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Inflammation in obesity-related disease

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Obesity and systemic inflammation

One of the most important realizations in the field of metabolic disease over the last decade is that obesity is associated with a state of chronic low grade systemic inflammation. Evidence from obese animals and humans demonstrates a clear association between weight regulation and inflammation, with abnormalities of numerous *in vitro* and *in vivo* measures of innate and adaptive immune function, including serum levels of inflammatory cytokines, and peripheral blood lymphocyte subpopulation frequencies and *in vitro* responses. These observations have profound clinical significance, as epidemiologic evidence demonstrates a strong correlation between systemic markers of inflammation and the most serious co-morbidities of obesity. Serum levels of inflammatory mediators, such as CRP, TNF-α, and IL-6 that are elevated in obesity, also predict the presence and severity of atherosclerosis, diabetes, steatohepatitis, and sleep apnea independent of body weight. Additional and compelling mechanistic evidence links the pathogenesis of obesity-related co-morbidities with inflammation; stimulation of the innate immune response with lipopolysaccharide induces insulin resistance, while aspirin, an inhibitor of inflammation, attenuates it. Furthermore, targeted disruption of NFκB signaling, a central regulator of inflammation, reverses insulin resistance in mice (1). Similar evidence implicates inflammation in the pathogenesis of atherosclerosis, steatohepatitis, sleep apnea, asthma, and osteoarthritis. Systemic inflammation therefore represents a common underlying factor in the pathogenesis of many serious, obesity-related, co-morbid diseases.

Adipose tissue- a primary in vivo site of inflammation in obesity

Adipose tissue is comprised not only of adipocytes, but also a stromovascular cell fraction which consists of a diverse population of lymphocytes, fibroblasts, endothelial and stromal cells, and preadipocytes, which along with adipocytes, serve as a rich source of cytokines and adipokines. Adipocytes themselves are closely related to fibroblasts and macrophages, and in fact, evidence supports their ability to transdifferentiate into macrophages *in vivo*. Adipose tissue should, therefore, in addition to its role as a storage depot for lipid, be considered an immune organ, and in this capacity, is a primary *in vivo* site of inflammation in obesity. Expression of positive regulators of inflammation is increased in subcutaneous adipose tissue from obese humans and mice, while calorie restriction causes a reversion of the adipose tissue transcriptome toward that similar to lean subjects, with down-regulation of pro-inflammatory cytokines and up-regulation of anti-inflammatory cytokines (2). Furthermore, the magnitude of the "inflammatory shift" in the adipose tissue transcriptome correlates with the presence and magnitude of obesity-related co-morbidities, including insulin resistance and steatohepatitis. Adding to its complexity of function, different anatomic depots of adipose tissue manifest distinct metabolic properties. While excess subcutaneous adipose tissue (SAT) imparts risk, excess visceral adipose tissue (VAT) is even more strongly predictive of obesity-

related co-morbidities and long-term mortality (3). Visceral lipectomy in rodents, and in a single trial in human bariatric surgery patients, ameliorates insulin resistance, while subcutaneous lipectomy has no such effect (4), observations which suggest fundamental differences between these tissue depots. The direct drainage of VAT venous effluent to the liver via the portal vein increases hepatic delivery of fatty acids and inflammatory mediators and may explain the detrimental effects of VAT without invoking other mechanisms. Nonetheless, important depot-specific qualitative differences in metabolism and gene expression have also been described. VAT, relative to SAT, demonstrates greater levels of lipolysis, expression of β-adrenergic receptor, steroid sensitivity, insulin resistance and, relevant to this discussion, expression of inflammatory cytokines. While the published literature is complicated by patient heterogeneity and study of different and likely functionally distinct anatomic sub-depots (e.g. epiploic, omental, mesenteric sub-depots within VAT, and deep and superficial SAT depots), a preponderance of data suggest that VAT manifests fundamental qualitative differences in metabolism and inflammation compared to SAT that contribute to its detrimental physiologic effects.

