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Chemerin—A new adipokine that modulates adipogenesis via its own receptor ☆

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Abstract

Chemerin, an 18 kDa protein secreted by adipose tissue, was reported to modulate immune system function through its binding to the chemerin receptor (chemerinR). We herein demonstrate that chemerin also influences adipose cell function. Our data showed that chemerin and chemerinR mRNA expressions were highly expressed in adipose tissues, and that their expression levels were up-regulated in mice fed a high-fat diet. Both chemerin and chemerinR mRNA expression dramatically increased during the differentiation of 3T3-L1 cells and human preadipocytes into adipocytes. Furthermore, recombinant chemerin induced the phosphorylation of extracellular signal-regulated kinases 1/2 (ERK 1/2) and lipolysis in differentiated 3T3-L1 adipocytes. Thus, the adipokine chemerin likely regulates adipocyte function by autocrine/paracrine mechanisms.

Keywords: Chemerin; Chemerin receptor; Adipogenesis; Adipokine

The discovery that adipose cells secrete leptin, which regulates food intake and energy homeostasis [1], confirmed the role of adipose tissue as a secretory organ. In addition to leptin, adipocytes were found to secrete adiponectin, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6); these factors were termed adipokines (or adipocytokines) [2,3]. Adipocytes are known to express receptors for TNF-α (TNFR1 and TNFR2) and adiponectin (adipoR1 and adipoR2), which reportedly modulate adipogenesis and lipid metabolism directly by autocrine and paracrine mechanisms [4,5]. Some adipokines, in particular TNF-α, IL-6, and IL-1β, are known to be produced by, and act upon, other cell types, most notably macrophages and other immune cells, and to play a role in immune and reproductive function [6–8].

Chemerin, also known as tazarotene induced gene 2 (TIG2) and retinoic acid receptor responder 2 (RARRES2) is an 18 kDa protein that was originally identified as the protein produced by the gene that was up-regulated by the RAR β/γ-selective anti-psoriatic synthetic retinoid tazarotene [9]. Recent evidence suggests that chemerin is a natural ligand of the chemerin receptor (chemerinR), also known as chemokine like receptor 1 (cmklr1, ChemR23, or GPCR-DEZ) [10,11]. The chemerin receptor, now termed chemerinR, was isolated and found to be an orphan G-protein coupled receptor (GPCR) that had been referred to as GPCR-DEZ in mice, and chemR23 in humans [12,13]. Chemerin is known to stimulate intracellular calcium release, phosphorylate extracellular signal-regulated kinase-1 and -2 (ERK 1/2), and to inhibit cAMP accumu-

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lation through its binding to Gi-coupled heterotrimeric G proteins [10]. However, the molecular mechanism and signaling pathways by which chemerin and chemerinR influence adipogenesis and adipocyte development have not been investigated. We herein examined the effects and mechanism of action of chemerin and its receptor in adipocytes.

Materials and methods

Animals. The mice were used C57BL/6J mice obtained from Charles River Japan. And then weighed and divided into two groups of six with approximately equal mean body weights. One group was fed the standard diet (Oriental Yeast, Chiba, Japan) containing 8.5% (w/w) fat, 43.7% carbohydrate, and 29.7% protein, with an energy content of 3.69 kcal/g, and the other received a high-fat diet for 11 weeks (4–15 weeks of age). The high-fat diet was contained 41% fat, 36% carbohydrate, and 23% protein, with an energy content of 4.33 kcal/g; its fat source was the same as that of the standard diet and it contained the same absolute amounts of protein and fiber as the standard diet. White adipose tissues and non-adipose tissues were rapidly frozen in liquid nitrogen, and stored at −80 °C until RNA extraction. All experiments were conducted in accordance with the Shinshu University Guide for the Care and Use of Experimental Animals.

Isolation of adipocytes and stromal-vascular (S-V) cells from adipose tissues. White adipose tissue from the perirenal and parametrial fat regions of 15-week-old female mice was separated from connective tissue and blood vessels. The adipose tissue was then divided into adipocyte and S-V cell fractions as previously described [14].

