Cell Metabolism
Perspective

Insulin Resistance in the Defense against Obesity

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In the face of the current obesity epidemic, the nature of the relationship between overnutrition and type 2 diabetes is of great importance. Obesity can be considered a state of excessive insulin action that elicits a series of cellular homeostatic responses, producing systemic insulin resistance. These responses occur in four steps: homologous desensitization to insulin action, leptin secretion, inflammation, and, finally, a counter-inflammatory phase that serves to conserve energy storage. The molecular mechanisms underlying these steps are discussed in the context of potential new therapeutic approaches.

It will not come as a shock to the reader that we are in the midst of a major worldwide epidemic of obesity and type 2 diabetes. The numbers are staggering, and with over 1.5 billion people now obese or overweight, the eventual impact of expected complications are predicted to take a major toll on public health (Swinburn et al., 2011; Wang et al., 2011b). The reasons for this epidemic remain obscure; several hypotheses have emerged, including increased food availability, adaptation to a sedentary lifestyle, changes in food content or nutritional value, intestinal dysbiosis, viral infection, low or high birth weight, evolutionary pressure, or all of the above. While I will leave it to others to sort through the origins of this phenomenon, one aspect is certain: the increased occurrence of metabolic disease can be traced to a positive energy balance in individuals.

What controls energy homeostasis in the face of excess caloric intake? It is well established that insulin is the major anabolic physiological agent and master regulator of energy storage (Saltiel and Kahn, 2001; Taniguchi et al., 2006). Upon ingestion of protein or carbohydrate, insulin is released from the β cells of the pancreas and, in turn, activates its receptor on fat, muscle and liver cells, increasing glucose, amino acid, and fatty acid uptake and storage, and also blocking breakdown. Insulin thus ensures efficient storage of energy so that it is available for mobilization during fasting, when insulin levels are low. However, chronic overnutrition, undernutrition, or other states of cellular stress can generate insulin resistance (Biddinger and Kahn, 2006; Doria et al., 2008; Olefsky and Glass, 2010; Saltiel, 2001), which is advantageous when energy mobilization is needed. Numerous longitudinal and crosspopulation studies have indicated a strong correlation between obesity and insulin resistance and, similarly, between insulin resistance and diabetes (Reaven, 2005a, 2005b; Stumvoll et al., 2005). Augmented synthesis and secretion of the hormone and expansion of β cell mass counter the increased demand for insulin until β cells can no longer compensate. Taken together, these observations suggest a linear pathway to type 2 diabetes, wherein overnutrition and excess energy accumulation in adipocytes, myocytes, and hepatocytes triggers signals that lead to insulin resistance and, finally, decreased insulin secretion.

Drilling down into the cause of type 2 diabetes has been difficult, and whether there is indeed a teleological explanation for the development of insulin resistance in obesity is unknown. Nevertheless, several questions face us. Why does insulin resistance develop after obesity or overnutrition, and how is it generated? Is insulin resistance cell-autonomous or is it a concerted effect of tissue crosstalk? How does obesity persist in the face of insulin resistance? I propose here that insulin resistance is the physiological response of cells to stressful situations in which it is advantageous to mobilize rather than store energy. One such situation is overnutrition, which is essentially a state of excessive insulin action. Thus, insulin resistance is a homeostatic response that reaches a pathological state as it becomes systemic and sustained. Furthermore, I propose that there are multiple, sequential stages by which this homeostatic response occurs. Outlined here are four steps in the defense against obesity (Figure 1). These steps include homologous desensitization of insulin signaling pathways, secretion of the adipostat leptin, generation of chronic inflammation, and, finally, counterinflammation, during which the evolutionary pressure to store energy eventually overcomes insulin resistance by co-opting insulin signaling pathways, so that insulin resistance fails as a response to limit obesity. Although I concede that this is an oversimplification of a complex process and does not take into account many aspects of receptor signaling, appetite regulation, genetics, β cell biology, and innate immunity, it is put forth as an overarching hypothesis in an attempt to unify some of the perplexing questions regarding obesity and insulin resistance.

