

Acta Med. Okayama, 2013
Vol. 67, No. 3, pp. 129–134

Copyright©2013 by Okayama University Medical School.

Acta Medica
Okayama

<http://escholarship.lib.okayama-u.ac.jp/amo/>

Review

Cell Cycle Abnormality in Metabolic Syndrome and Nuclear Receptors as an Emerging Therapeutic Target

Atsuko Nakatsuka^{*§}, Jun Wada, and Hirofumi Makino

*Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan*

In recent years, many researchers have emphasized the importance of metabolic syndrome based on its increasing prevalence and its adverse prognosis due to associated chronic vascular complications. Upstream of a cluster of metabolic and vascular disorders is the accumulation of visceral adipose tissue, which plays a central role in the pathophysiology. In the accumulation of adipose tissues, cell cycle regulation is tightly linked to cellular processes such as proliferation, hypertrophy and apoptosis. In addition, various cell cycle abnormalities have also been observed in other tissues, such as kidneys and the cardiovascular system, and they are critically involved in the progression of disease. Here, we discuss cell cycle abnormalities in metabolic syndrome in various tissues. Furthermore, we describe the role of nuclear receptors in cell growth and survival, and glucose and lipid metabolism in the whole body. Therapeutic strategies for modulating various cell cycles in metabolic disorders by targeting nuclear receptors may overcome obesity and its chronic vascular complications in the future.

Key words: nuclear receptor, cell cycle, metabolic syndrome, diabetic nephropathy

Recently, the population with metabolic syndrome has been increasing in Japan and in other developed and developing countries. In Japan, the national health survey in 2010 indicated that one-half of males and one-fifth of females from 40 to 74 years old meet the criteria of metabolic syndrome [1]. The concept of metabolic syndrome represents a cluster of atherosclerotic vascular risk factors such as hypertension, dyslipidemia, insulin resistance and glucose intolerance, which ultimately increases the risk of severe complications like cardiovascular, chronic kidney and cerebrovascular diseases. Upstream of the cluster of

metabolic disorders is the accumulation of visceral adipose tissue. A strategy for preventing the critical complications of metabolic syndrome is urgently required for public health and social medical cost reduction. To overcome metabolic syndrome and its related vascular complications, new insights into the mechanism and the identification of therapeutic targets are necessary. In the line of such considerations, we focus on findings regarding cell cycle regulation in metabolic syndrome. Cell proliferation, hypertrophy and apoptosis are controlled by cell cycle regulation, and cell cycle abnormality has been reported in various tissues under metabolic syndrome. In this review, we further consider the roles of nuclear receptors in the process of hypertrophy, proliferation and apoptosis of the cells and describe the emerging roles of modulators of nuclear receptors to control cell cycles

Received January 11, 2013; accepted March 14, 2013.

*Corresponding author. Phone: +81-86-235-7235; Fax: +81-86-222-5214

E-mail: atsuko-n@md.okayama-u.ac.jp (A. Nakatsuka)

§The winner of the 2012 Yuuki Prize of the Okayama Medical Association.

in metabolic syndrome.

Cell Cycle Abnormalities in Metabolic Syndrome

Cell cycle of adipocyte in metabolic syndrome.

The cell cycle abnormalities of adipocytes in obese patients have been investigated. In obesity, the large mass of adipose tissue is developed through an increase both in cell size and number. Various mechanisms involved in adipogenesis have been investigated, including cell cycle regulators, transcription factors, ligands of nuclear receptors, and signaling molecules. Sakai *et al.* reported an initial increase in adipocyte size followed by an increase in adipocyte number in white adipose tissue [2]. They showed that Skp2-dependent ubiquitination of p27^{Kip1} led to cell cycle progression, followed by an increase in the number of adipocytes during the development of obesity. p21^{Cip1} is also major cyclin-dependent kinase inhibitor and is associated with G₁ cell cycle arrest. Naaz *et al.* reported that both p27^{Kip1} and p21^{Cip1} deficiency produces adipocyte hyperplasia and obesity [3]. In contrast to that report, Inoue *et al.* demonstrated that p21^{Cip1} is induced during adipocyte differentiation, and promotes adipocyte hypertrophy and obesity-induced insulin resistance [4]. In addition, 3T3-L1 fibroblasts with deletion of p21^{Cip1} or embryonic fibroblast from p21^{-/-} mice impaired adipocyte differentiation, resulting in smaller adipocytes [4]. Thus, the regulation of adipocyte size and number may be quite complex.