Culture of 3T3-L1 cells and induction of differentiation. 3T3-L1 cells were purchased from ATCC (Manassas, VA, USA). Culture of 3T3-L1 cells and induction of differentiation was performed as previously described [14]. In another set of experiments, cells were treated with troglitazone (5 μM) for up to 7 days for up to 9 days during adipocyte differentiation.

Total RNA extraction and semi-quantitative RT-PCR. Total RNA was extracted from freshly dissociated adipocytes, S-V cells, adipose tissues and 3T3-L1 cells. Total RNA from human preadipocytes and differentiated adipocytes (20d) were purchased from Zen-Bio, Inc. (Research Triangle Park, NC). Semi-quantitative RT-PCR was performed in order to measure levels of chemerin, chemerinR, PPAR-γ2, and β-actin mRNA. The gene-specific primers are shown in Table 1. PCR products were resolved on a 1.2% agarose gel. The DNA was visualized by ethidium bromide staining and analyzed using NIH image software.

Protein preparation and Western blot analysis. The cells were washed with cold PBS, collected, and transferred to microfuge tubes. The cell pellets were lysed by vortexing for 10 s with 500 μL of 50 mM Tris (pH 8.0), 150 mM NaCl, 0.5% deoxycholate, 1% Nonidet P-40, 0.1% SDS, and a cocktail of mammalian proteinase inhibitors (Sigma Chemical Co., St. Louis, MO). After mixing, the solution was incubated for 10 min at 4 °C. The cell homogenate was spun at 10,000*g* in a tabletop centrifuge at 4 °C for 10 min. The supernatant was then transferred to a clean microfuge tube and stored at −80 °C until used in the blotting procedure. The proteins contained in the supernatant (70 μg per lane) were separated by denaturing gel electrophoresis. After the electrophoresis, the proteins were transferred to PVDF membranes in 50 mM Tris (pH 8.3), containing 380 mM glycine and 20% methanol at 15 V for 16 h. The membranes were washed twice in TBS containing 0.5% Tween 20 and blocked with 5% (w/v) nonfat dry milk in the above-mentioned wash buffer for 1 h at room temperature with constant agitation. The membranes were then washed 3 times for 5 min after which they were incubated with human chemerin antibody (mouse 7F6 monoclonal antibody, isotype IgG1) diluted 1:3000 in TBS containing 0.5% Tween 20 and 5% (w/v) nonfat dry milk (blocking buffer) for 16 h at 4 °C with constant agitation. The membranes were then again washed with blocking buffer and incubated with the secondary antibody (Goat anti-mouse IgG-HRP conjugate, 1:5000; Promega, Madison, WI) for 1 h at room temperature with constant agitation. The blots were developed with ECL Plus and visualized with Hyperfilm ECL (Amersham Pharmacia Biotech, Piscataway, NJ).

Determination of total and phosphorylated ERK. Total and phosphorylated ERK 1/2 were determined using polyclonal antibodies against total ERK 1/2 (1:1000) and phosphorylated ERK 1/2 (p44 and p42, 1:1000 dilution), respectively. To determine the effects of chemerin and chemerinR on ERK phosphorylation, 3T3-L1 cells were first grown in serum free DMEM containing 0.1% BSA for 6 h after which they were treated with mouse recombinant chemerin (PeproTech House, London, UK; 10^{-8} M). After treatment, the cells were lysed, the cell extracts were run on a 12.5% polyacrylamide gel, and Western blot analysis was performed.

Effects of chemerin in fully differentiated 3T3-L1 adipocytes. To investigate the effect of chemerin on the change of adipogenic genes, cells (3T3-L1 adipocytes that had differentiated for 10–15 days) were s treated with mouse chemerin (10^{-10} M) for 24 h. After then, culture medium was collected for analysis of glycerol and total RNA from the cells was extracted to measure the expression of PPAR-γ2 mRNA. The concentration of glycerol in culture medium was assayed using a kit from SIGMA (St. Louis, MO).

Statistical analysis. Results are presented as the percentage of control values (mean ± SEM) and represent data collected from at least three experiments. Data in each figure were compared using the Students *t*-test.