Step 1. Homologous Desensitization to Insulin Action

Homeostasis is a universal attribute of biological systems. Not surprisingly, homeostatic mechanisms exist to prevent fat, liver, and muscle cells from the overaccumulation of energy substrates. In the short term, once insulin target cells have reached a threshold, insulin-dependent energy storage is attenuated via acute feedback pathways that impinge on the insulin receptor to decrease its coupling to downstream targets (Figure 2). This kind of homologous desensitization is likely to occur via several mechanisms, including downregulation of the insulin receptor (Bar et al., 1979; Carpentier et al., 1985), increased expression or activity of protein tyrosine phosphatases that can inactivate the receptor or its substrates (Yip et al., 2010), or activation of phosphoinositide phosphatases, such as PTEN, SHIP2, or myotubularin that reduce levels of signaling phosphoinositides (Lazar and Saltiel, 2006).

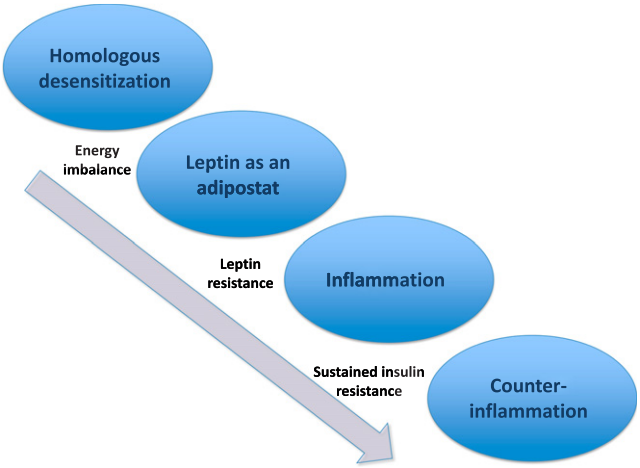

Figure 1. The Four-Step Response to Obesity

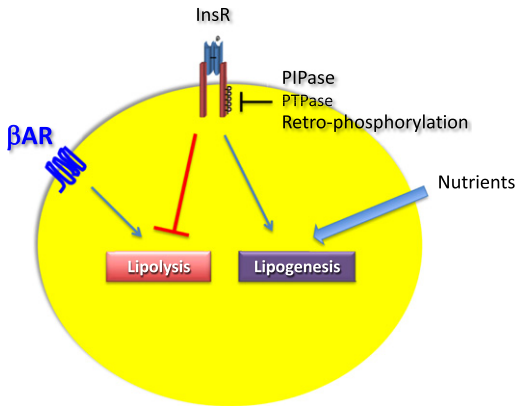

Figure 2. Step 1: Homologous Desensitization

Insulin increases nutrient uptake and storage as lipid in adipocytes through different pathways, including Akt and mTORC1. After sustained activation of its receptor, insulin signaling is downregulated through several mechanisms, including reduced cell-surface expression of its receptor, increased activity of tyrosine phosphatases (PTPases) and inositol lipid phosphatases (PIPases), and retrophosphorylation of insulin receptor substrates, reducing their tyrosine phosphorylation. Lipid accumulation can also produce substrate retro-phosphorylation via PKC's.

In addition to these mechanisms, desensitization can occur from retrophosphorylation events that reduce signaling from the receptor (Zick, 2005). Insulin receptor signaling is initiated upon the tyrosine phosphorylation of intracellular substrates, particularly the insulin receptor substrate (IRS) family of proteins. These tyrosine phosphorylation events are attenuated when IRS proteins are serine phosphorylated. This occurs on a number of sites, due to the activities of several different protein serine kinases (Aguirre et al., 2002; Hotamisligil et al., 1996; Zick, 2005). Some of these are stimulated by insulin itself, including the MAP kinase ERK, mTORC1, and S6 kinase. Thus, insulin can produce a negative feedback loop that diminishes the activity of a lipogenic or glycogenic pathway, representing the first line of defense against excessive insulin action.

