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Receptor for activated C-kinase 1, a novel binding partner of adiponectin receptor 1

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ABSTRACT

Adiponectin is an adipose tissue derived hormone with anti-diabetic and insulin-sensitizing properties. Two adiponectin receptors, AdipoR1 and AdipoR2, have recently been identified, yet the signaling pathways triggered through adiponectin receptors remain to be elucidated. Using a yeast two-hybrid screen, we identified an adaptor protein, receptor for activated protein kinase C1 (RACK1), as an interacting partner of human AdipoR1. RACK1 was confirmed to interact with AdipoR1 by co-immunoprecipitation and co-localization analysis in mammalian cells. The interaction was enhanced by adiponectin stimulation. In addition, the knockdown of RACK1 by RNA interference inhibited adiponectin-stimulated glucose uptake in HepG2 cells. These results suggest that RACK1 may act as a key bridging factor in adiponectin signaling transduction through interacting with AdipoR1.

Adiponectin/Acrp30 is an abundant adipocyte derived circulating plasma protein with insulin-sensitizing metabolic effects and vascular protective properties [1]. Studies in humans showed that plasma adiponectin level significantly decreased during obesity [2], insulin resistance [3] and type 2 diabetes [4]. In mice, targeted deletion of the adiponectin gene leads to insulin resistance [5], while replenishment of adiponectin increased insulin sensitivity [3,6]. These data suggest that adiponectin acts as an anti-inflammatory, insulin-sensitizing adipokine that protects against obesity-related metabolic disease.

The physiological effects of adiponectin on glucose and lipid metabolism in the liver and in the skeletal muscle are mediated by its 2 receptors (AdipoR1 and AdipoR2) that have been identified recently [7]. These receptors contain 7-transmembrane domains but are structurally and functionally distinct from G-protein-coupled receptors. The signaling pathways responsible for the metabolic effects of adiponectin have been only partially elucidated. AdipoR1 and AdipoR2 have been shown to be involved in adiponectin-activated AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor (PPAR)-α, and the p38 mitogen-activated protein kinase (MAPK) pathways [7]. However, the linkage between adiponectin receptors and the downstream signaling pathways is largely elusive.

To identify proteins that participate in the adiponectin-activated signaling pathways, a yeast two-hybrid screen was carried out using AdipoR1 as the bait and receptor for activated protein kinase C1 (RACK1) was identified as a potential AdipoR1-binding partner. RACK1 was reported to act as a scaffold protein providing the platform for protein–protein interactions and play a role in the recruitment of the binding partners to transmembrane receptors. We herein showed that RACK1 bound to AdipoR1 and modulated adiponectin-stimulated glucose uptake. These findings indicated an unidentified role of RACK1 in adiponectin signaling transduction.

Materials and methods

Plasmid construction. Full-length human AdipoR1 cDNA was amplified from human liver cDNA library (Invitrogen) by polymerase chain reaction (PCR) using primers AdipoR1-For (5′-ACGC*GTCG ACC*ATGTCTTCCCACAAAGG-3′) and AdipoR1-Rev (5′-ATTT*GCGG CCGC*TCAGAGAAGGGTGTCAT-3′) containing built-in SalI and NotI restriction sites and ligated into pDBLeu to generate the plasmid pDBLeu-AdipoR1.

The cDNA of AdipoR1 was released from pDBLeu-AdipoR1 by digesting with SalI/NotI and subcloned into the pCMV-Myc (Clontech) to create Myc-tagged fusion protein expression vector pMyc-AdipoR1. The cDNA fragment of human RACK1 was amplified from human liver cDNA library by PCR with primers RACK1-For (5′-G*G AATTC*AATGACTGAGCAGATG-3′) and RACK1-Rev (5′-G*AAGATCT* CTAGCGTGTGCCAATG-3′) and ligated into a eukaryotic vector of pFLAG-CMV2 (Sigma) to create FLAG-tagged fusion protein expression vector pFLAG-RACK1.