Table 1
Primers used for semi-quantitative reverse transcription polymerase chain reaction (RT-PCR)

	Gene			Length (bp)	Cycle	T_m[a] (°C)
Mouse	Chemerin	Forward	5′-TGCTTGCTGATCTCCCTA-3	345	25	60
		Reverse	5′-GACTATCCGGCCTAGAATTT-3′			
	ChemerinR	Forward	5′-CTGATCCCCGTCTTCATCAT-3′	376	25	58
		Reverse	5′-TGGTGAAGCTCCTGTGACTG-3′			
	PPAR-γ2	Forward	5′-TGGGTGAAACTCTGGGAGAT-3′	454	28	57
		Reverse	5′-CCATAGTGGAAGCCTGATGC-3′			
	β-Actin	Forward	5′-AGGTCATCACTATTGGCAAC-3′	363	27	57
		Reverse	5′-ACTCATCGTACTCCTGCTTG-3′			
Human	Chemerin	Forward	5′-GGAGGAATTTCACAAGCAC-3′	361	23	60
		Reverse	5′-GAACTGTCCAGGGAAGTAGA-3′			
	ChemerinR	Forward	5′-CTCCCAATCCATATCACCTA-3′	543	28	58
		Reverse	5′-GCAGAGGAAGAAGGTAATGA-3′			
	β-Actin	Forward	5′-AGGTCATCACCATTGGCAAT-3′	357	26	58
		Reverse	5′-ACTCGTCATACTCCTGCTTG-3′			

[a] T_m, melting temperature.

Results

Expression of chemerin and chemerinR in adipose tissues and mature adipocytes

First of all, we investigated the expression levels of chemerin and chemerinR mRNA in various tissues of mice using RT-PCR analysis. While chemerin and chemerinR mRNA transcripts were expressed ubiquitously in mice, they were expressed most highly in adipose tissue (Fig. 1A). Subsequently, whether chemerin and chemerinR mRNA were expressed in adipocytes and S-V cells, we determined the expression in these two cells. The expression of chemerin and chemerinR mRNA was significantly higher in adipocytes compared to S-V cells (Fig. 1B).

Up-regulation of chemerin and chemerinR mRNA expression in adipose tissues of mice fed a high-fat diet

After 11 weeks on a high-fat diet, the body weight of mice was 21% greater than that of mice that had been fed a normal diet. In addition, the respective weights of these animals' four different fat pads were approximately 2–3 times greater than were those in mice fed the normal diet. Levels of PPAR-γ2 mRNA, the adipose specific nuclear receptor, were also higher in mice fed the high-fat diet (Fig. 2), as were chemerin and chemerinR mRNA levels in the four different fat depots of mice fed the high-fat diet (Fig. 2).

Expression of chemerin and chemerinR in differentiating 3T3-L1 cells and human preadipocytes

The expression of chemerin and chemerinR mRNA was low in confluent 3T3-L1 cells. However, after they were hormonally stimulated to differentiate, expression increased markedly (Fig. 3A). PPAR-γ2 similarly increased during the differentiation of 3T3-L1 cells. Using a human monoclonal antibody, we also found that the expression of chemerin protein increased during hormone-induced differentiation (Fig. 3B). Similarly, both chemerin and chemerinR mRNA were highly expressed in human differentiated adipocytes compared to preadipocytes (Fig. 3C). The adipogenic expression patterns in human

