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Minireview

# The Pleiotropic Face of CREB Family Transcription Factors

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**cAMP responsive element-binding protein (CREB) is one of the most intensively studied phosphorylation-dependent transcription factors that provide evolutionarily conserved mechanisms of differential gene expression in vertebrates and invertebrates. Many cellular protein kinases that function downstream of distinct cell surface receptors are responsible for the activation of CREB. Upon functional dimerization of the activated CREB to *cis*-acting cAMP responsive elements within the promoters of target genes, it facilitates signal-dependent gene expression. From the discovery of CREB, which is ubiquitously expressed, it has been proven to be involved in a variety of cellular processes that include cell proliferation, adaptation, survival, differentiation, and physiology, through the control of target gene expression. In this review, we highlight the essential roles of CREB proteins in the nervous system, the immune system, cancer development, hepatic physiology, and cardiovascular function and further discuss a wide range of CREB-associated diseases and molecular mechanisms underlying the pathogenesis of these diseases.**

**Keywords:** cAMP responsive element, CREB, differential phosphorylation, neurodegenerative diseases, pleiotropic

## INTRODUCTION

The 43-kDa ubiquitous protein CREB belongs to the CREB/activating transcription factor (ATF) family, and has a conserved basic region/leucine zipper (bZIP) domain (Hai and Hartman, 2001; Sassone-Corsi, 1995). For transcriptional initiation, activation of CREB is primarily modulated by phosphorylation at the kinase-inducible domain (KID) in response to a variety of extracellular stimuli and mitogen stress signals (Fig. 1) (Montminy et al., 2004). Secondly, the active dimer of the CREB/ATF family binds to the conserved *cis*-acting cAMP responsive elements (CREs) 5′-TGACGT(C/G)A-3′ or 5′-CGTCA-3′ (Hai and Hartman, 2001; Impey et al., 2004), while the *Drosophila* CREB, dCREBB binds to the consensus sequence 5′-GTGACGT(A/C)(A/G)-3′ that is usually present in viral and cellular promoters, or within the promoters of target genes (Mayr and Montminy, 2001). Lastly, the CREB association with CREs promotes the recruitment of transcriptional machinery, such as CREB-binding protein (CBP), p300, and CREB-regulated transcription coactivators (CRTCs), to regulate transcription (Montminy et al., 1990).

CRTCs contain RNA-binding motifs, enhance transcriptional activity, also promote alternative splicing (pre-mRNA splicing) (Iourgenko et al., 2003). In particular, CRTCs are considered the key coactivators of CREB-regulated gluconeogenesis, lipid metabolism, synaptic plasticity, and mitochondrial biogenesis. Upon dephosphorylation, this signal-dependent co-activator

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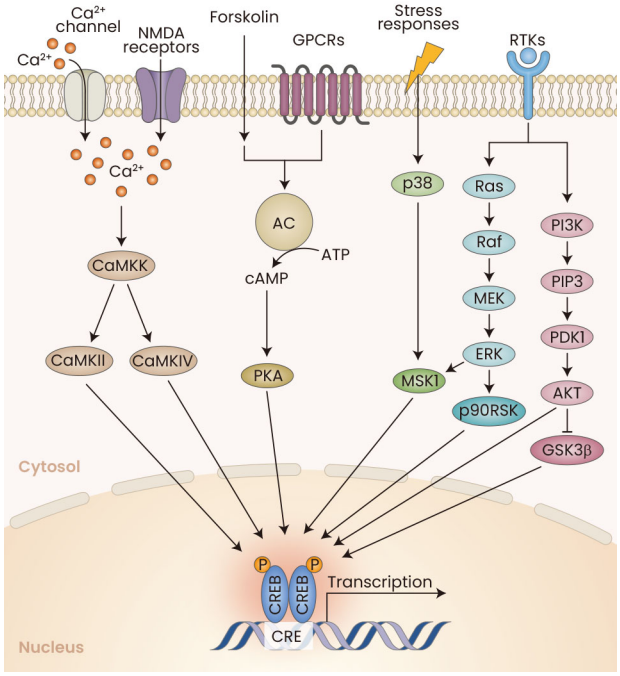