AdipoR1 cDNA was amplified with primers AdipoR1-GFP-For (5′-CCC*AAGCTT*CGATGTCTTCCCACAAAGG-3′) and AdipoR1-GFP-Rev (5′-CG*GGATCC*TCAGAGAAGGGTGTCAT-3′), and fused to the

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green fluorescent protein (GFP) cDNA sequence by cloning into the HindIII and BamHI sites of vector pEGFP-C1 (Clontech) to generate pGFP-AdipoR1. RACK1 cDNA was amplified with primers RACK1-DsRed2-For (5′-CCC*AAGCTT*CGATGACTGAGCAGATG-3′) and RACK1-DsRed2-Rev (5′-CG*GGATCCC*TAGCGTGTGCCAATG-3′), and fused to the DsRed2 cDNA sequence by cloning into the HindIII and BamHI sites of vector pDsRed2-C1 (Clontech) to generate pDsRed2-RACK1.

Yeast two-hybrid system. Yeast two-hybrid screening was performed according to the manufacturer's instructions (Invitrogen). Briefly, a bait strain was created by transforming pDBLeu-AdipoR1 which expresses AdipoR1 fused to the DNA-binding domain (DB) of the GAL4 transcriptional regulator (DB-AdipoR1) into *Saccharomyces cerevisiae* strain MaV204. The bait strain was then co-transformed with a human liver cDNA library constructed in the Gal4 activating domain (AD) vector pPC86 (Invitrogen). The co-transformants were plated onto SD minimal yeast media lacking histidine, leucine, and tryptophan (SD -His/-Leu/-Trp) plates, containing 20 mM 3-aminotriazole. Plates were incubated at 30 °C for 4–5 days and yeast colonies that grew on the triple deficient media were re-streaked onto fresh selective plates and assayed for β-galactosidase activity. Prey plasmids were isolated from yeast and electroporated into *Escherichia coli* DH5α cells. The 5′ end of each clone was sequenced using a vector primer. To confirm the interaction in yeast, purified prey plasmids were re-transformed with the pDBLeu-AdipoR1 or with the empty bait vector pDBLeu back into the yeasts and the colonies grown on SD minimal yeast media lacking leucine and tryptophan (SD -Leu/-Trp) plates were tested for β-galactosidase activity.

Cell culture and transfection. COS-7 cells and HepG2 cells were maintained in Dulbecco's modified Eagle's medium (Invitrogen) supplemented with 10% fetal bovine serum (Hyclone) at 37 °C. COS-7 cells were seeded in 100-mm plates and transfected the next day with appropriate plasmid DNA using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. HepG2 cells were seeded in 35-mm dishes with coverslip and then transfection was carried out.

Co-immunoprecipitation and Western blots. COS-7 cells were co-transfected with pFLAG-RACK1 together with pMyc, pMyc-AdipoR1 together with pFLAG, or pFLAG-RACK1 together with pMyc-AdipoR1. After 24 h, cells were washed twice with ice-cold phosphate buffered saline and lysed in 400 μl ice-cold lysis buffer (100 mM Tris–HCl, pH 7.5, 300 mM NaCl, 0.5% NP-40, 1 mM DTT) containing the protease inhibitor cocktail tablets (Sigma). The cell lysates were incubated at 4 °C for 30 min and centrifuged at 12,000 rpm for 10 min. Three hundred microliters of cell lysates was incubated with 1 μg of anti-FLAG antibody (Cell Signaling Technology) for 3 h, and then with 20 μl of protein A/G-agarose (Santa Cruz) at 4 °C for 1 h. After incubation, samples were centrifuged for 1 min at 1000 rpm. The protein A/G-agarose pellets were washed three times with the lysis buffer and resuspended in 20 μl SDS loading buffer, heated at 95 °C for 5 min, and separated by SDS–PAGE. Immunocomplexes were analyzed by Western blot using either anti-FLAG antibody or anti-myc antibody (Cell Signaling Technology), respectively, followed by anti-mouse IgG conjugated with HRP (Santa Cruz). Immunodetection was performed with an enhanced chemiluminescence (ECL) kit (Amersham).

