AIMing at Metabolic Syndrome
– Towards the Development of Novel Therapies for Metabolic Diseases via Apoptosis Inhibitor of Macrophage (AIM) –

Toru Miyazaki, MD, PhD; Jun Kurokawa; Satoko Arai, PhD

Metabolic syndrome (MetS) is a cascade of metabolic diseases, starting with obesity and progressing to atherosclerosis, and is often fatal because of serious cardiovascular problems such as heart/brain infarction and hemorrhage. Accumulating evidence has revealed a critical involvement of inflammatory responses triggered by lesional macrophages in the pathogenesis of MetS. Importantly, we found that macrophages are associated with disease progression, not only in the induction of inflammation but also in the production of apoptosis inhibitor of macrophages (AIM), which we initially identified as a soluble factor expressed by macrophages. In atherosclerotic plaques, AIM is highly expressed by foam macrophages and inhibits apoptosis of these cells, which results in the accumulation of macrophages, causing inflammatory responses within the lesion, and ultimately disease progression. In adipose tissue, macrophage-derived AIM is incorporated into adipocytes through CD36-mediated endocytosis, thereby reducing the activity of cytosolic fatty acid synthase. This unique response stimulates lipolysis, resulting in a decrease in adipocyte size, which is physiologically relevant to the prevention of obesity. The lipolytic response also stimulates inflammation of adipocytes in association with the induction of metabolic disorders subsequent to obesity. Thus, AIM is involved in the progression of MetS in both an advancing and inhibitory fashion. Regulation of AIM could therefore be therapeutically applicable for MetS. (Circ J 2011; 75: 2522–2531)

Key Words: Apoptosis inhibitor of macrophage (AIM); Chronic inflammation; Lipolysis; Macrophages; Metabolic syndrome

Metabolic Syndrome (MetS), Macrophages, and Apoptosis Inhibitor of Macrophage (AIM)

MetS comprises a variety of metabolic disorders such as obesity, type 2 diabetes, fatty liver dysfunction, and atherosclerosis. Importantly, these diseases form a cascade of events, occurring sequentially from obesity and progressing towards atherosclerosis, with the stresses of modern life often acting as a catalyst. Difficulties in understanding the events that bridge obesity and insulin resistance (IR) have recently been overcome to reveal that the chronic, low-grade inflammation observed in obese adipose tissue is responsible for triggering IR. This subclinical inflammatory state of adipose tissue is closely associated with IR both in adipose tissue and systemically, thus contributing to the development of multiple obesity-induced metabolic and cardiovascular diseases.1–5

Infiltration of a large number of classically activated inflammatory macrophages (M1 macrophages) into adipose tissue has been shown to be responsible for obesity-associated inflammation.6–8 Lean adipose tissue contains a resident population of alternative activated macrophages (also known as M2 macrophages) that suppress inflammation of both adipocytes and macrophages themselves, partly via the secretion of interleukin (IL)-10. Hence, obesity induces a switch in the macrophage activation state in adipose tissue towards M1 polarization, leading to inflammation.9–12 Despite this knowledge, the key factors that initiate macrophage recruitment into adipose tissue remain unknown.

In this review, we address this question by focusing on the AIM protein (also known as Sρ, Api6, and CD5L). Though AIM was initially identified as an apoptosis inhibitor that supports the survival of macrophages against various apoptosis-inducing stimuli,13 our recent studies revealed a new role for AIM in adipocytes in the initiation of macrophage recruitment into adipose tissue leading to subsequent metabolic disorders.

Initial Characterization of AIM

The AIM protein is a member of the scavenger receptor cysteine-rich superfamily13 (Figure 1). AIM is a secreted molecule produced solely by macrophages and has been detected in human and mouse blood at varying levels.13–18 AIM is a direct target for regulation by nuclear receptor LXR/RXR.
Figure 1. Expression regulation and an apoptosis inhibitory function of apoptosis inhibitor of macrophages (AIM). ApoE, apolipoprotein E; Fas, fatty acid synthase; oxLDL, oxidized low-density lipoprotein; LXR, liver X receptors; RXR, retinoid X receptors.