**Fig. 1. Signaling pathways that activate CREB.** Upon ligand binding, G protein-coupled receptors (GPCRs) can activate adenylyl cyclase (AC), converting ATP to cAMP that activates protein kinase A (PKA). The phosphorylation of CREB by PKA can promote target gene transcription through binding to cAMP response element (CRE). In addition, forskolin significantly induce activation of CREB by the stimulation of adenylyl cyclase. The binding of growth factors to receptor tyrosine kinases (RTKs) stimulates the activation of multiple protein kinases including MSK1, p90RSK, and AKT, which is then followed by phosphorylation and activation of CREB. In contrast, GSK3β-mediated phosphorylation can lead to inactivation of CREB. Stress inducers also activate CREB via p38 and MSK1. Furthermore, calcium influx via the calcium channels and NMDA receptors results in the activation of $Ca^{2+}$/CaMKs, such as CaMKII and CaMKIV, and PKA, upregulating CREB-target gene expression. CREB, cAMP responsive element-binding protein.

translocate into the nucleus to interact with CREB and modulates transcription (Wang et al., 2021). As of today, CRTC1, one of the three identified CRTCs, which is abundant in the brain, controls neuronal plasticity and overall memory formation (Parra-Damas et al., 2017). CRTC1 has also been shown to modulate energy balance (Altarejos et al., 2008). In addition, CRTC2 in the liver activates the gluconeogenic program (Han et al., 2017), whereas CRTC3 correlates to weight gain as it controls lipid metabolism and energy balance (Conkright et al., 2003).

Many pioneering experimental studies have demonstrated the link between cAMP, protein kinase A (PKA), the bZIP domain, and CREB (Ferraris et al., 2002). Earl Sutherland (Nobel laureate, 1971) was the first to discover the mechanism of action of the hormone epinephrine, and demonstrate that the activation of phosphorylase by epinephrine was triggered by cAMP, which is known as the second messenger. Functionally, the hormone-stimulated production of cAMP in the cell was actually triggered by an enzyme called adenylyl cyclase (Rall et al., 1956; Sutherland, 1972). In 1987, influential findings in PC12 cells demonstrated that CREB functions as a nuclear protein that binds to the CRE found in the *somatostatin* gene promoter (Quinn and Granner, 1990). So far CREB has been reported to be phosphorylated by up to 300 different types of stimuli. However, the pioneering studies on reversible phosphorylation (switching between different cellular processes to activate or regulate them) by Edmond Henri Fischer and Ed Krebs (Nobel laureate, 1992) identified PKA as being a primary element associated with cAMP action.

A pleiotropic signaling molecule CREB serves as a transcription factor, a neuron-associated molecule, a metabolic factor, and a factor involved in cell cycle and proliferation (Wen et al., 2010). A result of CREB activation is the transcription initiation of several distinct genes, including *c-Fos*, *BDNF*, several neuropeptide genes, as well as genes related to the mammalian circadian clock (*PER1* and *PER2*) (Purves et al., 2008). Cellular processes associated with CREB engagement include cell cycle progression, body's defense mechanism, and DNA repair (Sands and Palmer, 2008). Several other enzyme modifications are also carried out by CREB, such as glycosylation, ubiquitination, phosphorylation, and SUMOylation, contributing to the maintenance of physiological homeostasis (Lamarre-Vincent and Hsieh-Wilson, 2003). In fact, CREB is now recognized as one of the leading factors in neural development, synaptic plasticity in synapses, survival of neurons, neurotransmission, and overall memory (Belgacem and Borodinsky, 2017). Therefore, CREB signaling dysregulation is involved in a range of neuropathological and neurodegenerative diseases, including schizophrenia, Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD) (Amidfar et al., 2020). Contemporary studies also indicated that CREB plays a key role in integrating various physiological functions in non-neuronal cells. For example, CREB regulates glucose metabolism, lipid metabolism, energy balance, and fatty acid oxidation in hepatic cells, and also cardiac contraction, cardiac remodeling, and angiogenesis in cardiovascular cells (Yin et al., 2021). In addition, CREB reduces the inflammation-induced injury by suppressing oxidative stress in kidney cells, whereas it is well recognized for its regulation over pro-inflammatory and anti-inflammatory responses in immune cells (Portilla et al., 2002; Tran et al., 2011). Thus CREB are also involved in non-neuronal diseases like cancer, metabolic disorder (type 2 diabetes mellitus [T2DM]), hepatic disorder and lung fibrosis, and cerebral ischemic injury (Huang et al., 2015). Throughout our review, we first address the functional role of CREB in the nervous system, as well as non-neuronal tissues. In addition, we thoroughly discuss CREB activation and the evidence for and against it in different disease progression or remission scenarios.

