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Inflammation and insulin resistance: New targets encourage new thinking:

Galectin-3 and LTB_4 are pro-inflammatory molecules that can be targeted to restore insulin sensitivity.

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Summary

Galectin-3 and LTB_4 are pro-inflammatory molecules recently shown to directly cause insulin resistance in mouse and human cells. They are highly expressed in the obese state, and can be targeted both genetically and pharmacologically to improve insulin sensitivity in vivo. This expands on previous research showing that targeting inflammatory cytokines can be insulin sensitizing in animal models. However, translating these potential therapies into the human setting remains challenging. Here we review this latest research, and discuss how balancing their pleiotropic functions, the action of the microbiome, and the ability to identify relevant patient populations are vital considerations for successful anti-inflammatory insulin sensitizing therapy.

Keywords

galectin-3; inflammation; insulin resistance; leukotriene; macrophage; microbiome; obesity

Introduction

Obesity-associated insulin resistance is a characteristic precursor of type 2 diabetes mellitus, a disease that has now reached epidemic proportions [1, 2]. Since 1980 the number of people living with diabetes has risen from 108 million to 422 million, and at this rate of growth, global healthcare costs are expected to exceed $750 billion USD by 2040 [2]. Type 2 diabetes forms the vast majority of diabetes cases (up to 91%) [2], and so there is significant interest in identifying the causes of this condition and designing therapeutic strategies to treat the disease.

Over the past several decades, considerable research has been conducted showing that a wide range of pathways can lead to insulin resistance. These include toxicity of ectopic lipid, chronic inflammation, hormonal resistance [3] and, most recently, changes in bacteria resident in the gastrointestinal tract [4]. However, whether all of these are present in all

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patients and whether any pathways are dominant remains to be established. Indeed, even within a term such as “chronic inflammation” there is considerable diversity, with a large number of different cell types and an increasing number of inflammatory molecules shown to play causative roles in insulin-resistant animal models [5]. Many of these, such as Galectin-3 whose role in mouse and human insulin resistance we recently described [6], represent exciting potential therapeutic targets. However, despite promising pre-clinical work, clinical trials targeting single inflammatory molecules, such as TNF-α, to treat insulin resistance have thus far been disappointing [5, 7, 8]. This suggests that there remain significant gaps in our knowledge and approach that must be filled before utilizing anti-inflammatory therapies effectively. In this perspective we discuss the recent advances in inflammation-mediated insulin resistance, and highlight the importance of understanding patient heterogeneity, the contribution of the intestinal microbiome, and the pleiotropic nature of these inflammatory molecules in achieving clinical success. Our objective is not to provide an exhaustive review of the literature here, as many excellent versions of these have been recently published [9], but to raise questions and hypotheses that will help the scientific and medical community design strategies to succeed in the future.

Inflammation is a cause of insulin resistance: Evidence from obese mice and humans

The identification of a chronic inflammatory state caused by obesity was initially characterized based on increased concentrations of the molecule TNF-α in adipose tissue from obese mice and humans [10]. Subsequent to this, activation and recruitment of inflammatory macrophages was observed in obese adipose tissue [11, 12], and in the past decades a plethora of other immune cell types were shown to expand numerically and be activated in the obese state (outlined in Table 1) [5]. Indeed, observations have been extended beyond the adipose tissue to show immune activation in the liver [13], muscle [14], pancreas [15], and even central nervous system [14], and, based predominantly on genetic- or chemical-depletion, several of these immune cell types have been shown to make causative contributions to insulin resistance in animal models (see Table 1). Conversely, there are immune cell types that dominant numerically in these tissues of lean mice and humans, and indirectly offer protection against insulin resistance, by promoting an anti-inflammatory state (see Table 2). Mechanistically, many pro-inflammatory cytokines have been implicated in inducing insulin resistance, including TNF-α, IL-1β, IL-6, IFN-γ, GM-CSF, and IL-17 [10, 16–21]. Importantly, prospective studies in humans have also associated the plasma concentration of many of these cytokines with progression of obese individuals to a type 2 diabetic state [22]. Conversely, animal models have implicated type II immunity, including IL-4 and IL-5, with preserving a lean, insulin-sensitive tissue environment [23–25].