Adipocytokines

Aberrant expression of a wide range of cytokines and adipokines is a central feature of the inflammatory process within adipose tissue in obesity. While the term adipokine in the strictest sense refers to proteins expressed solely by adipocytes, such as leptin, lymphocytes comprise up to half of the non-adipocyte cell fraction of adipose tissue and are the source of many classic cytokines, such as TNF-α and IL-1, as well as mediators originally described as having a primary role in weight regulation, such as visfatin and resistin. In addition, many proteins are expressed by both lymphocytes and adipocytes, including adiponectin, IL-6, and monocyte chemotactic protein (MCP-1), reflecting the close relationship between adipocyte and hematopoietic lineages. Collectively, these "adipocytokines" demonstrate remarkable multiplicity of function and regulate diverse immune, endocrine, reproductive, and developmental processes. While a detailed review is beyond the scope of this discussion (5), a few generalizations deserve mention. Virtually all adipocytokines share important immunoregulatory activity. For example, despite its original classification as a satiety factor, leptin is a member of the long-chain helical cytokine family and regulates a variety of immune and inflammatory processes, including lymphocyte development, cytokine expression, proliferation, and apoptosis. Ob mice, which lack functional leptin, demonstrate profound defects in immune and inflammatory function, reinforcing leptin's important role within immune system. Virtually all other classically defined adipokines manifest similarly diverse immunoregulatory functions. Furthermore, in general, obesity is associated with an increase in expression of adipocytokines that promote inflammation, including leptin, TNF-α, IL-6, and resistin, and decreased expression of those which down-regulate inflammation, such as adiponectin, IL-1Ra and IL-10. The reciprocal regulation of pro and anti inflammatory adipocytokines is an important feature of adipose tissue-based inflammation. Another common feature of many adipocytokines is a central role in regulating insulin resistance. Among the classic cytokines, TNF-α has emerged as an important regulator of inflammation and insulin resistance in obesity. TNF-α levels are elevated in adipose tissue and serum in murine and human obesity. In addition to its role in inflammation, TNF-α induces insulin resistance in a wide range of cells, including adipocytes, through multiple mechanisms including down-regulation of expression and phosphorylation of insulin receptor, IRS-1 and IRS-2, and inhibition of GLUT 4 expression and translocation. While their exact *in vivo* roles in glucose homeostasis are unclear, other adipocytokines also regulate insulin resistance: resistin, IL-6, and MCP-1 induce insulin resistance, while leptin, adiponectin, and IL-10, in general, ameliorate it. These proteins represent a direct molecular link between inflammation and one of the most serious co-morbidities of obesity and reinforce the intimate relationship between the physiologic systems that regulate energy homeostasis and immune and inflammatory

function. Consistent with these observations, crosstalk occurs between the intracellular signaling pathways that regulate these processes. For example, the mitogen activated protein kinase JNK-1 and the NFκB-related signaling molecule IKKβ are central mediators of signaling pathways triggered by TNF-α, leptin, and numerous other adipocytokines, and regulate both inflammatory responses and glucose homeostasis. Of importance, activities of JNK-1 and IKKβ are increased in adipose tissue in obesity. Furthermore, JNK-1 and IKKβ have been implicated in the pathogenesis of atherosclerosis and steatohepatitis, suggesting a role in the pathogenesis of multiple obesity-related disease processes (6).

Just as cytokine-based therapy has proven effective for inflammatory bowel disease and rheumatoid arthritis, adipocytokine-based pharmacotherapy for metabolic disease is on the horizon. While trials of leptin therapy for obesity and TNF-α-based immunotherapy for diabetes in humans have been unsuccessful, other avenues show promise; immunoneutralization of IL-1, for example, improves insulin resistance and reduces systemic inflammation in humans (7), while targeting signaling molecules such as JNK and IKKβ provides the opportunity for even more highly tailored pharmacotherapy. Adipocytokines and their intracellular signaling pathways therefore represent exciting avenues for further study.

