Loutit, J.F., and Nisbet, N.W. (1982). Immunobiology *161*, 193–203.

Lowe, C., Yoneda, T., Boyce, B.F., Chen, H., Mundy, G.R., and Soriano, P. (1993). Proc. Natl. Acad. Sci. USA *90*, 4485–4489.

Sly, W.S., Whyte, M.P., Sundaram, V., Tashian, R.E., Hewett-Emmett, D., Guibaud, P., Vainsel, M., Baluarte, H.J., Gruskin, A., Al-Mosawi, M., et al. (1985). N. Engl. J. Med. *313*, 139–145.

Sobacchi, C., Frattini, A., Guerrini, M.M., Abinun, M., Pangrazio, A., Susani, L., Bredius, R., Mancini, G., Cant, A., Bishop, N., et al. (2007). Nat. Genet. *39*, 960–962.

Walker, D.G. (1975). Science *190*, 784–785.

The Rapidly Expanding Family of Adipokines

Ormond A. MacDougald[1,*] and Charles F. Burant[1,*]
[1]Departments of Molecular and Integrative Physiology and Internal Medicine, University of Michigan Medical School, Ann Arbor, MI 48109, USA
*Correspondence: macdouga@umich.edu (O.A.M.), burantc@umich.edu (C.F.B.)
DOI 10.1016/j.cmet.2007.08.010

Chemerin is a newly described adipokine with effects on adipocyte differentiation and metabolism in vitro. Its relationship with body mass index and aspects of the metabolic syndrome suggests a larger role for this protein in obesity-associated complications.

Adipose tissue biology has drawn much attention over the last several years, due in part to the increasing incidence of obesity and associated metabolic disorders and the hope that understanding the biology of fat will translate into a cure for bulging waistlines. Adipose tissue is recognized as an organ that not only stores energy but also acts as a multifunctional endocrine tissue. Adipocytes produce hormones (termed adipokines) that regulate systemic processes, including food intake and nutrient metabolism, insulin sensitivity, stress responses, reproduction, bone growth, and inflammation. A growing number of reports describe proteins that are secreted from adipocytes or preadipocytes. While leptin has systemic effects on appetite and metabolism and is undoubtedly the most studied secreted adipocyte protein, endocrine functions have been described for multiple adipokines. In addition, autocrine/paracrine factors from adipocytes influence adipose development and metabolism, vascularization, and recruitment of inflammatory cells. Two recent publications now add chemerin (aka RARRES2 or TIG2; Bozaoglu et al., 2007; Goralski et al., 2007) to the growing list of secreted adipocyte proteins. The data indicate that chemerin has local effects on adipogenesis and perhaps wider effects on metabolism and inflammation (Figure 1).

Chemerin is a secreted chemoattractant protein of ~16 kDa, synthesized as prochemerin and activated through serine protease C-terminal cleavage triggered as part of host survival defense (i.e., complement, fibrinolysis, coagulation, and from leukocyte granules) (Wittamer et al., 2003). Initially purified from biological fluids associated with inflammation (ovarian cancer ascites and rheumatoid arthritis synovial fluids), high levels of mRNA in adipose tissue suggest a role for chemerin in adipocyte biology (Bozaoglu et al., 2007; Goralski et al., 2007). Chemerin is expressed at very low levels in 3T3-L1 preadipocytes, but expression and secretion increase dramatically during adipogenesis in vitro (Bozaoglu et al., 2007; Goralski et al., 2007). Adipocytes purified from adipose tissue contain high levels of chemerin mRNA; however, substantial expression in stromal vascular cells suggests that production from nonadipocytes may also be important (Goralski et al., 2007). Chemerin mRNA expression is not altered in white adipose tissues of genetically obese *ob/ob* mice compared to lean controls, but it is increased in subcutaneous adipose tissue of fat sand rats (*P. obesus,* which are actually gerbils) with impaired glucose tolerance. Chemerin is also elevated in all adipose tissue depots in diabetic *P. obesus* relative to euglycemic lean controls (Bozaoglu et al., 2007). However, there was no change in expression in the stromal-vascular fraction with impaired glucose tolerance or diabetes. In humans, circulating levels of chemerin correlate with body mass index, plasma triacylglycerol concentrations, and blood pressure but are not altered by the presence of type 2 diabetes (Bozaoglu et al., 2007); the clinical significance of these findings are unclear.