Imaging with confocal microscopy. HepG2 cells seeded in 35 mm dishes were transfected with 1 μg pGFP-AdipoR1 and 1 μg pDsRed2-RACK1. After 24 h, the transfected HepG2 cells were treated with or without 5 μg/mL recombinant adiponectin (R&D systems) for 30 min, fixed with 4% paraformaldehyde at 4 °C and visualized with a Leica confocal microscopy (TCS-SP, Leica). Images were obtained with an excitation wavelength of 488 nm and an emission wavelength of 500–520 nm used for GFP, and an excitation wavelength of 543 nm and an emission wavelength of 550–570 nm used for DsRed2.

RNA interference. Chemically synthesized, double-stranded RACK1 siRNA (RACK1i) or negative control siRNA (NC) was purchased from Santa Cruz. siRNA transfection was carried out using the Lipofectamine 2000 transfection reagent (Invitrogen) according to the manufacturer's instructions. Protein expression was assessed by Western blotting with anti-RACK1 antibody (Santa Cruz) at 48 h post-transfection.

Glucose uptake assay. HepG2 cells cultured on 96-well black plates were transfected with RACK1 siRNA or negative control siRNA. Forty-eight hours after transfection, HepG2 cells were washed with DMEM for three times and incubated with 5 μg/mL recombinant adiponectin for 30 min. After adiponectin incubation, cells were incubated with 50 μM 2-(*N*-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose (2-NBDG) (Invitrogen) in PBS for 15 min, and then washed with additional PBS to remove excess 2-NBDG. Fluorescence in the cells was measured at an excitation wavelength of 485 nm and an emission wavelength of 535 nm with Tecan infinite M200 (Tecan). The fluorescence of control group transfected with scrambled siRNA and un-stimulated with adiponectin was normalized to 1.0. The fluorescence of other groups was compared with control group. The data are presented as means ± SD. Statistical differences between groups were determined using Student's *t*-test.

Results

RACK1 is one of the binding partners in yeast

To identify intracellular proteins interacting with the adiponectin receptor 1, yeast two-hybrid system was applied to screen a human liver cDNA library by using AdipoR1 as the bait. Pilot experiments showed that AdipoR1 itself had no transcription-activating property in the system. Out of 1×10^6 total transformants screened, 12 clones were found to grow on nutritional deficient plates and activate the β-galactosidase assay and three were identified as RACK1. The isolated clones comprise the full amino acids of RACK1. The plasmid pPC86-RACK1 was transformed back into the competent MaV203 cells along with the original bait plasmid pDBLeu-AdipoR1 or alternatively, with the bait vector pDBLeu. Transformants turned blue in X-gal analysis only when AdipoR1 and RACK1 were simultaneously expressed (Fig. 1A), demonstrating a true interaction between AdipoR1 and RACK1 in yeast.

Interaction of RACK1 and AdipoR1 in mammalian cells

To determine whether RACK1 interacts with AdipoR1 in mammalian cells, the expression constructs encoding FLAG-tagged RACK1 and Myc-tagged AdipoR1 were co-transfected into COS-7 cells. The cell lysates were subjected to immunoprecipitation assays with anti-FLAG antibody followed by Western blot analysis with anti-FLAG and anti-Myc antibody, respectively. Data showed that anti-FLAG antibody was able to precipitate Myc-AdipoR1 protein only in the presence of FLAG-RACK1 (Fig. 1B). As a control, the anti-FLAG antibody did not precipitate Myc-AdipoR1 in the absence of FLAG-RACK1. The result suggested that RACK and AdipoR1 are physically associated *in vivo*.

Co-localization of RACK1 and AdipoR1 in HepG2 cells

The data above strongly suggested that RACK1 is a binding partner of AdipoR1. To determine the localization of AdipoR1 with RACK1 in cells, their genes were tagged with *GFP* and *DsRed2* sequences, respectively, and co-transfected into HepG2 cells. The transfected cells were visualized with a confocal microscopy. Both

