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Highlights From the Latest in Diabetes Research

New Approach to Targeted Silencing of TNF-α and Osteopontin Expression in Adipose Tissue

The growing impact of the obesity epidemic promises that type 2 diabetes will remain a public health burden well into the future. Novel therapeutic strategies aimed at reducing diabetes risk are badly needed, and ones that focus on adipose tissue (AT) may be particularly useful because of the central role that this tissue plays in diabetes risk. It has been demonstrated that when macrophages gain access to AT and become activated, they secrete inflammatory cytokines that create a chronic state of inflammation. It has also been suggested that this state of ongoing inflammation increases diabetes risk. Indeed, an inverse association has been shown between macrophage numbers in visceral AT and insulin sensitivity. However, although there is a great deal of evidence supporting the idea that abnormalities of glucose metabolism result—at least in part—from chronic inflammation in AT, data that reflect a direct observation of this connection are absent from the literature. The reason for this gap is rather simple: It has not been possible to manipulate the expression of macrophage inflammatory genes in AT without impacting the expression of these genes in other tissues. Direct evidence of the role of AT-associated inflammation in glucose regulation could be demonstrated if there were a method to ablate these genes only in AT macrophages and relate this to improved glucose tolerance. A new study by Aouadi et al. not only shows a novel technique for silencing genes specifically in AT macrophages, it also demonstrates that obese mice whose tumor necrosis factor-α (TNF-α) and osteopontin were silenced in epididymal AT macrophages experienced improved glucose tolerance. The investigators injected glucan-encapsulated small interfering RNA particles (GeRPs) into obese mice and observed that they accumulated primarily in the AT but not in other tissues such as heart, liver, spleen, pancreas, lung, or kidney. Additional experiments indicated the injection of GeRPs resulted in significant depletion of TNF-α and osteopontin and an accompanying improvement in glucose tolerance. These intriguing findings support a direct role for AT inflammation in glucose dysregulation and suggest a potential application of gene-targeted therapy to improve insulin sensitivity. — *Helaine E. Resnick, PhD, MPH*

■ Aouadi et al. Gene silencing in adipose tissue macrophages regulates whole-body metabolism in obese mice. Proc Natl Acad Sci U S A 2013;110:8278–8283

New Review Examines Hypoglycemia-Associated Autonomic Failure

Successful treatment of diabetes often involves the need to balance aggressive control of blood glucose with avoidance of hypoglycemia. Although hypoglycemia can be caused by an absolute excess of therapeutic insulin, it occurs most often in individuals without marked insulin excess but whose defenses against hypoglycemia are compromised. Often these individuals have β-cell dysfunction characterized by a failure to lower insulin levels and increase glucagon secretion. Attenuation of epinephrine secretion is also commonly observed. These altered responses contribute to attenuation of responses to hypoglycemia, which can lead to hypoglycemia unawareness. In turn, the lack of awareness of hypoglycemia substantially increases the risk of subsequent hypoglycemic episodes, a cycle that can have serious consequences for the patient. This complex cycle of altered responses to hypoglycemia has been termed hypoglycemia-associated autonomic failure (HAAF), and it is the focus of a recently published review in *The New England Journal of Medicine*. The new report explores the mechanisms underpinning the loss of insulin and glucagon responses as well as those responsible for attenuation of sympathoadrenal responses. Significant attention is given to four hypotheses that could explain how the central nervous system mediates attenuation of sympathoadrenal responses. These include the systemic-mediator, brain fuel–transport, brain-metabolism, and cerebral-network hypotheses. The review emphasizes that attenuation of sympathoadrenal responses is a key feature of HAAF, and in the setting of β-cell failure of both insulin and glucagon responses, attenuation of neural responses not only causes hypoglycemia unawareness but it is also the cause of deficits in glucose counterregulation. — *Helaine E. Resnick, PhD, MPH*

■ Cryer. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2013;369:362–372

mTOR: A Messenger Between Immune Function and Metabolic Programming

mTOR is the target of rapamycin, a macrolide produced by *Streptomyces Hygroscopicus* bacteria. In mammals, the protein kinase mTOR signaling network integrates environmental cues (e.g.,