Signaling by chemerin is mediated by the seven-transmembrane-spanning G protein-coupled receptor (GPCR), chemokine like receptor-1 (CMKLR1). Expression of this receptor had been demonstrated in circulating plasmacytoid dendritic cells and tissue-resident macrophages. The new work shows that, like chemerin, CMKLR1 is highly expressed in adipose tissues, with slightly higher expression in adipocytes compared to stromal vascular cells. While Goralski et al. observed striking induction of CMKLR1 expression during 3T3-L1 adipogenesis, Bozaoglu et al. observed repression of this gene

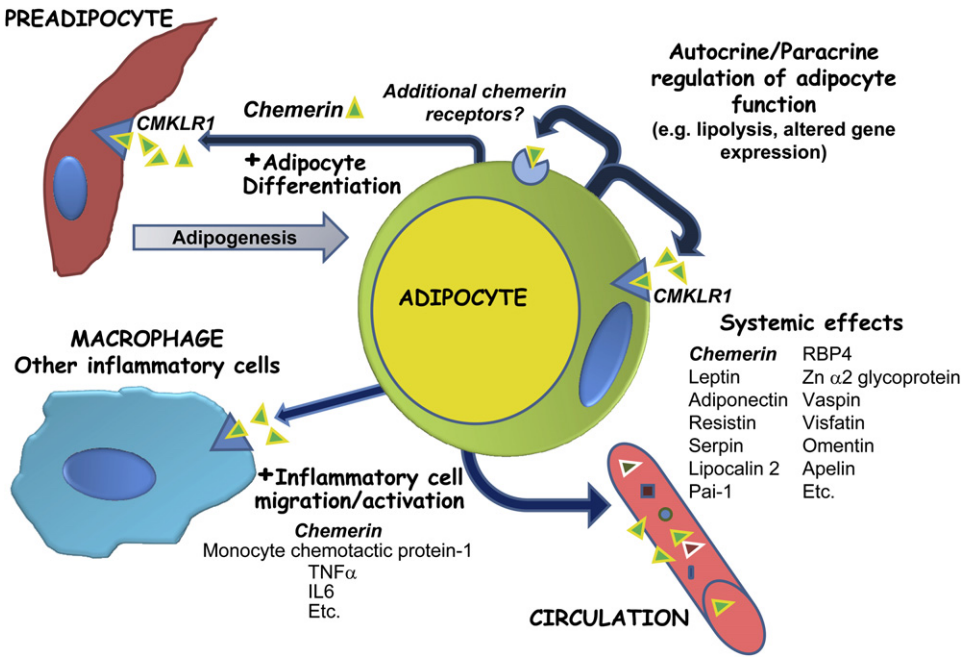

Figure 1. A Model for the Action of Chemerin, an Adipokine with Diverse Effects on Differentiation, Inflammatory Recruitment, and Metabolism

Local production regulates adipogenesis and through its receptor or possibly other receptors can modulate a variety of functions in mature adipocytes. Along with previously described adipokines, chemerin, through a paracrine effect, may participate in recruitment and activation of inflammatory cells in adipose tissue. Chemerin circulates at high levels in the serum and may have systemic effects on metabolism, similar to a host of other adipokines.

during preadipocyte differentiation. CMKLR1 is transcribed from two promoters (Martensson et al., 2005), which give rise to alternative noncoding first exons. Goralski et al. measured promoter 1a-specific transcripts, while Bozaoglu et al. measured expression of the coding region, shared by both promoters. Thus, the origin of the discrepant results is not clear.

CMKLR1 shares homology with a subfamily of chemoattractant receptors including C5L2. Activation of the latter by acylation-stimulating protein results in triacylglycerol synthesis by increasing esterification of fatty acids with glycerol phosphate. CMKLR1 and C5L2 are associated with various signaling events including calcium influx and transient phosphorylation of ERKs (Maslowska et al., 2006; Wittamer et al., 2003). CMKLR1 may be activated by other ligands, including a fatty-acid derivative resolvin E1, which possesses anti-inflammatory actions (Arita et al., 2007). Another fatty-acid-activated GPCR (i.e., GPR120) is also induced during differentiation and is required for adipogenesis (Gotoh et al., 2007). These data support a role for multiple GPCRs in adipocyte biology.

The initial characterization of chemerin and CMKLR1 pointed to chemoattractant functions, which may indeed be involved in the obesity-associated increase in macrophage infiltration of adipose tissue (Goralski et al., 2007). However, experiments reported by Goralski et al. have expanded the potential roles for these proteins to include modulation of adipocyte differentiation and metabolism. Knockdown of either chemerin or CMKLR1 during the early stages of 3T3-L1 adipogenesis resulted in a partial inhibition of adipocyte differentiation, as evidenced by decreased lipid accumulation and reduced expression of adipocyte markers such as PPARγ, adiponectin, perilipin, and GLUT4. Knockdown was accompanied by an increase in expression of IL6 with a trend toward increased expression of TNFα. Further, knockdown of chemerin resulted in decreased expression of CMKLR1, and vice versa, suggesting that endogenous signaling through this pathway maintains their expression through a positive feedback loop. Thus, it is somewhat surprising that knockdown of chemerin and CMKLR1 did not completely phenocopy each other. While chemerin or CMKLR1 knockdown partially inhibit adipogenesis, decreased CMKLR1 expression also results in a few large adipocytes with uncharacteristic perinuclear lipid accumulation (Goralski et al., 2007).

