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MINI REVIEW

Peroxisome Proliferactor Activated Receptor Gamma (PPAR-γ) Polymorphism Towards Obesity Endemic in Malaysia

EMILIA A*[1], ATIF AB*[1], ZAHRI MK[1], RAO USM[1], GOTAM K[3], HOLIFA SA[1], ESA AB RAHMAN[1], ZILFALIL AB[2]

[1]*Faculty of Medicine and Health Sciences, Universiti Sultan Zainal Abidin, Kuala Terengganu, Malaysia.*
[2]*Department of Paediatrics, School of Medical Sciences, Universiti Sains Malaysia, Malaysia.*
[3]*UCSI, School of Medical Sciences, Kuala Terengganu, Malaysia.*

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ABSTRACT

Obesity is pandemic and its associated co-morbidities, nowdays pose a major threat to global health systems. Obesity is often associated with adipose tissue dysfunction in which adiposity hypertrophy, adipose tissue hypo-perfusion and hypoxia, adipose tissue inflammation and macrophage infiltration are interrelated with each other in the pathophysiology and pathogenesis of obesity. Here we will discuss how genetic studies, through the discovery of peroxisome proliferactor-activated receptor gamma (PPAR-γ) have contributed to our understanding of the central pathways which govern the mechanism of how obesity develops in human. In Malaysia, we are still lacking information about the interaction of PPAR-γ polymorphism with obesity. We anticipate that future studies should emphasize more on genetic research, especially on lipid studies so that we could develop a most efficient and achievable targeted approach to the prevention and control of obesity accordingly.

There has been a growing concern of obesity pandemic as obesity pose a major threat to health systems around the world due to its significant relationship towards increasing morbidity and mortality to many of the metabolic disorders. Obesity results from an imbalance between excess food intake and energy expenditure, which leads to the accumulation of excess fat or white adipose tissue [1] around visceral and subcutaneous area [2].

Adipose tissue was described as a very active metabolic and endocrine organ which produces various factors with important endocrine functions including leptin, other cytokines, adiponectin, complement components, plasminogen activator inhibitor-1, proteins of renin angiotensin system [3] as well as resistin [3]. Excessive accumulation of adipose tissue especially in the visceral compartment leads to obesity, as well as other metabolic disorders such as insulin resistance, hyperglycemia, dyslipidemia, hypertension as well as prothrombotic and proinflammatory states [4].

Obesity was reported to be associated with adipose tissue dysfunction in which adipocyte hypertrophy, adipose tissue hypo-perfusion and hypoxia, adipose tissue inflammation and macrophage infiltration are interrelated with each other in the pathophysiology and pathogenesis of obesity [5]. Adipocyte was identified to play a central role in controlling energy and whole body lipid homeostasis [6] and the discovery of peroxisome proliferactor activated receptor (PPAR) family of transcription factors revealed that PPARs are major regulators of lipid and glucose metabolism, allowing adaptation to the prevailing nutritional environment [7]. Three isoforms of PPARs (α, β and γ) were described [7] and the latter was reported as the most adipose specific of the PPARs [8] as activation of PPAR-γ induces the differentiation of preadipocytes into adipocytes and stimulates triglyceride storage [7] which provides us some idea that PPAR-γ might be associated in the pathogenesis of obesity.

PPAR-γ is widely expressed in white and brown adipose tissue (both store large amounts of fatty acids) [7] and located on chromosome 3p25.2 and spans over 100 kb with 9 exons which gives rise to three isoforms namely PPAR-γ1, PPAR-γ2 and PPAR-γ3 as a consequence of alternate promoter usage and splicing [9]. Three genetic variants of the PPAR-γ gene were

*Corresponding Author

Dr. Atif Amin Baig
Faculty of Medicine and Health Sciences,
Universiti Sultan Zainal Abidin, Kuala Terengganu, Malayasia.
Phone: +6096225587
Email: atifamin@unisza.edu.my

reported. A Pro115Gln mutation which results in the conversion of proline to glutamine at position 115 of amino acid was demonstrated to be associated with increased BMI in obese subjects, as a result of active differentiation of adipocytes by PPAR-γ2 protein [10]. The CAC478CAT polymorphism, which causes the silent C to T substitution in exon 6 of the PPAR-γ gene, was reported not to be associated with all markers related with obesity. However, obese subjects bearing at least one CAT478 allele was shown to have higher plasma leptin levels than who did not, suggesting the idea that PPAR-γ gene might play a prominent role in regulating leptin levels among obese subjects [11]. The most prevalent Pro12Ala polymorphism results from a CCA to GCA missence mutation in codon 12 of exon B in PPAR-γ gene, which encodes the NH_2- terminus that defines the adipocyte specific PPAR-γ2 isoform [12]. PPAR-γ ligands exist in both synthetic and natural forms. Several unsaturated fatty acids, such as oleate, linoleate, eicosapentaenoic, and arachidonic acids as well as a prostanoid called 15-deoxy-δ-12, 14-prostaglandin J2 are natural ligands for PPAR-γ [8]. It has been reported that the members of the thiazolidinedione (TZD) family of antidiabetic compounds such as ciglitazone, pioglitazone, troglitazone and rosiglitazone are specific PPAR-γ ligands with a K_d in the 100 nmol/l range [13]. In fact, it is very interesting to note that these drugs were developed without realizing that they were ligands of PPAR-γ [7].