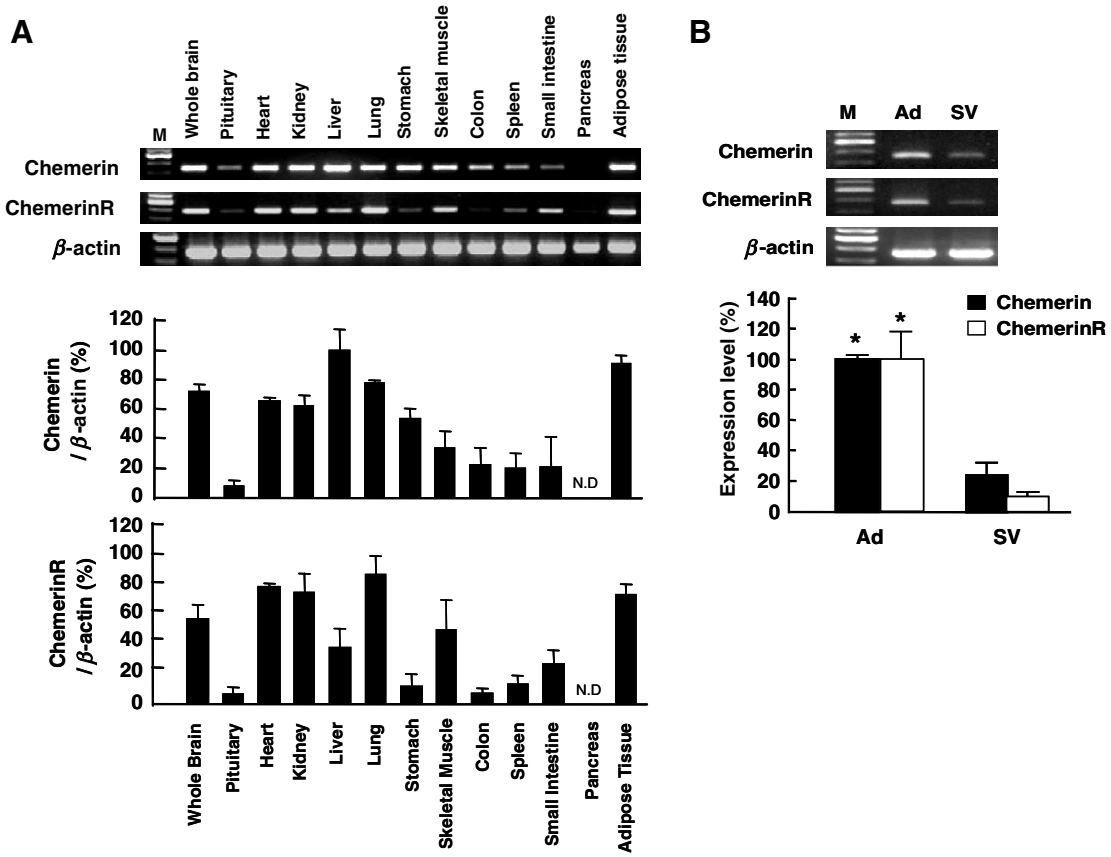

Fig. 1. (A) The levels of chemerin and chemerinR mRNA in various adult mouse tissues. (Upper panel) Representative ethidium bromide-stained agarose gel showing amplified chemerin, chemerinR, and β-actin with molecular markers. (Lower panel) Data were normalized using β-actin mRNA and expressed in percent form. The data represent the means ± SEM from six independent experiments. M, 100 bp molecular size ladder; ND, not detected. (B) The level of chemerin and chemerinR mRNA in adipocytes and S-V cells isolated from mesenteric adipose tissue. (Upper panel) Representative ethidium bromide-stained agarose gel showing amplified chemerin, chemerinR, and β-actin (363 bp) with molecular markers. (Lower panel) Data were normalized against β-actin and were expressed as a percent of the value obtained in adipocytes. The data represent the means ± SEM from three independent experiments. M, 100 bp molecular size ladder; Ad, adipocytes; S-V, stromal-vascular cells $^{*}P < 0.01$ vs. S-V cells.