Another important cell cycle regulator, p53, is well-known as a tumor suppressor gene, and its biological role in adipocyte differentiation has also been investigated. Upon DNA damage, the activation of p53 as the 'Guardian of the Genome' induces cell cycle arrest or removal of damaged cells through apoptosis. In adipocytes, p53 blocks clonal expansion and cell cycle progression rather than inducing apoptosis, and p53 represents a negative regulator for adipogenesis [5]. However, in later stages of adipocyte maturation, Bazuine *et al.* hypothesized that p53 protects adipocytes from reactive oxygen species and lipotoxicity induced cell damages by up-regulating cytoprotective genes to achieve conversion to large lipid-laden adipocytes [6]. In the setting of obesity *in vivo*, the increased expression of p53 in adipose tissues is critically involved in the development of senescence-

like changes including increased β -galactosidase activities and proinflammatory cytokines, which are ultimately linked to the development of insulin resistance [7]. Collectively, the involvement of cell cycle regulators in obesity is somewhat complex, depending, as has been shown, upon the stage of adipocyte differentiation *in vitro* and upon the animal model used for *in vivo* experiments; thus, further characterization of cell cycle regulators in metabolic syndrome is required in future studies.

Cell cycles of kidney cells in diabetic nephropathy.

The cell cycle of kidney cells had been well-investigated in diabetic nephropathy. Renal hypertrophy is one of the earliest abnormalities of diabetic nephropathy, and is the beginning of later irreversible structural changes, such as glomerulosclerosis and tubulointerstitial fibrosis [8]. Hyperglycemia increases the expression of p21^{Cip1} and p27^{Kip1} through a TGF- β dependent mechanism, which halts cell cycle at the G₁ stage (Fig. 1). In parallel, when *de novo* protein synthesis increases, extracellular matrix protein accumulation occurs, and consequently the glomeruli become hypertrophic [9]. Cell-cycle abnormalities of glomerular cells, such as mesangial cells, podocytes and endothelial cells, contribute to the morphological and physiological change of glomeruli. Similar to glomerular cells, the hyperglycemia-induced up-regulation of angiotensin II, TGF- β and cyclin-dependent kinase inhibitors such as p16^{INK4} and p27^{Kip1} cause cell-cycle arrest and hypertrophy of tubular cells, *i.e.* a senescence-like phenotype [10]. Unlike glomerular cells, however, a diabetic environment also increases the apoptosis of tubular cells and results in progression of tubular atrophy. The apoptosis is associated with increased expression of Bax and reduced expression of bcl-2, while up-regulation of p27^{Kip1} and p21^{Cip1} has been reported to limit the degree of apoptosis in tubular cells [8, 10]. Thus, the hypertrophy and atrophy of tubules are regulated in a yin and yang manner and the cycle regulators determine whether the cells exit the cell cycle in the late G₁ phase to apoptosis or remain in the G₁ phase [8].

Cell cycle abnormalities of the cardiovascular system.

