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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

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*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 G_1 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 G_1 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 G_1 phase to apoptosis or remain in the G_1 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

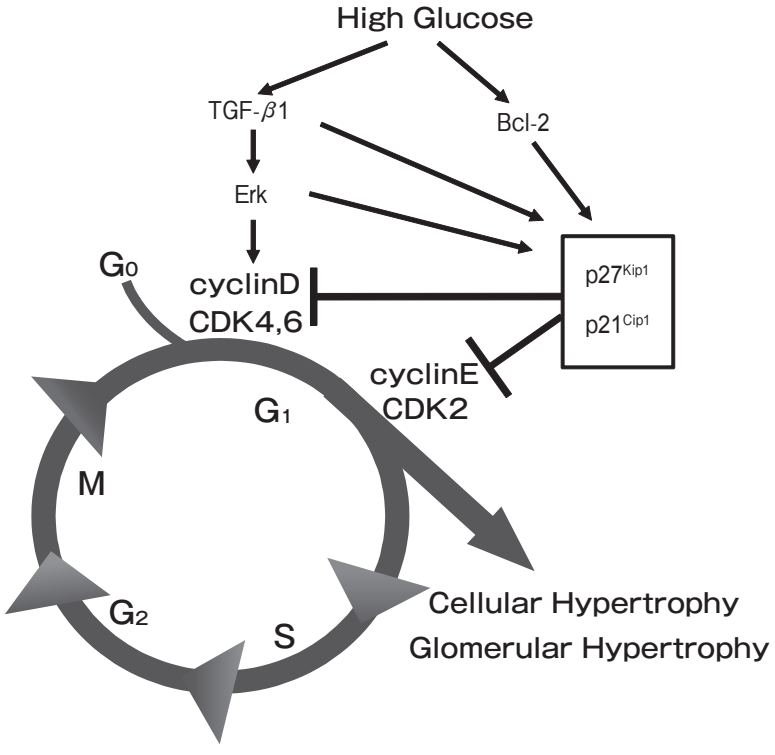

Fig. 1 Cell cycle abnormality in diabetic nephropathy. Erk, extracellular-signal-regulated kinase; CDK, cyclin dependent kinase; Bcl-2, B cell lymphoma-2; TGF-β1, transforming growth factor-β1.

apoptosis. Zhong *et al.* showed that high glucose increased the number of senescent cells, inhibited telomerase activity, increased the proportion of cells in the G_0/G_1 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, glycation 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 G_1 and G_2 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 cylcin 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 G_1 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 inflammatory cascade [23]. There are three subtypes of PPARs: PPARα, PPARγ and PPARδ. The tissue distribution and physiological function of the three subtypes are different. For example, PPARα locates in the liver, heart, muscle and kidney and plays a role for fatty oxidation; PPARγ is found in adipose tissue, macrophages and muscles and participates in adipogenesis and lipid storage; and PPARδ 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 G_0/G_1 switch gene 2 (G0S2) is one of direct PPARγ 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: RXRα, RXRβ and RXRγ. RXRα is expressed in the liver, kidney, spleen, placenta, and the epidermis; RXRβ ubiquitously; and RXRγ 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. RXRα deficiency in adipose tissue results in inhibition of preadipocyte differentiation and resistance to obesity. Loss of RXRα in the liver perturbs multiple metabolic pathways mediated by LXRα, PPARα, 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 PPARγ, 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 G_0/G_1 phase and decreased the S and G_2 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 $M/G_0 + G_1$ 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, PPARα 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 microvasuclar 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 PPARα, *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 PPARα and from differences in the expression levels of PPARα in the liver. The expression levels of PPARα 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 PPARα and PPARγ, 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.

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