Role of cAMP Response Element Binding Protein in Cardiovascular Remodeling

Good, Bad, or Both?

Toshihiro Ichiki

Abstract—The cAMP response element binding protein (CREB) is a ubiquitously expressed nuclear transcription factor that is activated by various extracellular stimuli. CREB is known to regulate the expression of genes important to cell proliferation, differentiation, adaptation, and survival in many cell types. Loss of CREB function by transgenic overexpression of dominant negative CREB or targeted deletion of the CREB gene revealed that CREB is involved in the differentiation of T lymphocytes, production of growth hormone, and the long-term potentiation of neuronal memory. The role of CREB in cardiovascular system is incompletely characterized and several controversies remain. A growing body of recent evidence, however, has suggested that CREB plays an important role in the cardiovascular remodeling process, including inflammation, cell migration, and apoptosis. Thus, CREB may be a possible target for the treatment of cardiovascular diseases such as atherosclerosis, restenosis, and reperfusion injury. (Arterioscler Thromb Vasc Biol. 2006;26:449-455.)

Key Words: cAMP response element binding protein • gene transcription • protein kinase • signal transduction

Regulation of gene expression is a critical mechanism for the normal differentiation and development of the organs as well as the pathological process of the diseases. Cells change the expression pattern of genes in response to extracellular signals. Protein kinases and transcription factors transmit the signals from the external stimuli to the genome, resulting in the modification of gene expression profile of the cells to accommodate to the environmental changes.

Many studies have reported the important roles of transcription factors in the development of cardiovascular diseases such as atherosclerosis, restenosis after balloon angioplasty, and reperfusion injury of the heart. Nuclear factor-κB and activator protein 1 are relatively well-studied redox-sensitive transcription factors involved in the various aspects of the cardiovascular disease process. The roles of other transcription factors in the cardiovascular diseases, however, largely remained to be determined.

The cAMP response element (CRE) binding protein (CREB) is a nuclear transcription factor and is ubiquitously expressed. CREB is known to be activated by various extracellular stimuli and play important roles in cell proliferation, differentiation, adaptation, and survival. Recent studies have indicated an important role of CREB in the development of the cardiovascular diseases.

Structure of CREB

CREB was originally isolated as a gene regulatory protein that bound to the CRE site of the somatostatin gene promoter region in response to an increase in the cellular cAMP level. The molecular weight of CREB is 43 kDa. Both mouse and human CREB genes are composed of 11 exons and 3 isoforms designated α, β, and Δ are produced through alternative splicing. These isoforms, expressed in most tissues, are functionally indistinguishable. As for its structure, CREB belongs to the leucine zipper class of transcription factors. CREB forms a homodimer through its leucine zipper domain and binds to DNA through a flanking basic domain containing many basic amino acid residues such as lysine and arginine. Together, these structures are called the bZIP domain (Figure 1). Another domain, the kinase inducible domain, containing serine 133, is necessary and sufficient for transcriptional activation of target genes. The glutamine-rich domains referred to as Q2 or constitutive activation domain and Q1 are necessary for the basal transcriptional activity. Activation of CREB requires phosphorylation of the serine residue at 133. The first kinase identified as being responsible for the phosphorylation of serine 133 is a cAMP-dependent protein kinase (protein kinase A [PKA]), which is activated by an increase in the intracellular cAMP level. On phosphorylation at serine 133, the CREB binding protein (CBP) is recruited to CREB. CBP is a transcriptional coactivator with histone acetyl transferase activity that activates gene transcription. CBP also induces acetylation of CREB, which increases its transcriptional activity.

However, it has been suggested that CREB phosphorylation dose not necessarily activate transcription of genes with
CRE in the promoter region. It is reported that promoter containing CRE and TATA box is activated stronger by cAMP than that with CRE but without TATA box. And it is reported that methylation of CRE site inhibits CREB binding. A recent analysis have also indicated that phosphorylation of CREB alone is not sufficient to activate target genes with CRE and suggested that the selective recruitment of CBP and perhaps other cofactors may determine the gene activation.