In metabolic syndrome, endothelial dysfunction gradually and insidiously progresses prior to the development of diabetes. Hyperinsulinemia, postprandial hyperglycemia, reactive oxygen species and hypertension assault endothelial cells and promote

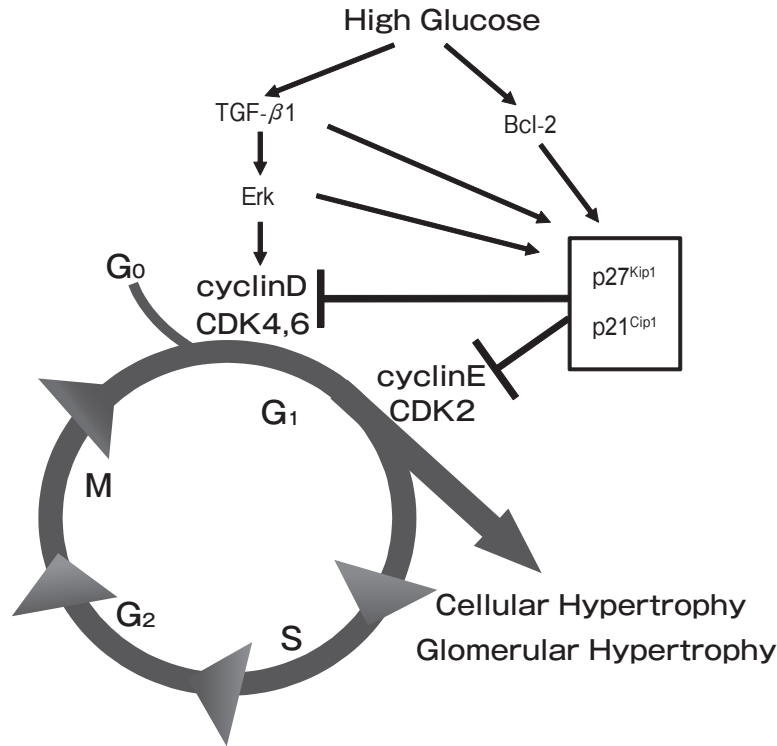


Fig. 1 Cell cycle abnormality in diabetic nephropathy. Erk, extracellular-signal-regulated kinase; CDK, cyclin dependent kinase; Bcl-2, B cell lymphoma-2; TGF-β1, transforming growth factor-β1.

apoptosis. Zhong *et al.* showed that high glucose increased the number of senescent cells, inhibited telomerase activity, increased the proportion of cells in the G₀/G₁ phase, reduced the proportion in the S phase, and decreased NO synthesis [11]. The abnormal proliferation of vascular smooth muscle cells (VSMC) is a key feature of the development of atherosclerosis and subsequent cardiovascular complications. Hyperglycemia, growth factors, and cytokines such as TNF-α trigger a mitogenic response, resulting in the activation of cell cycle progression and VSMC proliferation [12, 13]. Cardiomyocytes withdraw from the cell cycle and initiate hypertrophic growth soon after birth in mammals, and thus, a loss of cardiomyocytes without replication causes cardiac dysfunction. Among various diabetes-associated cardiovascular complications, diabetic cardiomyopathy presents heart failure without evidence of hypertension, coronary artery disease, valvular or congenital heart disease. The mechanism of diabetic cardiomyopathy is multifactorial, involving autonomic dysfunction, metabolic derangements, abnormalities in ion homeostasis, gly-

cation of interstitial proteins such as collagen, and interstitial fibrosis [14]. In an *in vivo* study, the expression of p21^{Cip1} and 14-3-3 σ, which are activated via p53 function, trigger cell-cycle arrest and DNA repair, preventing replication of mutated DNA and increasing the stress resistance of heart tissue, at least in early diabetes. However, the double cell-cycle arrest at G₁ and G₂ ultimately inhibits the replication of cells, and leads to tissue degeneration in the diabetic myocardium in later diabetes [15].

