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# Fanning the Flames of Obesity-Induced Inflammation

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The complex processes linking obesity to its deleterious health consequences are finally being unraveled. Inflammation is receiving increased attention for its potential role in the pathogenesis of disorders ranging from insulin resistance and type 2 diabetes (T2D) to steatohepatitis and cardiovascular disease (CVD). Recent back-to-back studies show that obesity perturbs inflammatory gene networks, and hint at causal relationships between inflammation and disease traits associated with the metabolic syndrome. Approaches used in these studies are distinct from classical genome-wide associational studies or tissue-specific mRNA expression profiling, as they rely on 'neural networks' and high-powered computational methods to interconnect genetic, genomic and environmental data into a 'causal' model.

Gene expression was assessed as a quantitative trait to predict which features of obesity promote disease. The first study revealed a tendency towards activation of an inflammation network in adipose tissue of Icelandic subjects with a higher body mass index[1]. Parallel results were found in the second study, which similarly analyzed adipose tissue and liver from obese and control mice[2]. A major strength of this approach is that individual state changes can be considered in the context of other changes occurring not only in the tissue being examined, but simultaneously in other tissues, and in the context of genetics, environmental determinants, and even over time. As a word of caution, however, these are early days in systems biology, and findings are limited by the quantity and accuracy of the data used to construct the networks.

The relatively unbiased approach used in these studies affirms a role for inflammation in the pathogenesis of metabolic diseases. The approach should also provide new biomarkers for obesity and related metabolic diseases. An additional major promise of such systems biology approaches is in their application to drug discovery. The administration of a drug provides a single perturbation that should influence multiple components of the system. The approach should provide valuable information about mechanisms of action, not only for the drug's beneficial effects but also for side effects that may limit utility. Identification of new biomarkers for assessing response to a drug should also provide avenues for personalized medicine, by tailoring interventions to an individual's underlying disease mechanisms.

How do these new findings fit the larger, emerging picture of obesity-induced inflammation? Epidemiological evidence relating inflammation to T2D and obesity has existed since the 1950s[3], but was not considered in terms of pathogenesis until the 1990s.

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The list of markers shown to be elevated in obesity includes white blood cell count and plasma concentrations of sialic acid, C-reactive protein (CRP), TNF-α, and IL-6, among other factors[3,4], and the list continues to grow.

TNF-α was hypothesized to mediate obesity-induced inflammation, because it is produced in adipose tissue and neutralization in mice curbed insulin resistance[5]. However, TNF-α neutralization trials in humans were negative[6], which dampened enthusiasm not only for TNF-α as a drug target in T2D, but for the 'inflammation hypothesis' of T2D. New discoveries continued to rekindle interest in this area of investigation despite these ongoing debates.

The discovery that obesity also activates intracellular pathways, including IKKβ/NF-κB and JNK[7,8], added fuel to the inflammatory hypothesis. Upregulation of the IKKβ/NF-κB axis leads to the excess production of multiple potential mediators of inflammation, whereas JNK activation impinges on insulin signaling through phosphorylation of serine residues of IRS-1. Stimuli potentially activating both IKKβ/NF-κB and JNK in obesity can be separated into extracellular ligands, such as proinflammatory cytokines TNF-α, IL-1β and IL-6 or fatty acids binding to TLRs -- and intracellular stimuli such ER or oxidative stress and ceramides[3]. Determining which processes initiate obesity-induced inflammation is an active area of investigation.

The discovery of macrophages in obese adipose tissue was another milestone towards better understanding obesity-induced inflammation[9,10]. Macrophages appear to accumulate in obese fat in response to adipocyte stress and death, possibly due to insufficient angiogenesis and hypoxia. Although incompletely understood, the macrophages may participate in the development insulin resistance, T2D and CVD through production of proinflammatory cytokines, chemokines, and other factors. Inhibition of NF-κB or JNK in macrophages improves insulin resistance[11,12].

