metabolically healthy obesity" (MHO) and may account for around 30% of the obese population [60]. Interestingly, the MHO phenotype is characterized by a more favourable body fat distribution with lower visceral fat and greater subcutaneous fat [42], by a lower ectopic fat depot in the liver [61], and by a less inflammatory profile with lower levels of circulating inflammatory markers [14, 42] compared to unhealthy obese phenotype. We have recently reported that the visceral adipose tissue of MHO phenotype is associated with lower activation of the NLRP3 inflammasome in infiltrating macrophages, and with a more favourable inflammatory and immunological profile compared to that of unhealthy obese phenotype [33] (Figure 3). Identification of the triggers that determine differential activation of the inflammasome between obesity phenotypes would likely help to better understand the physiopathology of obesity-related metabolic disorders. Fatty acids may be good candidates as saturated fatty acid can induce inflammatory cascades in macrophages and adipocytes

through the activation of NLRP3 inflammasome [58] whereas unsaturated fatty acids exert strong anti-inflammatory effects resulting in improved insulin sensitivity in obese and T2DM individuals [62]. Moreover, unsaturated and omega-3 fatty acids do not activate NLRP3 inflammasome [58, 59, 63] and can prevent its activation by other inducers [59]. The importance of unsaturated fatty acids in mediating inflammation is enhanced by a recent study showing a distinct fatty acid profile between MHO and unhealthy obese individuals, specifically for saturated fatty acids [64]. Further comparisons of these two groups are required to better identify potential mechanisms of protection against obesity-related insulin resistance and inflammation and to develop preventive and therapeutic strategies.

3.2. Adipocyte hypertrophy, hypoxia and cell death

Other hypothetical events have been proposed to initiate inflammatory process in adipose tissue. Obesity leads to an increased adipocyte size and hypertrophic adipocytes may produce themselves cytokines and chemokines [32], leading to macrophages recruitment. Adipocyte hypertrophy may also be responsible for hypoxia or even adipocyte death. Areas of hypoxia have been observed in expanding adipose tissue of obese mice and humans, as a result of insufficient vasculature and oxygen supply. Hypoxia can induce recruitment of macrophages and expression of pro-inflammatory cytokines in both adipocytes and immune cells, contributing to adipose tissue inflammation and dysfunction [31]. In the absence of additional nutrients supply, hypertrophy can also provoke adipocyte necrosis and the release of their cellular contents into the extracellular space triggering an inflammatory response. Particularly, some of the moribund or dead adipocytes become surrounded by macrophages to form the “crown-like structures” observed in expanding adipose tissue [29-31].

3.3. Endoplasmic reticulum stress

One other potential mechanism of NLRP3 activation in macrophages involves the endoplasmic reticulum, a major site for protein folding, maturation and trafficking. In obesity, the chronic excess nutrient intake generates endoplasmic reticulum stress due to an increase in synthetic demand, leading to activation of pro-inflammatory signaling pathways. Endoplasmic reticulum stress has been shown in adipose tissue of obese insulin resistant individuals and may be a cause for the development of insulin resistance and inflammation [65].

4. ANTI-INFLAMMATORY THERAPEUTIC PERSPECTIVES

Given the obvious link between inflammation and pathogenesis of T2DM, anti-inflammatory strategies have been proposed for its prevention and treatment. They are extensively reviewed elsewhere [66].

4.1. Anti-IL-1β

Considering the central role of NLRP3 inflammasome and IL-1β in the pathogenesis of T2DM, it is not surprising that the blockade of IL-1β activity has shown improvement in glucose control in prediabetic or T2DM populations. Studies conducted with IL-1 receptor antagonist (anakinra) or IL-1β antagonism (gevokizumab, canakizumab and LY2189102) have shown beneficial effects on glycated haemoglobin and β cell function in parallel to a decrease in systemic markers of inflammation [67-70]. Moreover, two studies have demonstrated persistent effects up to several weeks after treatment cessation with anakinra [71] or anti- IL-1β antibody [70]. Although the short duration of these studies does not provide definitive conclusions, data suggests that IL-1β blocking activity enhances glucose control in diabetic patients by improving the β-cell function and may even allow a partial generation these cells.

4.2. Salicylate and salsalate

Sodium salicylate and aspirin have demonstrated beneficial effects in the treatment of T2DM by improving glycaemic control through inhibition of NF-κB activity [72, 73]. Salsalate, prodrug of salicylate, which unlike aspirin and sodium salicylate does not lead to bleeding risk, can improve insulin sensitivity and glucose control in prediabetic and T2DM patients with a good safety profile [74, 75]. More particularly, a large randomized trial, the Targeting Inflammation with Salsalate in Type 2 Diabetes (TINSAL-T2D) trial, concluded that salsalate improves glucose control in T2DM patients with decrease in fasting glucose and glycated haemoglobin levels and enhances lipid profile [75]. These data suggest that NF-κB pathways may represent a novel therapeutic target for prevention and treatment of T2DM. More extensive studies are needed to confirm whether effects are sustainable with continued administration of these drugs.