Cell cycle abnormalities of cancer cells in metabolic syndrome. Elevated body-mass index (BMI) is associated with the risk of common cancers in adults [16]. The mechanisms have not been fully elucidated; however, the insulin and insulin-like growth factor (IGF) axis, sex steroids, and adipokines have been investigated as candidates for cancer growth in obesity [17]. Serum leptin levels were elevated in obese patients and leptin was reported to up-regulate cdk2 and cyclin D1 and accelerate cell cycle progression and cell proliferation in various cancer cell lines [18]. For example, leptin-induced cell-cycle progres-

sion and proliferation of breast cancer cell lines were associated with the enhanced expression of *c-myc* and cyclin D1 [18]. In the Bcl2-negative cell line, ZR-75-1, it was reported that leptin-induced cell proliferation is associated with inhibition of p53 and p21^{Cip1} [19]. Although leptin is regarded as a pro-carcinogenic adipokine, the treatment of a breast cancer cell line with leptin enhanced the antiproliferative action of cAMP-elevating agents and induced apoptosis. Such leptin-induced apoptosis is accompanied by the decrease of cyclin D1 and the increase of p27^{Kip1}, leading to cell cycle arrest at the G₁ phase, and the combination of leptin and cAMP-elevating agents may be beneficial for the treatment of cancers [20]. Adiponectin is also secreted from adipose tissues, and it stimulates phosphorylation of the serine/threonine kinase AMP-activated protein kinase (AMPK). AMPK is known to increase the expression of p21^{Cip1}, p27^{Kip1} and p53. In breast cancer cells, these cell cycle regulations by adiponectin are one of signaling pathways of anti-carcinogenic action [18].

Nuclear Receptors and Cell Cycles in Metabolic Syndrome

Nuclear receptors (NRs) are transcription factors that act as intracellular receptors for endocrine hormones and dietary lipids [21], and play an important role for regulating gene expression. NRs possess characteristic structures, which include N-terminal activation function 1 (AF1), DNA binding, ligand binding, and C-terminal AF2 domains. NRs bind to specific DNA sequence elements, namely, a consensus sequence (AGGTCA) that is constituted as a single element or as 2 tandem elements in a direct, everted or inverted repeat. Such a consensus sequence permits NR binding as monomers, homodimers or heterodimers. In mammalian species, there are 48 nuclear receptor genes. Peroxisome proliferator-activated receptor (PPAR), retinoid X receptor (RXR), liver X receptor (LXR), farnesoid X receptor (FXR) and thyroid hormone receptor (TR) are well-known regulators of glucose and lipid metabolism [21]. The retinoid acid receptor (RAR) functions as a heterodimer with RXR to regulate cell growth and survival [22].

PPARs are major NRs in the biology of metabolic syndrome, because they are associated with glucose and lipid metabolism, adipogenesis, and the inflamma-

tory cascade [23]. There are three subtypes of PPARs: PPAR α , PPAR γ and PPAR δ . The tissue distribution and physiological function of the three subtypes are different. For example, PPAR α locates in the liver, heart, muscle and kidney and plays a role for fatty oxidation; PPAR γ is found in adipose tissue, macrophages and muscles and participates in adipogenesis and lipid storage; and PPAR δ is ubiquitously expressed and plays a role in fatty acid oxidation and energy expenditure. After the ligands bind to PPARs, the PPARs heterodimerize with RXR, involving the detachment of corepressors, recruitment of coactivators, and subsequent binding to a PPAR response element (PPRE) on DNA that initiates the transcription of responsive genes. The G₀/G₁ switch gene 2 (G0S2) is one of direct PPAR γ target genes with a functional PPRE in its promoter [24]. G0S2 regulates the cell cycle, and the expression of G0S2 is associated with growth arrest, which is required for 3T3-L1 adipogenesis. In addition, G0S2 inhibits adipose triglyceride lipase activity and diminishes the rate of lipolysis in adipocytes.