Cellular mediators of inflammation within adipose tissue

The disorders in adipocytokine expression within adipose tissue are not surprisingly accompanied by aberrations in the frequency and function of immune and inflammatory effector cells. Among them, macrophages stand out as prime candidates for cellular mediators of inflammation. The frequency of adipose tissue-associated macrophages (ATM) is increased in obese humans and correlates directly with body mass index. Emphasizing the unique role of VAT in obesity-related inflammation, macrophage infiltration is two-fold greater in VAT than SAT in obese humans and associated with up-regulation of macrophage-specific inflammatory cytokines. Unique macrophage subpopulations are present in adipose tissue of obese but not lean mice (8), and ATM in obese humans express increased levels of inflammatory cytokines, including TNF-α, IL-6, and IL-1 (9). While the specific initiating event that leads to increased infiltration and a shift towards increased inflammatory responses by ATM in obesity is unknown, expression of MCP-1 and macrophage migration inhibitory factor are increased in adipose tissue in obesity and contribute to macrophage homing to adipose tissue, while cytokines secreted by adipocytes, ATM, and other lymphocytes in adipose tissue, including TNF-α and IL-6, have been implicated in potentiating ATM inflammatory responses. Emphasizing the clinical relevance of these observations, ATM and their cytokine products induce insulin resistance in adipocytes. Furthermore, obese knockout mice for either MCP-1 or its receptor CCR2 demonstrate decreases in ATM infiltration, inflammation, and insulin resistance, while the opposite is observed in mice with targeted over-expression of MCP-1 in adipose tissue. These data support a critical role for ATM in the link between inflammation and insulin resistance. While best studied within adipose tissue, macrophages play a role in obesity-related co-morbidities in other tissue beds as well. Macrophages with increased inflammatory properties contribute to atherosclerotic plaque progression, while abnormalities of bronchial macrophage phenotype have been described in patients with asthma. Macrophage infiltration of the liver has been described in murine obesity, and abrogation of hepatic macrophage infiltration with liposomal biphosphonates decreases histologic steatohepatitis in obese mice. Tissue macrophages and their cytokine products are therefore involved in the pathogenesis of multiple obesity-related inflammatory diseases. Finally, while ATM are clearly important mediators of adipose tissue inflammation, tissue lymphocytes of other lineages are also dysregulated. T-cell infiltration of adipose tissue is increased in murine and human obesity and associated with alterations in the expression of T-cell-related cytokines. The frequency and function of NK cells within adipose tissue is altered in murine obesity, along with aberrations in NKT and gamma-delta T-cells, although these cell types are less well-

studied than ATM and classic T-cells. Despite a central role for ATM, alterations in phenotype and function affect a wide variety of adipose tissue-associated lymphocytes.

Adipose tissue inflammation and systemic metabolic disease

While adipose tissue is a central site of inflammation in obesity, the resultant metabolic sequelae are systemic. What are the mechanisms by which inflammation within adipose tissue influences other organ systems? One such mechanism is the intimate anatomic association between VAT and the liver. Increased VAT leads to increased delivery of free fatty acids, inflammatory adipocytokines to the liver via the portal venous system, phenomena that are directly implicated in the pathogenesis of hepatic steatosis and steatohepatitis. As a result, alterations in inflammatory cytokine expression and lymphocyte function similar to those observed in adipose tissue are also present in the liver. Hepatic inflammation in turn influences metabolism and disease pathogenesis in other organ systems. For example, mice genetically engineered to over-express NFκB in the liver exhibit insulin resistance not only locally within hepatic tissue, but in skeletal muscle as well, suggesting *in vivo* communication between these tissues through humoral mediators. The liver is, therefore, an important secondary anatomic site of inflammation in obesity.

