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Molecular Mechanisms of Obesity and Diabetes: At the Intersection of Weight Regulation, Inflammation, and Glucose Homeostasis

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Abstract Obesity is a major health crisis, and diabetes is one of its most serious sequelae. Obesity is associated with a state of chronic systemic inflammation that is a primary etiologic factor in the development of insulin resistance and diabetes. This inflammatory state is based in adipose tissue and mediated in large part by tissue macrophages and their cytokine and adipokine products. Recent research has identified specific molecular mediators of the link between inflammation and insulin resistance in obesity. Study of these mediators and the specific mechanisms underlying inflammation and insulin resistance in obesity holds the promise for novel pharmacotherapy for obesity-related metabolic disease.

Obesity and diabetes: looming epidemics, evolutionary underpinnings

Obesity and its related comorbidities exact an enormous toll on society. Over 30% of Americans are obese and this epidemic is increasing [1]. Insulin resistance is one of the most serious sequelae of obesity, and by 2030 it is estimated that over 30 million people in the United States will suffer from type 2 diabetes [2]. These twin epidemics threaten to bankrupt the public health system. Bariatric surgery represents an effective treatment for obesity and its comorbidities, including diabetes, for which it has been labeled a surgical cure. Nonetheless, bariatric surgery is associated with a finite morbidity and mortality, not all obese patients are candidates for surgery, and most importantly, it is simply not feasible to consider providing surgical therapy to what may comprise more than a third of the US population. Effective pharmacotherapy for obesity-related metabolic disease, especially diabetes, is necessary to avoid a serious impending public health crisis, a goal that requires an understanding of the molecular mechanisms underlying obesity-related disease.

What explains the close association between obesity and insulin resistance? The "thrifty gene" hypothesis posits that a propensity for peripheral insulin resistance and obesity may have coevolved as a protective response to the shift to a more carnivorous diet with more frequent periods of famine during the Ice Age which spanned the last 1–2 million years of primate evolution [3]. Under such conditions, peripheral insulin resistance protects organisms from acute hypoglycemia during periods of prolonged fasting, while a propensity to store energy as fat protects against starvation. This theory is supported by modern observations that document a higher prevalence of insulin resistance in societies that have only recently transitioned from a hunter-gatherer (i.e., Ice Age-similar) lifestyle to an agrarian lifestyle, such as Pima Indian and Australian Aboriginal cultures [4, 5]. Europeans, in contrast, who adopted an agrarian lifestyle thousands of years earlier, have a much lower prevalence of insulin resistance, suggesting a reduction in the selective pressure for insulin resistance in the most recent phase of human evolution with a shift back toward a more stable and less carnivorous food supply. While debated, and while alternative theories exist [6], the thrifty gene hypothesis nonetheless provides a plausible albeit likely incomplete explanation for the close relationship between obesity and insulin resistance in modern humans.

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The systemic inflammatory state in obesity

Obesity in both animals and humans is associated with a state of chronic systemic inflammation manifested by increased serum levels of inflammatory cytokines as well as alterations in peripheral blood lymphocyte frequencies and function [7–10]. Similar aberrations are present at the tissue level, including alterations in inflammatory transcript levels and lymphocyte distribution and function in adipose, liver, and other tissue beds [11, 12]. Most importantly, this inflammatory diathesis is the primary underlying cause of virtually all serious obesity-related comorbidities, including diabetes, atherosclerosis, steatohepatitis, asthma, and allergy [13–17]. Inflammation underlies the pathogenesis of these diseases in lean patients as well, albeit at lower frequencies, and therefore represents a root cause of a broad range of metabolic disease.