In RXRs, there are 3 subtypes: RXR α , RXR β and RXR γ . RXR α is expressed in the liver, kidney, spleen, placenta, and the epidermis; RXR β ubiquitously; and RXR γ in skeletal muscle and cardiac muscle, the anterior pituitary, and to a lesser extent the brain [25]. A RXR knockout model indicated that RXR has various physiological functions. RXR α deficiency in adipose tissue results in inhibition of preadipocyte differentiation and resistance to obesity. Loss of RXR α in the liver perturbs multiple metabolic pathways mediated by LXR α , PPAR α , constitutive androstane receptor β , pregnane X receptor and FXR. RXRs play roles in diverse physiological processes including cell proliferation, differentiation, and apoptosis and metabolism; therefore, RXR isotypes have been referred to as master regulators. On the promoter region of p21^{Cip1}, there is a binding site of RAR/RXR, and retinoids are thought to activate transcription of p21^{Cip1}. Collectively, nuclear receptors are involved in various central biological mechanisms such as development, metabolism, cell growth, differentiation, and immunity [26, 27]. Nuclear receptors, such as PPARs, RXRs and RARs, control cell cycles through regulating the expression of cell cycle-associated genes, and modulate cell proliferation, apoptosis and hypertrophy.

Nuclear Receptors Modulator in Metabolic Syndrome

In a clinical setting, nuclear receptor modulators are widely prescribed in the treatment for dyslipidemia and diabetes in patients with metabolic syndrome. For example, thiazolidinediones (TZDs), which are ligands for PPAR γ , are used as insulin sensitizers for type 2 diabetes and fatty liver. TZDs are implicated in apoptosis, cell proliferation, and cell-cycle regulation. In diabetic nephropathy, pioglitazone, one of the TZDs, inhibited cell hypertrophy and reversed high glucose-induced G₁-phase cell cycle arrest, *i.e.* increased the G₀/G₁ phase and decreased the S and G₂ phases. Pioglitazone suppressed high glucose-induced phosphorylation of p44/42 mitogen-activated protein kinase and reduced Bcl-2 and p27^{Kip1} protein levels in glomeruli [9]. However, pioglitazone promotes adipogenesis and obesity. Pioglitazone increased the M + late M population and the M + late M/G₀ + G₁ ratio, indicating that pioglitazone increased proliferation activities by completing the cell cycle [28]. Recently, pioglitazone has received attention for its oncogenic potency in bladder cancer. Meta-analysis revealed that the evidence is limited and the usage of pioglitazone is not prohibited in many countries except France [29].

Fibrates, PPAR α agonists, are mainly used as hypolipidemic drugs. In the Fenofibrate Intervention in Event Lowering in Diabetes (FIELD) study, fenofibrate treatment significantly reduced diabetic retinopathy and suppressed albuminuria progression [30]. In addition, it was reported that fenofibrate reduced not only microvascular complications but also macrovascular complications. However, in rodent models, one may concern about the potency of hepatocellular carcinoma by fibrate through modulation of cell-cycle regulatory genes by PPAR α , *i.e.* up-regulation of mRNA and protein for cyclin-dependent kinase (CDK)-1, CDK-4 and *c-myc*. However, in clinical results from humans, there is no increase in the incidence of hepatocellular carcinoma associated with the use of fibrates. This discrepancy derives from structural differences between human and mouse PPAR α and from differences in the expression levels of PPAR α in the liver. The expression levels of PPAR α may be sufficient for humans to receive beneficial effects of the drugs; however, they are low enough to avoid the activation

of the genes responsible for the hepatocarcinogenic effect of fibrates [31].

Conclusion and Future Directions

Nuclear receptor modulators provide diverse beneficial effects such as insulin-sensitizing action, the correction of dyslipidemia, and the prevention of micro- and macro-angiopathies by modulating cell-cycle abnormalities in metabolic syndrome. In clinical setting, TZDs and fibrates are used as therapeutic modalities for lipid and glucose metabolic abnormalities; however, the adverse effects of TZDs on edema, osteoporosis, obesity, and oncogenesis of the urinary bladder and the deleterious effects of fibrates on renal function are also concerns. The dark side of TZDs and fibrates may also derive from the modulation of cell cycle, such as the increased number of newly developed adipocytes and the subsequent expansion of adipose tissues by TZDs. In future development of nuclear receptor modulators, dual agonists targeting PPAR α and PPAR γ , and PPAR pan-agonists should be carefully screened to avoid unexpected adverse effects, since nuclear receptors regulate fundamental biological processes of the cells, such as the cell cycle.