4.3. Anti-TNFα

TNFα was the first pro-inflammatory cytokine implicated in pathogenesis of obesity-related insulin resistance and T2DM [28]. However, TNF-α antagonism has not demonstrated significant improvement on insulin sensitivity in patients with metabolic syndrome [76] or T2DM [77, 78], but these pilot studies were probably underpowered as they were conducted on a short-time period in a limited number of patients. Further longer and bigger studies are warranted, especially because TNF-α antagonism treatment in non-diabetic patients with rheumatoid polyarthritis improves their insulin sensitivity [79].

CONCLUSIONS

The concept of T2DM as an inflammatory disease has recently emerged and seems to be confirmed by accumulating evidences. A number of studies have shown that abdominal obesity is associated with systemic low grade inflammation leading to insulin resistance and metabolic disorders. Moreover, systemic inflammatory markers can predict development of T2DM and cardiovascular diseases in the general population, and should be therefore used more widely in clinical practice to detect individuals at risk. Adipose tissue appears to play a central role in the induction of inflammation as over-nutrition leads to changes in its cellular composition and production of pro-inflammatory cytokines and chemokines. A local inflammation is also observed in the liver and skeletal muscle but its role in obesity-related metabolic disorders still needs to be determined. Recent evidence implicates the inflammasome NLRP3 in the pathogenesis of metabolic syndrome and T2DM. In pancreas activation of NLRP3 inflammasome by high levels of glucose and fatty acids and subsequent release of IL-1β lead to β cells dysfunction and apoptosis, insulin deficiency and progression to T2DM. NLRP3 inflammasome is also activated in macrophages infiltrating visceral adipose tissue from obese patients with metabolic disorders, and contributes to local inflammation, defect in adipogenesis and insulin resistance. The exact events and triggers that promote inflammatory cascade activation still need to be determined. Because an imbalance in inflammatory profile and inflammasome activation has been detected in visceral adipose tissue of metabolically healthy and unhealthy obese persons, study of these phenotypes may help to better understand the molecular mechanisms, identify signal dangers in obesity and develop preventive and therapeutic strategies. Targeting inflammation, especially NLRP3 inflammasome, may offer potential novel therapeutic perspectives in T2DM prevention and treatment.

Conflict of Interest Statement

None

REFERENCES

[1] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640-5.
[2] Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006;116:1793-801.
[3] Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011;11:98-107.
[4] Chawla A, Nguyen KD, Goh YP. Macrophage-mediated inflammation in metabolic disease. Nat Rev Immunol. 2011;11:738-49.
[5] Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011;11:85-97.
[6] Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. Diabetologia. 1997;40:1286-92.
[7] Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol. 1999;19:972-8.
[8] Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrinol Metab. 2000;85:3338-42.
[9] Haffner S, Temprosa M, Crandall J, Fowler S, Goldberg R, Horton E, et al. Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. Diabetes. 2005;54:1566-72.
[10] Bruun JM, Helge JW, Richelsen B, Stallknecht B. Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects. Am J Physiol Endocrinol Metab. 2006;290:E961-7.
[11] Belalcazar LM, Haffner SM, Lang W, Hoogeveen RC, Rushing J, Schwenke DC, et al. Lifestyle intervention and/or statins for the reduction of C-reactive protein in type 2 diabetes: from the look AHEAD study. Obesity. 2013;21:944-50.
[12] Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA. High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes. 2002;51:455-61.
[13] Natali A, Toschi E, Baldeweg S, Ciociaro D, Favilla S, Sacca L, et al. Clustering of insulin resistance with vascular dysfunction and low-grade inflammation in type 2 diabetes. Diabetes. 2006;55:1133-40.
[14] Phillips CM, Perry IJ. Does inflammation determine metabolic health status in obese and nonobese adults? J Clin Endocrinol Metab. 2013;98:E1610-9.
[15] Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes. 2003;52:1799-805.
[16] Spranger J, Kroke A, Mohlig M, Hoffmann K, Bergmann MM, Ristow M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes. 2003;52:812-7.