Further complicating our understanding of the role of chemerin in adipocyte biology are the data obtained from mature adipocytes. Knockdown of chemerin or CMKLR1 in adipocytes does not cause dedifferentiation as assessed by lipid accumulation, or expression of PPARγ and adiponectin (Goralski et al., 2007). The positive feedback loop between chemerin and CMKLR1 is not operative in differentiated 3T3-L1 cells, as knockdown of either mRNA does not influence expression of the other. However, chemerin appears to be required for expression of a subset of adipocyte genes because knockdown decreases expression of perilipin, GLUT4,

adiponectin, and leptin mRNAs. Although not explained by the analyses performed, chemerin has complex effects on lipolysis in that knockdown of chemerin decreases basal glycerol release, while addition of purified recombinant chemerin inhibits lipolysis in response to a β-agonist. While decreased lipolysis is consistent with effects of chemerin to lower intracellular cAMP (Wittamer et al., 2003), what is surprising is that knockdown of CMKLR1 does not block the effects on lipolysis of purified chemerin (Goralski et al., 2007). Nor does it cause the changes in adipocyte gene expression observed with knockdown of chemerin. Together with the observation that knockdown of CMKLR1 does not completely phenocopy the loss of ligand during adipogenesis, these data suggest alternate chemerin receptors or "spare receptors" such that decreasing expression of CMKLR1 by ~80% is not sufficient to inhibit chemerin signaling (Goralski et al., 2007). Assessment of other downstream signals, such as Erk activation or cAMP generation, will be helpful in defining the potential for additional receptor subtypes. The finding by Bozaoglu et al. of a marked reduction in CMKLR1 in 3T3-L1 adipocytes does not preclude autocrine and paracrine effects of chemerin on mature adipocytes.

New adipokines with diverse biological effects are now identified on a regular basis (e.g., lipocalin 2; Yan et al., 2007). How do the proposed biological actions of chemerin fit in with the rest of the adipokine family? Chemerin disruption has some effect on adipogenesis in vitro, but regulation of gene expression and lipolysis in mature adipocytes suggests a wider role in lipid and carbohydrate metabolism, and perhaps insulin sensitivity (Figure 1). However, consistent with the finding that chemerin containing conditioned media from adipocytes increases migration of CMLKR1-expressing lymphocytes (Goralski et al., 2007) and increased circulation of chemerin with obesity (Bozaoglu et al., 2007), the primary role of chemerin may be in the inflammatory response associated with metabolic stress. Further functional analysis awaits an understanding of how chemerin is regulated in vivo, not only in adipose tissue, but in other tissues that are central to metabolic homeostasis, such as liver. Development of models with tissue-specific gain or loss of function for chemerin and/or CMKLR1 will provide additional insight into chemerin biology. However, even these results will require cautious interpretation, as it is clear that no single adipokine is *the* answer for how fat cells cause complications associated with obesity, including insulin resistance. Indeed, the multitude of adipokines and their overlapping biological effects suggests that it is the integration of their actions, in the context of other genetic and environmental factors, that will determine weight and associated health. In the end, conquering bulging bellies and chronic complications will require attacks on multiple pathways.

REFERENCES

Arita, M., Ohira, T., Sun, Y.P., Elangovan, S., Chiang, N., and Serhan, C.N. (2007). J. Immunol. *178*, 3912–3917.

Bozaoglu, K., Bolton, K., McMillan, J., Zimmet, P., Jowett, J., Collier, G., Walder, K., and Segal, D. (2007). Endocrinology. Published online July 19, 2007. 10.1210/en.2007–0175.

Goralski, K.B., McCarthy, T.C., Hanniman, E.A., Zabel, B.A., Butcher, E.C., Parlee, S.D., Muruganandan, S., and Sinal, C.J. (2007). J. Biol. Chem. Published online July 16, 2007. 10.1074/jbc.M700793200.

Gotoh, C., Hong, Y.H., Iga, T., Hishikawa, D., Suzuki, Y., Song, S.H., Choi, K.C., Adachi, T., Hirasawa, A., Tsujimoto, G., et al. (2007). Biochem. Biophys. Res. Commun. *354*, 591–597.

Martensson, U.E., Bristulf, J., Owman, C., and Olde, B. (2005). Gene *350*, 65–77.

Maslowska, M., Legakis, H., Assadi, F., and Cianflone, K. (2006). J. Lipid Res. *47*, 643–652.

Wittamer, V., Franssen, J.D., Vulcano, M., Mirjolet, J.F., Le Poul, E., Migeotte, I., Brezillon, S., Tyldesley, R., Blanpain, C., Detheux, M., et al. (2003). J. Exp. Med. *198*, 977–985.

Yan, Q.W., Yang, Q., Mody, N., Graham, T.E., Hsu, C.H., Xu, Z., Houstis, N.E., Kahn, B.B., and Rosen, E.D. (2007). Diabetes. Published online July 16, 2007. 10.2337/db07–0007.