References

1. Matsuzawa Y: Metabolic syndrome--definition and diagnostic criteria in Japan. *J Atheroscler and Thromb* (2005) 12: 301.
2. Sakai T, Sakaue H, Nakamura T, Okada M, Matsuki Y, Watanabe E, Hiramatsu R, Nakayama K, Nakayama KI and Kasuga M: Skp2 controls adipocyte proliferation during the development of obesity. *J Biol Chem* (2007) 282: 2038-2046.
3. Naaz A, Holsberger DR, Iwamoto GA, Nelson A, Kiyokawa H and Cooke PS: Loss of cyclin-dependent kinase inhibitors produces adipocyte hyperplasia and obesity. *FASEB J* (2004) 18: 1925-1927.
4. Inoue N, Yahagi N, Yamamoto T, Ishikawa M, Watanabe K, Matsuzaka T, Nakagawa Y, Takeuchi Y, Kobayashi K, Takahashi A, Suzuki H, Hasty AH, Toyoshima H, Yamada N and Shimano H: Cyclin-dependent kinase inhibitor, p21WAF1/CIP1, is involved in adipocyte differentiation and hypertrophy, linking to obesity, and insulin resistance. *J Biol Chem* (2008) 283: 21220-21229.
5. Hallenborg P, Feddersen S, Madsen L and Kristiansen K: The tumor suppressors pRB and p53 as regulators of adipocyte differentiation and function. *Expert Opin Ther Targets* (2009) 13: 235-246.
6. Bazuine M, Stenkula KG, Cam M, Arroyo M and Cushman SW: Guardian of corpulence: a hypothesis on p53 signaling in the fat cell. *Clinical lipidology* (2009) 4: 231-243.
7. Minamino T, Orimo M, Shimizu I, Kunieda T, Yokoyama M, Ito T,