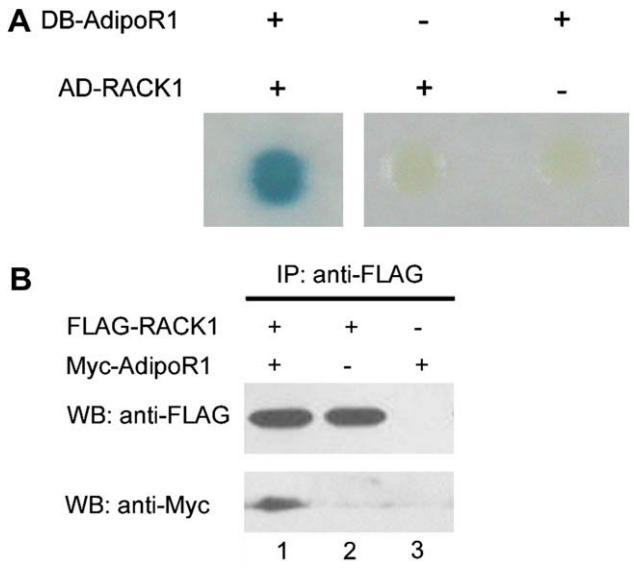

Fig. 1. RACK1 interacted with AdipoR1 in yeast cells. (A) Yeast transformants expressing GAL4 activating domain (AD) or AD-fused RACK1 (AD-RACK1) together with GAL4 DNA-binding domain (DB) or DB-fused AdipoR1 (DB-AdipoR1) were subjected to X-gal analysis. The β-galactosidase-positive colony (blue staining) indicates a positive interaction inside the cells. (B) COS-7 cells was transfected with pFLAG-RACK1 (lane2), pCMV-AdipoR1 (lane3), respectively, or both together (lane1). Twenty-four hours later, cells were lysed and immunoprecipitated with anti-FLAG antibodies. The immunoprecipitates were divided into two parts and analyzed by Western blot with anti-FLAG or anti-Myc antibodies (top and bottom panels). (For interpretation of color mentioned in this figure the reader is referred to the web version of the article.)

proteins showed correct localization. DsRed2-RACK1 displayed cytoplasm localization and GFP-AdipoR1 distributed predominantly in the cell membrane. A small fraction of RACK1 and AdipoR1 are co-localized in the cell membrane. When the cells were stimulated with adiponectin, there was much more co-localization of AdipoR1 and RACK1 in the cell membrane compared to non-treated cells. The finding that the interaction between AdipR1 and RACK1 was responsive to adiponectin stimulation suggested RACK1 might participate in adiponectin signaling transduction (Fig. 2).

RACK1 was involved in adiponectin-stimulated glucose uptake

Adiponectin enhances glucose uptake. To test whether RACK1 has a role in adiponectin-stimulated glucose metabolism, the expression of RACK1 in HepG2 cells were knocked down by siRNA. Western blot showed that RACK1 expression was efficiently suppressed (Fig. 3A). RACK1-suppressed HepG2 cells and the control group were then incubated with adiponectin and the uptake of 2-NBDG, a metabolizable fluorescent derivative of glucose, was measured. As expected, adiponectin stimulation could markedly increase glucose uptake, about 1.55 ± 0.17-fold higher compared to the un-stimulated group. Adiponectin-stimulated glucose uptake was reduced to 0.72 ± 0.17-fold when the RACK1 expression was knocked down (Fig. 3B), indicating that RACK1 was involved in adiponectin-stimulated glucose uptake.

Discussion

As adiponectin has shown significant anti-diabetic, anti-atherogenic and anti-inflammatory properties, elucidating the adiponectin signaling pathway is essential to harness the therapeutic application of this hormone. Adiponectin receptors should play important roles in adiponectin signaling transduction. However, little is known about its direct interacting partners. Not until recently, the adaptor protein APPL1 (Adaptor Protein containing Pleckstrin homology domain, Phosphotyrosine binding domain and Leucine zipper motif) has been identified as the first signaling molecule that binds to the adiponectin receptor 1 directly and positively mediates adiponectin signaling in muscle cells [8]. The present study identified RACK1 as another novel interaction partner of AdipoR1.

