Inflammation and Metabolic Syndrome

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Sangye Gyamtso, a seventeenth century Tibetan scholar, noted that, “overeating ... causes illness and shortens lifespan”. Thus, without even an understanding of a biochemical pathway, early scholars recognized excess weight as harmful to health. Indeed, obesity predisposes individuals to a host of health complications, including insulin resistance, hypertension, and dyslipidemia, which collectively constitute the metabolic syndrome. Due to the massive and sustained increase in obesity and the prevalence of the metabolic syndrome worldwide, extensive efforts have been devoted to better understand the cellular events that mediate these pathologies.

Inflammation and Metabolic Syndrome

The term inflammation as used in the context of obesity and metabolism is applied to explain the phenomenon of higher levels of circulating pro-inflammatory factors (e.g. C-reactive protein (CRP), TNFα, Interleukin-1β (IL-1β), etc.) with fat mass expansion, rather than an actual redness and swelling of a particular area resulting from infection. Hotamisligil et al. were the first to discover the molecular link between obesity and inflammation when they identified adipose tissue as a site of proinflammatory cytokine synthesis and excretion. Since that time, scientists have found inflammation to be connected with all aspects of the metabolic syndrome. Various definitions exist that identify the metabolic syndrome, though essentially all include central obesity, dyslipidemia, hypertension, glucose intolerance, and insulin resistance. While the constellation of problems may seem somewhat benign, the consequences are very real—those with the syndrome have roughly four times the risk of dying from cardiovascular complications and have double the risk of all-cause mortality. As such, efforts have focused on understanding the etiology with particular attention on the molecular mechanisms that lead to disease onset. A milestone was reached when it was discovered that obesity is associated with a chronic inflammatory state that exacerbates several prominent diseases, including all facets of the metabolic syndrome. In fact, elevated circulating CRP levels are so consistently correlated with the metabolic syndrome that some have recommended the inclusion of a proinflammatory state as one of the syndrome’s components.

Central Obesity

While most discussions with obesity and inflammation assume the perspective of obesity causing inflammation due to adipose-released cytokines, there is an undercurrent of thinking that inflammation may exacerbate obesity. Cani et al. found that mice receiving a continuous infusion of bacterial lipopolysaccharide (LPS), a proinflammatory innate immune response activator, experienced similar weight gain as littermates fed a high-fat diet. This might explain why mice lacking a functional LPS response (CD14 or TLR4 mutant mice) are protected from diet-induced obesity. Interestingly, LPS-induced weight gain occurs without an increase in energy intake, indicating that dietary fat content is not sufficient to explain obesity. A possible link is the unexpected role of gut bacteria in regulating host energy homeostasis. Obesity is considered by some to be an inflammatory disease, where changes in gut bacterial content and function are considered mediating elements driving adiposity and metabolic disturbances. Not only does high-fat diet increase LPS absorption from the gut, which has been shown exacerbate obesity, but substances known to nourish non-LPS-containing bacteria, known as prebiotics, have been shown to actually reduce adiposity. These and similar efforts have been beneficial in helping the scientific community identify means to treat metabolic problems. Kim et al. suggest directing treatment towards inflammation via a dual approach consisting of pharmacological and dietary methods. For example, nutraceuticals can be used as a safe therapeutic means to combat insulin resistance. Exercise has also been shown to be an important therapeutic method. Teixeira et al. found that the proinflammatory cytokines, IL-6 and TNFα, as well as hyperuricemia all decreased in response to exercise, leading...
them to conclude that exercise is “anti-inflammatory in nature”, although whether this anti-inflammatory effect is necessary for exercise-induced weight loss is unknown.

**Dyslipidemia**

Inflammation leads to harmful changes in lipid metabolism. Dyslipidemia refers to an abnormal amount of lipid in the blood. Much of the evidence linking inflammation to dyslipidemia revolves around the TNF\(\alpha\), the prototypical pro-inflammatory molecule. A host of correlational evidence exists, wherein patients with dyslipidemia also exhibit elevated plasma TNF\(\alpha\) levels and interventions that improve lipid profile correlate with reduced plasma TNF\(\alpha\). In fact, the correlation is so consistently observed that some suggest TNF\(\alpha\) be used as a marker for familial combined hyperlipidemia. Further, TNF\(\alpha\) treatment in mice elicits an acute increase in plasma triglyceride and prolonged administration of recombinant human TNF\(\alpha\) reduces beneficial HDL cholesterol.