Figure 2. Apoptosis inhibitor of macrophages (AIM) induces lipolysis in adipocytes. FFA, free fatty acid; rAIM, recombinant AIM.
heterodimers, so is produced when macrophages incorporate oxidized low-density lipoprotein (LDL), but not native or acetylated LDL. Based on these findings, we observed that AIM is expressed in lipid-laden macrophages at atherosclerotic lesions, and this induction is associated with atherosclerosis by supporting the survival of macrophages within lesions. Indeed, atherosclerotic plaques were markedly reduced in size in mice doubly deficient for AIM and LDL receptor (AIM−/−LDL−/−) compared with AIM+/−LDL−/− mice fed a high-cholesterol diet. Other studies have shown that AIM appears to be multifunctional and is effective in cell types other than macrophages, including B and natural killer (NK) T lymphocytes.

AIM harbors 3 cysteine-rich domains, resulting in a complex protein structure. The average detected AIM concentration in human and mouse blood varies according to the antibodies used for analysis by ELISA or Western blotting (Miyazaki, unpublished data). In addition, especially in human blood, different types of AIM structure seem to be present in different populations, based on the variable recognition patterns of blood AIM by an AIM-specific antibody (Miyazaki, unpublished data). Therefore, it is essential to evaluate the particular antibody being used for AIM analysis. It is also noteworthy that functional AIM variants exist, because recombinant AIM (rAIM) proteins generated in different host cell types show a wide range of diversity in both structure and function (Miyazaki, unpublished data). In addition to the host cell type, the production efficiency and functional activity of the rAIM protein appear largely dependent on several conditions, including strength of promoter activity of the expression vector, cell culture conditions, including amount and type of fetal bovine serum (FBS), purification method, including the type of antibody being used, and presence and location of a protein tag. Because of the difficulties experienced in obtaining large quantities of the correct AIM protein, it is also difficult to generate sufficient AIM antibodies; indeed, some rAIM and commercially available antibodies are not fully functional. This makes detailed study of AIM complicated. Although the mechanisms underlying such AIM structural variance are unclear, these could be investigated by analyzing possible associations between AIM structure and disease susceptibility.

**AIM Induces Lipolysis in Adipocytes, Suppressing Increased Fat Mass**

Besides the apoptosis inhibitory effect, we previously identified a novel AIM function within adipocytes. We initially observed a more accelerated weight increase of both visceral and subcutaneous fat tissue in AIM−/− mice fed a high-fat diet (HFD: fat kcal 60%) for 12 weeks compared with AIM+/− mice. Consistently, visceral fat adipocytes were larger in obese AIM−/− mice than in obese AIM+/− mice, and this was corrected by the intraperitoneal administration of rAIM. Interestingly, both obese AIM−/− and AIM+/− mice showed comparable metabolic rates (such as body temperature, oxygen consumption, and food intake), as well as locomotor activity. Thus, AIM appeared to influence adipose tissue mass by specifically affecting adipocytes. It is also noteworthy that the serum level of AIM was markedly increased in mice receiving a HFD. However, it is unclear whether this increase in the blood AIM levels is brought about by advanced AIM expression in macrophages or other unknown mechanisms.
We next assessed the effect of AIM in adipocytes using the 3T3-L1 preadipocyte cell line (Figure 2). When differentiated 3T3-L1 adipocytes in culture were challenged with rAIM, the size of the lipid droplets within the cells and the number of cells containing lipid droplets were remarkably decreased.\(^{26}\) When adipocytes were treated with rAIM, the amount of glycerol and free fatty acids (FFA) in the supernatant increased significantly. Supernatant viscosity was also markedly enhanced by the administration of rAIM, perhaps because of the increased glycerol content. Thus, AIM induces a lipolytic response resulting in the liberation of droplet components such as glycerol and fatty acids from the cells.\(^{27,28}\)

To support these in vitro observations, basal levels of serum FFA and glycerol were lower in obese AIM–/– mice than in obese AIM+/+ mice. Therefore, AIM induces lipolysis in adipocytes, resulting in the regulation of fat and body weight.

**AIM Functions in a Lack-of-Signaling Manner**

In most cases, a secreted protein binds to its specific receptor and mediates signal transduction to affect the target cell. Interestingly, however, this is not the case for AIM. Exogenous AIM secreted by macrophages is incorporated into adipocytes where it functions directly. When differentiated 3T3-L1 adipocytes, expressing high levels of peroxisome proliferator-activated receptor \(\gamma 2\) (PPAR\(\gamma 2\)),\(^{29}\) are treated with rAIM, rAIM accumulates within the cytoplasm, forming multiple dots within the intracellular compartment (Figure 3A Left). Incorporated rAIM colocalizes with early endosomes, but not with late endosomes or recycling endosomes. Therefore, AIM is endocytosed into adipocytes and is thereafter transported into the cytosol during endosome maturation. Notably, rAIM is not incorporated into immature preadipocytes that are negative for PPAR\(\gamma 2\) expression (Figure 3A Right). This specific colocalization of AIM with endosomes was supported by electron microscopy and AIM immunolabeling (Figure 3B).