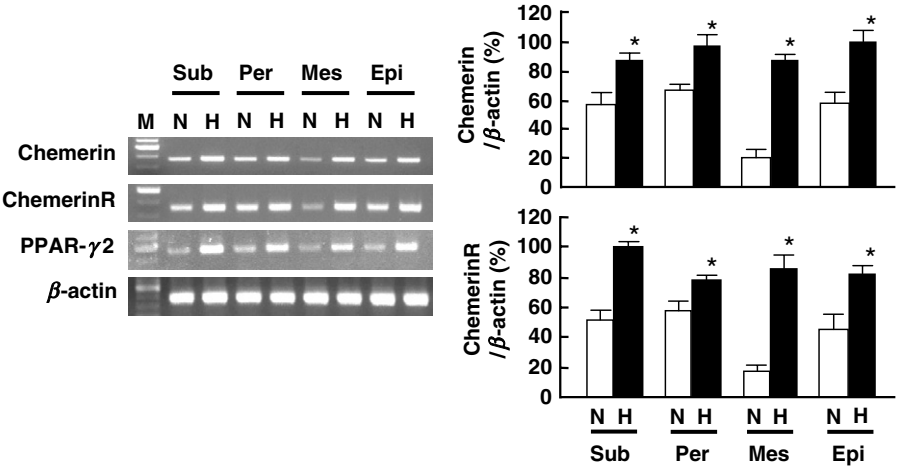

Fig. 2. Levels of chemerin, chemerinR, and PPAR-γ2 mRNA in four different regional fat depots of mice fed normal (N) or high-fat (H) chow. (Left panel) Representative ethidium bromide-stained agarose gel showing amplified chemerin, chemerinR, PPAR-γ2, and β-actin with molecular markers. (Right panel) Data were normalized using β-actin mRNA and were expressed as a percent. The data represent the means ± SEM from six independent experiments. M, 100 bp molecular size ladder; Sub, subcutaneous fat; Per, perirenal fat; Mes, mesenteric fat; Epi, epididymal fat $^{*}P < 0.05$ vs. mice fed normal diet.