RACK1 was originally identified on the basis of its ability to bind the activated form of protein kinase C [9], to stabilize the active form of protein kinase C, and to facilitate its protein trafficking within the cell [10]. RACK1 is a 36-kDa cytosolic protein that is composed of seven WD40 motifs, which are predicted to form a 7-bladed propeller structure important in protein–protein interactions [9]. The individual WD40 repeats can simultaneously interact with different signaling molecules, which allow RACK1 to integrate inputs from distinct signaling pathways. Signaling molecules that bind to RACK1 can be classified into two main groups: cytosolic signaling proteins and membrane receptors. Through its

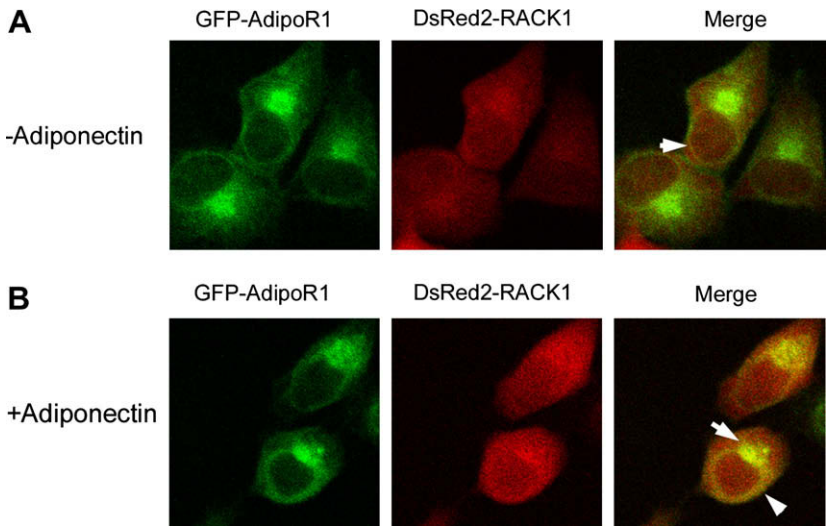

Fig. 2. Co-localization of AdipoR1 and RACK1 in HepG2 cells. HepG2 cells transiently transfected with expression plasmids encoding GFP-AdipoR1 and DsRed2-RACK1 were stimulated with (A) or without (B) adiponectin for 30 min. Cells were fixed and images were obtained with a confocal microscopy. Each picture shows the GFP-AdipoR1 image (left panel), the DsRed2-RACK1 image (middle panel) and the merged image (right panel) of the cells in the same field.

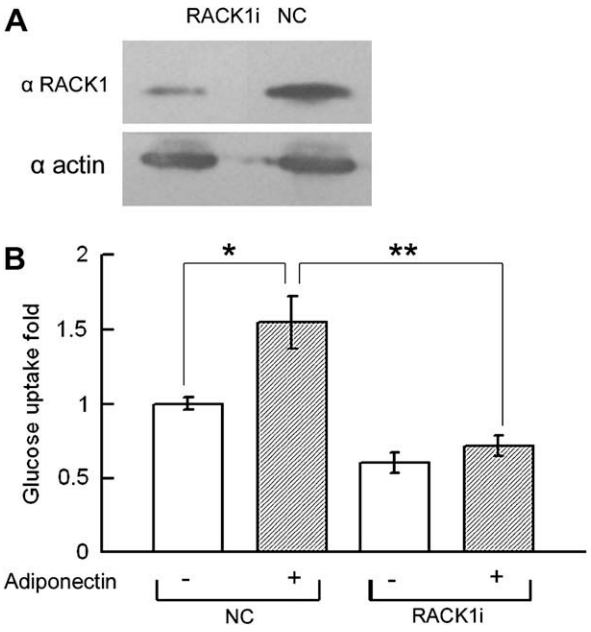

Fig. 3. The role of RACK1 in glucose uptake. HepG2 cells were transfected with RACK1 siRNA (RACK1i) or negative control siRNA (NC). RACK1 interfering efficiency was detected by Western blot analysis. The RACK1-suppressed HepG2 cells and control cells were stimulated with or without adiponectin for 30 min. Cells were incubated with 50 μM 2-NBDG in PBS for 15 min and the fluorescence were measured. The error bars represent means ± SD from four independent experiments. $^{*}P < 0.05$ and $^{**}P < 0.01$.