Adipocytokines may influence other organ systems via hormonal effects. Many of the same mediators which are increased in adipose tissue in obesity are also increased in serum, suggesting an adipose tissue source. Despite well-established hormonal effects of adipokines with respect to satiety, however, whether similar hormonal mechanisms are active with respect to immune and inflammatory function is uncertain, as are hormonal effects for classic adipose tissue-derived cytokines. For example, while exogenous TNF-αhas well-described widespread systemic effects, a paucity of data support the hypothesis that adipose tissue is a primary source of systemic, bioactive TNF-α *in vivo*. TNF-α levels are lower in venous than arterial blood from SAT, and adipose tissue expresses high levels of soluble TNFR, which may sequester TNF-α within tissues. Current data, therefore, do not convincingly establish a hormonal effect of adipose-tissue-derived TNF-α. More compelling evidence exists for a hormonal role for IL-6; up to one third of circulating IL-6 is thought to be derived from adipose tissue, but distinguishing between hormonal and paracrine effects *in vivo* has proven difficult. Specific hormonal activities of adipocytokines are therefore as of yet not well-established but are certainly plausible.

Finally, excess lipid itself contributes to systemic inflammation in obesity. Increased dietary fat intake is thought to overwhelm adipocyte storage abilities, leading to increased circulating free fatty acids and subsequent ectopic lipid deposition in virtually all tissues, with widespread physiologic consequences. Lipids are cytotoxic to most cells: lipid deposition in pancreatic islets has been implicated in the pathogenesis of diabetes, while lipid deposition within endothelial cells contributes to hypertension, in part by inducing resistance to the vasodilatory effects of insulin. Lipid accumulation in hepatocytes defines steatosis and is a causal agent in the progression of steatosis to steathohepatitis, while in skeletal muscle, ectopic lipid deposition has been associated with peripheral insulin resistance. Indirect evidence of the role of adipose tissue as a protective buffer against the systemic effects of lipids is provided by observations in humans and animals with lipodystrophy, in whom adipose tissue is absent and associated with widespread ectopic lipid deposition and severe insulin resistance, which in mice is reversed by transplantation of healthy adipose tissue. The mechanisms of lipid cytotoxicity are not fully understood, but free fatty acids uncouple oxidative phosphorylation and increase mitochondrial production of reactive oxygen species, as well as induce stress responses in endoplasmic reticulum. In addition to these cytotoxic effects, lipids also play an important role in direct activation of the innate immune system via Toll-like receptor (TLR) signaling. TLRs play an important role in regulating innate immune responses to both infectious and sterile

inflammatory stimuli, and free fatty acids are important ligands for TLR-2 and TLR-4. TLRs therefore represent a direct molecular link between hyperlipidemia, a central clinical feature of obesity, and activation of the innate immune system. TLR-2 and TLR-4 are expressed in a wide range of cells, including macrophages and adipocytes, and upon binding free fatty acids, activate NFκB, upregulate inflammatory cytokine expression and induce insulin resistance. TLRs play a role in other co-morbidities of obesity as well; human TLR gene polymorphisms are associated with decreased susceptibility to atherosclerosis, diabetes, and cancer, while over-expression of TLR-4 in vascular endothelial cells exacerbates and under-expression attenuates atherosclerosis. TLR signaling has also been implicated in steatohepatitis; a TLR-4 agonist exacerbates and TLR-2 deficiency ameliorates steatohepatitis in mice. These examples stress the importance of TLR signaling in mediating the effects of excess lipid on obesity-related inflammation and disease pathogenesis (10).

The root cause of inflammation in obesity

The underlying events that initiate inflammation within adipose tissue remain unknown. A leading hypothesis implicates adipose tissue hypoxia in the genesis of inflammation (11), a finding confirmed in murine obesity and reversed with weight loss. What causes adipose tissue hypoxia? Adipocyte enlargement is a paradigmatic histologic feature of human obesity, and adipocytes are one of the few cell types that can enlarge to sizes greater than the effective diffusion distance of oxygen. Enlarged adipocytes may therefore be susceptible to hypoxia due to an oxygen diffusion barrier presented by intra-cytoplasmic lipid. Furthermore, adipocyte enlargement has been linked to inflammation and insulin resistance: enlarged adipocytes express higher levels of inflammatory cytokines and exhibit greater levels of insulin resistance than small adipocytes. Despite these observations, at least one study demonstrates that hypoxia affects both large and small adipocytes equally, prompting a search for causes other than diffusion defects. Alterations in blood flow to adipose tissue have also been implicated. Post-prandial blood flow to adipose tissue is normally increased from fasting levels, a mechanism thought to play an important role in clearing circulating lipids after a meal. This response is blunted in obesity, which may lead to decreased lipid uptake, exacerbating ectopic lipid deposition as well as contributing to adipocyte hypoxia.

