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New pathways to control inflammatory responses in adipose tissue

Rand T. Akasheh¹, Jingbo Pang¹, Jason M. York¹, and Giamila Fantuzzi

Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, IL, 60612

Abstract

Obesity is characterized by the presence of chronic inflammation in adipose tissue, particularly in the visceral compartment, that has been causally linked to development of obesity-associated co-morbidities. This link can be either direct or indirect, through induction of insulin resistance. This review summarizes recent evidence on potential pharmacological targets of adipose tissue inflammation, with emphasis on mediators that are being studied for intervention in chronic inflammatory diseases and are therefore viable therapeutic candidates. Specifically, we discuss evidence on the role of the inflammasome and its downstream products as a potential target for anti-inflammatory strategies as well as T regulatory cells and mediators involved in the resolution phase of inflammation, such as resolvins, protectins, annexin A1 and galectins as potential targets for novel agonist therapies.

Introduction

Obesity affects a considerable proportion of the world population, with rates increasing at a rapid pace in children and adults in both the developed and developing world [1]. Increased adiposity, particularly when adipose tissue is located in the visceral compartment, increases morbidity and mortality rates through elevated risk of development of several chronic conditions, such as type 2 diabetes, cardiovascular disease, osteoarthritis, dementia and cancer, while also exacerbating severity of various acute diseases [2]. A common thread to explain the contribution of obesity to development of these disparate co-morbidities is the presence of chronic, low grade inflammation that has been implicated as a causal factor in several obesity-associated pathologies. The inflammation of obesity likely directly increases risk of type 2 diabetes by contributing to development of insulin resistance which, in turn, secondarily influences susceptibility and severity of other conditions [3]. Thus, an important key to understanding the pathophysiology of obesity-associated co-morbidities is to identify mechanisms leading to development of insulin resistance, with inflammation being one of the most likely intermediaries.

In this review we summarize recent evidence on potential targets for modulation of the inflammatory response in obesity, with emphasis on those pathways involved in development of dysregulated glucose homeostasis. Rather than aiming at providing comprehensive coverage of each mediator participating in obesity-associated inflammation,

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Corresponding author: Giamila Fantuzzi, PhD, Department of Kinesiology and Nutrition, University of Illinois at Chicago, 1919 W Taylor Street MC517, Chicago, IL 60612, Phone: 312-413-5398, giamila@uic.edu.

¹These authors equally contributed to this manuscript.

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we discuss a selected group of cells and molecules that are being targeted for pharmacological intervention for treatment of chronic inflammatory conditions and could therefore represent viable targets in the context of metabolic disease. Without neglecting to address the role of pro-inflammatory mediators, we specifically focus on pathways that participate in the resolution phase of inflammation, when a complex network of cells and molecules actively apply a break to the inflammatory response [4]. Mediators in this category can be targeted by novel, agonist strategies that offer the likelihood of less severe side-effects compared to the standard anti-inflammatory approaches currently employed [4]. However, for agonist strategies to be effective, the responders – cells, receptors and the cellular transcription machinery -need to be present and responsive. An example of failed agonist strategy (outside the field of inflammation) has been the attempt to use exogenous leptin for weight loss before fully developing and acknowledging the concept of leptin resistance in obesity [5]. Thus, the basic biology of the anti-inflammatory and pro-resolution networks in obesity needs to be carefully studied and understood in order to design rational pharmacological interventions. Figure 1 illustrates potential targets for agonist and antagonist intervention to reduce inflammation in obesity.

Leukocyte subpopulations

The expanded adipose tissue of obese individuals, particularly the intra-visceral compartment, is infiltrated by several types of leukocytes, most prominently macrophages and subpopulations of T lymphocytes with pro-inflammatory activity [6]. Our understanding of the exact kinetics of infiltration and characterization of specific subpopulations of leukocytes in adipose tissue is rapidly evolving. However, the concept that adipocyte hypertrophy leads to changes in the populations of leukocytes present in adipose tissue, with a switch towards pro-inflammatory leukocytes and a reduction in anti-inflammatory ones, is well established [6].

T regulatory lymphocytes

T regulatory (Treg) cells are a population of lymphocytes with potent immunosuppressive and anti-inflammatory activities [7]. Stimulation of endogenous production or transfer of these cells is being investigated as a potential tool in a variety of conditions characterized by autoimmunity and/or chronic inflammation, as well as to induce tolerance in recipients of organ and tissue transplants [7].