Galectin-3 and LTB_4: New targets for anti-inflammatory therapy in insulin resistance

An analysis of gene expression in $CD11c^+$ macrophages isolated from obese adipose tissue highlighted the breadth of inflammatory pathways activated in the obese state, suggesting

that novel targets may exist beyond the classical pro-inflammatory cytokines already discovered [26]. In particular, Galectin-3 expression is elevated in $CD11c^+$ macrophages isolated from the adipose tissue of insulin-resistant obese mice, but not after these mice had been switched to a normal chow diet and become insulin sensitive [6]. Galectin-3 could also be found at high levels in circulating plasma of obese mice and humans compared to lean counterparts, correlating with insulin resistance and body mass index (BMI) [6]. Although many cell types can produce Galectin-3 we were able to show, using chemical depletion and bone marrow chimeras, that non-hematopoietic cells and most likely macrophages were the dominant source of the increase in circulating Galectin-3 found during obesity [6]. Importantly, exposing adipocytes, hepatocytes or muscle cells to Galectin-3 in vitro was sufficient to cause insulin resistance and Galectin-3 administration in vivo caused mice to become glucose intolerant and insulin resistant [6]. Furthermore, Galectin-3-knockout or Galectin-3-heterozygote mice, which have reduced circulating Galectin-3 levels, remained more insulin sensitive than their wild-type littermates when exposed to a high fat diet or aging [6]. These data demonstrate that Galectin-3 is a pro-inflammatory molecule upregulated in obesity and capable of causing insulin resistance.

It should be noted that varying results exist regarding the metabolic phenotype of Galectin-3-knockout mice, most likely due to Galectin-3's pleiotropic nature across a number of metabolically relevant systems described below, which may contribute more or less to the overall phenotype given the specific environmental, genetic and technical conditions. Using multiple methods, we found Galectin-3 to be causative for insulin resistance, without impacting body weight. Specifically, Galectin-3-deficient mice, and wild-type mice administered with a Galectin-3 inhibitor, were insulin sensitive, whereas administration of recombinant Galectin-3 made mice insulin resistant, and in vitro treatment of hepatocytes, adipocytes or myocytes with galectin-3 resulted in insulin resistance [6]. This is broadly similar to data reported by Baek et al., who found Galectin-3-deficient mice to be insulin sensitive, although in their study this was also accompanied by reduced body weight [27]. In contrast, Pang et al. found that a different strain of Galectin-3-deficient mice had increased body weight, fasting hyperglycemia and glucose intolerance compared to non-littermate control mice, but with no difference in insulin sensitivity [28]. Greater weight gains in Galectin-3-deficient mice compared to controls were also reported by Pejnovic et al. [29]. Finally, Darrow and Shohet reported hyperglycemia in Galectin-3-deficient mice with reduced plasma insulin levels, indicative of β-cell dysfunction, but no change in insulin sensitivity [30]. Varying data also exists in humans, where a study of 20 type 2 diabetics in Japan with a BMI of 28 ±3 found Galectin-3 to be associated with reduced plasma insulin levels and insulin sensitivity, but not BMI [31], in contrast to our findings in lean and obese Americans whose BMI ranged from 20–50, and included both diabetics and non-diabetics. These results suggest that targeting Galectin-3 in humans may have most relevance in defined patient populations at certain stages of diabetes etiology e.g. in the obese pre-diabetic stage. Furthermore, data has indicated that that Galectin-3 can facilitate the clearance of advanced glycation end-products (AGE) from the blood [32], restrain macrophage inflammatory responses to microbial ligands [33], and maintain intestinal immune tolerance [34], all of which could impact the metabolic state. The challenges

presented by the pleiotropic nature of inflammatory molecules and the appropriate selection of patient populations are discussed further below.

Another novel molecule recently highlighted as playing a key role in inflammation-induced insulin resistance is the leukotriene B_4, (LTB_4) [35, 36]. Macrophage infiltration to insulin-sensitive tissues is a critical feature of obesity and conditioned media obtained by culturing adipocytes from obese mice ex vivo is sufficient to induce macrophage migration. The CCR-2-MCP-1 axis has been implicated in driving this process. However, monocyte CCR2-deficiency or whole body MCP-1-deficiency only reduces macrophage accumulation in adipose tissue by approximately 40%, suggesting that additional chemoattractive signals play a role [37]. Neutralization of LTB_4 within adipocyte-conditioned media is sufficient to block macrophage migration almost entirely indicating that LTB_4 is a significant chemoattractant in this context [36]. LTB_4 signals through the receptor BLT-1, and either pharmacological-inhibition or genetic-deletion of BLT-1 was sufficient to reduce monocyte-infiltration and adipose tissue inflammation in obese mice [36]. Interestingly, exposure of hepatocytes or myocytes to LTB_4 in vitro was also sufficient to induce insulin-resistance, indicating the LTB_4 is capable of directly inducing insulin resistance in these cell types, independent of its effect on macrophage migration [36].