CREB was initially thought to be selective in mediating gene transcription in response to extracellular stimuli that elevate the intracellular cAMP level. It was reported that a reporter gene driven by the CRE sequence (TGACGTCA) was not affected by growth factors that activate receptor tyrosine kinases. However, subsequent studies using a specific antibody against CREB phosphorylated at serine 133 showed that CREB is activated by a wide range of extracellular stimuli through distinct signaling pathways. Many of these pathways involve mitogen activated protein kinases (MAPKs). p90RSK is one of the CREB kinases downstream of these pathways that involve mitogen and stress-activated protein kinases (MAPKs). p38MAPK, the kinase was named mitogen-activated protein kinase 2 (MAPKAP-2). Another pathway involves calcium. Calmodulin-dependent protein kinases I, II, and IV also phosphorylate CREB at serine 133 in response to an elevation of intracellular [Ca\(^{2+}\)] level. A recent study suggests that Akt/protein kinase B also phosphorylates CREB downstream of phosphatidylinositol 3-kinase.

The signaling pathways that activate CREB are summarized in Figure 2.

**Function of CREB**

To clarify the role of CREB, several types of dominant negative mutants of CREB gene have been developed. CREB also plays an important role in the metabolic control. A recent report showed that inhibition of CREB function by targeted gene disruption or overexpression of a dominant negative CREB induced fasting hyperglycemia and reduced expression of gluconeogenic genes such as phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G6Pase), and fructose-1,6-bisphosphatase (FBPase).

**Figure 1.** Structure of CREBα. The structure of CREBα is shown. Q1 and Q2 represent glutamine-rich regions. Q2 is also called as constitutive activation domain (CAD). KID represents kinase inducible domain and contains serine 133, the phosphorylation of which is required for the activation of CREB. bZIP contains the basic region and the leucine zipper important for DNA binding and dimerization, respectively. NLS indicates nuclear localization signal. The number indicates amino acid residues.

**Figure 2.** Signaling pathways that activate CREB. Several protein kinase pathways involved in CREB activation are shown. Some of the signaling cross-talks are not indicated for the simplicity. RTK, receptor tyrosine kinase; GPCR, G-protein coupled receptor; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; CAMK, calmodulin-dependent protein kinase; PKA, protein kinase A; AC, adenylyl cyclase.

CREBM1, in which the serine residue at 133 is replaced with alanine, is unphosphorylatable but still can bind to CRE sites of target genes. CREBM1 thus inhibits CRE-dependent gene transcription by preventing wild-type CREB and other CRE-binding protein from accessing CRE sites. Another mutant, K-CREB, was made by the replacement of lysine at 287 in the DNA binding domain with leucine, a modification that impairs DNA binding. A-CREB, with a mutation in the bZIP domain, is also reported to work as a dominant negative molecule.

Transgenic mice expressing the dominant negative CREB gene driven by a tissue-specific promoter have revealed the function of CREB in the specific tissues or organs. In the pituitary gland, overexpression of dominant negative CREB by the growth hormone gene promoter induced atrophy of the gland because of a decrease in the number of growth hormone-producing cells resulting in growth retardation. Similarly, T lymphocyte-specific expression of dominant negative CREB by CD2 gene promoter induced apoptosis of T lymphocytes when the cells were challenged with a mitogen such as concanavalin A or an anti-CD3 antibody. Targeted deletion was also used to study the function of CREB. Mice with targeted deletion of CREB gene showed impairment in the long-term memory. Other apparent abnormalities, however, were not observed in CREB knockout mice. The almost normal phenotype of CREB deficient mice is explained by the compensation of CREB deficiency with an upregulation of CREM. CREB also plays an important role in the metabolic control. A recent report showed that inhibition of CREB function by targeted gene disruption or overexpression of a dominant negative CREB induced fasting hyperglycemia and reduced expression of gluconeogenic genes such as phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G6Pase), and fructose-1,6-bisphosphatase (FBPase).
phenoxypruvate carboxykinase and glucose-6-phosphatase.\textsuperscript{25} It was found that CREB induced expression of gluconeogenic genes by the nuclear receptor coactivator PGC1–1, suggesting the important role of CREB-induced PGC-1 activation in the pathogenesis of type II diabetes. It is also reported that CREB-deficient mice show a fatty liver phenotype and elevated expression of peroxisome proliferator activated receptor (PPAR)\textsubscript{γ}.