- Nojima A, Nabetani A, Oike Y, Matsubara H, Ishikawa F and Komuro I: A crucial role for adipose tissue p53 in the regulation of insulin resistance. *Nat Med* (2009) 15: 1082–1087.
8. Wolf G: Cell cycle regulation in diabetic nephropathy. *Kidney Int Suppl* (2000) 77: S59–66.
 9. Okada T, Wada J, Hida K, Eguchi J, Hashimoto I, Baba M, Yasuhara A, Shikata K and Makino H: Thiazolidinediones ameliorate diabetic nephropathy via cell cycle-dependent mechanisms. *Diabetes* (2006) 55: 1666–1677.
 10. Tang SC and Lai KN: The pathogenic role of the renal proximal tubular cell in diabetic nephropathy. *Nephrol Dial Transplant* (2012) 27: 3049–3056.
 11. Zhong W, Zou G, Gu J and Zhang J: L-arginine attenuates high glucose-accelerated senescence in human umbilical vein endothelial cells. *Diabetes Res Clin Pract* (2010) 89: 38–45.
 12. Chan KC, Wang CJ, Ho HH, Chen HM and Huang CN: Simvastatin inhibits cell cycle progression in glucose-stimulated proliferation of aortic vascular smooth muscle cells by up-regulating cyclin dependent kinase inhibitors and p53. *Pharmacol Res* (2008) 58: 247–256.
 13. Tammali R, Saxena A, Srivastava SK and Ramana KV: Aldose reductase regulates vascular smooth muscle cell proliferation by modulating G1/S phase transition of cell cycle. *Endocrinology* (2010) 151: 2140–2150.
 14. Boudina S and Abel ED: Diabetic cardiomyopathy revisited. *Circulation* (2007) 115: 3213–3223.
 15. Golubnitschaja O, Moenkemann H, Trog DB, Blom HJ and De Vriese AS: Activation of genes inducing cell-cycle arrest and of increased DNA repair in the hearts of rats with early streptozotocin-induced diabetes mellitus. *Med Sci Monit* (2006) 12: BR68–74.
 16. Renehan AG, Tyson M, Egger M, Heller RF and Zwahlen M: Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* (2008) 371: 569–578.
 17. Novosyadlyy R and LeRoith D: Hyperinsulinemia and type 2 diabetes: impact on cancer. *Cell Cycle* (2010) 9: 1449–1450.
 18. Jarde T, Perrier S, Vasson MP and Caldefie-Chezet F: Molecular mechanisms of leptin and adiponectin in breast cancer. *Eur J Cancer* (2011) 47: 33–43.
 19. Chen C, Chang YC, Liu CL, Chang KJ and Guo IC: Leptin-induced growth of human ZR-75-1 breast cancer cells is associated with up-regulation of cyclin D1 and c-Myc and down-regulation of tumor suppressor p53 and p21WAF1/CIP1. *Breast Cancer Res Treat* (2006) 98: 121–132.
 20. Naviglio S, Di Gesto D, Romano M, Sorrentino A, Illiano F, Sorvillo L, Abbruzzese A, Marra M, Caraglia M, Chiosi E, Spina A and Illiano G: Leptin enhances growth inhibition by cAMP elevating agents through apoptosis of MDA-MB-231 breast cancer cells. *Cancer Biol Ther* (2009) 8: 1183–1190.
 21. Shulman AI and Mangelsdorf DJ: Retinoid x receptor heterodimers in the metabolic syndrome. *N Engl J Med* (2005) 353: 604–615.
 22. Altucci L, Leibowitz MD, Ogilvie KM, de Lera AR and Gronemeyer H: RAR and RXR modulation in cancer and metabolic disease. *Nat Rev Drug Discov* (2007) 6: 793–810.
 23. Guri AJ, Hontecillas R and Bassaganya-Riera J: Peroxisome proliferator-activated receptors: bridging metabolic syndrome with molecular nutrition. *Clin Nutr* (2006) 25: 871–885.
 24. Zandbergen F, Mandard S, Escher P, Tan NS, Patsouris D, Jatkoa T, Rojas-Caro S, Madore S, Wahli W, Tafuri S, Müller M and Kersten S: The G0/G1 switch gene 2 is a novel PPAR target gene. *Biochem J* (2005) 392: 313–324.
 25. Pinaire JA and Reifel-Miller A: Therapeutic potential of retinoid x receptor modulators for the treatment of the metabolic syndrome. *PPAR Res* (2007) 2007: 94156.
 26. Gronemeyer H, Gustafsson JA and Laudet V: Principles for modulation of the nuclear receptor superfamily. *Nat Rev Drug Discov* (2004) 3: 950–964.
 27. Teboul M, Guillaumond F, Grechez-Cassiau A and Delaunay F: The nuclear hormone receptor family round the clock. *Mol Endocrinol* (2008) 22: 2573–2582.
 28. Nakatsuka A, Wada J, Hida K, Hida A, Eguchi J, Teshigawara S, Murakami K, Kanzaki M, Inoue K, Terami T, Katayama A, Ogawa D, Kagechika H and Makino H: RXR antagonism induces G0/G1 cell cycle arrest and ameliorates obesity by up-regulating the p53–p21 (Cip1) pathway in adipocytes. *J Pathol* (2012) 226: 784–795.
 29. Ferrara A, Lewis JD, Quesenberry CP, Jr, Peng T, Strom BL, Van Den Eeden SK, Ehrlich SF and Habel LA: Cohort study of pioglitazone and cancer incidence in patients with diabetes. *Diabetes Care* (2011) 34: 923–929.
 30. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C and Laakso M; FIELD study investigators: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* (2005) 366: 1849–1861.
 31. Roberts-Thomson SJ: Peroxisome proliferator-activated receptors in tumorigenesis: targets of tumour promotion and treatment. *Immunol Cell Biol* (2000) 78: 436–441.