## CREB FUNCTIONS IN THE NERVOUS SYSTEM

A large amount of experimental data suggests that CREB modulates adult hippocampal neurogenesis leading to increased neuronal survival and postnatal hippocampal neurogenesis, improvement of memory formation and several

**Table 1**. Dysregulated CREB signaling in neurobiological disorders

| Neurologic disorders | Associated molecules | Underlying mechanisms of pathogenesis | Reference |
|---|---|---|---|
| Huntington's disease | CREB<br>CBP | Reduced CREB-mediated transcription led to a reduction in energy metabolism and subsequently neuronal death or overall effect on life expectancy. | (Landles and Bates, 2004) |
| Rubinstein-Taybi syndrome | CBP | Reduced transcriptional activity of CREB results in skeletal abnormalities and cognitive deficits. | (Hallam and Bourtchouladze, 2006) |
| Coffin-Lowry syndrome | RSK2 | Reduced CREB activity impairs cognitive performance. | (Harum et al., 2001) |
| Alzheimer's disease | CREB<br>CBP<br>CRTC1 | Reduced CREB phosphorylation results in lower transcriptional activity, which in turn affects synaptic plasticity and ultimately causes loss of synapse.<br>Downregulation of CREB/CBP target genes (for example, *c-Fos* and *BDNF*) contributes to memory loss and age-related neurodegeneration observed in conditional knockout mice lacking both PS1 and PS2.<br>Selective suppression of CRTC1-regulated memory genes, such as *c-Fos* and *BDNF*, is associated with memory impairment found in AD mouse model. | (Amidfar et al., 2020; Eggert et al., 2022) |
| Schizophrenia | CREB | Aberrant patterns of CREB activation and function are found in bipolar disorder and schizophrenia. Schizophrenia susceptibility genes, such as *Akt*, *GSK3b*, and *neuregulin 1*, upregulate the CREB activity in normal brain. | (Wang et al., 2018) |
| Autism | CREB | *CREB*-deficient mice dissociate locomotor activity from anxiety-like behavior. In addition, downregulation of PKA/CREB/BDNF induces neurodevelopmental toxicity. | (Liu et al., 2021) |
| Drug addiction, epileptic seizures, depression, suicide | CREB | Chronic activation or hyper-phosphorylation of CREB significantly reduces the number of hippocampal neurons and induces neural imbalance between excitation and inhibition observed in sporadic epileptic seizures. | (Fisher et al., 2017) |

CREB, cAMP responsive element-binding protein; CBP, CREB-binding protein; CRTC, CREB-regulated transcription coactivator.

cognitive processes, including recognition memory, synapse, or neuronal plasticity, as well as fear conditioning memory development, and in addition, neurite outgrowth, and neuroprotection (Cameron and Glover, 2015; Kida et al., 2002). To this end, cognitive disorders, including HD, Rubinstein–Taybi syndrome (RTS), Coffin–Lowry syndrome (CLS), AD, and PD are reported as CREB-modulated disease (Table 1) (Amidfar et al., 2020).

## Neuronal function

### *Neuroprotection*

A growing body of evidence has demonstrated that CREB regulates neuroprotection by upregulating neurotrophins and anti-apoptotic genes, and detoxifying reactive oxygen species in neurons. CREB modulates immediate–early genes, for instance *c-Fos*, *leptin*, *IAPs*, *BDNF* and *nNOS*, *insulin-like growth factor 1* (*IGF-1*), *pituitary adenylate cyclase-activating polypeptide*, and *B cell lymphoma-2* (*Bcl-2*). They have all found to have an impact on neuronal viability and neural development (Tabuchi et al., 2002). *BDNF* is an established target gene for CREB that contributes profoundly to the development of neuronal circuits and the activity-dependent survival of existing neurons. BDNF contributes to sympathetic neuronal survival via CREB-induced expression of the anti-apoptotic *Bcl-2* (Riccio et al., 1999). Another study demonstrates that CREB-regulated anti-apoptotic Bcl-2 family member, *myeloid cell leukemia sequence 1*, is required for cortical neurogenesis and neuronal survival after DNA damage (Arbour et al., 2008). Nerve growth factor binding to its cognate receptor has been shown to result in the activation of RSK2 kinase, thereby phosphorylating CREB at Ser-133, which is required for the *Bcl-2* expression (Xing et al., 1996). *BDNF* knockout animal models showed either progressive atrophy of neurons or the degeneration of specific neurons, leading to the severe impairment of synaptic transmission and long-term potentiation (Bianchi et al., 1996). Several studies confirm that low BDNF levels are the probable cause for neuronal dysfunction in AD, as disease progression induces symptoms of synapse loss and cognitive decline (Amidfar et al., 2020). In experimental studies, increasing BDNF levels can reduce the risk of memory deficits and cognitive dysfunction in AD patients, as well as reduce the amount of amyloid beta peptide (Aβ) aggregation in the brain (Hampel et al., 2021). Clinical studies show that the overexpression of BDNF and its receptor tyrosine kinase-coupled receptor (TrkB) in the hippocampus can reverse memory impairment. Several studies also suggest that both *BDNF* and *TrkB* are target genes of CREB that may contribute to memory formation and neuroprotection (Amidfar et al., 2020). Overall, the evidence suggests