CREB also regulates 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) (HMG-CoA) synthase gene expression. HMG-CoA synthase is the rate-limiting enzyme of cholesterol biosynthesis, which converts acetoacetyl-CoA and acetyl-CoA into HMG-CoA. Cholesterol depletion induced HMG-CoA synthase gene expression, which is dependent on CREB and sterol regulatory element-binding proteins.\textsuperscript{27}

Cell survival is another critical function of CREB. Nerve growth factor-dependent survival of neuronal cells is mediated through PPAR\textsubscript{γ} upregulation and inhibition of gluconeogenesis.\textsuperscript{26} In this study it was found that CREB activated the expression of the Hairy Enhancer of Split (HES-1) gene, a transcriptional repressor. On activation, HES-1 downregulates hepatic PPAR\textsubscript{γ} expression. Therefore, it was suggested that CREB antagonists may enhance insulin sensitivity through PPAR\textsubscript{γ} upregulation and inhibition of gluconeogenesis.

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Role of CREB in the Cardiovascular System

Role of CREB in the Heart

Transgenic mice with cardiac myocyte-specific expression of dominant negative CREB driven by the α-myosin heavy chain gene promoter showed impaired contractile response to isoproterenol stimulation as well as dilatation of the 4 chambers of the heart, mimicking idiopathic dilated cardiomyopathy.\textsuperscript{30} Although histological analysis revealed both atrophic and hypertrophied muscle fibers, as well as significant interstitial fibrosis, apoptosis of cardiac myocytes was not observed in this model. In another study, a brief ischemic injury of the heart led to CREB activation via PKA.\textsuperscript{31} Interestingly, it was found that PKA was activated in 2 phases. In an early response, the activation of PKA was mediated by Ca-independent phospholipase A2. However, in the late response, the adenylate cyclase/cAMP pathway activated PKA. Despite these findings, it is not yet clear whether the activation of CREB is protective for cardiac function in this ischemia-reperfusion model. Cardiac pacing for 2 hours in dogs decreased CREB content in the ventricle, which was dependent on angiotensin II (Ang II) and calcium.\textsuperscript{32} It has also been found that cardiac pacing for 3 weeks reduced CRE binding activity in the Kv4.3 gene promoter and transient outward potassium current. These changes are associated with long-term cardiac memory, which includes nonpathological cardiac remodeling, modulation of repolarization, and drug actions on the heart.

In a study using cultured cells, hypoxia-induced apoptosis of cultured neonatal cardiac myocytes was prevented by insulin-like growth factor-1 (IGF-1).\textsuperscript{33} The antiapoptotic effect of IGF-1 involves PI3-kinase–dependent and ERK kinase MEK–dependent activation of CREB. These data indicate that CREB plays an important role in the maintenance of normal function and structure of the heart.

Role of CREB in the Endothelial Cells

Endothelial dysfunction induces the expression of cell adhesion molecules on the endothelial surface, which recruits monocytes into subendothelial space. Monocytes, then, differentiate into macrophages. Vascular smooth muscle cell (VSMC) in the media also migrates into subendothelial space. These cells with production of matrix components form atheromatous plaque.\textsuperscript{34} In contrast to atheromatous plaque, neointima formed after balloon injury is mainly composed of VSMC derived from the media.

To date, there is evidence to support a role for CREB in angiogenesis and the inflammatory response. Vascular endothelial growth factor induced CREB phosphorylation in endothelial cells.\textsuperscript{35} This activation of CREB was mediated by the p38MAPK/mitogen-activated and stress-activated protein kinase 1 and protein kinase C/p90RSK pathways. Therefore, it is suggested that CREB may be involved in the expression of genes important to angiogenesis.