[17] Herder C, Baumert J, Thorand B, Koenig W, de Jager W, Meisinger C, et al. Chemokines as risk factors for type 2 diabetes: results from the MONICA/KORA Augsburg study, 1984-2002. Diabetologia. 2006;49:921-9.
[18] Festa A, D'Agostino R, Jr., Tracy RP, Haffner SM, Insulin Resistance Atherosclerosis S. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes. 2002;51:1131-7.
[19] Wang X, Bao W, Liu J, Ouyang YY, Wang D, Rong S, et al. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2013;36:166-75.
[20] Blake GJ, Ridker PM. Inflammatory bio-markers and cardiovascular risk prediction. J Intern Med. 2002;252:283-94.
[21] Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation. 2003;107:391-7.
[22] Jager A, van Hinsbergh VW, Kostense PJ, Emeis JJ, Yudkin JS, Nijpels G, et al. von Willebrand factor, C-reactive protein, and 5-year mortality in diabetic and nondiabetic subjects: the Hoorn Study. Arterioscler Thromb Vasc Biol. 1999;19:3071-8.
[23] Saito I, Folsom AR, Brancati FL, Duncan BB, Chambless LE, McGovern PG. Nontraditional risk factors for coronary heart disease incidence among persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Ann Intern Med. 2000;133:81-91.
[24] Best LG, Zhang Y, Lee ET, Yeh JL, Cowan L, Palmieri V, et al. C-reactive protein as a predictor of cardiovascular risk in a population with a high prevalence of diabetes: the Strong Heart Study. Circulation. 2005;112:1289-95.
[25] Soinio M, Marniemi J, Laakso M, Lehto S, Ronnemaa T. High-sensitivity C-reactive protein and coronary heart disease mortality in patients with type 2 diabetes: a 7-year follow-up study. Diabetes Care. 2006;29:329-33.
[26] Kengne AP, Batty GD, Hamer M, Stamatakis E, Czernichow S. Association of C-reactive protein with cardiovascular disease mortality according to diabetes status: pooled analyses of 25,979 participants from four U.K. prospective cohort studies. Diabetes Care. 2012;35:396-403.
[27] Lowe G, Woodward M, Hillis G, Rumley A, Li Q, Harrap S, et al. Circulating inflammatory markers and the risk of vascular complications and mortality in people with type 2 diabetes and cardiovascular disease or risk factors: The ADVANCE Study. Diabetes. 2014;63:1115-23.
[28] Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest. 1995;95:2409-15.
[29] Cancello R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, et al. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes. 2005;54:2277-86.
[30] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112:1796-808.
[31] O'Rourke RW, White AE, Metcalf MD, Olivas AS, Mitra P, Larison WG, et al. Hypoxia-induced inflammatory cytokine secretion in human adipose tissue stromovascular cells. Diabetologia. 2011;54:1480-90.
[32] Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. J Clin Endocrinol Metab. 2007;92:1023-33.

[33] Esser N, L'Homme L, De Roover A, Kohnen L, Scheen AJ, Moutschen M, et al. Obesity phenotype is related to NLRP3 inflammasome activity and immunological profile of visceral adipose tissue. Diabetologia. 2013;56:2487-97.
[34] Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest. 2007;117:175-84.
[35] Fujisaka S, Usui I, Bukhari A, Ikutani M, Oya T, Kanatani Y, et al. Regulatory mechanisms for adipose tissue M1 and M2 macrophages in diet-induced obese mice. Diabetes. 2009;58:2574-82.
[36] Wentworth JM, Naselli G, Brown WA, Doyle L, Phipson B, Smyth GK, et al. Pro-inflammatory CD11c+CD206+ adipose tissue macrophages are associated with insulin resistance in human obesity. Diabetes. 2010;59:1648-56.
[37] Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, et al. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med. 2009;15:930-9.
[38] Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med. 2009;15:914-20.
[39] Winer S, Chan Y, Paltser G, Truong D, Tsui H, Bahrami J, et al. Normalization of obesity-associated insulin resistance through immunotherapy. Nat Med. 2009;15:921-9.
[40] Deiuliis J, Shah Z, Shah N, Needleman B, Mikami D, Narula V, et al. Visceral adipose inflammation in obesity is associated with critical alterations in tregulatory cell numbers. PLoS One. 2011;6:e16376.
[41] Jagannathan-Bogdan M, McDonnell ME, Shin H, Rehman Q, Hasturk H, Apovian CM, et al. Elevated proinflammatory cytokine production by a skewed T cell compartment requires monocytes and promotes inflammation in type 2 diabetes. Journal of immunology. 2011;186:1162-72.
[42] Koster A, Stenholm S, Alley DE, Kim LJ, Simonsick EM, Kanaya AM, et al. Body fat distribution and inflammation among obese older adults with and without metabolic syndrome. Obesity. 2010;18:2354-61.
[43] Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev. 2013;93:359-404.
[44] Serfaty L, Lemoine M. Definition and natural history of metabolic steatosis: clinical aspects of NAFLD, NASH and cirrhosis. Diabetes Metab. 2008;34:634-7.
[45] Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, et al. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nat Med. 2005;11:183-90.
[46] Huang W, Metlakunta A, Dedousis N, Zhang P, Sipula I, Dube JJ, et al. Depletion of liver Kupffer cells prevents the development of diet-induced hepatic steatosis and insulin resistance. Diabetes. 2010;59:347-57.
[47] Nguyen MT, Favelyukis S, Nguyen AK, Reichart D, Scott PA, Jenn A, et al. A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via Toll-like receptors 2 and 4 and JNK-dependent pathways. J Biol Chem. 2007;282:35279-92.
[48] Fink LN, Oberbach A, Costford SR, Chan KL, Sams A, Bluher M, et al. Expression of anti-inflammatory macrophage genes within skeletal muscle correlates with insulin sensitivity in human obesity and type 2 diabetes. Diabetologia. 2013;56:1623-8.
[49] Maedler K, Sergeev P, Ris F, Oberholzer J, Joller-Jemelka HI, Spinas GA, et al. Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. J Clin Invest. 2002;110:851-60.