Negative feedback in insulin signaling can also acutely result from lipogenesis. Several studies have demonstrated that diacylglycerides, in particular, lead to activation of protein kinase C isoforms that may also catalyze serine phosphorylation of IRS proteins, resulting in their decreased tyrosine phosphorylation (Kim et al., 2004). It is possible that this phenomenon explains the acute insulin resistance that has been observed upon lipid infusion in rodents or humans, which may be a model of short-term receptor desensitization (Itani et al., 2002; Samuel et al., 2010; Savage et al., 2007).

Step 2. Leptin as an Adipostat

Perhaps the most important discovery of the last quarter century in metabolic research concerns the role of leptin as a feedback regulator of energy storage (Friedman, 2004; Friedman and Halaas, 1998), thus exposing the role of adipocytes as endocrine cells (Figure 3). Although leptin is not the only counterregulatory hormone for insulin, it stands alone as an adipostat that responds directly to energy status in the adipocyte (Badman and Flier, 2007). Although the molecular mechanisms involved in the regulation of leptin synthesis and secretion have not been elucidated, there is clear evidence that levels of the hormone fall during starvation and are elevated with feeding (Spiegelman and Flier, 2001). Once released into the circulation, leptin acts on receptors, located primarily in the hypothalamus, to produce three major effects that are catabolic and, thus, directly opposed to insulin action. First, leptin represses appetite, reducing nutrient intake and availability (Spiegelman and Flier, 2001). Second, acting via the sympathetic nervous system, leptin increases activity of the hepatic AMP-activated protein kinase (AMPK), producing a cascade of phosphorylation events that results in reduced lipogenesis and increased fatty acid oxidation (Kahn et al., 2005; Minokoshi et al., 2002). Finally, sympathetic activation also causes increased β-adrenergic activity in both brown and white fat cells, stimulating lipolysis and expression of uncoupling protein 1, thus coordinately increasing fatty acid generation from triglyceride and oxidation via cAMP production (Collins et al., 1996; Halaas et al., 1997; Rosenbaum and Leibel, 2010).

Although leptin is perhaps the most potent anorexic hormone that responds directly to nutritional status, states of obesity in both humans and rodents are commonly associated with leptin resistance and high leptin levels (Myers et al., 2010). As such, leptin has not proven to be an effective anti-obesity agent in obese patients (Tam et al., 2011). However, when administered to mice (Halaas et al., 1995; Pelleymounter et al., 1995) or to patients with mutations in the leptin gene (Farooqi et al., 2007) or lipodystrophy (Oral et al., 2002), the hormone not only reverses obesity, but also has profound antidiabetic effects with dramatically improved insulin resistance. This illustrates well the apparent paradox in which insulin resistance can be overcome by administration of an agent that effectively opposes insulin action. Likewise, metformin and other biguanides mimic part of leptin's indirect action in the liver by activating AMP-activated kinase (AMPK) (Hardie, 2003; Zhou et al., 2001), whereas β3 adrenergic agonists can mimic leptin's indirect actions at the adipocyte by increasing lipolysis and fat oxidation (Grujic et al., 1997). Both agents improve insulin resistance, even though they act in a manner that is diametrically opposed to the anabolic effects of the hormone.

