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RESEARCH HIGHLIGHT

AIMP1 negatively regulates PPARγ: Implication in adipogenesis

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The regulation mechanism of peroxisome proliferator-activated receptor γ (PPARγ) known as key determinant in adipogenesis is important for understanding the cause of lipid metabolic disorders and glucose metabolic syndromes. In a recent paper published in Journal of Cell Science, we demonstrated that aminoacyl-tRNA synthetase-interacting multifunctional protein 1 (AIMP1) is a novel negative regulator of PPARγ Although AIMP1 is originally found as an associated factor within multi-tRNA synthetase complex for translation, it has been shown to play regulatory roles in diverse cellular processes. Now AIMP1 is shown to negatively regulates PPARγ-mediated transcription through direct interaction with DNA-binding domain of PPARγ and inhibits adipogenesis. These results suggest that AIMP1 functions as a novel inhibitor of PPARγ, raising the possible linkage between translation and adipogenesis.

Keywords: AIMP1; aminoacyl-tRNA synthetase; PPARγ; adipogenesis

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Negative regulation of adipogenesis by AIMP1

AIMP1 has been identified as one of non-enzymatic factors associated with multi-aminoacyl-tRNA synthetase (ARS) complex, which consists of nine different aminoacyl-tRNA synthetase enzymes [1, 2] and three non-enzymatic factors [3, 4]. AIMP1 regulates the stability of the ARS complex through protein-protein interaction [5, 6]. It is also highly detected in pancreatic □ cells, from which it is secreted to maintain glucose homeostasis [7]. AIMP1 knockout mice show hypoglycemia *in vivo* [7]. During adipogenic differentiation of 3T3-L1 cells, the expression of genes encoding ten different tRNA synthetases, glutamyl-prolyl-tRNA synthetase (EPRS), methionyl-tRNA synthetase (MRS), isoleucyl-tRNA synthetase (IRS), valyl-tRNA synthesis (VRS), tryptophanyl-tRNA synthetase (WRS), aspartyl-tRNA synthetase (DRS), arginyl-tRNA synthetase (RRS), leucyl-tRNA synthetase (LRS), glycyl-tRNA synthetase (GRS), and histidyl-tRNA synthetase (HRS), and that of genes encoding two AIMPs, AIMP2 and AIMP3 was decreased. These findings suggest that aminoacyl-tRNA synthesis and ATP consumption is decreased during adipogenesis. However, the expression pattern of the gene encoding AIMP1 was different from that of genes encoding AIMP2 and AIMP3. The mRNA and protein expression of AIMP1 shows dynamic alteration during adipogenesis in which mRNA expression maximizes at 4-6 days and protein expression peaks at 6-8 days after differentiation [8]. During adipogenesis, AIMP1 is clearly localized in the nucleus. Accumulation of intracellular lipid

and triglyceride (TG) content was increased in AIMP1-deficient MEF and preadipocyte transfected with AIMP1 siRNA. Reversely, overexpression of AIMP1 in 3T3-L1 preadipocyte and mouse epididymal fat pads attenuated adipogenesis.

Negative regulation of PPARγ by AIMP1

PPARγ belongs to the nuclear hormone receptor super family [9]. PPARγ forms a heterodimer with retinoid X receptor (RXR) and ligand binding to either PPARγ or RXR can change the conformation of this heterodimer, favoring release of co-repressors and recruitment of co-activators [10]. This heterodimer induces the expression of target genes via specific binding with PPAR response elements (PPREs) in thepromoter regions. AIMP1 interacts with the DNA binding domain of PPARγ and inhibits its transcriptional activity. The complex between PPARγ and AIMP1 prevented the binding of PPARγ to PPRE and inhibits the expression of target genes such as aP2, LPL, and glycerol kinase (Gyk) [8].

The potential application of AIMP1 as a therapeutic target

We identified AIMP1 as a novel inhibitor of PPARγ which is a key master regulator of adipogenesis. The enhancement of AIMP1 expression by chemicals or gene introduction or PPARγ inhibition by AIMP1 mimetics may suppress lipid accumulation and attenuates the risks of obesity. Thus, the understanding of the regulation of PPARγ by AIMP1 provides a novel pharmacological space to deal with metabolic syndrome such as obesity.

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Conflict of interest

The authors declare there is no conflict of interest.

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