Receptor CD36 links a risk-associated allele to obesity and metabolic disorders

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Mice harboring a particular allele of the human brain-derived neurotropic factor (BDNF<sup>M/M</sup>) develop extreme obesity and insulin resistance when fed a high-fat diet. The underlying mechanisms of this genetic risk factor for obesity are unclear. In the current issue of JBC, Yang et al. report that pharmacological inhibition of integral membrane protein CD36 significantly reduces body weight gain and improves glucose tolerance in BDNF<sup>M/M</sup> mice. Targeting CD36 may therefore be a promising strategy to improve metabolic dysfunctions and normalize risk factors in obese individuals. 

Obesity is a major health risk that can contribute to life-threatening metabolic complications including dyslipidemia and type 2 diabetes (1). The pathogenesis of obesity involves complex interactions between environmental and genetic factors, leading to dysregulated energy balance. Genetic variants, including single-nucleotide polymorphisms (SNPs)<sup>2</sup>, account for 40–70% of the heritability of body mass index (BMI) (2). One such SNP that is associated with body weight regulation is a mutation in the gene for brain-derived neurotrophic factor (BDNF).

BDNF plays a critical role in nervous system development and function, including the regulation of energy intake and expenditure (3). One common polymorphism in the <em>BDNF</em> gene is a substitution of a valine with a methionine at codon 66 (Val<sup>66</sup>Met SNP) (4). The Val<sup>66</sup>Met allele has been associated with several disorders, including early seizures, obsessive-compulsive disorder, eating disorders, and obesity in humans (5).

Yang et al. (6) used a unique mouse model containing the human <em>BDNF Val</em><sup>66</sup><em>Met</em> variant and found that, consistent with observations in humans, BDNF<sup>M/M</sup> mice fed a normal diet had significantly increased body weight relative to BDNF<sup>V/V</sup>, controls by 6 weeks of age. When subsequently fed a high-fat diet for 8 weeks, the BDNF<sup>M/M</sup> mice became extremely obese with elevated fasting glucose levels and impaired glucose tolerance, implying the development of insulin resistance. The authors specifically investigated the connection between these phenotypes and the expression of integral membrane protein CD36, a multifunctional receptor with documented links to obesity-associated metabolic disorders. They found that, compared with controls, BDNF<sup>M/M</sup> mice had significantly increased levels of CD36 mRNA and protein, including the soluble form (sCD36), which is a marker of insulin resistance in diabetes (7). Thus, changes in BDNF were correlated with changes in CD36 and associated metabolic phenotypes.

CD36, a class B scavenger receptor, functions as a fatty acid transporter to promote fatty acid uptake. CD36 is thought to mediate cross-talk between adipocytes and macrophages in obese mice by facilitating cytokine secretion from macrophages (8). To identify the role of CD36 in the development of obesity in BDNF<sup>M/M</sup> mice, Yang et al. (6) used salvianolic acid B (SAB), a specific CD36 antagonist, in experiments both <em>in vitro</em> and <em>in vivo</em> (9). Although chronic administration of SAB into diet-induced obese (DIO) WT mice had no effect on total body weight during the experimental period (8 weeks), it significantly reduced the accumulation of visceral fat and improved glucose tolerance relative to DIO mice receiving the vehicle. Importantly, these beneficial effects were abolished in CD36 knockout mice, further confirming that SAB counteracts insulin resistance and visceral obesity through its effect on CD36 function.

Yang et al. (6) then asked whether the inhibition of CD36 by SAB would provide greater benefits in the obesity-prone BDNF<sup>M/M</sup> mice. As predicted, relative to what occurred in vehicle-treated DIO BDNF<sup>V/V</sup> mice, chronic SAB infusion significantly decreased weight gain, reduced lipid accumulation in both adipose tissue and liver, and improved insulin sensitivity in BDNF<sup>M/M</sup> mice. SAB treatment also significantly decreased the expression of genes for CD36, F4/80, and monocyte chemoattractant protein-1 (MCP-1) in adipose tissue of the DIO BDNF<sup>M/M</sup> mice, suggesting that SAB treatment counteracts obesity-induced macrophage infiltration and inflammation in adipose tissue.