immune signals and metabolic cues) to control anabolic and catabolic processes. mTOR interacts with other proteins to form mTOR complex 1 (mTORC1) and 2 (mTORC2). These complexes have different sensitivities to rapamycin as well as upstream inputs and downstream outputs. The aim of a new report by Zeng et al. was to uncover the missing link between immunological signal sensing and immune function activation by T_{reg} cells. Since mTOR signaling has been shown to regulate T-cell differentiation and function, the investigators speculated that mTOR signaling may play a role in the regulation of naturally occurring T_{reg}-cell homeostasis and function. The new report concluded that mTORC1 signaling is an important determinant of T_{reg}-cell function in mice. This was supported by the observation that naturally occurring T_{reg} cells had elevated mTORC1 activity compared with naïve T cells at steady state, and that signals through the T-cell antigen receptor (TCR) and interleukin-2 can promote mTORC1 activation and suppress T_{reg}-cell function. These observations suggested a direct relationship between mTORC1 and T_{reg} suppressive activity. Moreover, disruption of mTORC1 through T_{reg}-specific deletion of the essential component of the regulatory-associated protein of mTOR (raptor) leads to a profound loss of T_{reg}-cell suppressive activity in vivo and fatal inflammatory responses that are indicative of a loss of T_{reg} function. Using functional genomics and comparing gene expression profiles of T_{reg} cells from $Cd4^{cre}Rptor^{fl/fl}$ and wild-type mice, the investigators determined that mTORC1 promotes cholesterol/lipid biosynthesis in T_{reg} cells with the mevalonate pathway playing a pivotal role in coordinating T_{reg}-cell proliferation and upregulation of T_{reg}-cell surface effector molecules (i.e., CTLA4 and ICOS) to maintain T_{reg}-cell function integrity. Finally, they provided evidence that mTORC1 maintains T_{reg}-cell function partly through inhibiting the mTORC2 pathway. Findings from this research provide a fundamental understanding of how immunological signals are sensed and integrated by T_{reg}-cell function. Adhering to its ancient role in coordinating signals from the extracellular milieu to corresponding changes in the intracellular processes, mTORC1-dependent metabolic programming appears to be the central mechanism that T_{reg} cells use to link immunological inputs to metabolic activity and function. This may be a central mechanism that has evolved and been preserved to maximize our adaptation to the volatility of the environment. — *Jenny Tong, MD, MPH*

■ Zeng et al. mTORC1 couples immune signals and metabolic programming to establish T_{reg}-cell function. Nature 2013;499:485–490

From Mast Cell Stabilizer to Metabolic Wonder Drug?

Chronic, low-grade inflammation in liver and fat—accompanied by local secretion of cytokines and chemokines—attenuates insulin action. The nuclear factor-κB (NF-κB) signaling pathway plays an important role in this process. NF-κB activation is triggered by phosphorylation of the regulatory protein IκB. IKK-ε and TANK-binding kinase 1 (TBK1) are the noncanonical IκB kinases (IKKs). Unlike IKK-α and IKK-β, their role in NF-κB activation has been unclear. A new report by Reilly et al. shows that both high-fat diet (HFD) and chronic tumor necrosis factor (TNF)-α treatment increased TBK1 and IKK-ε kinase activity and expression levels in mouse liver and adipose tissue. Perhaps the most important aspect of the newly published work was the demonstration of the metabolic benefits of amlexanox, a selective TBK1 and IKK-ε inhibitor that is currently approved for the treatment of mouth ulcers and asthma. In mice, 4 weeks of amlexanox treatment prevented HFD-induced obesity (DIO) and induced a 10-g weight loss, which was accompanied by a reduction in fat mass. Dose escalation did not lead to further weight loss, but discontinuation of the drug restored weight gain. While food intake was not altered by amlexanox, an increase in energy expenditure and thermogenesis were observed in the obese mice. Importantly, amlexanox treatment also improved glucose tolerance and insulin sensitivity (particularly in the liver) in DIO and *ob*/*ob* mice. Furthermore, TBK1 and IKK-ε inhibition reduced lipogenesis, and most impressively, it reversed hepatic steatosis in obese mice. In adipose tissue, amlexanox reduced inflammation and promoted energy expenditure. Overall, the findings from this research support a role of IKK-ε and TBK1 in the counterinflammation process that is responsible for energy storage in the presence of insulin resistance. Disrupting this process with amlexanox treatment appears to lead to increased energy expenditure and improved insulin sensitivity. But it is not clear how amlexanox, a mast cell stabilizer, can increase energy expenditure and reduce lipid storage. Also unknown is whether the desirable metabolic benefits observed in mice treated with this agent can be replicated in humans. — *Jenny Tong, MD, MPH*

■ Reilly et al. An inhibitor of the protein kinases TBK1 and IKK-ε improves obesity-related metabolic dysfunctions in mice. Nat Med 2013;19:313-321

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