Obesity-related inflammation is often considered a disorder of the innate immune system. Monocytes, macrophages, and neutrophils are the classic cellular effectors of innate immunity. They rely on non-MHC-restricted pattern-recognition receptors and do not generate clonal responses or memory. Adaptive immunity, in contrast, is characterized by MHC-restricted antigen presentation resulting in clonal antigen-specific memory, with T cells and B cells acting as its primary effector cells. In reality, significant crosstalk exists between innate and adaptive immune systems, and indeed disorders of both innate and adaptive immunity have been implicated in obesity-related inflammation. For example, while macrophages, paradigmatic innate effector cells, are indeed central mediators of inflammation in obesity [12], T cells have also been implicated [18, 19]. Obesity-related inflammation therefore appears to involve aberrations in both innate and adaptive immune systems.

While generally thought of as an acute response to trauma or infection, inflammation is also a response to the ongoing processes of cell turnover associated with aging [20]. In this capacity, the inflammatory response regulates fundamental processes intrinsic to cellular homeostasis, including proliferation, necrosis, and apoptosis. In keeping with the task of regulating tissue turnover, inflammatory responses are triggered by not only exogenous stimuli, such as foreign bodies or infectious antigens, but by endogenous stimuli as well, such as the by-products of cell necrosis and apoptosis. Free fatty acids represent an important example relevant to obesity. Free fatty acids, systemic levels of which are elevated in obesity, are primary ligands for Toll-like receptors, central regulators of the innate immune response [21, 22]. Free fatty acids and Toll-like receptors therefore act as a direct link between the systems that regulate body weight and inflammation.

At the molecular level, the intracellular signaling pathways that govern inflammation and glucose homeostasis demonstrate significant crosstalk and share multiple signaling mediators. At the cellular level, adipocytes and macrophages are closely related and likely evolved from a common primordial precursor cell [23], further evidence of the parallel evolution of inflammation and metabolic systems. What is the evolutionary rationale for this intimate relationship? Immune and inflammatory responses require significant energy expenditure and therefore certainly co-evolved to fine-tune responses to available energy resources. More specifically, physiologic stress during our evolution most often took the form of traumatic or infectious insults and thus required vigorous inflammatory responses. Furthermore, as stated earlier, such stress in the last 1–2 million years of primate evolution was likely often associated with low caloric intake, in which case maintenance of adequate blood glucose levels is a priority [3]. These observations suggest a mechanism for the coselection of robust inflammatory responses along with a propensity for insulin resistance and provide an evolutionary explanation for the twin epidemics of obesity and diabetes.

Adipose tissue-based inflammation

Obesity-related inflammation originates in adipose tissue, as evidenced in part by observations that inflammation is present in adipose tissue in the early stages of murine obesity prior to its development in the liver and other organs [18, 24]. Adipose tissue inflammation is characterized by a diffuse lymphocytic infiltrate that includes macrophages, T cells, and other lymphocyte subsets [12, 18, 19]. Within this diverse infiltrate, adipose tissue macrophages (ATM) play a central role in the inflammatory process. ATM are increased in number and predisposed to an inflammatory phenotype in murine and human obesity [12, 25, 26] and are a dominant source of many inflammatory cytokines, expression of which is altered in obesity, including elevated tissue levels of TNF-α, IL-6, IL-1, and CCL-2 [11]. Obesity is also associated with alterations in adipokine levels within adipose tissue, including leptin, adiponectin, resistin, and visfatin, all of which share diverse immunoregulatory functions in addition to their roles in regulating body weight. The net effect of these alterations is a chronic low-grade state of heightened inflammation within adipose tissue. Finally, adding yet further complexity, anatomic depot-specific differences are another important characteristic of adipose tissue inflammation, as the inflammatory state appears to be greater in visceral relative to subcutaneous adipose tissue [27]. These observations are paralleled by strong epidemiologic evidence that links visceral adiposity with an increased risk of metabolic syndrome, numerous individual obesity-related comorbidities, and mortality [28, 29]. Visceral adipose

tissue is therefore a particularly important anatomic site for pathogenic inflammation in obesity.