These studies are two examples of inflammatory mediators that represent novel targets to treat insulin resistance. However, they should be considered as part of a much wider milieu of different positive and negative inflammatory mediators active in the obese state, including the cytokines cited above, and extending towards lipids, microbial ligands, bile acid derivatives, and nuclear hormone receptor ligands, whose roles continue to be described. LTB_4, for example, is one member of a large family of lipid mediators, which have well-established positive or negative impacts on inflammation, but whose role in insulin resistance remains relatively understudied. Indeed, genetic- or pharmacological-inhibition of 5-lipoxygenase, the enzyme responsible for the production of many of this family, has a beneficial impact on insulin sensitivity [38], and administration of Lipoxin A_4 to diet-induced obese mice can reduce adipose tissue inflammation [39].

Many molecular mechanisms can lead to insulin resistance

Inflammatory mediators cause insulin resistance by a variety of molecular mechanisms, reinforcing the diversity apparent in this system, and again LTB_4 and Galectin-3 illustrate this. TNF-α and other inflammatory mediators activate serine/threonine kinases, such as JNK or IKKβ, which phosphorylate and inhibit components of the insulin signaling pathway, including the Insulin Receptor (IR), Insulin Receptor Substrate 1 (IRS1), and Protein Kinase B (AKT). In addition, inflammation also activates a program of gene expression, such as is controlled by the transcription factor NF-κB, resulting in the upregulation of suppressor proteins such as SOCS3, which can bind to the IR blocking IRS recruitment [40]. NF-κB also represses transcription of components of insulin signaling including IRS1, AKT, and GLUT4, an important transporter required for glucose uptake [41, 42]. LTB_4 acts in part in this same fashion, however in addition LTB_4 also stimulates hepatic lipogenic gene expression, and ceramide and diacylglycerol accumulation, which are also known to induce insulin resistance [36]. A similar impact on ceramide synthesis was

observed in response to free fatty acid infusion, suggesting an intersection of these inflammatory pathways with lipotoxicity [43]. Galectin-3 inhibits insulin signaling by a further novel mechanism namely binding directly to the insulin-receptor itself [6]. Thus, inflammatory mediators coming from many different sources can induce insulin resistance by diverse mechanisms.

Moving forward: Considerations for translation

The clear evidence that inflammatory pathways are elevated in obesity and can induce an insulin-resistant state makes them attractive therapeutic targets. However, there are challenges that must be considered and overcome in order to make this a success. Here we discuss three in particular: i) Beyond TNF-α: Are there advantages to targeting these new molecules? ii) Patient heterogeneity: How can we identify patient populations most-likely to benefit from a given therapy? iii) Pleiotropic effects: How can we balance the actions of inflammatory mediators across different tissues in the body? Can we tailor therapies to maximize the net benefit from all these actions for human metabolism? Others challenges such as a requirement for greater analysis of large human population cohorts and a perceived over reliance on murine studies have been previously discussed and we refer the reader to these [44].

Beyond TNF-α: Are there advantages to considering these new targets?

Of the candidate cytokines implicated in insulin resistance, therapies targeting TNF-α and IL-1β have progressed to clinical trials. Targeting IL-1β, while showing promising efficacy against type 2 diabetes overall, has shown a primary effect on preserving beta cell function, not restoring insulin sensitivity [45–47]. Targeting of TNF-α alone in obese individuals yielded little effect on insulin sensitivity in shorter-term protocols [7, 8], although recent analysis of insulin sensitivity in rheumatoid arthritis patients under-going more chronic anti-TNF-α therapy suggested improvement in six out of eight studies [48]. It is notable that rheumatoid arthritis patients have a much higher plasma concentration of TNF-α than obese individuals and this may be one reason why targeting TNF-α is more effective in these groups. Furthermore, the concentration of TNF-α used to bring about insulin resistance in vivo (e.g. > 600 pg/ml in rats [49], > 15 pg/ml in humans [50]) and in vitro (e.g. 1,000–2,000 pg/ml in cultured adipocytes [51]) is generally much higher than that found in the circulation of obese people (undetectable to 7 pg/ml [52–54]), although recent data suggests concentrations in obese type 2 diabetics can be higher (100 pg/ml [53]). This is in contrast to Galectin-3, which can induce insulin resistance directly in all three insulin-target cells at physiological concentrations, giving reason to believe targeting these may offer greater therapeutic benefit [6]. Furthermore, it is notable that small molecule inhibitors already exist to target both LTB_4 and Galectin-3 and both have been used to restore insulin sensitivity in vivo [36, 6] and this may offer pharmacokinetic benefits over antibody-mediated TNF-α targeting.