Inflammatory cytokine-induced expression of cyclooxygenase-2 (COX-2) in endothelial cells is also dependent on CRE and CREB.\textsuperscript{36} It was found that a mutation in the CRE site of COX-2 gene promoter abolished the upregulation of the promoter activity in response to proinflammatory mediators such as interleukin (IL)-1β and tumor necrosis factor-α. These data suggest that CREB mediates vascular inflammatory response, which plays a critical role in the progression of vascular remodeling.

Role of CREB in the VSMCs

It has been reported that Ang II induced IL-6 gene expression in VSMCs.\textsuperscript{37} The deletion and mutation analysis of the IL-6 gene promoter revealed that CRE site was critical for the induction of IL-6 gene promoter activity by Ang II. Then it was examined whether Ang II induced phosphorylation of CREB. Ang II induced phosphorylation of CREB after 5 or

<table>
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<th>Table 1. Some Target Genes of CREB</th>
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<tr>
<td>Metabolic</td>
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<tr>
<td>HMG-CoA synthase, PEPCK, G6Pase, lactate dehydrogenase</td>
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<tr>
<td>Transcription</td>
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<tr>
<td>NF-IL6, CREB, STAT3, c-Fos, PGC-1, Per1</td>
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<td>Neurotransmitters</td>
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<td>Enkephalin, calcitonin gene related peptide, glucagon, vasopressin</td>
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<td>Cell cycle</td>
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<td>Retinoblastoma, PCNA, cyclin A, cyclin D1</td>
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<td>Cell survival</td>
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<td>Bcl-2, GADD34</td>
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<td>Growth factors</td>
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<tr>
<td>Insulin, TNF-α, brain-derived neurotrophic factor, fibroblast growth factor 6</td>
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<td>Immune regulation</td>
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<td>T-cell receptor α, interleukin 2, IL-6, Cox2</td>
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<tr>
<td>Structural</td>
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<td>Nonmuscle myosin heavy chain, fibronectin, αA-cristallin</td>
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Modified from Mayr and Montminy.\textsuperscript{1}
Ang II type 1 receptor (AT1-R) involves ectodomain shedding of pro heparin binding-epidermal growth factor (pro HB-EGF) to release HB-EGF through activation of a disintegrin and metalloproteinase (ADMA). The released HB-EGF, then activates epidermal growth factor (EGF) receptor, resulting in the activation of ERK and p38MAPK. SHC, Grb2, and SOS are adaptor proteins. Other abbreviations are indicated in the legend to Figure 2.

10 minutes of stimulation. It was also found that CREB phosphorylation was blocked by PD98059, a MEK inhibitor, and by SB203580, a p38 MAPK inhibitor. AG1478, an inhibitor of epidermal growth factor (EGF) receptor, also blocked Ang II-induced CREB phosphorylation. Recent studies have shown that ectodomain shedding of pro heparin binding-EGF (pro HB-EGF) and transactivation of EGF receptor by the released HB-EGF play an important role in Ang II type 1 receptor (AT1-R) signaling. AG1478 also inhibited Ang II-induced activation of ERK and p38MAPK, indicating that the activation of Ang II receptor induces transactivation of the EGF receptor. This cascade continues with the activation of ERK and p38MAPK downstream from the EGF receptor, and then these MAPKs induce the phosphorylation of CREB (Figure 3). A role for CREB in VSMCs was then suggested by experiments involving the inhibition of CREB by adenosine-mediated overexpression of CREBM1 (AdCREBM1), a dominant negative form of CREB by adenovirus-mediated overexpression. In these experiments, it was observed that AdCREBM1 attenuated Ang II-induced CREB phosphorylation and CREB-mediated VSMC survival and proliferation is dependent on CREB.

Similarly, thrombin also induced phosphorylation of CREB through ERK and p38MAPK in VSMCs. The thrombin-induced hypertrophy and hyperplasia of VSMCs were dependent on the CREB activation. Lin et al reported that activation of α-adrenergic receptor by norepinephrine induced phosphorylation of CREB through PKA in VSMC. Therefore, these data suggest that the signals from several different G protein coupled receptors (GPCRs) converge on the CREB pathway, which supports the idea that CREB plays a pivotal role in GPCR signal transduction.