What initiates inflammation within adipose tissue? One hypothesis suggests that as lipid stores increase, adipocytes hypertrophy to a size greater than the diffusion distance of oxygen, inducing a state of cellular hypoxia [30]. Separate data also implicate dysregulation of adipose tissue blood flow in this hypoxic state [31, 32]. Adipose tissue hypoxia in turn induces cell necrosis, the by-products of which induce inflammation [33]. Consistent with this theory, macrophages congregate near necrotic adipocytes in inflamed adipose tissue [34]. In addition, surviving hypoxic adipocytes upregulate a broad array of hypoxia-inducible genes, including hypoxia-inducible factor-1α, which in turn activate NFκB and other inflammatory pathways [33]. Hypoxia also induces endoplasmic reticulum and oxidative stress as well as mitochondrial dysfunction, processes that have also been linked to activation of inflammation [35]. Hypoxia therefore appears to play an important role in the initiation of inflammation within adipose tissue.

Adipose tissue inflammation, insulin resistance, and diabetes

Diabetes represents a paradigm of an inflammatory metabolic disease, and the systems that regulate glucose homeostasis and inflammation are intimately related. As early as the late 19th century it was noted that aspirin, a potent inhibitor of inflammation, ameliorates diabetes [36–38]. Epidemiologic data accumulated over the past few decades demonstrate a strong association between serum inflammatory markers and type 2 diabetes [39, 40]. In 1993, Hotamisligil et al. [41] showed that adipose tissue-derived TNF-α directly induced systemic insulin resistance in mice. Prior to this discovery, inflammatory cytokines such as TNF-α were thought to be expressed primarily by lymphocytes in peripheral blood and dedicated lymphoid and recticuloendothelial organs. Hotamisligil's work was one of the earliest demonstrations that adipose tissue-derived inflammatory cytokines regulate systemic glucose homeostasis. Subsequent research shows that surgical visceral (but not subcutaneous) lipectomy in obese mice and humans ameliorates diabetes [42–44], stressing the importance of adipose tissue and its inflammatory products in the pathogenesis of systemic insulin resistance.

Cytokines and adipokines are dominant molecular mediators within adipose tissue that bridge the link between inflammation and glucose homeostasis and, as suggested above, TNF-α is of particular importance. Adipose tissue and systemic TNF-α levels are increased in both murine and human obesity and correlate with metabolic syndrome as well as with multiple individual obesity-related comorbidities [45–47]. Compelling mechanistic data also implicate TNF-α in glucose metabolism. Obese TNF-α knockout mice, for example, are protected from insulin resistance [48, 49], and in vivo neutralization of TNF-α ameliorates diabetes in obese rats [41, 50]. TNF-α exerts its effects on glucose metabolism via multiple mechanisms, including regulation of expression and phosphorylation of insulin signaling molecules, including the insulin receptor itself, as well as its proximal signaling mediators IRS-1, IRS-2, Akt, and the glucose transporter GLUT4 [51]. In addition, TNF-α regulates lipolysis, adipogenesis, and multiple other physiologic functions within adipose tissue. These diverse effects position TNF-α as a central mediator of metabolism within adipose tissue.

Adipose tissue is a rich source of numerous other cytokines such as IL-6, IL-1, and CCL-2 that regulate both inflammation and glucose metabolism and that have been implicated in obesity-related insulin resistance. In addition, adipose tissue-derived adipokines share with their cytokine cousins diverse inflammatory and glucoregulatory functions. Leptin, for example, was initially defined as a satiety factor but subsequently was shown to regulate both inflammation and insulin resistance. A member of the long-chain helical cytokine family, leptin regulates proliferation, apoptosis, and differentiation of multiple lymphocyte lineages. Leptin also regulates glucose metabolism, in general acting as an insulin agonist. Numerous other adipokines, including adiponectin, resistin, and visfatin, share distinct inflammatory and glucoregulatory functions, and together with cytokines, orchestrate inflammation and glucose homeostasis within adipose tissue.