Given the range of inflammatory mediators now shown to be capable of inducing insulin resistance and the range of mechanisms by which they act, there is also the possibility that there is some redundancy in the system. Indeed, a recent study in mice has showed that

IL-1β causes insulin resistance partly in a TNF-α-independent fashion suggesting that there may be benefit to targeting both these cytokines [55]. If this is the case, combination therapies or therapies that act more broadly to suppress inflammation may offer greater benefit. For example, Salsalate is broadly thought to inhibit NF-KB and showed efficacy in a recent trial [56]. Broader characterization of inflammation in obese individuals both before and after candidate anti-inflammatory treatment would be useful for the interpretation of results and optimizing potential combination strategies, especially in the event that insulin resistance remains after treatment.

Patient heterogeneity: How do we identify those most likely to benefit?

The immune response is not a fixed entity in all people, but is adaptable to the precise set of stimuli to which we are exposed, and the context in which these stimuli are received. This "context" encompasses individual genetics, diets, lifestyles and even life-history of each patient in ways that are still incompletely understood. This has clear advantages when it comes to tailoring our response to resist infection, however it presents clear challenges when it comes to the population-wide targeting of inflammation to treat diseases where the context can be heterogeneous. For example, we know that individuals become obese and insulin resistant in a variety of different ways, and their individual lifestyle is a significant factor. Therefore, the precise set of stimuli driving inflammation in each patient and the precise nature of their response could well be very different. It is therefore critical that we are able to understand these sources of variation, and to identify patients that will respond to a given therapy.

A good place to begin the search for such biomarkers may be the inflammatory pathways themselves. Plasma concentrations of Galectin-3 increase in mice as they age, and so, genetic depletion of Galectin-3 has little effect on insulin sensitivity in lean young mice, but significantly enhances insulin sensitivity in older mice [6]. Furthermore, Galectin-3 levels are higher in obese individuals and correlate with BMI and the measure of insulin resistance, HOMA-IR [6]. Therefore, Galectin-3 itself may act as a biomarker to identify patients who may best respond to anti-Galectin-3 therapy. As others have previously suggested, large human cohorts in which multiple inflammatory parameters are assessed are required in order to better characterize the nature of systemic inflammation in obese individuals, how it varies, and to inform clinical trial design and interpretation [44].

One major source of variation in biology, which has recently come to the fore and is especially relevant in the obese/insulin resistant context, is the intestinal microbiome [57]. The microbiome is composed of 100 trillion microorganisms, contains 100 times more genetic material than our own genome and is, to a large extent, unique to each individual [58]. Control of our microbial community is achieved by the intestinal epithelium and immune system, as well as ecological dynamics responsive to factors, such as the diet, and this overall balance is critical for our health [57]. Indeed, the microbiome has a profound impact on the development of the immune system and inflammatory disease [59]. Evidence suggests that obesity and a high fat diet put the homeostatic balance controlling the microbiome under a particular strain, resulting in changes in species composition [60], intestinal immune cell depletion [61–63], and even penetration of bacteria or bacterial

products into the circulation [64, 65]. In preliminary human studies, the concentration of LPS or bacterial DNA (16s rDNA) in the blood has been associated with progression to a type 2 diabetic state [64]. However, the concentration of 16s rDNA in individuals progressing to diabetes is variable (mean = 0.15 ± 0.25 ng/μl, median = 0.076 ng/μl) with some individuals progressing with a low or undetectable level of 16s rDNA in the blood [64]. Whether or not an individual has systemic bacterial penetration is an important question to answer when considering anti-inflammatory therapy for insulin resistance for two main reasons. Firstly, bacteria and their products are critical immune stimuli and so the nature of systemic inflammation may well be altered by their presence or absence in the circulation, thus causing heterogeneity within the patient population. Secondly, if an individual is susceptible to infection from the microbiota, then administering an anti-inflammatory therapy at all carries a risk of exacerbation, and indeed forms of intestinal immune-suppression resulting from a high fat diet [61–63] or genetic-manipulation [66] have been associated with intestinal permeability and exacerbation of glucose intolerance in mice. It may be that in these cases a form of probiotic or antibiotic therapy will be necessary to correct the state of dysbiosis in the intestine and restore barrier function, prior to, or concurrent with, treating the systemic inflammatory state. Further work to understand what enables microbial factors to penetrate beyond the intestine in some individuals, the prevalence of this in the population, and the role that specific immune mediators play in controlling this, will provide vital knowledge required to bring anti-inflammatory therapies for insulin resistance to the clinic.