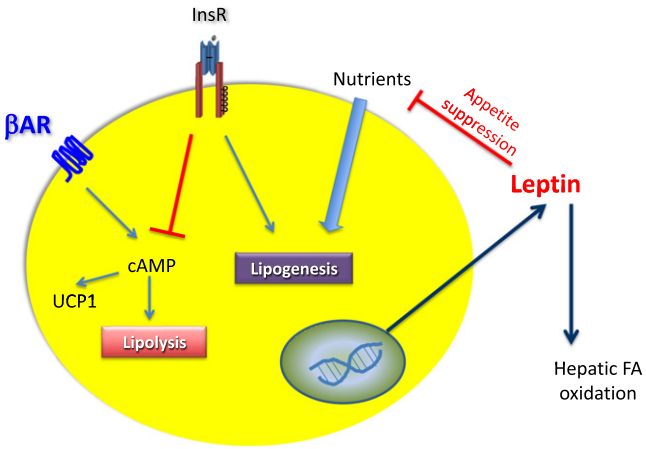

Figure 3. Step 2: Leptin as an Adipostat
Adipocytes sense size or lipid stores through an unknown mechanism and, in turn, secrete the hormone leptin. Leptin binds to receptors in the hypothalamus, which activates neuronal pathways that 1) reduce appetite; 2) activate hepatic fatty acid oxidation while reducing lipogenesis; and 3) increase sympathetic activity, resulting in release of norepinephrine to activate the β-adrenergic receptors in adipocytes.

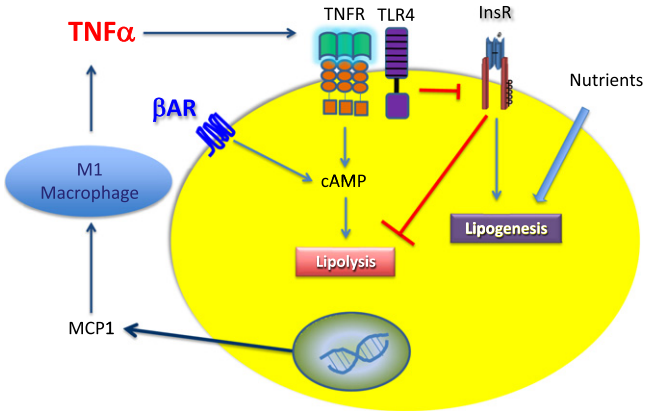

Figure 4. Step 3: Inflammation
As leptin resistance occurs, the adipocyte continues to expand and store lipid. At some point, through mechanisms that are not well understood, chemokines, such as MCP1, are released that recruit M1-polarized proinflammatory macrophages to adipose tissue. These macrophages, in turn, secrete TNF-α, IL-6, and other proinflammatory cytokines that bind to receptors on adipocytes. At the same time, Toll receptors are activated, perhaps in response to local increases in fatty acids. Together, these receptors initiate MAP kinase pathways that increase lipolysis and desensitize insulin action via the mechanisms described in Figure 2.

Step 3. Inflammation

Although receptor desensitization and leptin both oppose insulin action to limit excess energy accumulation, the development of leptin resistance and other adaptive responses ensures that energy storage continues in the face of continued overnutrition. It is difficult to ascertain the precise temporal relationship of these different biological events (Lee et al., 2011), but careful high-fat diet feeding studies in rodents suggest that the next line of defense against obesity is inflammation (Li et al., 2010b; Olefsky and Glass, 2010). Compelling evidence has accrued that both genetic and dietary forms of rodent obesity are accompanied by generation of a low-grade inflammation in adipose and liver tissue (Gregor and Hotamisligil, 2011; Hotamisligil, 2010; Lumeng and Saltiel, 2011). Moreover, there is now considerable reason to conclude that in many cases the generation of inflammation may be a key link between obesity and sustained insulin resistance. Almost all rodent models of obese insulin resistance are associated with chronic inflammation, and there has been a strong correlation between insulin resistance and inflammatory markers in studies of several patient groups (Aron-Wisnewsky et al., 2009; Blackburn et al., 2006; Festa et al., 2002; Pradhan et al., 2001). This inflammation is generally low-grade and accompanied by macrophage switching from a type 2 to type 1 polarization state (Lumeng et al., 2007a; Odegaard and Chawla, 2011; Schenk et al., 2008), as well as the presence of additional inflammatory cells (Feuerer et al., 2009; Nishimura et al., 2009; Winer et al., 2009, 2011). Additionally, coculture studies (Lumeng et al., 2007b) using neutralizing antibodies directed against different proinflammatory cytokines have demonstrated in vitro that inflammatory signals can desensitize cells to insulin via different mechanisms. Inhibition of inflammatory signaling by knockout of key pathways in obese mice, including components of NF-κB (Arkan et al., 2005) and JNK (Hirosumi et al., 2002) pathways, as well as numerous other proinflammatory signaling molecules, scaffolding proteins, and cytokines, can disrupt the link between obesity and insulin resistance (Holland et al., 2007; Hotamisligil, 2010; Lesniewski et al., 2007; Nakamura et al., 2010; Saberi et al., 2009; Shi et al., 2006; Summers, 2010; Vandanmagsar et al., 2011; Wellen et al., 2007). Likewise, different anti-inflammatory pharmacological approaches can also reduce insulin resistance in rodents (Hundal et al., 2002), and recent data indicates that the NF-κB inhibitor salsalate may produce antihyperglycemic effects in patients (Goldfine et al., 2010).