Such direct functioning in the absence of signaling is unusual for a secreted molecule, with only a limited number of previously reported examples, including fibroblast growth factors 1 and 2,\(^{30,31}\) epidermal growth factor,\(^{32}\) and some plant and bacterial toxins,\(^{33,34}\) in which the cytosolic delivery of exogenous proteins mediates biological effects in mammalian cells. In addition, in dendritic cells some exogenous antigens can access the cytosol via similar machineries for intracellular transport where they are presented by major histocompatibility complex class I molecules.\(^{35,36}\) Additional experiments are necessary to clarify the mechanism responsible for AIM translocation from the endosomal compartment to the cytosol.

The internalization of exogenous AIM is mediated by the scavenger receptor CD36, which promotes the internalization of various molecules, including lipoproteins and fatty acids,\(^{37,38}\) and is expressed by adipocytes and macrophages, the target cells for AIM. Indeed, incorporation of rAIM was drastically decreased in the presence of CD36-neutralizing antibody. In addition, when rAIM was intravenously injected into CD36–/– mice, its incorporation into adipocytes in fat tissue was markedly less in CD36–/– mice than in CD36+/+ mice.\(^{39}\) Interestingly, the CD36–/– phenotype is not equivalent to that of AIM–/– mice,\(^{39-41}\) because of the wide-ranging scavenging characteristic of CD36, which allows CD36–/– mice to show a complicated phenotype caused by the deficient incorporation of multiple molecules.
AIM Targets Fatty Acid Synthase to Induce Lipolysis

Following the understanding that macrophage-derived AIM enters into adipocytes via CD36-mediated endocytosis (Figure 3C), the next question was how does it induce lipolysis. The first clue was provided by immunoprecipitation–mass spectrometry analysis using lysates from 3T3-L1 adipocytes treated with rAIM. AIM was shown to associate with fatty acid synthase (FAS), which is highly expressed in adipose tissue and catalyzes the synthesis of saturated fatty acids, such as palmitate, from acetyl-CoA and malonyl-CoA precursors. Previous studies have highlighted critical roles for FAS in biological aspects such as early embryogenesis, in addition to its use as a metabolic substrate. The association of AIM and FAS was subsequently confirmed in vitro by HEK293T cell lysates overexpressing FAS and AIM, and in vivo following the coprecipitation of FAS and AIM from fat tissue lysates in obese AIM−/− mice injected with rAIM. Additional in vitro studies revealed that AIM binds to specific domains within FAS, which are involved in the elongation of fatty acid chains, the terminal release of synthesized palmitate, as well as stabilization of FAS dimerization. It is well known that FAS is highly functional as a dimerized form, whereas monomeric FAS possesses little or no activity. Apparently owing to AIM binding, the proportion of dimerized FAS was significantly reduced in 3T3-L1 adipocytes treated with rAIM.

AIM association was shown to result in a remarkable reduction in the enzymatic activity of FAS, similar or even greater than that induced by the specific FAS inhibitor, C75, when used at a functional concentration (25 μmol/L). Consistently, FAS activity was significantly increased in the epididymal fat of AIM−/− mice compared with AIM+/+ mice, and this activity was subsequently decreased following supplementation of rAIM via direct injection. Thus, through association with multiple regions of FAS, AIM decreases FAS activity both functionally and structurally. Because treatment of 3T3-L1 adipocytes with AIM or C75 has similar consequences, the lipolytic effect of AIM on adipocytes must be through suppression of FAS activity. Indeed, rAIM (5 μg/ml) and C75 (25 μmol/L) were found to induce an increase in the efflux of glycerol and FFA at comparable levels from 3T3-L1 adipocytes. AIM and C75 also similarly prevented preadipocyte morphological differentiation and the suppression of the dif-

