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HIF-2α Blows Out the Flames of Adipose Tissue Macrophages to Keep Obesity in a Safe Zone

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In 1993, Hotamisligil et al. (1) broke new ground by linking immune response and metabolism. A striking observation in this early study was the upregulation of the inflammatory cytokine tumor necrosis factor-α in adipose tissue (AT) of obese and insulin-resistant animals. Although adipocytes were thought to be the major source of inflammatory cytokines in fat, Weisberg et al. (2) later showed that macrophages accumulate in the AT of obese animals, creating a state of low-grade inflammation that could trigger insulin resistance. Since then, the concept of "immunometabolism" has gradually evolved, and many types of immune cells have been shown to contribute to AT inflammation and insulin resistance (3). For instance, macrophages secrete proinflammatory cytokines and other factors, which could impair insulin sensitivity. In light of this evidence, it has been suggested that decreasing inflammation in AT could attenuate the diabetic state. In support of this idea is the fact that anti-inflammatory drugs appear to have provided proof-of-concept that inflammation is linked to the deleterious effects of insulin resistance in animals (4,5). Paradoxically, recent studies suggest that inflammation is also required for maintaining AT homeostasis (6–8). These complex findings emphasize the need for a more nuanced understanding of the role immune cells play in the development of insulin resistance.

Adipose tissue macrophages (ATMs) have been categorized into two distinct populations: proinflammatory (M1) and anti-inflammatory (M2). While ATM subpopulations have overlapping inflammatory profiles, it is generally accepted that a polarization of M2 macrophages toward an M1 phenotype occurs in the AT of obese animals. Importantly, the AT microenvironment seems to play a major role in this phenotypical switch (9). One of the signals triggering this ATM polarization is hypoxia, which has been of particular interest in recent years (10). The lack of de novo angiogenesis during the large AT expansion that occurs in obesity leads to a reduced blood flow and increased oxidative stress in this tissue in animals (7). However, whether this hypothesis has application in human AT is still controversial (11). At the molecular level, hypoxia stimulates the transcriptional activity of the hypoxia-inducible factor, HIF-1α. In turn, this factor controls the expression of inducible nitric oxide synthase (iNOS), which is involved in nitric oxide (NO) production (12). Excessive NO production in AT promotes inflammation, thereby contributing to the impairment of insulin sensitivity in obesity (9). HIF-2α is another hypoxia-responsive component of the HIF family that is also expressed in macrophages (13). HIF-1α and HIF-2α have been shown to play opposite roles in the regulation of macrophage function in vitro and in vivo (14). This raises the important question that Choe et al. (15) address in this issue of *Diabetes*: How do these two isoforms regulate ATM phenotype and its consequence on whole-body metabolism?

Choe et al. demonstrate that M2 macrophages express high levels of HIF-2α in the AT of obese mice. It has been recently shown that HIF-1α and HIF-2α antagonize each other in the regulation of NO production, resulting in different effects on the macrophage inflammatory profile (14). iNOS produces NO by metabolizing its substrate, the amino acid L-arginine (16). Arginase 1 (ARG1) is highly expressed in M2 macrophages and competes with iNOS for their common substrate, L-arginine, to produce ornithine and urea (17). Therefore, ARG1 activity can decrease NO production via the limitation of arginine availability (18). Choe et al. provide evidence that HIF-2α could partially prevent obesity-associated inflammatory response and insulin resistance through activation of ARG1 (Fig. 1). Accordingly, in gain- and loss-of-function experiments, macrophage HIF-2α prevented

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See accompanying article, p. 3359.