These results are very informative and raise a number of questions. First, although Yang et al. (6) clearly documented increased CD36 gene expression in BDNF<sup>M/M</sup> mice, what is the molecular mechanism mediating this effect of the BDNF variant? Second, because BDNF exerts its catabolic actions mainly within the hypothalamus, where CD36 is also expressed (10), is the influence of the BDNF variant on adiposity mediated through a central or peripheral action? Further investigation is...
needed to determine if central CD36 is involved in the development of obesity induced by genetic BDNF variability. Finally, how can this knowledge be exploited for the treatment of obesity and insulin resistance?

Yang’s innovative studies lay the groundwork for furthering our understanding of the connection between a common BDNF variant and CD36. BDNFM/M stimulates CD36 gene expression, and the consequently increased level of CD36 underlies the progression of obesity-associated metabolic dysfunctions through increasing lipid accumulation and inflammation (Fig. 1). These experiments also clearly make the case that CD36 is a key player in the development of high-fat diet-induced obesity and type 2 diabetes.

References
1. Kahn, B. B., and Flier, J. S. (2000) Obesity and insulin resistance. J. Clin. Invest. 106, 473–481 CrossRef Medline
2. El-Sayed Moustafa, J. S., and Froguel, P. (2013) From obesity genetics to the future of personalized obesity therapy. Nat. Rev. Endocrinol. 9, 402–413 CrossRef Medline
3. Xu, B., and Xie, X. (2016) Neurotrophic factor control of satiety and body weight. Nat. Rev. Neurosci. 17, 282–292 CrossRef Medline
4. Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., and Weinberger, D. R. (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112, 257–269 CrossRef Medline
5. Rosas-Vargas, H., Martínez-Ezquerro, J. D., and Bienvenu, T. (2011) Brain-derived neurotrophic factor, food intake regulation, and obesity. Arch. Med. Res. 42, 482–494 CrossRef Medline
6. Yang, J., Park, K. W., and Cho, S. (2018) Inhibition of the CD36 receptor reduces visceral fat accumulation and improves insulin resistance in obese mice carrying the BDNF-Val66Met variant. J. Biol. Chem. 293, 13338–13348 CrossRef Medline
7. Handberg, A., Norberg, M., Stenlund, H., Hallmans, G., Attermann, J., and Eriksson, J. W. (2010) Soluble CD36 (sCD36) clusters with markers of insulin resistance, and high sCD36 is associated with increased type 2 diabetes risk. J. Clin. Endocrinol. Metab. 95, 1939–1946 CrossRef Medline
8. Kennedy, D. J., Kuchibhotla, S., Westfall, K. M., Silverstein, R. L., Morton, R. E., and Febbraio, M. (2011) A CD36-dependent pathway enhances macrophage and adipose tissue inflammation and impairs insulin signaling. Cardiovasc. Res. 89, 604–613 CrossRef Medline
9. Bao, Y., Wang, L., Xu, Y., Yang, Y., Wang, L., Si, S., Cho, S., and Hong, B. (2012) Salvianolic acid B inhibits macrophage uptake of modified low density lipoprotein (mLDL) in a scavenger receptor CD36-dependent manner. Atherosclerosis 223, 152–159 CrossRef Medline
10. Mouillé, V. S., Le Foll, C., Philippe, E., Kassis, N., Roux, C., Marsollier, N., Bui, L.-C., Guissard, C., Dairou, J., Lorsignol, A., Pépincaud, L., Levin, B. E., Cruciani-Guglielmacci, C., and Magnan, C. (2013) Fatty acid transporter CD36 mediates hypothalamic effect of fatty acids on food intake in rats. PLoS ONE 8, e74021 CrossRef Medline