interaction with protein kinase C or Src kinases [11], RACK1 can function as a critical adaptor protein mediating cross-talk between serine/threonine and tyrosine kinase signaling pathways. RACK1 also serves as an adaptor for PKC-mediated JNK activation [12]. RACK1 can also bind to the stress-responsive MTK1 MAPKKK and facilitates its activation [13]. Receptors that bind to RACK1 include the cytoplasmic domain of the β-subunit of the integrin receptor [14], the common β-chain of the interleukin-5/interleukin-3/granulocyte macrophage colony-stimulating factor receptor [15] and type II bone morphogenetic protein receptor [16]. These reports suggest that RACK1 acts as a scaffold protein providing the platform for protein–protein interactions essential in the recruitment of its binding partners to transmembrane receptors. Therefore, it is reasonable to speculate that RACK1 plays a role in recruitment of the downstream signaling molecules to AdipoR1.

RACK1 interacts with its binding partners in 2 ways (1) in a constitutive fashion such as with the cAMP-specific phosphodiesterase PDE4D5 [17] or (2) in a stimulus-dependent fashion such as with protein kinase C isoforms [10]. The interaction between RACK1 and AdipoR1 reported here represents a stimulus-dependent interaction in that there was much more significant co-localization of AdipoR1 and RACK1 in the cell membrane with adiponectin stimulation.

To investigate the physiological and biological functions of RACK1, we knocked down the expression of RACK1 in HepG2 cells and observed the reduced glucose uptake. It was reported that adiponectin-activated AMPK, PPAR-α, and p38 MAPK pathways and subsequently increased fatty-acid oxidation or glucose consumption [18]. It is possible that RACK1 may be involved in one or more of these signaling pathways and regulate adiponectin-stimulated glucose uptake. Further studies are needed to test these possibilities.

In summary, we have identified RACK1 as another signaling molecule that binds to the adiponectin receptor 1. In light of the important role of RACK1 as a scaffold protein in signaling transduction, the molecular interaction between RACK1 and AdipoR1 may partly account for the mechanism adiponectin-activated signaling and action.