The molecular underpinnings of obesity-induced inflammation have been studied extensively. Proinflammatory adipose tissue macrophages (ATMs) infiltrate fat during the later stages of obesity (Figure 4). Alterations in ATM content and polarization state appear to occur coincident with the development of insulin resistance, but evidence has accumulated that other changes in the innate immune system may precede these events, and ATMs may be effectors of a coordinated inflammatory response that includes the accumulation of Th1 polarized $CD4^+$ T cells and the loss of Tregs, as well as the appearance of B cells, NK cells, NKT cells, eosinophils, neutrophils, and mast cells (Lumeng and Saltiel, 2011; Olefsky and Glass, 2010).

The primary signals in adipocytes and hepatocytes that trigger this inflammatory response remain a point of contention. Studies have implicated ER stress (Hotamisligil, 2010), adipose tissue hypoxia (Hosogai et al., 2007), enhanced lipolysis (Kosteli et al., 2010), and adipocyte death (Cinti et al., 2005). However, although blocking these signals in some cases may prevent inflammation and development of sustained insulin resistance, these changes occur fairly late in the progression of the disease and probably are not initiating events. In this regard, a leading hypothesis for how inflammation is initiated from within fat and liver tissue remains the secretion of chemokines, such as MCP1, Rantes, and others (Weisberg et al., 2006). The signals that lead to release of these hormones remain unknown, but

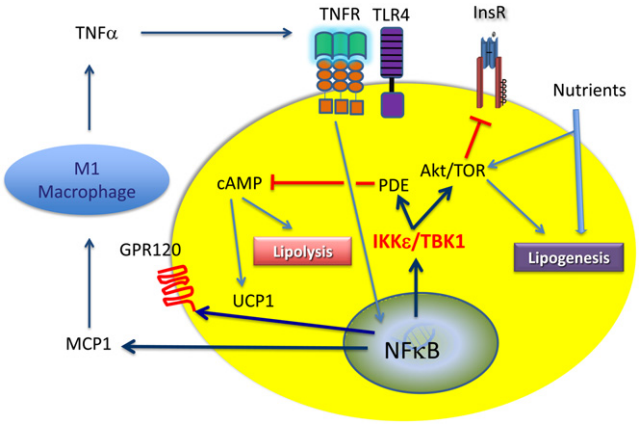

Figure 5. Step 4: Counter-Inflammation
One major attribute of inflammation in obesity is that it is sustained and low-grade. This is due in part to counter-inflammatory pathways that are activated by cytokines, such as increased expression of the GPR120 receptor for anti-inflammatory fatty acids. NF-κB activation also increases the expression of the noncanonical IKKs, IKKε and TBK1, which co-opt insulin signaling pathways to increase lipogenic and decrease lipolytic programs in the absence of insulin action.