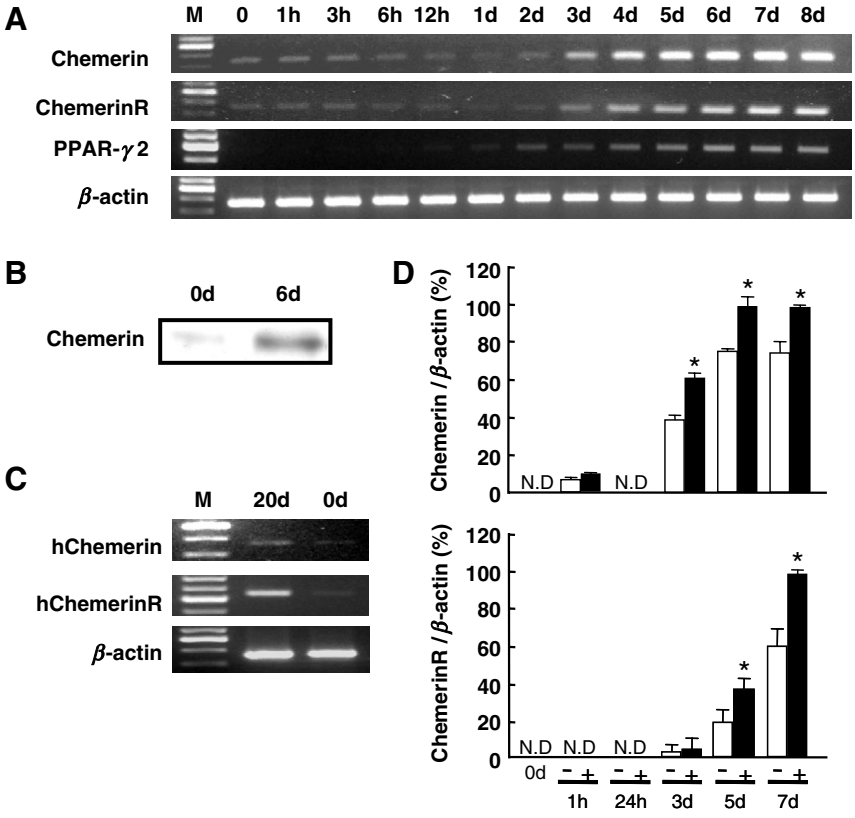

Fig. 3. (A) The levels of chemerin, chemerinR, and PPAR-γ2 mRNA during the differentiation of 3T3-L1 cells. Representative ethidium bromide-stained agarose gel showing amplified chemerin, chemerinR, PPAR-γ2, and β-actin with molecular markers. β-Actin was used as the internal control. M, 100 bp molecular size ladder. (B) Expression of chemerin protein during 3T3-L1 cell differentiation. 3T3-L1 cells were grown to 2 day post-confluency, after which they were allowed to differentiate into adipocytes in differentiation medium. Total proteins were extracted from the cells when they were post-confluent (0d) and 6 days after they had differentiated (6d), after which they were blotted with human anti-chemerin antibodies. (C) Chemerin and chemerinR mRNA levels in human differentiated adipocytes (20 day) and preadipocytes (0 day). Representative ethidium bromide-stained agarose gel show amplified chemerin, chemerinR, and β-actin with molecular markers. β-Actin was used as the internal control. M, 100 bp molecular size ladder. (D) The levels of chemerin and chemerinR mRNA in 3T3-L1 cells treated with (+) or without (−) troglitazone (5 μM) during their differentiation. (Upper panel) Representative ethidium bromide-stained agarose gel showing amplified chemerin, chemerinR, PPAR-γ2, and β-actin with molecular markers; the hours (h) and days (d) of differentiation are indicated at the top. (Lower panel) Data were normalized against β-actin and were expressed in percent form. The data represent the means ± SEM from three independent experiments. M, 100 bp molecular size ladder; ND, not detected $^{*}P < 0.05$ vs. untreated.

samples were confirmed in our previous reports [14]. Troglitazone, a PPAR-γ2 agonist, treatment significantly increased the expression of PPAR-γ2 starting 3 days after differentiation. Similarly, chemerin and chemerinR mRNA levels were significantly up-regulated by troglitazone treatment (Fig. 3D).

Functional roles of mouse recombinant chemerin in differentiated 3T3-L1 cells

The previous study showed that chemerin stimulate ERK 1/2 phosphorylation via chemerinR that coupled with Gi class G proteins [10]. Treatment with human recombinant chemerin clearly stimulated ERK 1/2 phosphorylation in differentiated 3T3-L1 cells (Fig. 4A); total ERK 1/2 was used as the control. The time-course study revealed that maximal stimulation of ERK 1/2 phosphorylation occurred 3 min after the addition of chemerin, and then decreased by 5 min.

The treatments of chemerin (10^{-10} M) for 24 h in the differentiated 3T3-L1 adipocytes significantly decreased the levels of PPAR-γ2 compared with control (Fig. 4B). The glycerol release in culture medium for 24 h was significantly increased by the treatment of chemerin (Fig. 4C).