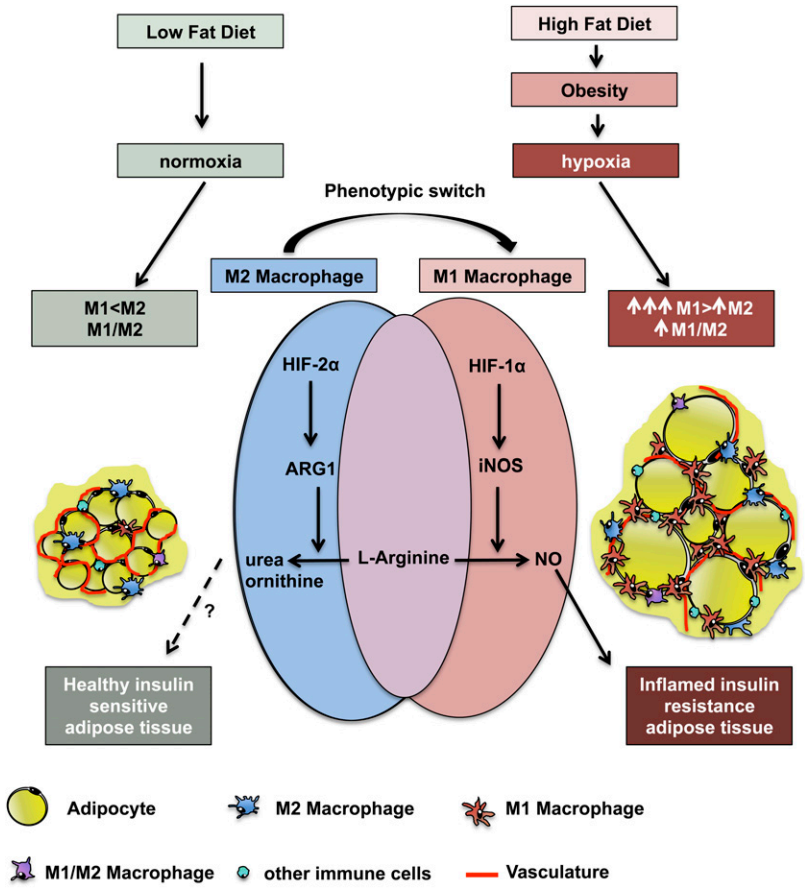

Figure 1—Hypothetical model for HIF-2α regulation of macrophage inflammatory phenotype and AT insulin sensitivity. High-fat diet–induced obesity is associated with AT hypoxia, which stimulates HIF-1α activity and the production of NO via iNOS. Excess production of NO in the AT promotes a phenotypical switch from M2 macrophages toward M1. Thus, increased HIF-1α activity leads to AT inflammation and insulin resistance. HIF-2α, by inducing the expression of ARG1, decreases the production of NO, maintaining the M2 phenotype. Therefore, HIF-2α may promote insulin sensitivity by preventing AT inflammation.

insulin resistance in adipocytes, which was induced by co-culture with macrophages or inflammatory signals. These findings raise other interesting questions. Are these effects mediated by ARG1? Would genetic manipulation of *arg1* mimic the effect of *hif2α* silencing or overexpression? In vivo, Choe et al. demonstrate that *hif2α* haplodeficiency exacerbates AT inflammation and insulin resistance induced by high-fat feeding. These findings support macrophage HIF-2α as a protective factor for AT homeostasis and insulin sensitivity.

Perhaps the most interesting finding in this study is that macrophages in the AT can express a beneficial factor, HIF-2α, in response to a stress stimulus such as hypoxia in the obese state. This observation is consistent with other studies showing a dual role for macrophages in regulation of whole-body metabolism. This shifts the paradigm that ATMs are exclusively detrimental to insulin sensitivity (8,19). However, whether hypoxia actually induces HIF-2α in ATMs of obese animals is still unclear. Although expression of HIF-2α was increased in the AT of obese mice compared with lean controls, where hypoxia has been previously observed, the signal that regulates *hif2α* expression or transcriptional activity is unknown. Similar to previously published studies (14,20), it would be interesting to test whether hypoxia or cytokine treatment, such as the anti-inflammatory cytokine interleukin-4, actually affects HIF-2α levels or activity in ATMs. Taken as a whole, the findings by Choe et al. provide evidence that HIF-2α plays an important role in maintaining ATMs in an anti-inflammatory state, but whether macrophage-specific HIF-2α is actually contributing to the regulation of obesity insulin resistance remains unclear. Depletion of macrophages in AT failed to decrease HIF-2α expression while restoring normal glucose tolerance, suggesting that HIF-2α expressed by other cells or organs could contribute to the observed phenotype. The specific contribution of ATM HIF-2α to AT and whole-body insulin sensitivity remains to be demonstrated.

Choe et al. (15) have provided evidence that a tightly controlled balance in HIF activity might play an important role in regulation of AT inflammation and insulin sensitivity. The new study raises the crucial question of whether macrophages are actually physiological or pathological components of the AT. This is particularly

important as it is still unclear whether anti-inflammatory drugs represent a valid therapeutic approach for metabolic disease in humans. Recently, particular attention has been drawn to the role of hypoxia-induced fibrosis in regulation of AT function and systemic metabolic impairment in humans (21). Similar to HIF-1α, an obvious question is whether HIF-2α is involved in AT remodeling.

Answering these questions may lead to the discovery of new therapeutic approaches for metabolic diseases.

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