Adipose tissue of lean individuals is enriched with Treg, with a significant decline observed in obesity in both mice and humans [8,9]. However, data demonstrating reduced Treg numbers and activity in obese adipose tissue need to be reconciled with observations indicating increased presence of Treg in peripheral blood of morbidly obese individuals [10], perhaps indicating defective recruitment of Treg to adipose tissue rather than ineffective generation of these cells in immune organs. The transcription factor peroxisome proliferator-activated receptor γ is a critical mediator of adipose tissue-associated Treg, with these cells presenting unique activities, such as lipid handling, compared to Treg present in other tissues [11]. The potential therapeutic effect of modulating Treg to affect obesity-associated pathologies is underscored by observations indicating that adoptive transfer of Treg improves insulin sensitivity and kidney damage in mouse models of type 2 diabetes [12].

Pattern-recognition receptors

Several families of pattern-recognition receptors (PRR), with Toll-like receptors (TLRs) being the best characterized, are involved in binding and responding to pathogen- and danger-associated molecular patterns, leading to activation of innate immune and

inflammatory responses [13]. The observation that mice deficient in TLR4, the receptor for lipopolysaccharide, are protected from the deleterious effects of high-fat diets provided the initial link between PRR and metabolic disease [14]. Understanding of this connection has been further refined with involvement of other members of the TLR family in obesity and insulin resistance, with data indicating that saturated fatty acids activate TLRs as well as with observations that are beginning to clarify the complex cross-talk between the gut microbiota and TLRs in modulating adiposity and insulin resistance [15,16].

The inflammasome

Inflammasomes are multimolecular intracellular PRR involved in activation of the pro-inflammatory cytokines interleukin (IL)-1 β and IL-18 [17]. There are several different types of inflammasomes; activation of a particular type is dependent on the specific agonist involved [17]. Regardless of the initiating stimulus, the end result of inflammasome assembly and activation is the maturation of pro-IL-1 β and pro-IL-18 into their active forms *via* the enzyme caspase-1 [17]. Both animal and human studies implicate the inflammasome in development of obesity itself, as well as its associated chronic inflammatory state [18–21]. Genetic deletion or pharmacological inhibition of the NLRP3 inflammasome results in reduced weight gain and adipocyte size, protection from obesity-induced insulin resistance and pancreatic damage, lower hepatic triglyceride levels as well as reduced macrophage infiltration and overall adipose tissue inflammation in murine models of diet-induced obesity (DIO) [18–22]. In obese individuals with type 2 diabetes, weight loss leads to reduced activation of the inflammasome in adipose tissue [20]. One of the pathways leading to activation of the inflammasome in obesity is elevation of fatty acids and ceramides, although additional mechanisms are probably involved [20]. Due to the involvement of inappropriate activation of the inflammasome in the pathogenesis of several chronic inflammatory diseases, pharmacological inhibition of this pathway and its downstream effectors IL-1 β and IL-18 is actively being pursued and may thus represent a potential strategy for controlling inflammation in obesity by antagonistic approaches [23].

Pro-resolution mediators

The resolution phase of inflammation is a tightly controlled, active process involving a complex network of mediators that are only recently beginning to be clearly identified and studied [24]. Defective engagement of pro-resolving mechanisms represents a potential mechanism leading to chronicization of inflammation in obese adipose tissue.

Resolvins and protectins

Resolvins and protectins are omega-3 fatty acid-derived lipid mediators that actively stimulate resolution of inflammation [25]. Reduced amounts of selected members of the resolvins and protectins family are observed in obese compared to lean adipose tissue [26,27], with data suggesting increased elimination of these mediators through upregulation of specific metabolizing enzymes as the most likely mechanism for the reduced levels observed in obesity [26]. Administration of resolvins and protectins mimics the insulin-sensitizing and antisteatotic effects of omega-3 fatty acids in mice, while reducing macrophage infiltration in adipose tissue of obese and diabetic mice [28,29]. Importantly, treatment with exogenous resolvins and protectins increases production of adiponectin, an adipokine with beneficial effects on glucose and fat metabolism [27].

Annexin A1

Annexin A1 (ANXA1), a member of the annexins superfamily of calcium- and phospholipid-binding proteins that participates in the resolution of inflammation, is widely expressed in tissues and present in soluble form in biological fluids and plasma [30].