Figure 5. Apoptosis inhibitor of macrophages (AIM) is required for macrophage recruitment into obese adipose tissue. (A) Many inflammatory type macrophages stained with a pan-macrophage antibody F4/80 (green signals) and an IL-6 antibody (red signals) were observed in obese AIM−/− adipose tissue (Upper panels), whereas far fewer macrophages were found in obese AIM−/− adipose tissue (Lower panels). (B) Systemic rAIM injection into AIM−/− mice efficiently reconstituted the infiltration of macrophages into the adipose tissue (Left panels), while BSA injection as a negative control did not (Right panels). BSA, bovine serum albumin; HFD, high-fat diet; IL, interleukin.
fertile upregulation of mRNA levels for “fat genes” such as C/EBPα, PPARγ2, CD36, and GLUT4. Figure 4 summarizes the effects of AIM on adipocytes to reduce cell size.

**How Does Reduced FAS Activity Lead to Lipolysis?**

It is of interest that AIM is the first identified natural inhibitor of FAS. Systemic FAS inhibition via the administration of C75 decreases the production of neuropeptide Y in the mouse hypothalamus, resulting in a marked loss of appetite and overall decreased body weight. However, Aim−/− and Aim+/− mice show comparable levels of food intake, suggesting that AIM may not have a neurologic effect. This may be related to a requirement for a specific endocytotic process mediated by CD36, the expression of which is not reported in hypothalamic cells. Obviously, the lipolytic effect of AIM is a direct effect of FAS inhibition on adipocytes, which decreases the size and number of lipid droplets, thereby decreasing adipocyte size.

Lipolysis usually occurs during periods of energy deprivation. Under fasting conditions, adipocytes undergo lipolysis via the hormone-dependent stimulation of a G protein-coupled receptor/cyclic AMP (cAMP)-dependent signaling cascade, followed by phosphorylation of protein kinase A (PKA) which activates hormone-sensitive lipase (HSL). Simultaneously, the level of adipose triglyceride lipase (ATGL) mRNA also increases. Interestingly, however, despite the lipolytic consequences, neither rAIM nor C75 upregulates the phosphorylation of PKA or the levels of ATGL and HSL mRNA in 3T3-L1 adipocytes. Thus, unlike conditions of starvation, inhibition of FAS might activate an unknown cAMP/PKA-independent lipolytic pathway. Indeed, lipolysis caused by AIM/FAS inhibition is a slow and mild process contrasting with that observed in starvation, which occurs rapidly and robustly. Further studies are required to identify the mechanisms involved in AIM/FAS-dependent lipolysis.

**Lipolysis and Macrophage Recruitment Into Obese Adipose Tissue**

Although the mechanism that promotes the infiltration of inflammatory macrophages into obese adipose tissue has been unknown, recent studies have shown that saturated fatty acids released from adipocytes in response to various metabolic consequences of cell hypertrophy, including reduced mitochondrial function, ER stress, and increased rates of basal lipolysis, may contribute to macrophage recruitment. In particular, a critical role for lipolysis has been suggested, showing that it promotes macrophage infiltration into adipose tissue during both obesity and weight loss. On the other hand, several reports have emphasized the importance of the chemokine, MCP-1, following the analysis of MCP-1-deficient mice or transgenic mice overexpressing MCP-1 in adipocytes. However, many unanswered questions remain, including “What is the key factor that induces lipolysis along with obesity?” “What promotes MCP-1 expression in obese adipose tissue?” “What links lipolysis and MCP-1”?, and “Is lipolysis brought about by AIM involved in this event, and if so, how?”

**No Adipose Tissue Macrophage Accumulation in the Absence of AIM**

As so far described, adipocyte hypertrophy is more advanced in Aim−/− mice than in Aim+/− mice, and the overall mass of visceral fat and body weight is markedly greater. Interest-ingly, however, the obesity-associated infiltration of inflammatory macrophages (M1 macrophages) into adipose tissue was dramatically suppressed in AIM−/− mice compared with Aim+/− mice after a 12-week HFD (Figure 5A). In addition, the intraperitoneal administration of rAIM induced the accumulation of M1 macrophages in adipose tissue in obese Aim−/− mice (Figure 5B). Thus, the presence of AIM is indispensable for obesity-associated recruitment of adipose tissue macrophages.