At the cellular level, ATM play a central role in glucose homeostasis within adipose tissue and are a primary source of TNF-α and other diabetogenic inflammatory cytokines. ATM and their cytokine products induce insulin resistance in adipocytes in vitro [52] and are both sufficient and necessary for murine diabetes in vivo. Obese mice with adipose tissue-targeted knockdown of CCR2, the receptor for macrophage chemotactic protein (CCL2, aka MCP-1), do not develop an ATM infiltrate and demonstrate markedly improved insulin sensitivity [53], while overexpression of CCL2 in adipose tissue increases ATM infiltration and induces diabetes [54]. ATM are therefore central effectors of inflammation and insulin resistance in obesity. Interestingly, macrophages and adipocytes are closely related and may have evolved from a common ancestral cell [55]. These observations suggest a cellular basis for the intimate coevolution of the physiologic systems that regulate glucose homeostasis and inflammation in response to their respective primary stimuli, nutritional status and stress.

The systemic effects of adipose tissue-based inflammation are likely mediated by multiple mechanisms, including

hormonal effects of adipose tissue-based cytokines and adipokines on remote tissues as well as direct cytotoxic effects of excess circulating lipid on a wide range of tissues. A dominant mechanism by which adipose tissue exerts its systemic effects is the portal venous communication between visceral adipose tissue and liver which delivers adipose tissue-derived inflammatory products, including cytokines and free fatty acids, directly to the liver, inducing both hepatic and systemic insulin resistance [56, 57]. This intimate anatomic association, along with its central role in regulating glucose metabolism, establishes the liver as an important secondary in vivo site of inflammation and insulin resistance in obesity. The close relationship between visceral adipose tissue and the liver extends beyond anatomy to phylogeny. Drosophila lacks a liver but instead possesses a "fat body," a modified adipose tissue depot that carries out functions attributed to the liver in higher organisms [58], suggesting a common phylogenetic heritage. The "hepatic-visceral adipose tissue axis," closely tied together by its intimate anatomic relationship, likely evolved to allow for precise regulation of hepatic control of systemic glucose homeostasis based on information regarding energy stores and inflammation provided by visceral adipose tissue.

Molecular mechanisms of inflammation and insulin resistance: avenues toward pharmacotherapy for metabolic disease

The multiple cytokine and adipokine ligands, effector cells, and intracellular signaling mediators that collectively regulate glucose homeostasis and inflammation and the wide range of tissues in which these processes unfold together comprise a signaling network that, while daunting in its complexity, provides rich opportunities for tailored pharmacotherapy for diabetes and metabolic syndrome. Cytokines and adipokines are among the most obvious targets for such therapy. Leptin-based therapy for diabetes has not proven effective in the treatment of type 2 diabetes in humans, likely because of systemic leptin resistance [59]. Similarly, early trials in humans with type 2 diabetes demonstrated a lack of efficacy of anti-TNF-α and anti-TNF-receptor antibodies [60–63]. That said, more recent trials of long-term treatment with anti-TNF-α antibodies in patients with rheumatoid arthritis and insulin resistance show promise, with documented improvements in glucose homeostasis [64–66]. Therapy directed at other cytokines also demonstrates potential: Treatment with a recombinant IL-1-receptor antagonist ameliorates diabetes in humans [67] and represents an early step toward cytokine- and adipokine-based pharmacotherapy.

Recent study has also focused on the numerous intracellular signaling mediators that regulate inflammation and glucose homeostasis, of which PPAR-γ and IKK-β are promising candidates. The transcription factor PPAR-γ is active primarily in adipose tissue and regulates inflammation, insulin resistance, lipolysis, and adipogenesis. PPAR-γ activity is generally associated with beneficial effects on metabolism, including increased insulin sensitivity and reduced lipolysis. PPAR-γ gene mutations in humans are associated with severe insulin resistance and metabolic syndrome [68], testament to its central role in maintaining normal glucose homeostasis. One of the many mechanisms by which TNF-α mediates its effects on glucose homeostasis is through inhibition of PPAR-γ expression and induction of inhibitory PPAR-γ serine phosphorylation. PPAR-γ-based therapy already exists in the form of the thiazolidinedione family of drugs, which act as PPAR-γ agonists. The beneficial effects of these drugs on metabolic disease are secondary to multiple mechanisms, which include important effects on inflammation. PPAR-γ inhibits NFκB directly and has diverse effects on other inflammatory mediators as well [69]. PPAR-γ activation also induces a shift in adipose tissue macrophages to a less inflammatory phenotype [70]. Further study of PPAR-γ has the potential to provide tailored anti-inflammatory therapy for diabetes and other metabolic disease beyond what currently exists in the form of thiazolidinediones.