One mechanism that explains TNF\(\alpha\)'s impact on dyslipidemia is via free fatty acid (FFA) production. In general, three sources of FFA are thought to exist: i) dietary FFA, ii) TAG lipolysis, and iii) de novo FFA synthesis; TNF\(\alpha\) has been shown to impact lipolysis and de novo FFA synthesis. TNF\(\alpha\) administration has been shown to activate adipocyte lipolysis, greatly increasing circulating FFA and TAG. Scratching beneath the surface, Sethi et al. found that the lipolytic effects of TNF\(\alpha\) required TNF\(\alpha\) receptor 1 (TNFR1). The pleiotropic TNF\(\alpha\) initiates signaling down multiple canonical proinflammatory pathways and a particular role for the MAPK pathways has been implicated in mediating the anti-lipolytic effects of TNF\(\alpha\). Of the three known MAPK, namely p44/42, c-Jun N-terminal kinase (JNK), p38, only p44/42 and JNK are necessary for TNF\(\alpha\)-induced inhibition of lipolysis.

In addition to impacting lipolysis, TNF\(\alpha\) alters FFA synthesis in the liver. In fact, this effect is so potent that TNF\(\alpha\) has been implicated in the etiology of hepatic steatosis, also known as non-alcoholic fatty liver disease. Endo et al. found that TNF\(\alpha\) acutely and robustly accelerated fat accumulation in mouse liver. Additionally, mice treated with lipopolysaccharide (LPS), which activates immune pathways, similarly induced hepatic fat accumulation. However, further implicating TNF\(\alpha\), pretreatment of mice with an anti-TNF\(\alpha\) antibody attenuated these deleterious effects. An important factor in hepatic fat synthesis is the sterol regulatory element binding protein-1c (SREBP-1c), which synthesizes a host of lipogenic enzymes. SREBP-1c mediates hepatic lipogenesis in response to both TNF\(\alpha\) and LPS. Interestingly, TNF\(\alpha\) may explain risk of developing fatty liver in humans. In analyzing a cohort of humans with steatosis, Tokushige et al. observed that those with advanced hepatic steatosis had elevated TNF\(\alpha\) receptors.

**Hypertension**

The role of inflammation in causing hypertension involves several possible mechanisms, both direct and indirect. Focusing on a direct mechanism, CRP inhibits formation of nitric oxide by endothelial cells, which could promote vasoconstriction, platelet activation, oxidation, and thrombosis. An additional direct effect may be the CRP-induced upregulation of angiotensin receptors and enhanced plasminogen activator inhibitor-1 expression in endothelial cells, all of which could induce atherogenesis and elevate blood pressure. Indirectly, inflammation can result in hypertension via inflammation-induced insulin resistance. Insulin is a powerful vasodilator and a loss of insulin sensitivity leads to reduced vasodilation. Scheede-Bergdahl et al. found that vasodilation in response to prolonged insulin infusion is lessened in individuals with type 2 diabetes. Importantly, they note that this difference is not a result of diminished vascular capacity since non-insulin vasodilators cause similar forearm blood flow responses in both type 2 diabetic and non-diabetic subjects. Interestingly, in patients with the metabolic syndrome, hyperinsulinemia does not enhance responsiveness to vasodilators, suggesting the importance of effective insulin responsiveness in vasodilation.
Insulin Resistance

Due to the magnitude of published research exploring the relationship between inflammation and insulin resistance, as well as the robust role of insulin resistance in the metabolic syndrome (discussed later), special emphasis is warranted.

The pioneering discovery by Hotamisligil et al. that gave rise to the exploration of inflammation and obesity was centered around the observation that excess adipose tissue yields a pro-inflammatory state via pro-inflammatory secretagogues that induce systemic insulin resistance. The landmark paper was soon followed by evidence mechanistically linking inflammatory pathways with altered insulin receptor signaling. Briefly, normal insulin signaling initiates phosphorylation of tyrosine residues of the insulin receptor substrate-1 (IRS-1) subsequent to activation of the insulin receptor. This and other proximal signaling events are reduced in response to insulin in obesity and was considered to be the central dysfunction underlying insulin resistance. The altered insulin signaling in response to inflammatory mediators like TNFα involved the phosphorylation of IRS-1 on serine residues. Whereas tyrosine phosphorylation propogates the insulin signal downstream of IRS-1, serine phosphorylation stops the signal in its tracks, preventing downstream signaling and reducing insulin’s effects. However, cognizant of the fact that TNFα alone is not sufficient to explain IRS-1 serine phosphorylation, efforts continued to find the mediating kinase. Several have been implicated, namely JNK, the inhibitor of κB kinase β (IKKβ), and protein kinase C (PKC).