The difference in macrophage accumulation in fat in the presence or absence of AIM is not predominantly because of the anti-apoptotic effect of AIM, because the apoptotic state of macrophages (and also of adipocytes) is comparable between obese Aim−/− and Aim+/− epididymal adipose tissue, as assessed by TUNEL staining. Recent reports showed that T cells are also recruited to adipose tissue, and that accumulation of a CD8+ T cell population appears to precede macrophage infiltration. However, the number of CD8+ (as well as CD4+) T cells in epididymal fat did not differ significantly between Aim−/− and Aim+/− mice fed a HFD for 6 weeks, which is the early phase of obesity prior to macrophage accumulation.

The lipolytic state of adipose tissue, which progressed along with an increase in blood AIM levels under HFD conditions, was previously shown to be suppressed in Aim−/− mice. Thus, an increase in AIM may induce vigorous lipolysis in obese adipose tissue, thereby stimulating macrophage recruitment. To test this idea, we investigated whether AIM itself attracts macrophages, but found that it showed no chemotactic activity in a macrophage migration assay using RAW264.1 mouse macrophage cells. By contrast, conditioned medium from 3T3-L1 adipocytes that had been challenged with rAIM for 72 h (AIMCM) efficiently attracted macrophage cells. A comparable effect was observed with conditioned medium from cells treated with the specific FAS inhibitor, C75 (C75CM). Furthermore, conditioned medium from 3T3-L1 adipocytes treated with rAIM in the presence of a CD36-neutralizing antibody to inhibit AIM-dependent lipolysis did not efficiently attract macrophages, suggesting that AIM-induced lipolysis in adipocytes appears to be responsible for macrophage recruitment.

**Bona Fide Scenario to Attract Macrophages Into Adipose Tissue**

Previous work has demonstrated that saturated fatty acids activate Toll-like receptor (TLR) 4, and that this response is tightly associated with obesity-induced inflammation. Thus, it is plausible that an increase in blood AIM induces vigorous lipolysis in obese adipose tissue, and that saturated fatty acids effluxed from adipocytes as a result of lipolysis might activate chemokine production in adipocytes via the stimulation of TLR4 in a paracrine/autocrine fashion. Indeed, palmitic acid (PA) and stearic acid (SA), the major fatty acids comprising triglyceride droplets and well known stimulators of TLR4, were identified as the components released by adipocytes in response to lipolysis induced by AIM or C75. Consistently, both AIMCM and C75CM efficiently activated the TLR signaling cascade and chemokine production in 3T3-L1 adipocytes, inducing degradation of IκBα and production of chemokines such as MCP-1, CCL5/RANTES, MCP-2, and MCP-3. Similar effects of TLR activation and chemokine production were observed when 3T3-L1 adipocytes were treated with PA and SA.

The essential role of TLR4 was corroborated in 2 ways.
First, suppression of TLR4 expression by siRNA significantly reduced production of MCP-1 in 3T3-L1 adipocytes. Second, intravenous injection of rAIM into wild-type and TLR4-/- mice was assessed according to the state of lipolysis and chemokine production in epididymal adipose tissue. In wild-type and mutant mice, rAIM did induce lipolysis, as shown by increased blood FFA and glycerol levels. By contrast, induction of mRNA for chemokines by rAIM injection was significantly less efficient in TLR4-/- than in wild-type mice. Thus, in summary, AIM-induced lipolysis provoked an efflux of saturated fatty acids, including PA and SA, from adipocytes, which stimulated chemokine production in both adipocytes and resident macrophages via TLR4 activation, resulting in M1 macrophage migration (Figure 6). Consistent results were obtained in vivo in obese AIM+/+ and AIM-/- mice after 12 weeks on a HFD. In epididymal fat, phosphorylation levels of JNK, representing the state of TLR activation, were decreased in AIM-/- mice compared with AIM+/+ mice. In addition, chemokine mRNA levels were lower in AIM-/- compared with AIM+/+ adipose tissue. Overall, these results strongly indicate that AIM-induced lipolysis is the initiating step for macrophage recruitment into obese adipose tissue.

**No Inflammation or IR in Obese AIM-/- Mice**

As a consequence of the abolished infiltration of inflammatory macrophages, the progression of obesity-associated inflammation is prevented both locally and systemically in obese AIM-/- mice. In adipose tissue, mRNA levels for proinflammatory cytokines such as tumor necrosis factor α (TNFα), IL-6 and IL-1β, were significantly lower in AIM-/- than in AIM+/+ mice after a HFD for 12 weeks. Consistent with this finding, serum levels of TNFα and IL-6 were lower in AIM-/- mice compared with AIM+/+ mice.

