Cell Metabolism
Previews

The work of Haschemi et al. (2012) provides further evidence of differential metabolic reprogramming of immune cells in response to differentiation signals. These results raise the key question of whether the metabolic changes in macrophages simply reflect a general response to microbial stimuli or whether metabolic flux directly influences cellular differentiation programs to shape inflammatory immune responses. If the latter is true and metabolic patterning can direct lineage specification, then how may this phenomenon occur? Many transcription factors including NF-κB contain redox-sensitive Cys residues (Nishi et al., 2002) and can be influenced by the cellular redox state. Maintenance of a high NADH:NAD$^+$ ratio induced by LPS stimulation (and suppressed by CARKL) may enhance NF-κB binding activity and favor M1 macrophage differentiation. Another possibility is that changes in metabolic flux may influence epigenetic imprinting. Recent work has shown that metabolic enzymes can affect histone acetylation and demethylation activity (Lu et al., 2012; Wellen et al., 2009), which may impact cell-differentiation programs. It is unclear whether S7P possesses signaling properties beyond its role as a PPP intermediate. Further exploration of how signal-transduction pathways downstream of immune and cytokine receptors influence cellular metabolism may help us understand how metabolism may impact cellular differentiation and effector function in the immune system.

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Hidden Variant of ChREBP in Fat Links Lipogenesis to Insulin Sensitivity

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The ChREBP transcription factor is regulated by glucose and plays a role in insulin sensitivity, but the mechanism underlying these effects remains unclear. In a recent *Nature* article, Herman et al. (2012) show that a shorter ChREBP isoform (ChREBP-β) links glucose transport to lipogenesis in white adipose tissue.

The quest for the molecular factor mediating the transcriptional effects of glucose remained unfruitful until ChREBP (carbohydrate responsive element binding protein) was cloned in 2001 (Yamashita et al., 2001). Glucose modifies ChREBP at the posttranslational level (Bricambert et al., 2010; Guinez et al., 2011) and stimulates its nuclear translocation, thereby promoting binding to a ChREBP binding site (ChoRE) present on its target genes, which include glycolytic and lipogenic genes. The relationship of ChREBP with insulin resistance is complex: whereas its inhibition in liver of obese mice counteracts fatty liver and systemic insulin resistance (Dentin et al., 2006), ChREBP overexpression, by modifying hepatic fatty acid composition, promotes a state of hepatic steatosis that is dissociated from insulin resistance (Benhamed et al., 2012). Furthermore, ChREBP is also expressed in white adipose tissue (WAT), a target site of insulin resistance in obesity-related diseases. Decreased glucose transport and metabolism in adipocytes together with alterations in

the release of fatty acids, cytokines, or adipokines are potential inducers of systemic insulin resistance, suggesting a potential role for ChREBP in this tissue. In a recent issue of *Nature*, Herman and colleagues (Herman et al., 2012) report that ChREBP links lipogenesis—de novo fatty acid synthesis in WAT— to insulin sensitivity, and reveal the existence of a natural ChREBP variant that may help transmit the transcriptional effects of glucose.

Using mouse models of adipose specific overexpression (OX) and deletion (KO) of the glucose transporter GLUT4, the authors identify ChREBP as a key mediator of GLUT4 effects and a central modulator of lipogenesis in WAT (Figure 1A). GLUT4-OX mice show enhanced glucose tolerance and insulin sensitivity. Even fed with a high-fat diet (HFD), these mice are protected against glucose intolerance, possibly due to the persistence of WAT lipogenesis. The induction of lipogenesis in WAT of GLUT4-OX mice was abrogated, however, when these mice were crossed with ChREBP-deficient (ChREBP-KO) mice. Importantly, GLUT4-OX/ChREBP-KO mice showed a reversal of enhanced glucose tolerance and insulin sensitivity that was independent of a change in circulating free fatty acids or an alteration in glucose transport rates. These results suggest that beneficial lipids (lipokines) secreted by adipose tissue upon activation of lipogenesis can affect whole-body insulin sensitivity (Cao et al., 2008). In support of this idea, the authors provide evidence that ChREBP presence correlates with insulin sensitivity in humans (nondiabetic and obese patients). The exact contribution of ChREBP to the phenotype of GLUT4-OX mice under HFD will require further analysis, however. In the absence of ChREBP, HFD-fed GLUT4-OX mice would be expected to become severely glucose and insulin intolerant
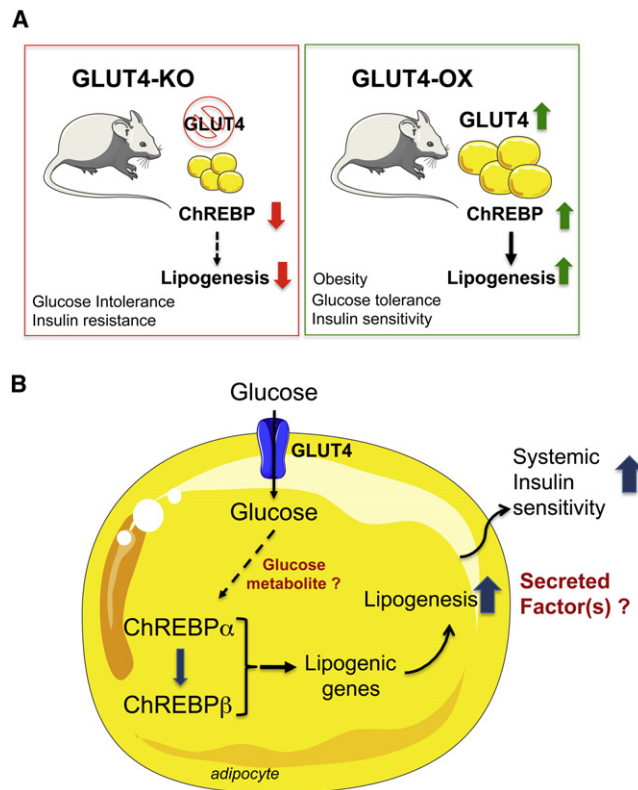
Figure 1. ChREBP Exerts Beneficial Effects on Systemic Insulin Sensitivity through Its Control of de novo Lipogenesis
(A and B) ChREBP expression is reciprocally regulated in white adipose tissue (WAT) in mouse models of GLUT4 overexpression (GLUT4-OX) and deletion (GLUT4-KO) (A). Summary of their phenotypes in relationship to lipogenesis (de novo fatty acid synthesis) or systemic insulin sensitivity is shown (B). Glucose stimulation induces ChREBP-α, which then transcriptionally activates ChREBP-β (a shorter and more potent isoform). The beneficial effects of ChREBP on glucose homeostasis most likely result from upregulation of lipogenesis in adipose tissue or from the release of beneficial adipokines or lipokines.

