

## Visfatin – A New Visceral Fat Adipokine

Employing the method of differential display of expressed genes (by analysis of 8800 gene products utilizing cDNA probes) in paired samples of subcutaneous and visceral fat donated from 2 female volunteers, the investigators identified an adipokine that is synthesized primarily by visceral fat and termed this molecule “visfatin.” They subsequently found that the visfatin had been previously identified as “pre-B cell colony-enhancing factor” (PBEF). This is secreted by the liver, bone marrow, and muscle, is a growth factor for early stage B lymphocytes, and down-regulates apoptosis of neutrophils. The investigators demonstrated that: 1) expression of PBEF/visfatin increased during adipocyte differentiation *in vitro* with increased secretion of this protein into medium; 2) plasma concentrations of visfatin correlated with the volume of visceral fat in humans and mice but not the quantity of subcutaneous fat; 3) plasma levels of visfatin increased as the amount of fat accumulated in a mouse model of obesity; and 4) visfatin values rose rapidly in mice ingesting a high-fat diet. Subsequently, the authors observed that intravenous administration of visfatin led to a dose-dependent decline in glucose concentrations without affecting insulin values in intact and diabetic mice. Complete knock-out of the visfatin gene was lethal. In heterozygotic (visfatin<sup>+/-</sup>) animals, basal plasma glucose values were elevated, glucose tolerance was impaired, while there was no difference in size or insulin levels. *In vitro*, visfatin had several insulin-like actions including: enhancement of glucose uptake, suppression of glucose release, accumulation of triglycerides, and induction of gene markers of adipocyte differentiation (PPAR $\gamma$ , fatty acid synthase, adiponectin, and so forth). The investigators also showed that visfatin bound to the insulin receptor and induced its autophosphorylation, as well as phosphorylation of a number of downstream products consistent with induction of the insulin/insulin

receptor signal transduction pathway. Most interestingly, they demonstrated that visfatin did not bind to the same segment of the insulin receptor as insulin (extracellular  $\alpha$  subunit), although the binding site on the insulin receptor to which visfatin adheres was not identified. The authors concluded that visfatin has insulin-like effects and may be of physiological significance in the regulation of glucose homeostasis.

Fukuhara A, Matsuda M, Nishizawa M, et al. Visfatin: A protein secreted by visceral fat that mimics the effects of insulin. *Science*. 2005;307:426-430.

**Editor's Comment:** *This exciting discovery adds yet another factor to the many that regulate glucose and lipid homeostasis and to the list of adipocyte products that includes leptin, adiponectin, resistin, tumor-necrosis factor- $\alpha$ , and interleukin-6.<sup>1</sup> Although visfatin has many insulin-like qualities, its serum concentrations are lower than those of insulin and do not change acutely after eating. Inasmuch as visfatin is primarily secreted as the quantity of visceral fat increases, it may serve as a (less than optimal) compensatory mechanism for the deleterious effects of increased visceral adiposity. It is of interest that visfatin, like other non-peptidal small molecules, such as modified benzoquinones, can cross the plasma membrane and interact with and activate the insulin receptor tyrosine kinase.<sup>2</sup> These agents are active orally in animal models of type 2 diabetes mellitus; they increase insulin sensitivity and also exert other central and peripheral effects.*

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### References

1. Hug C, Lodish HF. *Science*. 2005;307:36-37.
2. Strowski MZ, Li Z, Szalkowski D, et al. *Endocrinology*. 2004;145:5259-5268.

**Growth, Genetics & Hormones** is supported by an unrestricted educational grant from **Genentech, Inc.**

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