Activation of the insulin signaling pathway was studied after the intravenous injection of insulin in AIM-/- and AIM+/+ mice fed a HFD for 12 weeks. Substantial insulin-stimulated phosphorylation of AKT and GSK3β protein kinases was observed in adipose tissue, skeletal muscle (gastrocnemius), and liver in AIM-/- mice in contrast to markedly diminished phosphorylation levels in AIM+/+ mice. Thus, insulin sensitivity was maintained in obese AIM-/- mice. In line with this, whole-body glucose tolerance and IR observed in obese AIM+/+ mice were ameliorated in obese AIM-/- mice, as shown by intraperitoneal glucose and insulin tolerance tests. Thus, AIM-/- mice showed advanced obesity compared with AIM+/+ mice after a 12-week HFD, but still showed normal glucose tolerance.

**Conclusion**

Is AIM Beneficial or Detrimental for MetS?

AIM is incorporated into adipocytes and induces lipolysis via the reduction of FAS enzymatic activity. This decreases lipid droplet storage within adipocytes, which resists the augmentation of adipose tissue mass on overfeeding. Indeed, the weight increase of visceral fat in mice fed a HFD was accelerated in AIM+/+ mice, and suppressed by the systemic administration of rAIM. Thus, AIM appears to be a beneficial molecule that impedes the progression of obesity, suggesting that it might be a promising target for next-generation anti-obesity drugs. Intriguingly, however, when this lipolytic effect is excessive...
(ie, when an increased level of AIM targets hypertrophic adipocytes), it triggers chronic inflammation via the recruitment of macrophages into adipose tissue, leading to IR. In this regard, AIM is certainly detrimental for metabolic disorders. Thus, during early periods of MetS prior to prominent obesity and with limited lipid storage in adipocytes, AIM can help prevent the progression of obesity through lipolysis; in obese conditions, anti-AIM therapy should prevent the development of metabolic diseases such as diabetes and cardiovascular events, as observed in AIM⁻/⁻ mice.

One of the criteria for assessing whether AIM or anti-AIM therapy should be administered is the blood AIM level, based on the observation that this increases in line with the progression of obesity in mice fed with HFD. However, 2 things are noteworthy. First, because AIM has a complicated structure, it is possible that a considerable proportion of blood AIM undergoes unsuccessful protein folding, resulting in limited or even no function. In addition, the presence of glycosylation is likely, in particular for murine AIM. Indeed, murine AIM has 3 or 4 regions susceptible to N-glycosylation, and both murine and human AIM proteins have several regions for O-glycosylation. Further, the molecular weights of both murine and human AIM are markedly larger than those estimated from their amino acid sequences, suggesting that they are heavily glycosylated. This modification may also influence the function of AIM. Therefore, not only the amount but also the activity of blood AIM should be evaluated. Second, unlike mice fed with HFD, the body mass index and AIM level are not always parallel in humans (Miyazaki, unpublished data), possibly because of the wide variation in eating habits, as some foods may induce obesity without a remarkable increase in blood AIM, and vice versa. Thus, it is relevant to study some foods that may induce obesity without a remarkable increase in blood AIM, possibly because of the wide variation in eating habits, as some foods stimulate AIM production while interfering with its efficient folding and glycosylation. Thus, the evaluation of blood AIM activity together with blood AIM levels is therefore again necessary.

Practically, however, it may be difficult to clearly establish the threshold of blood AIM level or activity, which decides the agonist or antagonist to be used. To this end, large-scale cohort studies for the association of blood AIM and the incidence and levels of disease are certainly required. In the meantime, a set of parameters including blood AIM needs to be defined. In addition, development of a simple method that can maintain the AIM level at a reasonable level via modulation of the expression or protein stability of AIM is required.

Perspectives

We have shown that AIM prevents the progression of obesity via lipolysis, and acts as a key factor in the initiation of obesity-associated chronic inflammation leading to IR. Future efforts to establish a diagnosis via the measurement of the blood AIM level and the therapeutic application of both AIM (AIM agonists) and anti-AIM (AIM antagonists) will further progress the development of treatments to prevent the onset of metabolic disorders brought about by the modern lifestyle.

Acknowledgments

We thank to Drs K. Nakashima and T. Kadokawa, Ms M. Mori, K. Morita, and M. Ohba for their assistance and discussion.

References