probably involve some kind of energy-sensing mechanism. One interesting possibility is that mechanotransduction pathways may be involved, particularly in adipose tissue. The extracellular matrix limits the expansion of fat cells during obesity (Chun et al., 2006; Kim et al., 2007). Moreover, adipose tissue shows signs of fibrosis in obese states (Spencer et al., 2011), characterized by production of collagen VI (Pasarica et al., 2009), and mice lacking collagen VI become morbidly obese on high-fat diet, without any evidence of inflammation or insulin resistance (Khan et al., 2009). Thus, it is possible that matrix-dependent signaling senses a physical limit of fat-cell expansion, initiating activation of pathways that lead to chemokine secretion.

It is worth considering that these adaptive immune responses might be beneficial, and function to preserve metabolic homeostasis, particularly when other adaptive responses, such as leptin, have failed. Inflammation is generally associated with a catabolic state, leading to energy mobilization to combat infection and other stresses. The inflammatory cells that infiltrate liver and adipose tissue release proinflammatory cytokines that generally activate catabolic pathways (Figure 4). For example, TNF-α, originally identified because of its potent catabolic actions (Torti et al., 1985), can increase lipolysis via MAP kinase pathways in adipocytes (Souza et al., 2003) while also producing serine phosphorylation of IRS proteins to block insulin signaling, using the same pathways involved in homologous desensitization. Pattern recognition receptors that might respond to bacterial products or even fatty acids can similarly activate different MAP kinase pathways (Dunne and O'Neill, 2003). At the same time, other proinflammatory signaling pathways that have been implicated in obesity, including ER stress (Hotamisligil, 2010) and ceramide synthesis (Summers, 2010), as well as JNK and NF-κB activation (Arkan et al., 2005; Hirosumi et al., 2002), can potentiate these phosphorylation pathways while promoting the secretion of more inflammatory cytokines and chemokines to prolong or amplify inflammatory signals.

In addition to correlations between the degree of inflammation and insulin resistance (Ortega Martinez de Victoria et al., 2009), it is also interesting to note that both patients and rodents with the most extreme forms of obesity can be relatively sensitive to insulin and, similarly, lack notable signs of inflammation (Bogardus et al., 1985). Likewise, treatment of mice and diabetic patients with PPARγ-activating thiazolidinediones (Patsouris et al., 2009) or constitutive activation of PPARγ in fat cells by deletion of corepressors (Li et al., 2011b) can block sensing of proinflammatory signals, as well as recruitment of inflammatory cells in adipose tissue, whereas activation of this nuclear receptor is often associated with weight gain and expansion of adipose tissue (Lu et al., 2011). Taken together, these data suggest that inflammation may represent another line of defense against excess nutrient storage, mainly by blocking or counteracting insulin action.

Step 4. Counter-Inflammation

The inflammatory response induced by obesity in liver and fat tissue includes most of the expected cell types, but lacks many of the cardinal signs of classic inflammation (i.e., dolor, rubor, calor, tumor). This has led Hotamisligil et al. (Gregor and Hotamisligil, 2011) to coin the term "meta-inflammation" to describe the low-grade, sustained nature of obesity-induced inflammation. How is it that this particular inflammatory response fails to resolve, and why does the resulting insulin resistance fail to stop continued energy storage? One possible explanation may lie in the homeostatic response to inflammation itself, or counter-inflammation, which attenuates the extent to which inflammatory signals are effective (Figure 5).