Importantly for patients with T2D or CVD, these recent discoveries promise potential new avenues for treatment. Despite the earlier failures with TNF-α blockers, it now appears that inflammation will provide viable therapeutic targets. Two approaches are already being validated in clinical trials, anti-inflammatory salicylates and IL-1 blockade. The salicylates are atypical members of the non-steroidal anti-inflammatory class of drugs, which target NF-κB as opposed to the cyclooxygenase enzymes, Cox1 and Cox2. Salsalate, a salicylate prodrug, has been shown to have glucose lowering efficacy in small trials[13], with larger TINSAL-T2D trials ongoing (www.TINSAL-T2D.org). The recombinant IL-1 receptor antagonist anakinra, currently approved for use in rheumatoid arthritis, also improves glycemia in patients with T2D[14]. IL-1 blockade and salsalate are both likely to improve β cell function and insulin resistance, although anakinra reportedly targets β cells and salsalate effects have focused on insulin sensitivity[13,14].

While it is too early to say whether salicylate or anakinra will go the distance, these approaches have already served to validate inflammation as a pharmacological target in T2D. Moreover, these approaches are vastly different from one another, as anakinra is an injected biological that binds extracellular IL-1 proteins, whereas salicylate (salsalate) is an

orally active small molecule that acts in cells to inhibit transcription. This suggests that numerous nodes or points within inflammation networks may be targeted in diabetes - which is good news, as the therapeutic area of inflammation is rich in molecular targets that have already received great attention from the pharmaceutical industry.

Of course salsalate and anakinra target inflammation systemically, while potential targets identified by the back-to-back studies of Schadt and Stefansson and colleagues are restricted to adipose tissue. Unless the studies are expanded to other tissues, which is both feasible and a strength of the approach, the potential targets they identify will be in adipose tissue. Modulation of these targets could have systemic effects and even β cell effects, but this needs to be shown. The authors pointed out that several genes already related to obesity, *Zfp90, C3ar1, Hsd11b1* and *Tgfbr2*, were identified by and thus validated their approach. They also studied 3 additional genes, *Lpl, Lactb* and *Ppm1l*, which they identify as "previously unknown obesity genes," although lipoprotein lipase (Lpl) is certainly well known to researchers in the field. The independent ablation of each of these genes leads to an overweight or obese phenotype.

Additional studies will determine whether these are *bona fide* drug targets or 'just' research tools. But it is certain that these types of systems biology, network analysis approaches will prove to be invaluable in the hunt for safer and more efficacious drugs that are tailored to obese subjects and patients with diabetes.

## Reference List


1. Emilsson V, et al. Genetics of gene expression and its effect on disease. Nature. 2008; 452:423–428. [PubMed: 18344981]
2. Chen Y, et al. Variations in DNA elucidate molecular networks that cause disease. Nature. 2008; 452:429–435. [PubMed: 18344982]
3. Shoelson SE, Lee J, Goldfine AB. Inflammation and Insulin Resistance. J Clin Invest. 2006; 116:1793–1801. [PubMed: 16823477]
4. Pickup JC, Crook MA. Is type II diabetes mellitus a disease of the innate immune system? Diabetologia. 1998; 41:1241–1248. [PubMed: 9794114]
5. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-α: Direct role in obesity-linked insulin resistance. Science. 1993; 259:87–91. [PubMed: 7678183]
6. Bernstein LE, Berry J, Kim S, Canavan B, Grinspoon SK. Effects of etanercept in patients with the metabolic syndrome. Arch.Intern.Med. 2006; 166:902–908. [PubMed: 16636217]
7. Yuan M, et al. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of *Ikk*β. Science. 2001; 293:1673–1677. [PubMed: 11533494]
8. Hirosumi J, et al. A central role for JNK in obesity and insulin resistance. Nature. 2002; 420:333–336. [PubMed: 12447443]
9. Weisberg SP, et al. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003; 112:1796–1808. [PubMed: 14679176]
10. Xu H, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003; 112:1821–1830. [PubMed: 14679177]
11. Arkan MC, et al. IKK-beta links inflammation to obesity-induced insulin resistance. Nat.Med. 2005; 11:191–198. [PubMed: 15685170]
12. Solinas G, et al. JNK1 in hematopoietically derived cells contributes to diet-induced inflammation and insulin resistance without affecting obesity. Cell Metab. 2007; 6:386–397. [PubMed: 17983584]

13. Goldfine A, et al. Use of Salsalate to Target Inflammation in the Treatment of Insulin Resistance and Type 2 Diabetes. Clinical and Translation Science. 2008; 1:36–43.

14. Larsen CM, et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N.Engl.J Med. 2007; 356:1517–1526. [PubMed: 17429083]