Fibrosis is important for vascular remodeling. It was reported that fibronectin gene expression by 12(s)-hydroxyeicosatetraenoic acid [12(s)-HETE] in VSMCs is also mediated by CREB. I2(s)-HETE induced CREB phosphorylation, leading to fibronectin gene expression through p38MAPK.

Although infection with AdCREBM1 for 2 or 3 days did not affect the survival of VSMCs, longer incubation induced the apoptosis of VSMCs. The apoptosis induced by AdCREBM1 is accompanied by the downregulation of Bcl-2, an antiapoptotic gene, the expression of which is regulated by CRE sequence in its promoter.

The expression of CREB after balloon angioplasty was examined. Interestingly, in intact rat carotid artery, CREB expression was barely detectable by immunohistochemistry. The expression and phosphorylation of CREB that were detectable were observed mainly in the neointimal α-SM actin-positive cells. These data suggest that proliferating neointimal VSMCs express CREB and that CREB is activated in these cells, an event which may play a role in the neointimal formation. Infection with AdCREBM1 after balloon injury led to reduced neointimal formation accompanied by increased terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) positive cells and decreased BrdU incorporation in the neointima. These data support the idea that activation of CREB is critically involved in proliferation and survival of neointimal VSMC.

More recently, it was reported that stimulation with tumor necrosis factor-α induced phosphorylation of CREB via p38MAPK in VSMCs. It was found that dominant negative CREB inhibited the tumor necrosis factor-α-induced expression of Rac1 and migration of VSMC, suggesting that inhibition of VSMC migration may be involved in the attenuation of neointimal formation by CREBM1 overexpression.

Another group recently showed that low-density lipoprotein (LDL)-induced mitogenesis of VSMCs is accompanied by an upregulation of neuron-derived orphan receptor 1 (NOR1), which is dependent on CREB activation and its binding to the CRE site of the NOR1 gene promoter. Because it was also found that antisense oligonucleotide against NOR1 inhibited LDL-induced DNA synthesis, it was suggested that the CREB-NOR1 pathway plays a critical role in LDL-induced VSMC proliferation. These results seem to be consistent with ours and generally support the idea that CREB mediates VSMC survival and proliferation.

Several articles, however, reported opposite results. Watson et al reported that oxidative stress, induced by a high glucose concentration, increased chemokinesis and accelerated entry into the cell cycle with a concomitant decrease in the CREB content of the VSMCs. They also showed that the CREB content of blood vessels from diabetic rats was lower than normal rats, and that treatment with rosiglitazone, an insulin sensitizer, restored the expression level of CREB toward that of nondiabetic normal rats. It was also reported that high levels of glucose or reactive oxygen species decreased CREB content and activity of VSMCs while increasing their PDGF receptor expression. Thus CREB content is low and PDGF receptor expression is high in the blood vessels of diabetic rats compared with nondiabetic rats. Although the CREB content has not been examined, it was reported that the oxidative stress induced phosphorylation of CREB at serine 133 in VSMCs. The same response has also
been reported by another group in PC12 cells, a pheochromocytoma cell line.50 Therefore, taking our results together with apparently contradictory results just discussed, it appears that oxidative stress activates CREB in the short term but decreases its expression level in the long term.

Klemm et al reported that the CREB content of the aorta and pulmonary artery was high in proliferation-resistant medial VSMCs and low in proliferation-prone regions.51 It was also reported that chronic hypoxia led to a decrease in CREB content and enhancement of proliferation. Another series of studies by the same group also seems to contradict our results. In particular, these data contradict our immunohistochemical analyses of rat carotid artery that found that CREB content was increased in neointimal αSM actin-positive cells,44 which are generally accepted as proliferating VSMCs originating from the media. This immunohistochemical data were corroborated by a Western blot analysis, indicating that proliferating VSMCs have a higher content of CREB. Klemm et al51 examined the pulmonary vascular bed indicating that proliferating VSMCs have a higher content of CREB. Klemm et al also showed that small molecule named KG501 bound to CREB-binding site of CBP.56 Best et al showed that small molecule named KG501 bound to CREB-binding site and could inhibit CREB:CBP interaction, resulting in the attenuation of target gene induction in AdCREBM1-infected arteries.