[50] Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. Annu Rev Immunol. 2009;27:519-50.
[51] Schroder K, Zhou R, Tschopp J. The NLRP3 inflammasome: a sensor for metabolic danger? Science. 2010;327:296-300.
[52] Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol. 2010;11:136-40.
[53] Boni-Schnetzler M, Boller S, Debray S, Bouzakri K, Meier DT, Prazak R, et al. Free fatty acids induce a proinflammatory response in islets via the abundantly expressed interleukin-1 receptor I. Endocrinology. 2009;150:5218-29.
[54] Masters SL, Dunne A, Subramanian SL, Hull RL, Tannahill GM, Sharp FA, et al. Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1beta in type 2 diabetes. Nat Immunol. 2010;11:897-904.
[55] Stienstra R, van Diepen JA, Tack CJ, Zaki MH, van de Veerdonk FL, Perera D, et al. Inflammasome is a central player in the induction of obesity and insulin resistance. Proc Natl Acad Sci U S A. 2011;108:15324-9.
[56] Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med. 2011;17:179-88.
[57] Koenen TB, Stienstra R, van Tits LJ, Joosten LA, van Velzen JF, Hijmans A, et al. The inflammasome and caspase-1 activation: a new mechanism underlying increased inflammatory activity in human visceral adipose tissue. Endocrinology. 2011;152:3769-78.
[58] Wen H, Gris D, Lei Y, Jha S, Zhang L, Huang MT, et al. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat Immunol. 2011;12:408-15.
[59] L'Homme L, Esser N, Riva L, Scheen A, Paquot N, Piette J, et al. Unsaturated fatty acids prevent activation of NLRP3 inflammasome in human monocytes/macrophages. J Lipid Res. 2013;54:2998-3008.
[60] Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med. 2008;168:1617-24.
[61] Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, et al. Identification and characterization of metabolically benign obesity in humans. Arch Intern Med. 2008;168:1609-16.
[62] Summers LK, Fielding BA, Bradshaw HA, Ilic V, Beysen C, Clark ML, et al. Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improves insulin sensitivity. Diabetologia. 2002;45:369-77.
[63] Yan Y, Jiang W, Spinetti T, Tardivel A, Castillo R, Bourquin C, et al. Omega-3 fatty acids prevent inflammation and metabolic disorder through inhibition of NLRP3 inflammasome activation. Immunity. 2013;38:1154-63.
[64] Perreault M, Zulyniak MA, Badoud F, Stephenson S, Badawi A, Buchholz A, et al. A distinct Fatty Acid profile underlies the reduced inflammatory state of metabolically healthy obese individuals. PLoS One. 2014;9:e88539.
[65] Cnop M, Foufelle F, Velloso LA. Endoplasmic reticulum stress, obesity and diabetes. Trends Mol Med. 2012;18:59-68.
[66] Esser N, Paquot N, Scheen A. Anti-inflammatory agents to treat or prevent type 2 diabetes, metabolic syndrome and cardiovascular disease. Expert opinion on investigational drugs. 2014. In press
[67] Larsen CM, Faulenbach M, Vaag A, Volund A, Ehses JA, Seifert B, et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med. 2007;356:1517-26.