Counter-inflammation can be expressed in different forms. In the first, classical response, inflammatory pathways can feedback-inhibit themselves, toning down their response in a cell-autonomous manner. This is particularly well established with the NF-κB and p38 pathways, in which there are feedback signals that block upstream phosphorylation events in immune cells (Delhase et al., 1999), particularly involving the TAB/TAK axis (Clark et al., 2011). During obesity, proinflammatory macrophages increase their expression of GPR120, a receptor for anti-inflammatory omega-3 fatty acids, thus inducing sensitization to a feedback signal (Oh et al., 2010). There are also genes induced by NF-κB that can feedback-inhibit the pathway, particularly the noncanonical kinases IKKε and TBK1 (Kawai and Akira, 2007). Indeed, macrophages isolated from IKKε knockout mice are hyperresponsive to activation by TNF-α and LPS (unpublished data). Additionally, the intriguing and confusing observations regarding the role of IL-6 in regulating insulin sensitivity may also reflect a counter-inflammatory process in which IL-6 expression during obesity induces the expression of anti-inflammatory cytokines, such as IL-10 (Allen and Febbraio, 2010). Thus, one intriguing possibility is that these counter-inflammatory processes maintain inflammation in a low-grade state, prohibiting its resolution.

Although counter-inflammatory mechanisms can tone down inflammation in macrophages, how about the catabolic effects of inflammatory cytokines in liver and fat cells? Interestingly, the noncanonical IKKs, IKKε and TBK1, are induced during obesity but do not appear to function as IκB kinases in this setting (Chiang et al., 2009). Moreover, anti-inflammatory

treatments, such as TZDs or omega-3 fatty acids, reduce expression of these kinases (unpublished data), suggesting that they are induced by inflammatory cytokines, rather than participating in inflammation. In this regard, both kinases contain NF-κB sites in their promoters and are markedly induced by both TNF and LPS (Kravchenko et al., 2003).

The first clue to the counter-inflammatory role of the noncanonical IKKs came from knockout studies of IKKε. Deletion of the IKKε gene rendered mice partially resistant to weight gain, insulin resistance, steatosis, and the long-term inflammation produced by high-fat diet (Chiang et al., 2009); this has been reproduced by administration of an IKKε/TBK1 inhibitor to diet-induced obese or Ob/ob mice (unpublished data). Similar observations have been made after knockout of the mTORC1 adaptor protein, Raptor (Polak et al., 2008), as well as S6 Kinase 1 (Um et al., 2004). One interpretation of these results is that different counter-inflammatory events are activated in order to favor long-term energy conservation. In this regard, insulin receptor resistance in liver and adipose tissue is often accompanied by elevations in basal signaling patterns or expression of signaling molecules (Wan et al., 2011b; Yang et al., 2003), and deletion of Akt can prevent obesity by increasing energy expenditure (Wan et al., 2011a). In liver, the observation of mixed insulin resistance, in which the antigluconeogenic effects of insulin are attenuated, whereas while lipogenesis is preserved, may be an example of this phenomenon (Li et al., 2010a). Moreover, obesity is associated with desensitization to sympathetic activation in white and brown fat (Seals and Bell, 2004), resulting in decreased lipolysis and fat oxidation. The mechanisms underlying these counter-inflammatory changes are uncertain, but they may also occur as a consequence of increased nutrient signaling (Wang et al., 2011a). In either event, the co-opting of anabolic signaling pathways by counter-inflammatory kinases like IKKε and TBK1, or nutrient activation of mTORC1, can generate insulin-independent, constitutive activation of lipogenic and glycogenic pathways, while subsequently promoting feedback inhibition of insulin receptor signaling. Thus, these insulin-like effects can paradoxically block insulin action.

Should We Rethink the Treatment of Metabolic Disease?

These observations raise important questions about the treatment of obesity and type 2 diabetes. Although there is little doubt that insulin resistance is a key factor in the generation of type 2 diabetes, it may be overly simplistic to think that merely improving or mimicking insulin action would provide an effective solution to this problem. If insulin resistance is indeed a normal physiological response to overnutrition at the cellular level, new approaches may be needed to block energy storage or allow energy utilization as a more effective method to treating this devastating disease. Although this seems to be a paradoxical approach to the treatment of insulin resistance, it may be the best bet in developing new weapons in the fight against this epidemic.

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