due to a marked decrease in WAT lipogenesis.

An important finding of the study by Herman and colleagues (Herman et al., 2012) is the identification of a novel variant of ChREBP named ChREBP-β. The authors, with the goal of understanding the transcriptional regulation of ChREBP, searched the ChREBP genomic region for carbohydrate response elements (ChoREs), representing potential ChREBP-binding sites. They found two such elements, leading them to the identification of two separate promoters, corresponding to two variants of ChREBP: an 864 amino-acid protein called ChREBP-α, and a 687 amino-acid protein called ChREBP-β. ChREBP-β appears to be less abundant than ChREBP-α but is a potent transactivator

exhibiting a transcriptional activity 20-fold higher than that of ChREBP-α. Interestingly, the ChREBP-β protein structure closely resembles a ChREBP mutant previously shown to localize to the nucleus and to activate target gene expression independent of glucose concentrations (CA-ChREBP) (Li et al., 2006). CA-ChREBP lacks the first 196 amino acids, which include the low-glucose inhibitory domain (LID). The LID domain, when present inhibits the glucose response of ChREBP under low glucose concentrations. ChREBP-β, which is missing the first 177 amino acids (most of the LID), indeed shares common features with CA-ChREBP, namely a constitutively high transcriptional activity. ChREBP-β, but not ChREBP-α, was highly sensitive to GLUT4-mediated glucose uptake in WAT. Interestingly, ChREBP-β, but not ChREBP-α, was decreased under HFD in subcutaneous WAT, suggesting that only this isoform is predictive of insulin sensitivity in this tissue.

In summary, the work by Kahn and colleagues demonstrates that ChREBP is a central regulator of lipogenesis in WAT, and that its activity may promote insulin sensitivity. The authors had previously proposed that retinol-binding protein 4, an adipokine, may mediate whole-body insulin resistance in GLUT4-KO mice (Yang et al., 2005). The relationship between ChREBP, WAT lipogenesis, and retinol-binding protein was not investigated in the current work, however. Future lipidomics analyses may uncover which lipid species act as the mediators of ChREBP-dependent insulin sensitivity, and may lead to novel therapeutic treatments. Researchers in the field may now also want to take another look at ChREBP western blots to check whether they can detect ChREBP-β at the expected size of 75.5 kDa. The identification of this new ChREBP variant raises many new

questions. The fact that ChREBP-α does not upregulate itself but potently induces expression of ChREBP-β through the ChoRE sequence identified in exon 1b implies the existence of a two-step mechanism in which glucose, perhaps through a product of glucose metabolism (potentially glucose 6-phosphate), first activates ChREBP-α, which would in turn stimulate ChREBP-β, a much more potent transcriptional activator (Figure 1B). This mechanism appears redundant under physiological conditions and raises further questions. If one considers that ChREBP-α is able "to do the job," why does it need to induce ChREBP-β to stimulate similar panels of target genes? Is ChREBP-β only substantially induced in case of hyperglycemia as part of an amplification phenomenon when ChREBP-α nuclear concentrations reach sufficient levels? Are ChREBP-α and ChREBP-β corecruited, in association with Mlx (ChREBP heterodimerization partner (Ma et al., 2006), on the ChoRE of their target genes? Could ChREBP-α and ChREBP-β regulate different clusters of genes by recruiting specific cofactors? One thing is clear: we still have a lot to learn about these fascinating transcription factors, and selective overexpression or deletion of ChREBP-α and ChREBP-β (by targeting exon 1b) coupled with gene-set analysis could help unravel their respective physiological and transcriptional functions.

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