[68] Ridker PM, Howard CP, Walter V, Everett B, Libby P, Hensen J, et al. Effects of interleukin-1beta inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation. 2012;126:2739-48.
[69] Cavelti-Weder C, Babians-Brunner A, Keller C, Stahel MA, Kurz-Levin M, Zayed H, et al. Effects of gevokizumab on glycemia and inflammatory markers in type 2 diabetes. Diabetes Care. 2012;35:1654-62.
[70] Sloan-Lancaster J, Abu-Raddad E, Polzer J, Miller JW, Scherer JC, De Gaetano A, et al. Double-blind, randomized study evaluating the glycemic and anti-inflammatory effects of subcutaneous LY2189102, a neutralizing IL-1beta antibody, in patients with type 2 diabetes. Diabetes Care. 2013;36:2239-46.
[71] Larsen CM, Faulenbach M, Vaag A, Ehses JA, Donath MY, Mandrup-Poulsen T. Sustained effects of interleukin-1 receptor antagonist treatment in type 2 diabetes. Diabetes Care. 2009;32:1663-8.
[72] Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, et al. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. Science. 2001;293:1673-7.
[73] Hundal RS, Petersen KF, Mayerson AB, Randhawa PS, Inzucchi S, Shoelson SE, et al. Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. J Clin Invest. 2002;109:1321-6.
[74] Koska J, Ortega E, Bunt JC, Gasser A, Impson J, Hanson RL, et al. The effect of salsalate on insulin action and glucose tolerance in obese non-diabetic patients: results of a randomised double-blind placebo-controlled study. Diabetologia. 2009;52:385-93.
[75] Goldfine AB, Fonseca V, Jablonski KA, Pyle L, Staten MA, Shoelson SE, et al. The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomized trial. Ann Intern Med. 2010;152:346-57.
[76] Paquot N, Castillo MJ, Lefebvre PJ, Scheen AJ. No increased insulin sensitivity after a single intravenous administration of a recombinant human tumor necrosis factor receptor: Fc fusion protein in obese insulin-resistant patients. J Clin Endocrinol Metab. 2000;85:1316-9.
[77] Ofei F, Hurel S, Newkirk J, Sopwith M, Taylor R. Effects of an engineered human anti-TNF-alpha antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. Diabetes. 1996;45:881-5.
[78] Dominguez H, Storgaard H, Rask-Madsen C, Steffen Hermann T, Ihlemann N, Baunbjerg Nielsen D, et al. Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obese patients with type 2 diabetes. J Vasc Res. 2005;42:517-25.
[79] Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. Ann Rheum Dis. 2005;64:765-6.

Figure 1. Adipose tissue inflammation in pathogenesis of metabolic syndrome and type 2 diabetes

Obesity induces adipocyte hypertrophy and changes in stromovascular cell composition with their phenotypic activation to a pro-inflammatory state. Cells from the adaptive immune system interact with adipose tissue macrophages to modify their activation state. In lean adipose tissue, T helper type 2 and regulatory T lymphocytes promote a M2 macrophage polarization, which maintain an anti-inflammatory state. Eosinophils may also induce a M2 macrophage polarization. In obesity and type 2 diabetes, adipose tissue is characterized by an enrichment of macrophages and T lymphocytes with a shift from an anti-inflammatory to a pro-inflammatory state. Cytotoxic CD8+, T helper type 1 and T helper type 17 lymphocytes stimulate M1 macrophage polarization. Other cells, including B lymphocytes and mast cells, are also increased in obese adipose tissue and may contribute to obesity-induced inflammation. In obesity, the imbalance among immune cells results in production of chemokines and pro-inflammatory cytokines, which promote systemic inflammation and peripheral insulin resistance.

Abbreviations: IL: interleukin; TNFα: tumor necrosis factor alpha; T2DM: type 2 diabetes mellitus; Treg : regulatory T lymphocytes.

Figure 2. The NLRP3 inflammasome

NLRP3 inflammasome is an intracellular multiprotein complex formed through the interaction of NLRP3, the protein adaptor ASC and the pro-caspase-1, leading to caspase-1 activation. One activated, caspase-1 cleaves the inactive precursor of IL-1β (pro-IL-1β) into its biological active form which is secreted. NLRP3 activation requires a two-step process. First or "priming" signal acts on TLR or cytokines receptors and converges on the activation of NFκB pathway and transcriptional expression of inflammasome components, including NLRP3 and pro-IL-1β. The second or "activating" signal is then able to directly induce NLRP3 inflammasome formation and instigates caspase-1 activation. The second signal includes various PAMPs and DAMPs.