It has been reported that adipocyte differentiation involves the communication between extracellular signals and extracellular matrix (ECM) environment to the nucleus, leading to a orderly regulation of adipocyte-specific gene expression resulting in the mature adipocyte that is highly specialized for storing energy and homeostasis [14]. Thus, PPAR-γ must cooperate with C/EBP family of transcription factor to transactivate adipocyte genes to regulate adipocyte differentiation [14]. Accumulated evidence stated that C/EBP-α function in adipocyte differentiation. Even though C/EBP-α is not very adipocyte specific, C/EBP-α is expressed before the transcription of most adipocyte-specific genes is initiated. CCAAT/enhancer binding protein-α binds and transactivates the promoters of adipocyte genes as aP2, SCD1, GLUT-4, PEPCK, leptin and insulin receptor [14]. Hwang and colleagues [15] reported that mutation of the C/EBP-α site in adipocyte genes would terminate transactivation process. Besides playing a role in adipocyte differentiation thus increased adipocyte numbers, activation of PPAR-γ stimulates fatty acids storage in mature adipocytes through several steps; release of fatty acids from the triglycerides contained in the lipoprotein particles through the transactivation of lipoprotein lipase, intracellular fatty acid transport (aP_2), acyl-CoA synthase, and fatty acid esterification by stimulating PEPCK gene, which provides α-glycerophosphate [16-19].

It was reported that PPAR-γ expression is increased in visceral adipose tissue of obese subjects relative to subcutaneous adipose tissue, suggesting the idea that altered expression of PPAR-γ might play a role in adipose tissue distribution and expansion [20]. Since PPAR-ɣ was identified as a central regulator for adipocyte differentiation and body fat mass is a potent determinant of insulin sensitivity and type 2 diabetes, the Pro12Ala polymorphism effect on susceptibility for obesity has become of major interest [12]. In two independent cohort study of obese Caucasian (BMI range 18.6 – 43.2kg/m^2 and 24.2 – 76.8 kg/m^2), Pro12Ala polymorphism missense mutation was found to be associated with increased BMI, suggesting that Ala12 isoform might contribute to the genetic susceptibility for the metabolic disorders in obesity [21]. Norman and colleagues [22] reported that in Pima Indians, a population with a very high prevalence of obesity, suggestive linkage (logarithm of odds = 2.0) with percentage body fat was located at chromosome 3p24.2-p22, near the region locating the PPAR-ɣ gene (3p25 – p24.2). Other studies in selected populations with a relatively small sample sizes also supported the idea that increased weight gain is associated with the Ala allele [23-25]. However, Deeb *et al* [26] reported that Pro12Ala polymorphism was associated with decreased receptor activity, lowered BMI and improved insulin sensitivity in Finns subjects while no difference in Japanese [27]. Different findings for the Pro12Ala variant depends on the superimposition of environmental factors, suggesting the so-called "gene-environment" interaction might well hinged on genetic variations, such as those occurring in the transcription factor PPAR-γ [12].

Based on our extensive literature review we found that there are no reported studies being conducted to show any possible interaction of PPAR-γ polymorphism and obesity in Malaysian subjects so far. Since obesity pose the biggest health challenges around the world, it is very crucial to have more focus on the genetic approaches to have better understanding on the current genetic trends of human obesity, especially in the extended roles of PPAR-γ in the regulation of lipid metabolism. Therefore, we suggested that more genetic research should be conducted on the association of the PPAR-γ and its polymorphism on the regulation of lipid homeostasis as well as adipose tissue dysfunction in order to provide us a detailed structural framework of pathophysiological mechanism involved in the development and maintenance of obesity. It is important for us to take note that having better understanding on the status and pattern of obesity at molecular level in any ethnicity or sub-ethnicities is crucial for effective obesity intervention to improve our quality of life and health. In addition, Stumvoll and Ha¨ring [12] suggested that further studies should be conducted on the likely interaction PPAR-γ polymorphism with independent modulators such as obesity, ethnicity, ratio of unsaturated to saturated fatty acids as well as other common genetic polymorphisms such that the understanding of how specific modulation of PPAR-γ influences metabolism in humans might accelerate the development of novel pharmacological agents useful for preventing and treating type 2 diabetes and related disorders.

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Authors Column

Dr. Atif Amin Baig is a medical lecturer and a molecular geneticist working with biochemical, genetics and rare disease disorders. Curretly, he has been working on obesity with his team. Obesity is a heriditary disorder which has been a public health issue globally with its significant contribution towards increasing the morbidity and mortality to many of the metabolic disorders. There is a need of studying the obesity related genes in multiethnic and multicultural Malaysian population to predict the health risk and to improve the quality of life in Malaysian population towards health and economical well being of the country.