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References

[1] A.H. Berg, T.P. Combs, P.E. Scherer, ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism, Trends Endocrinol. Metab. 13 (2002) 84–89.
[2] M. Cnop, P.J. Havel, K.M. Utzschneider, D.B. Carr, M.K. Sinha, E.J. Boyko, B.M. Retzlaff, R.H. Knopp, J.D. Brunzell, S.E. Kahn, Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex, Diabetologia 46 (2003) 459–469.
[3] T. Yamauchi, J. Kamon, H. Waki, Y. Terauchi, N. Kubota, K. Hara, Y. Mori, T. Ide, K. Murakami, N. Tsuboyama-Kasaoka, O. Ezaki, Y. Akanuma, O. Gavrilova, C. Vinson, M.L. Reitman, H. Kagechika, K. Shudo, M. Yoda, Y. Nakano, K. Tobe, R. Nagai, S. Kimura, M. Tomita, P. Froguel, T. Kadowaki, The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity, Nat. Med. 7 (2001) 941–946.
[4] K. Hotta, T. Funahashi, Y. Arita, M. Takahashi, M. Matsuda, Y. Okamoto, H. Iwahashi, H. Kuriyama, N. Ouchi, K. Maeda, M. Nishida, S. Kihara, N. Sakai, T. Nakajima, K. Hasegawa, M. Muraguchi, Y. Ohmoto, T. Nakamura, S. Yamashita, T. Hanafusa, Y. Matsuzawa, Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients, Arterioscler. Thromb. Vasc. Biol. 20 (2000) 1595–1599.
[5] N. Maeda, I. Shimomura, K. Kishida, H. Nishizawa, M. Matsuda, H. Nagaretani, N. Furuyama, H. Kondo, M. Takahashi, Y. Arita, R. Komuro, N. Ouchi, S. Kihara, Y. Tochino, K. Okutomi, M. Horie, S. Takeda, T. Aoyama, T. Funahashi, Y. Matsuzawa, Diet-induced insulin resistance in mice lacking adiponectin/ACRP30, Nat. Med. 8 (2002) 731–737.
[6] A.H. Berg, T.P. Combs, X. Du, M. Brownlee, P.E. Scherer, The adipocyte-secreted protein Acrp30 enhances hepatic insulin action, Nat. Med. 7 (2001) 947–953.
[7] T. Yamauchi, J. Kamon, Y. Ito, A. Tsuchida, T. Yokomizo, S. Kita, T. Sugiyama, M. Miyagishi, K. Hara, M. Tsunoda, K. Murakami, T. Ohteki, S. Uchida, S. Takekawa, H. Waki, N.H. Tsuno, Y. Shibata, Y. Terauchi, P. Froguel, K. Tobe, S. Koyasu, K. Taira, T. Kitamura, T. Shimizu, R. Nagai, T. Kadowaki, Cloning of adiponectin receptors that mediate antidiabetic metabolic effects, Nature 423 (2003) 762–769.
[8] X. Mao, C.K. Kikani, R.A. Riojas, P. Langlais, L. Wang, F.J. Ramos, Q. Fang, C.Y. Christ-Roberts, J.Y. Hong, R.Y. Kim, F. Liu, L.Q. Dong, APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function, Nat. Cell Biol. 8 (2006) 516–523.
[9] D. Ron, C.H. Chen, J. Caldwell, L. Jamieson, E. Orr, D. Mochly-Rosen, Cloning of an intracellular receptor for protein kinase C: a homolog of the beta subunit of G proteins, Proc. Natl. Acad. Sci. USA 91 (1994) 839–843.
[10] D. Mochly-Rosen, B.L. Smith, C.H. Chen, M.H. Disatnik, D. Ron, Interaction of protein kinase C with RACK1, a receptor for activated C-kinase: a role in beta protein kinase C mediated signal transduction, Biochem. Soc. Trans. 23 (1995) 596–600.
[11] B.Y. Chang, K.B. Conroy, E.M. Machleder, C.A. Cartwright, RACK1, a receptor for activated C kinase and a homolog of the beta subunit of G proteins, inhibits activity of src tyrosine kinases and growth of NIH 3T3 cells, Mol. Cell Biol. 18 (1998) 3245–3256.
[12] P. Lopez-Bergami, H. Habelhah, A. Bhoumik, W. Zhang, L.H. Wang, Z. Ronai, RACK1 mediates activation of JNK by protein kinase C [corrected], Mol. Cell 19 (2005) 309–320.
[13] K. Arimoto, H. Fukuda, S. Imajoh-Ohmi, H. Saito, M. Takekawa, Formation of stress granules inhibits apoptosis by suppressing stress-responsive MAPK pathways, Nat. Cell Biol. 10 (2008) 1324–1332.
[14] J. Liliental, D.D. Chang, Rack1, a receptor for activated protein kinase C, interacts with integrin beta subunit, J. Biol. Chem. 273 (1998) 2379–2383.
[15] N. Geijsen, M. Spaargaren, J.A. Raaijmakers, J.W. Lammers, L. Koenderman, P.J. Coffer, Association of RACK1 and PKCbeta with the common beta-chain of the IL-5/IL-3/GM-CSF receptor, Oncogene 18 (1999) 5126–5130.
[16] A. Zakrzewicz, M. Hecker, L.M. Marsh, G. Kwapiszewska, B. Nejman, L. Long, W. Seeger, R.T. Schermuly, N.W. Morrell, R.E. Morty, O. Eickelberg, Receptor for activated C-kinase 1, a novel interaction partner of type II bone morphogenetic protein receptor, regulates smooth muscle cell proliferation in pulmonary arterial hypertension, Circulation 115 (2007) 2957–2968.
[17] S.J. Yarwood, M.R. Steele, G. Scotland, M.D. Houslay, G.B. Bolger, The RACK1 signaling scaffold protein selectively interacts with the cAMP-specific phosphodiesterase PDE4D5 isoform, J. Biol. Chem. 274 (1999) 14909–14917.
[18] T. Kadowaki, T. Yamauchi, Adiponectin and adiponectin receptors, Endocr. Rev. 26 (2005) 439–451.