Abbreviations: ASC: apoptosis-associated speck-like protein containing a caspase-recruitment domain; DAMPs: danger-associated molecular pattern; IL-1β : interleukin-1β ; NFκB : nuclear factor-kappa B ; NLRP3 : nucleotide-binding oligomerization domain-like receptor family pyrin domain containing-3; PAMPs: pathogen-associated molecular patterns; TLR: toll-like receptor

Figure 3. Adipose tissue inflammatory profile imbalance between metabolically healthy and unhealthy obese

Compared to metabolically healthy obesity (MHO) phenotype, the visceral adipose tissue of metabolically unhealthy obesity (MUO) phenotype is characterized by a higher NLRP3 inflammasome activation in macrophages infiltrating visceral adipose tissue and a decrease number of anti-inflammatory regulatory T lymphocytes. This imbalance in the inflammatory profile may explain why metabolically healthy obese are at lower risk of developing type 2 diabetes, NAFLD and cardiovascular diseases. The triggers that determine differential inflammasome activation remains to be identified. Fatty acids, glucose and uric acid may be good candidates.

Abbreviations: MHO : metabolically healthy obesity; MUO: metabolically unhealthy obesity; NAFLD: nonalcoholic fatty liver disease; NLRP3 : nucleotide-binding oligomerization domain-like receptor family pyrin domain containing-3; T2DM: type 2 diabetes mellitus