IKK-β is a ubiquitous intracellular inflammatory signaling mediator that activates NFκB as well as other tissue-specific transcriptional responses that regulate inflammation and glucose homeostasis. Not only is IKK-β an important positive regulator of inflammation [71], but recent data also demonstrate an important role in the regulation of central hypothalamic control of body weight and systemic insulin resistance [72]. IKK-β is therefore a pivotal player at the interface of weight regulation, glucose homeostasis, and inflammation. Hepatic overexpression of IKK-β induces diabetes in mice [73], while targeted knockdown of IKK-β in the liver in obese mice ameliorates insulin resistance due to increased hepatic insulin sensitivity. These animals nonetheless eventually develop diabetes due to muscle and adipose tissue insulin resistance. In contrast, obese mice with targeted knockdown of IKK-β in myeloid cells are completely protected from diabetes [13]. These data suggest a central role for IKK-β within myeloid-derived effector cells such as macrophages in regulating systemic insulin resistance. IKK-β-based therapy is being actively pursued. Aspirin is a powerful inhibitor of IKK-β, and it is this effect that is primarily responsible for its beneficial effects on diabetes [74]. Salicylate inhibition of IKK-β ameliorates diabetes in mice [73], and tailored small-molecule pharmacotherapy directed toward IKK-β and related signaling mediators is an area of ongoing

research [71] that represents the next frontier in therapeutics for metabolic disease.

Identification and targeting of specific diabetogenic macrophage subpopulations [75] is another important avenue of research. Among their many effects, PPAR-γ agonists induce a shift in macrophages to a less inflammatory phenotype. While the magnitude of the contribution of this specific mechanism to their clinical effects is unknown, thiazolidinediones may nonetheless represent an early step toward pharmacotherapy directed at manipulating macrophage phenotype [70]. Other strategies may also yield macrophage-targeted therapy. As mentioned above, mice with adipose tissue-specific knockdown of macrophage homing molecules demonstrate improved insulin sensitivity, which suggests the possibility of therapy based on manipulation of tissue macrophage homing.

Summary

Obesity is associated with a state of chronic systemic inflammation that has its genesis in adipose tissue. This inflammatory state has broad systemic effects, including insulin resistance and diabetes. This review has addressed but a few of the many avenues of research studying the underlying mechanisms that bridge inflammation and glucose homeostasis. Other areas of research include therapy based on hypoxia-inducible and endoplasmic reticulum stress-related mediators, as well as mediators of mitochondrial dysfunction.

The physiologic processes that regulate inflammation and glucose homeostasis are closely linked and coevolved to produce finely tuned responses to stress and nutritional status. Recent discovery of a role for IKK-β in the regulation of hypothalamic control of body weight suggests that the central physiologic systems that control body weight also evolved in concert with these processes and that manipulation of common mediators may allow for simultaneous treatment of obesity, diabetes, and other inflammatory comorbidities. Bariatric surgery is an effective therapy for obesity, and surgically induced weight loss contributes to the resolution of systemic inflammation and its comorbid sequelae [76]. Given the impracticality of providing surgery to all potential candidates, however, the challenge moving forward is to translate our understanding of the intimate relationship between obesity, inflammation, and glucose homeostasis into cost-effective pharmacotherapy for diabetes and other metabolic diseases.

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