How does adipose tissue hypoxia lead to inflammation? Adipocyte hypoxia may induce cell necrosis, with release of cell byproducts that recruit macrophages and other phagocytic cells and induce inflammatory responses. ATM in obese mice and humans congregate predominantly near necrotic adipocytes, supporting such a theory. In addition, surviving hypoxic adipocytes up-regulate hypoxia-inducible genes, including hypoxia-inducible factor -1, which in turn induces expression of inflammatory cytokines through activation of NFκB. In addition, hypoxia may contribute to oxidative stress and related abnormalities in the endoplasmic reticulum, mechanisms that have also been implicated in the genesis of inflammation in adipocytes. Further research will be necessary to define the exact roles of these phenomena in contributing to the initiation of inflammation within adipose tissue.

Conclusion

Systemic inflammation is a primary underlying cause of many serious, obesity-related co-morbid diseases, and adipose tissue is a dominant *in vivo* site of inflammation in obesity. ATM are important mediators of inflammation within adipose tissue, but other lymphocyte and adipocyte-related cell types and their cytokine and adipokine products also contribute to the inflammatory process. Adipose tissue inflammation influences other organ systems through multiple mechanisms, including a direct, anatomic communication with the liver, potential humoral effects of adipocytokines, and lipid-mediated cellular toxicity and activation of the innate immune system. While the inciting cause of inflammation within adipose tissue is

unknown, adipocyte hypoxia appears to be an important contributor. Other potential contributing factors include oxidative stress and resultant defect in endoplasmic reticulum and mitochondrial function, and genetic and epigenetic influences. Elucidation of the underlying mechanisms of inflammation in obesity has the potential to provide therapy for a wide range of inflammatory disease processes. The plasticity of the macrophage phenotype provides opportunities for macrophage-based immunotherapy, while cytokines, adipokines, TLRs, lipids, and their intracellular signaling mediators represent promising avenues for pharmacotherapy with potentially broad implications for the treatment of metabolic diseases.

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References

1. Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, Shoelson SE. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. Science 2001;293 (5535):1673–7. [PubMed: 11533494]
2. Cancello R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, Bouloumie A, Barbatelli G, Cinti S, Svensson PA, Barsh GS, Zucker JD, Basdevant A, Langin D, Clement K. 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(8):2277–86. [PubMed: 16046292]
3. Carey VJ, Walters EE, Colditz GA, et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. Nurses' Health Study. Am J Epidemiol 1997;145:614–19. [PubMed: 9098178]
4. Thorne A, Lonnqvist F, Apelman J, Hellers G, Arner P. A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. Int J Obes Relat Metab Disord 2002;26(2):193–9. [PubMed: 11850750]
5. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6(10):772–83. [PubMed: 16998510]
6. de Luca C, Olefsky JM. Inflammation and insulin resistance. FEBS Lett 2008;582(1):97–105. [PubMed: 18053812]
7. Larsen CM, Faulenbach M, Vaag A, Vølund A, Ehses JA, Seifert B, Mandrup-Poulsen T, Donath MY. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med 2007;356(15):1517–26. [PubMed: 17429083]
8. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117(1):175–84. [PubMed: 17200717]
9. Zeyda M, Farmer D, Todoric J, Aszmann O, Speiser M, Györi G, Zlabinger GJ, Stulnig TM. Human adipose tissue macrophages are of an anti-inflammatory phenotype but capable of excessive pro-inflammatory mediator production. Int J Obes (Lond) 2007;31(9):1420–8. [PubMed: 17593905]
10. Misch EA, Hawn TR. Toll-like receptor polymorphisms and susceptibility to human disease. Clin Sci (Lond) 2008;114(5):347–60. [PubMed: 18230059]
11. Trayhurn P, Wang B, Wood IS. Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity? Br J Nutr 2008 Apr 9;:1–9.