Figure 1

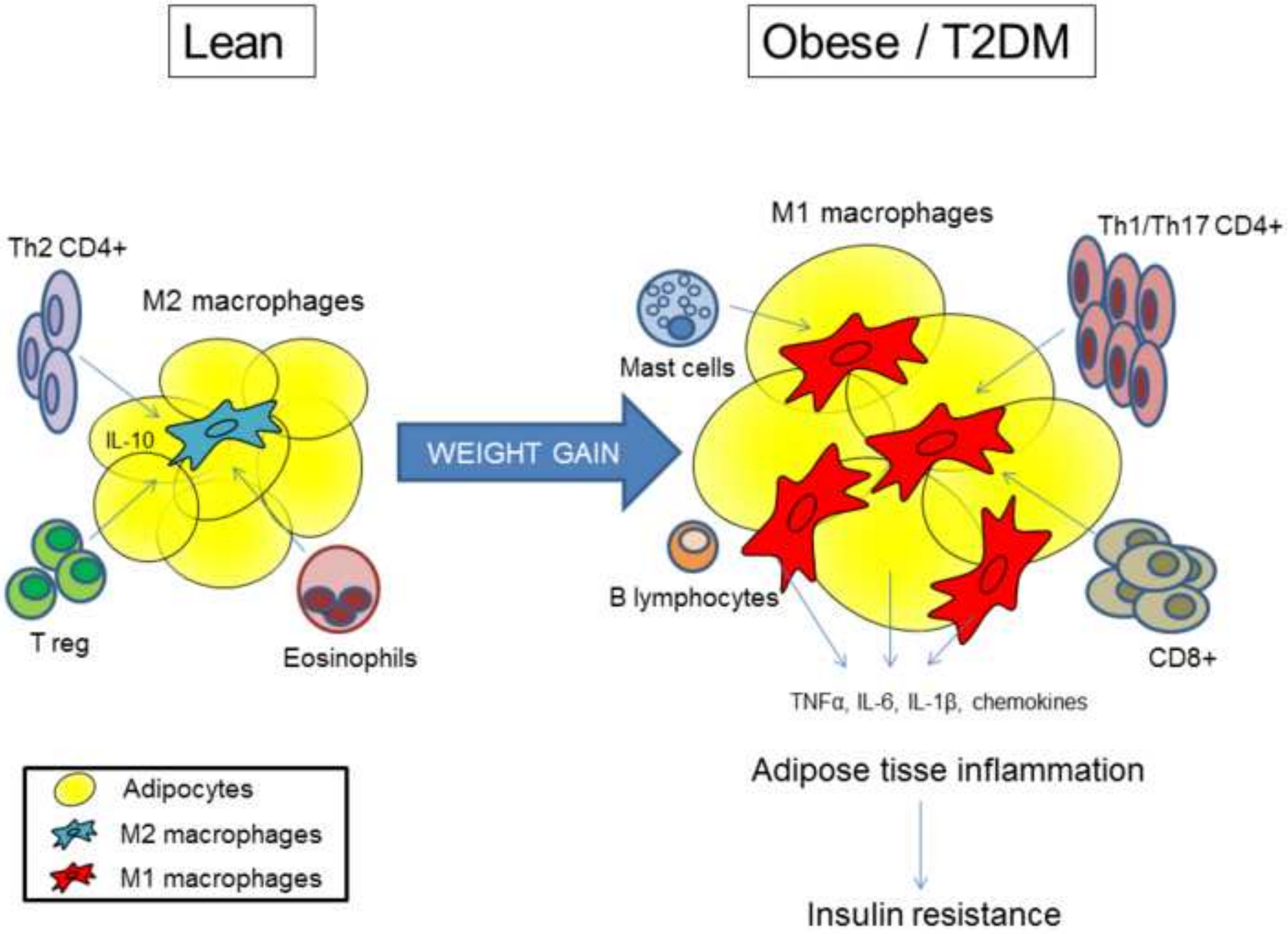

Lean
Obese / T2DM
Th2 CD4+
M2 macrophages
IL-10
T reg
Eosinophils
WEIGHT GAIN
M1 macrophages
Th1/Th17 CD4+
Mast cells
B lymphocytes
CD8+
TNFα, IL-6, IL-1β, chemokines
Adipose tisse inflammation
Insulin resistance
Adipocytes
M2 macrophages
M1 macrophages