JNK is a well-known serine kinase and its activation in response to inflammatory signals and obese states prompted further research. Not only are JNK-deficient mice resistant to obesity-induced insulin resistance, but TNFα-induced IRS-1 serine phosphorylation is also prevented when JNK activity is blunted. Nuclear factor κB (NF-κB) is a primary transcription factor responsible for synthesis of a host of inflammatory cytokines. For NF-κB to function, it must be liberated from its cytosolic jailer by the action of IKKβ (i.e. when IKKβ is active, NF-κB is active). Distinct from its indirect role in initiating cytokine transcription, IKKβ, a serine kinase, is upregulated in obesity and IKKβ null mice are protected from diet-induced insulin resistance. Moreover, Yuan et al. revealed that inhibition of IKKβ improved insulin signaling by preventing IKKβ-mediated IRS-1 serine phosphorylation.

The PKC family is large and involved in many processes as second messengers. Certain PKC isoforms (β and η) are implicated in mediating fatty acid-induced insulin resistance via serine IRS-1 phosphorylation, while another isoform (ε) enhances the inhibitory effect of TNFα on insulin signaling. TNFα is thought to induce PKCε translocation to the cell membrane, placing it in proximity to IRS-1 and serine phosphorylating and ultimately inhibiting IRS-1. A commonly cited pathway that activates PKC is the formation of the lipid diacylglycerol (DAG), though the inhibitory effect of DAG-activated pathways
on insulin signaling is debated. Though DAG may not be important in this conversation, recent findings suggest that indeed a lipid may mediate inflammation-induced insulin resistance. Work performed at the Duke-National University of Singapore Graduate Medical School revealed that ceramide, a sphingolipid well-known to mediate insulin resistance in obese states, is synthesized not only in response to hyperlipidemic conditions, but also inflammatory stimuli. In particular, pro-inflammatory LPS was shown to induce insulin resistance in control models (animals and cells), but had no effect when ceramide formation was blocked. Additionally, in the absence of functioning inflammatory receptors (e.g. toll-like receptor 4), animals were protected from LPS- and lipid-induced insulin resistance, indicating that ceramide may be necessary in inflammation-induced insulin resistance.

**Insulin Resistance and Metabolic Syndrome**

The distinct factors of the metabolic syndrome are often present in groups, with many people having more than one of the conditions. This phenomenon suggests a common abnormality rather than coincidence. The parallel increase in prevalence among populations of the metabolic syndrome and insulin resistance is not coincidental. Indeed, the association is so tight that the metabolic syndrome is also known as the “insulin resistance syndrome”, which questions where insulin resistance fits in defining the metabolic syndrome. Is insulin resistance merely one of many factors that identify the metabolic syndrome or is it fundamentally responsible in the pathogenesis of the other factors (Figure 1)? It seems the latter may be the case.

**Central Obesity**

A conversation regarding obesity and insulin resistance can be confusing and cyclical. For the sake of brevity, a popular concept is that obesity precedes insulin resistance (via inflammatory pathway activity, see above); though evidence certainly exists that insulin resistance can exacerbate obesity. An interesting example is the reduced hypothalamic sensitivity to insulin and leptin in response to diets high in saturated fats (palmitic acid), which inhibits insulin’s and leptin’s ability to regulate appetite and body weight. Interestingly, this effect is less pronounced in diets high in mono-unsaturated oleic acid, which fails to induce insulin resistance.

**Dyslipidemia**

Of the multiple insulin-sensitive tissues in the body, evidence suggests that muscle and liver insulin resistance may play a role in mediating dyslipidemia, albeit to varying degrees, with the liver being a dominant factor. Regarding the relatively minor role of muscle insulin resistance, Peterson et al. found that muscle insulin resistance reduces glycogen formation, redirecting carbohydrates to the liver for de novo lipogenesis with eventual increases in circulating lipids. Thus, even muscle-derived dyslipidemia requires the actions of the liver.