Pleiotropic effects: How can we balance these for net benefit?

Related to the concept of patient heterogeneity is evidence that the efficacy of targeting a given inflammatory mediator on insulin sensitivity can vary across studies. As mentioned above, Galectin-3 is a good example of this, with physiological effects across many metabolically relevant systems and contrasting data regarding its role in obesity and insulin resistance in the literature. However, it is far from the only pro-inflammatory target for insulin resistance that has pleiotropic effects or for which varying efficacies have been noted. We hypothesize that the actions across systems ultimately compete and thus the net outcome depends on which system is most dominant in the conditions tested. This might be impacted by age, gender, microbiome, and diet, to name but a few factors. IL-6, for example, promotes adipose tissue inflammation and can induce insulin resistance, especially in hepatocytes, but also has catabolic effects by promoting energy expenditure, so that mice in which IL-6 is targeted actually develop obesity and associated insulin resistance with age [18]. Any effort to target IL-6 to treat insulin resistance, would need to balance or discriminate between these different factors. One recent study by Kraakman et al., attempted to do this by targeting specifically IL-6 *trans*-signaling, whereby IL-6 is bound by soluble IL-6R in circulation and is targeted to inflammatory cells expressing gp130 [67]. Targeting this aspect of IL-6-signalling, but leaving membrane-bound IL-6R signaling intact, resulted in resolution of adipose tissue inflammation without exacerbation of obesity and insulin resistance [67]. However, although the negative consequences of targeting IL-6 signaling were prevented, this method was not sufficient to improve insulin sensitivity overall [67].

Conclusions and outlook

In summary, obesity-associated inflammation is a diverse process, and the targeting of inflammatory molecules, such as Galectin-3 and LTB_4, to restore insulin sensitivity in patients holds promise. However, to fulfill such potential we must address gaps in our knowledge regarding the function of these molecules across different metabolically-relevant tissues and determine how this balance is altered by patient heterogeneity, especially with regard to the action of the gastrointestinal tract and the microbiome. Lastly, we will require the technical skill to modify the balance ourselves for optimal therapeutic benefit, such as by combination therapies, or by dietary or probiotic intervention. This challenge is scientifically broad and therefore will require collaboration across the fields of metabolism, immunology, microbiology, and the involvement of medical and pharmaceutical professionals to achieve the ultimate goal of clinical success.

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Abbreviation

BMI body mass index

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Table 1

Summary of immune cell types implicated in causing insulin resistance

Cell type	Model system	Reference
M1 Macrophages	Clodronate liposome- or diphtheria toxin-mediated inflammatory macrophage depletion restores insulin sensitivity.	[68] [69]
$CD8^+$ T cells	Adoptive transfer of $CD8^+$ T cells worsens insulin resistance Genetic-ablation of $CD8^+$ T cells protects from insulin resistance	[70]
$CD4^+$ Th1 cells	T cell depletion with anti-CD3 antibody protects against insulin resistance.	[71]
$CD4^+$ Th17 cells	IL-17-deficeint mice are insulin sensitive Accumulation of Th17 cells in adipose tissue from obese humans	[72][73]
B cells	B cell-depletion protects against insulin resistance Transfer of IgG antibodies from obese to lean mice causes insulin resistance	[74]
Neutrophils	Neutrophil elastase-deficient mice are protected from insulin resistance	[75]

Table 2

Summary of immune cell types implicated in preserving insulin sensitivity

Cell type	Model system	Reference
$CD4^+$ Th2 cells	Adoptive transfer of predominantly Th2 cells protects against insulin resistance	[71]
$CD4^+$ Treg cells	Treg cell-depletion leads to adipose tissue inflammation And adoptive transfer of Treg cells improves glucose tolerance	[76]
Eosinophils	Eosinophil-deficient mice display insulin resistance	[24]
Group II Innate Lymphoid Cells (ILC2)	ILC2-deficient mice display insulin resistance	[23]
M2 macrophages	Macrophage-specific deletion of PPAR-γ or PPAR-β/δ results in M2 macrophage depletion from adipose tissue and insulin resistance.	[77] [25]