Another possibility is that inhibition of CREB function in macrophages or ECs may affect neointimal formation, which was not excluded in our study as pointed out by Reush and Klemm.53 Because CREB regulates COX2 gene expression in response to inflammatory cytokines in ECs as previously described,56 inhibition of CREB function in ECs may contribute to the attenuated neointimal formation in AdCREBM1-infected arteries.

An alternative interpretation of the current discrepancy may be explained by the context-dependent role of CREB activation. We now know that CREB is activated by cAMP signaling, growth factor signaling, and GPCR signaling. Generally speaking, the former inhibits cardiovascular remodeling, whereas the latter 2 accelerate it. These observations to date, therefore, suggest that CREB is involved in cardiovascular remodeling process both positively and negatively. Other transcription factors concomitantly activated by certain extracellular stimuli may determine the role of CREB to be either good or bad for cardiovascular remodeling. One of the examples is Hex, a homeobox gene transcription factor involved in nonmuscle myosin heavy chain-B gene expression in the neointima after balloon injury.54 It was reported that CREB strongly activated nonmuscle myosin heavy chain-B gene expression induced by Hex, suggesting that Hex works as a transcriptional modulator of CRE-dependent gene transcription. The overall response of the blood vessel to stress or environmental changes may be dependent on the protein kinase pathways that activate CREB and other transcription factors that work in collaboration with CREB. The possible roles of CREB in cardiovascular remodeling are summarized in Table 2.

### Therapeutic Implication

A recent study showed that introduction of the CRE-transcription factor decoy oligonucleotide inhibited growth of MCF-7 breast cancer cells.55 In this study, it was found that stabilization and activation of p53, a tumor suppressor gene, may contribute to this growth inhibition. Because it was shown that inhibition of CREB function by dominant negative molecule attenuates neointimal formation,44 it may thus be possible that the CRE decoy oligonucleotide also inhibits vascular remodeling. Because oral administration of oligonucleotide is ineffective, efficient drug delivery system such as a drug-eluting stent is necessary for the clinical application of the decoy oligonucleotide.

In contrast to vascular remodeling, activation of CREB may be beneficial to support the viability of cardiac myocytes because IGF-1-mediated inhibition of apoptosis of cardiac myocytes is dependent on CREB activation.33 Because it is reported that vascular endothelial growth factor also activates CREB, CREB activation may be useful for the therapeutic angiogenesis.35

Another study used NMR-based screening approach to find compounds that bound to CREB-binding site of CBP.56 Best et al showed that small molecule named KG501 bound to CREB-binding site and could inhibit CREB:CBP interaction, resulting in the attenuation of target gene induction in response to cAMP agonist. As mentioned previously, it was suggested that CREB antagonist may be used as an insulin sensitiser.56 However, it is also possible that the putative CREB antagonist may impair neuronal memory if it passes the blood–brain barrier. Therefore, tissue specific delivery or action is necessary for the clinical application of the putative CREB antagonist.

Modification of gene expression profile is a key cellular mechanism to adapt to the environmental changes. Although the short-term effect of adaptation is beneficial, the long-term effect may be deleterious and cause pathological process of the diseases. Recent studies have indicated that angiotensin receptor antagonist57 and HMG-CoA reductase inhibitors58...
improve the prognosis of patients with cardiovascular diseases. However, the efficacy of these drugs is limited. The drugs acting on the transcription factors such as nuclear factor-κB, activator protein 1 and CREB to restore the gene expression pattern to normal pattern may be helpful for the treatment of the cardiovascular diseases with concomitant administration of angiotensin receptor antagonist or HMG-CoA reductase inhibitors.

Conclusions
CREB plays an important role in the regulation of a number of genes involved in the maintenance of normal cellular function as well as stress responses. Although the role of CREB in the cardiovascular remodeling is still controversial, it seems that CREB is critically involved in this process. Further efforts to clarify the reason for the apparent discrepancies and to identify the target genes of CREB involved in the cardiovascular remodeling are needed.

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