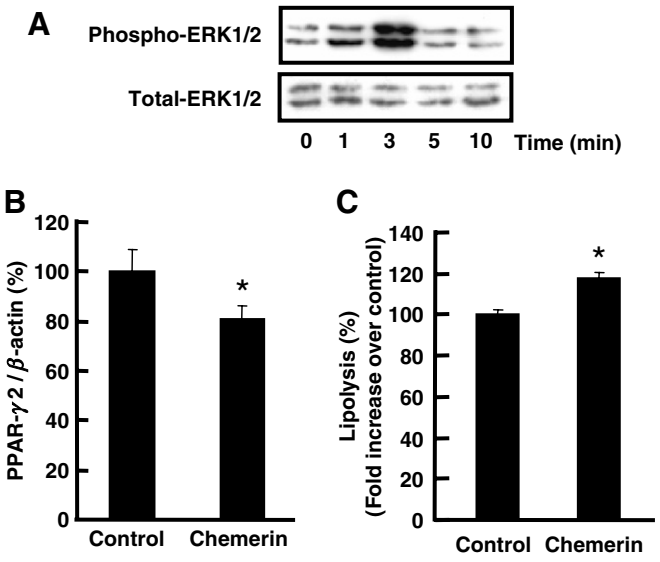

Fig. 4. (A) Effects of chemerin on ERK 1/2 phosphorylation in differentiated 3T3-L1 adipocytes. The cells were serum-starved for 6 h to reduce their basal levels of ERK 1/2, after which they were treated with 10^{-8} M mouse recombinant chemerin. Cell extracts were run on a 12.5% polyacrylamide gel and Western blotted with total and phospho-specific ERK antibodies. (B) Effects of chemerin on PPAR-γ2 mRNA expression in differentiated 3T3-L1 adipocytes. Mouse chemerin (10^{-10} M) were treated for 24 h in 3T3-L1 adipocytes differentiated for 10–15 days. Data were normalized against β-actin and were expressed in percent form. All data are expressed as the means ± SEM fold increase over control values. $^{*}P < 0.05$ vs. control. (C) Effects of chemerin on lipolysis in differentiated 3T3-L1 adipocytes. Cells were incubated with mouse recombinant chemerin (10^{-10} M) for 24 h, and then culture medium was collected. Accumulation of glycerol was measured as an index of lipolysis. All data are expressed as the means ± SEM fold increase over control values. $^{*}P < 0.01$ vs. control.

Discussion

Chemerin is known to be produced by the liver and to act as a chemotactic agent through its binding to chemerinR, which is expressed at high levels on immune cells such as plasmacytoid dendritic cells and macrophages [10,15–17]. To date, however, the status of chemerin expression in adipose tissues has not elucidated. Our results suggest that chemerin regulates adipose tissue function in an autocrine/paracrine manner through its binding to chemerinR. The expression of chemerin and chemerinR mRNA was higher in mature adipocytes compared to S-V cells suggesting that the former may be their primary site of expression. Adipocytes as well as preadipocytes and macrophages appear to be involved in the local production of proinflammatory cytokines and chemokines such as IL-6, TNF-α, and monocyte chemoattractant protein-1 [6,8,18,19]. Resolvin E1, a newly discovered bioactive oxygenated product of eicosapentaenoic acid that has anti-inflammatory effects, was also reported to activate chemerinR [20]. Thus, the binding of ligands to chemerinR on adipocytes may play a role not only in lipid metabolism but also immune system function.

The gene expression patterns of a host of adipocyte-derived genes, such as PPAR-γ2, are known to be regulated by nutritional factors [2,21]. Our results showing up-regulation of both chemerin and chemerinR mRNA in four different regional fat pads in mice fed a high-fat diet not only support the notion that chemerin expression is regulated by nutrients but also that the binding of chemerin to its receptor on fat cells plays a role in the regulation of adipose tissue growth and energy homeostasis.

It is well known that hormone-induced differentiation of 3T3-L1 cells is primarily mediated by the three transcription factors, PPAR-γ2, C/EBP-α, and C/EBP-β. Our results showed that the expression of chemerin and chemerinR mRNA was up-regulated during the differentiation of 3T3-L1 cells and human preadipocytes into adipocytes. Furthermore, we found that the expression of chemerin protein was also up-regulated in differentiating 3T3-L1 cells. The expression of both the chemerin and chemerinR genes in differentiating 3T3-L1 cells was also up-regulated by troglitazone. Promoter analysis revealed the existence of Sp1, C/EBP, GATA-1, and GATA-2 binding sites in the promoter region of the mouse and human chemerinR gene [22]. In addition, it was shown that the stimulatory effect of PPAR-γ2 on adipogenesis was mediated by C/EBP-α [23]. Thus, the up-regulation of chemerinR mRNA by troglitazone treatment may have been due to the activation of C/EBP-α. These suggest that the expression of chemerin and chemerinR mRNA is controlled by adipogenic transcription factors in adipocytes.

Our data suggested that chemerin showed the lipolytic effect in differentiated 3T3-L1 adipocytes. ERK 1/2 phosphorylation is known to directly promote the activation of hormone sensitive lipase (HSL) activation and to stimulate lipolysis in mature adipocytes [24]. However, it has

been also reported that cAMP-dependent PKA activation is the major pathway of lipolysis [25,26]. The expression pattern of chemerin and chemerinR suggests the possibility that its up-regulation during differentiation may relieve transcriptional stimulation on other adipogenic genes, mediating the lipolytic effects via its own receptor. The foregoing notwithstanding, the pathways that mediate the lipolytic effects of chemerin via chemerinR in adipocytes are still unclear.

In summary, chemerin appears to regulate both adipocyte differentiation and lipid metabolism. The chemerinR is highly expressed in adipocytes, supporting its role in the mediation of the autocrine/paracrine effects of chemerin.

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