Figure 2

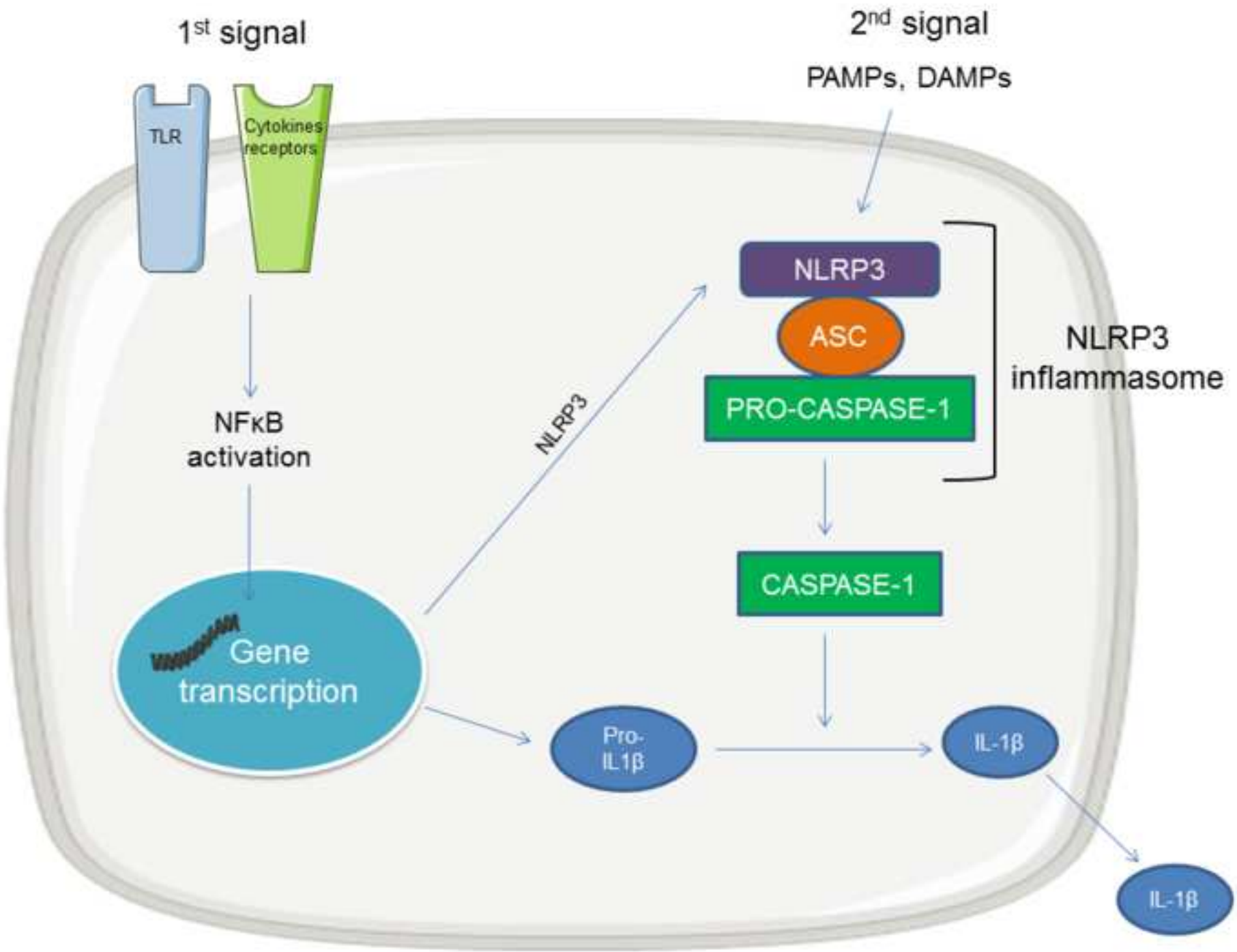
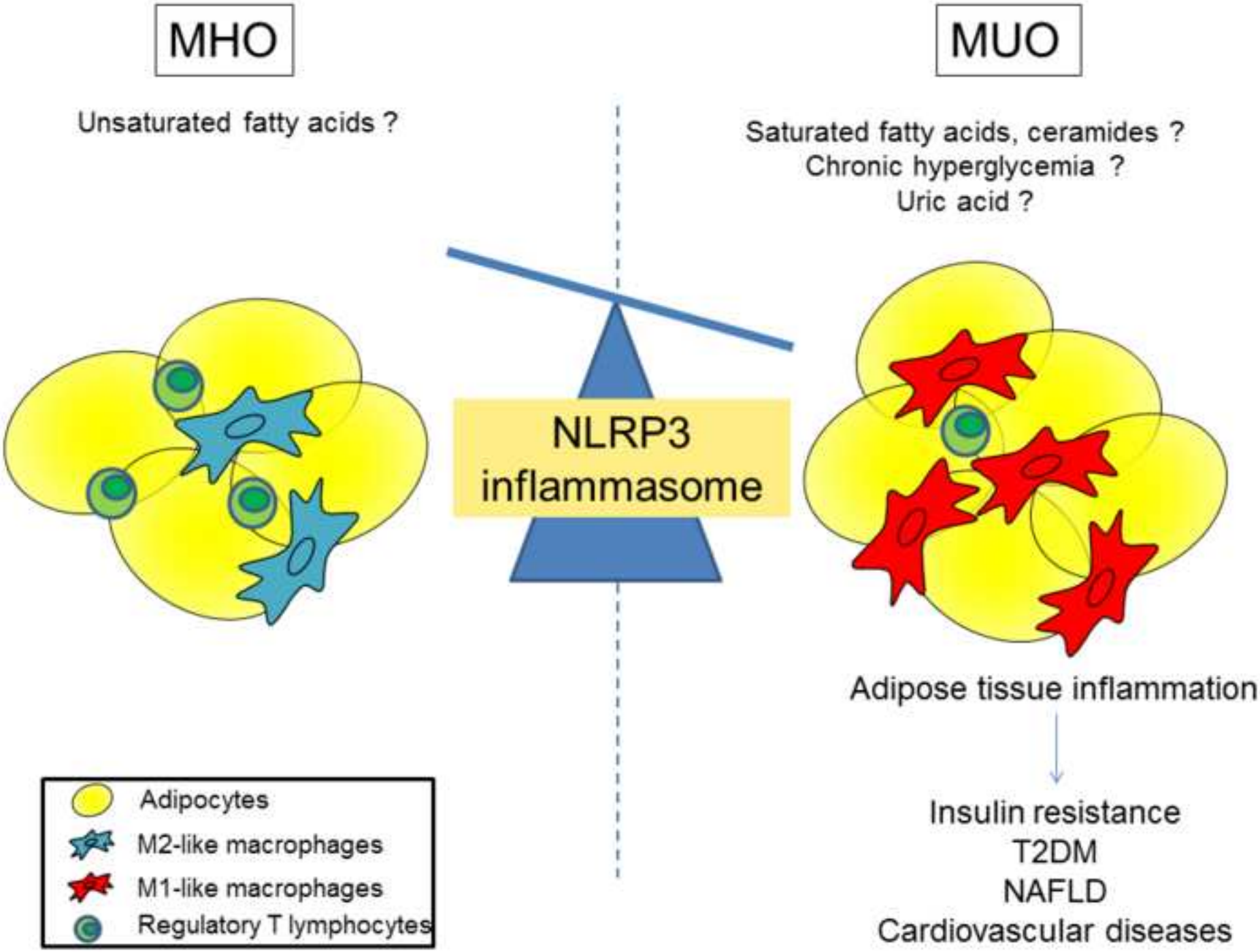

1st signal
2nd signal
PAMPs, DAMPs
TLR
Cytokines receptors
NLRP3
ASC
PRO-CASPASE-1
NLRP3 inflammasome
NFκB activation
NLRP3
CASPASE-1
Gene transcription
Pro-IL1β
IL-1β
IL-1β

Figure 3


MHO
MUO
Unsaturated fatty acids ?
Saturated fatty acids, ceramides ?
Chronic hyperglycemia ?
Uric acid ?
NLRP3
inflammasome
Adipose tissue inflammation
Insulin resistance
T2DM
NAFLD
Cardiovascular diseases
Adipocytes
M2-like macrophages
M1-like macrophages
Regulatory T lymphocytes