Expression and production of ANXA1 are regulated by glucocorticoids in a complex manner in cells of the innate and acquired immune response, with ANXA1 being an important mediator of the anti-inflammatory effects of these steroid hormones [31]. In fact, ANXA1 KO mice develop a more severe phenotype and resistance to glucocorticoid treatment as compared to WT controls in models of acute and chronic inflammatory diseases [32,33]. In models of DIO, ANXA1 KO mice exhibit increased adiposity, associated with blunted lipolysis, elevated hepatic lipogenesis and insulin resistance (Manuscript in preparation). In humans, plasma ANXA1 levels are inversely correlated with markers of adiposity, suggesting loss of this potentially protective factor with increased obesity [34]. However, analysis of the transcriptome in human white adipose tissue reveals increased ANXA1 expression in obese subjects [35]. The latter findings parallel data from our laboratory demonstrating increased ANXA1 expression in adipose tissue of DIO mice compared with lean animals (Manuscript in preparation). A possible explanation for these apparently contradictory findings is that ANXA1 may be sequestered inside the expanded, poorly vascularized adipose tissue of obesity, which may limit its access to the systemic circulation. Whether obesity is associated with increased or decreased activity of ANXA1 in adipose tissue remains to be established.

Because of its important role in the resolution of inflammation, ANXA1 is being actively investigated as a target for agonist strategies to control inflammation. However, the complex biology of ANXA1 makes it a difficult protein to study. For example, ANXA1 is highly regulated at the post-transcriptional and conformational level [36], and gives rise to short peptides when cleaved. While some of these peptides share some of ANXA1's anti-inflammatory effects, others exhibit proinflammatory actions [37]. Thus, a more complete understanding of the role and regulation of ANXA1 is necessary before considering this protein as a pharmacological target in obesity-related inflammation.

Galectins

Galectins are a family of proteins characterized by conserved carbohydrate-recognition domains which bind β -galactosides [38]. The diverse members of the galectin family participate not only in the resolution of inflammation, but are also involved in host-pathogen interactions, angiogenesis, tumor development and progression, cell migration, wound healing and more [38]. Production of several members of the galectin family, including galectin-1, -3, -9 and -12, is altered in obesity and diabetes in both animals and humans [39–41]. A functional role for members of the galectin family in modulating obesity and its associated inflammation and metabolic dysregulation has been demonstrated using KO mouse models. Specifically, deletion of galectin-1 in mice leads to increased adiposity without alterations in glucose metabolism [40]. A more dramatic phenotype is observed in galectin-3 KO mice, that develop increased adiposity and marked glucose intolerance, coupled with altered inflammatory responses and upregulation of the receptor for advanced glycation end products in the DIO model [42,43]. Data indicate that galectin-3 KO mice develop more severe pathology in a variety of models of metabolic disease, including atherosclerosis and kidney damage, suggesting an important protective effect of galectin-3 in response to nutrient overload and dysregulated metabolism [44,45]. In contrast to the protective effect of galectin-3 against obesity and associated morbidities, deletion of galectin-12, which is exclusively produced by adipocytes and whose expression is inhibited by tumor necrosis factor α and other insulin-resistance-inducing mediators [46], results in reduced adiposity and improved insulin resistance in DIO mice [47]. As can be surmised by the above discussion, given the extreme diversity of activities exerted by galectins, the potential impact of modulating this family of mediators in obesity and its co-morbidities needs to be carefully assessed using specific pharmacological tools.

Conclusion

Despite strong experimental evidence indicating a causative role of adipose tissue inflammation in obesity-associated co-morbidities, particularly in insulin resistance, standard anti-inflammatory interventions to reduce metabolic disease in humans have not been particularly effective [6]. Although part of this discrepancy may be due to the inadequacy of experimental models of obesity and metabolic disease that limit translatability of rodent studies, the relatively limited armamentarium of anti-inflammatory compounds available for human use may also have contributed to the less-than-stellar effects of clinical trials that have used anti-inflammatory strategies [6]. Identification of new potential targets, particularly those that entail modulation of novel pathways and mediators, may open fresh strategies for intervention.

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Highlights

- The inflammasome is involved in chronic inflammation in obese adipose tissue
- There are reduced numbers of T regulatory cells in adipose tissue in obesity
- Protectins and resolvins ameliorate inflammation in obese adipose tissue
- Circulating levels of annexin A1 are reduced in obese individuals
- Galectins are differentially involved in adipose tissue inflammation in obesity

Figure 1. Agonist and antagonist strategies to inhibit adipose tissue inflammation in obesity
 Agonist strategies aim at targets that actively induce resolution of inflammation or exert anti-inflammatory effects. Targets of agonist strategies discussed in the article include induction of endogenous or transfer of exogenous T regulatory cells, as well as administration of molecules mimicking the activity of resolvins, protectins, Annexin A1 or selected members of the galectin family. For these strategies to be effective, the necessary targets of these molecules (cells, receptors and transcriptional machinery) need to be present and responsive in adipose tissue of obese individuals. In contrast to the agonist strategy, antagonism of pro-inflammatory pathways can be directed against the inflammasome and/or its downstream products. Additional potential targets not discussed in this article are listed under both strategies.