**Hepatic insulin resistance is an interesting phenomenon.** Whereas some insulin-dependent functions are indeed affected with hepatic insulin resistance such as gluconeogenesis, other functions, such as hepatic lipogenesis, remain potently influenced by insulin, which explains the liver’s ability to synthesize new lipids from carbohydrate spill-over from the muscle despite identifiable insulin resistance. Li et al. identified the mTORC1 complex as the point of bifurcation, which is required for insulin-mediated increase in lipogenesis, but is not necessary for insulin-stimulated suppression of gluconeogenesis. Further, to identify the specific role of hepatic insulin resistance, independent of other peripheral factors, Biddinger et al. found that mice lacking the liver insulin resistance, which exhibit pure hepatic insulin resistance, develop a heavily proatherogenic lipoprotein profile, with reduced HDL cholesterol and increased VLDL cholesterol levels. Moreover, when fed a high-fat diet, in addition to exhibiting pronounced hypercholesterolemia, 100% of mice lacking a liver insulin receptor developed severe atherosclerosis.

**Hypertension**

Roughly half of all individuals suffering with hypertension are insulin resistant and severity of insulin resistance accurately predicts blood pressure. Indeed, Baron et al. found almost 20 years ago that insulin sensitivity is inversely correlated with blood pressure. These findings were soon followed with evidence highlighting how insulin impacts vasodilation (via increased nitric oxide release). Interestingly, in a reversal of supposed roles, while virtually all research on the effects of nitric oxide focus strictly on vasodilation, it may also impact insulin sensitivity. Mice with targeted disruptions in endothelial and neuronal nitric oxide synthase, which suffer from hypertension, experience significantly reduced total and hepatic insulin sensitivity, suggesting that nitric oxide plays a role in modulating insulin function and carbohydrate metabolism.

**Conclusion**

The metabolic syndrome is a prevalent problem worldwide, affecting upwards of 20%-60% of adults in countries of the Asia-Pacific region. The sustained surge of individuals suffering from the metabolic syndrome has grabbed the attention of biomedical scientists who seek to better understand its origins. A fruit of these labors is the discovery of the intimate relationship between the metabolic syndrome and chronic inflammation. While it is well established that inflammation plays a prominent role in the etiology of the metabolic syndrome, this may perhaps be true only insofar as inflammation induces insulin resistance, with insulin resistance serving as the primary mediator of inflammation-induced metabolic disturbances. With our current knowledge, future research efforts will reveal effective treatments to address the intertwined roles of inflammation and insulin resistance with a concentration on the treatment and prevention of the metabolic syndrome.
References


Benjamin Bikman began his academic career studying Exercise Physiology at Brigham Young University in Utah, USA from 1999-2005. While there, Dr. Bikman’s research interests subtly shifted. Rather than exploring the mechanisms that mediate the cellular adaptations to exercise, he began to focus on the molecular mechanisms that are altered with adaptations to obesity. He completed his thesis exploring the effects of aging and exercise on the chronic systemic inflammation that accompanies weight gain and obesity. He then joined the laboratory of G. Lynis Dohm at East Carolina University in North Carolina, USA where he obtained his doctoral degree in Bioenergetics. His dissertation work focused on the exploration of obesity- and inflammation-induced insulin resistance, concentrating particularly on the interaction between the metabolic and immune systems. Following his doctoral degree in 2008, Dr. Bikman sought to work with Dr. Scott Summers, a leader in the area of insulin resistance, who was at the University of Utah who then moved his lab to Duke-NUS in Singapore. While at Duke-NUS, Dr. Bikman continued to focus on insulin resistance and helped establish the current paradigm of the etiology of obesity-induced insulin resistance. Dr. Bikman very recently joined the faculty of his alma mater and is an Assistant Professor in the Physiology and Developmental Biology Department at Brigham Young University.

M. Andrew Bressler, an undergraduate at Brigham Young University in Molecular Biology, works as a student research assistant in the Laboratory of Obesity and Metabolism under Dr. Bikman. His future plans include medical school and a career as an ophthalmologist where he hopes to make a difference. Andrew grew up in Rexburg, Idaho as part of a close family consisting of his parents and five siblings. Andrew believes that molecular approaches and methods will constitute much of the future of medicine in order to better diagnose and treat diseases.