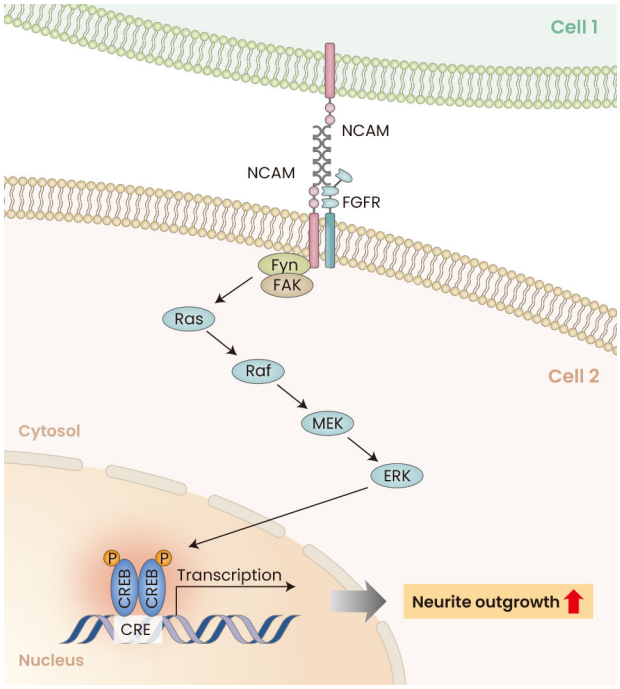


**Fig. 2. CREB-mediated neurite outgrowth.** CREB activation is required for neural cell adhesion molecule (NCAM)-mediated neurite outgrowth. Homophilic interactions of NCAM activate Fyn and FAK kinases that results in the sequential activation of Ras, Raf, MEK, and ERK, finally phosphorylating CREB. Activation of CREB consequently induces target gene expression responsible for neurite outgrowth. CREB, cAMP responsive element-binding protein; FGFR, fibroblast growth factor receptor; CRE, cAMP response element.

that CREB improves memory and acts as a neuroprotective modulator through a variety of underlying mechanisms.

### *Neurite outgrowth*

Neural cell adhesion molecules (NCAMs) have been shown to promote neurite outgrowth through at least two mechanisms: (1) triggering the activation of FGFR, and (2) interacting with Fyn and focal adhesion kinase (FAK) to create intracellular signaling complexes (Fig. 2) (Ditlevsen et al., 2008). The intracellular interaction partners Fyn and FAK phosphorylate NCAM and transiently activate CREB and some of CREB upstream regulators, including ERK1/2, when they interact with NCAM (Fig. 2). It has been shown that CREB promotes the activation of target genes involved in axonal outgrowth, survival, and synaptic transmission in neuronal cells. In a genome-wide screen, miR132 was identified as a neuronal CREB target whose expression is highly induced by neurotrophins, leading to neurite outgrowth (Vo et al., 2005).

### *Memory formation*

In almost two decades of research, CREB has been regarded as the master memory gene, which modulates the expression of a set of memory genes that are crucial for the growth of neurons, synaptic plasticity, and the overall survival of the neurons (Tully et al., 2003). An initial study on mollusk *Aplysia* demonstrated that serotonin and cAMP are involved in synaptic facilitation, behavioral sensitization, and long-term facilitation (LTF) (Castellucci et al., 1980). These mechanistic insights demonstrate the inevitability and sufficiency of cAMP-PKA-CREB for neurogenic gene expression, synaptic facilitation, learning, and memory consolidation (Kaang et al., 1993). Besides *Aplysia*, a wide range of behavioral tests have been carried out in fruit flies to determine the functional consequence of cAMP-CREB in the transcriptional pathway, which is sufficient for LTF, as well as for learning and memory (Gonzalez and Montminy, 1989). In 1992, two different research groups, Smolik et al. (1992) and Abel et al. (1992), reported that dCREBA is also a member of the leucine zipper family, which can bind to CREs and activate transcription. It is interesting to observe that dCREBA possesses CaMKII sites, but no PKA phosphorylation site. In 1993, Usui and colleagues isolated dCREBB/CREBB-17A as a novel CRE-binding protein, which possesses multiple transcripts (Usui et al., 1993). Among the 7 different alternatively spliced isoforms, *dCREBB-a* & *dCREBB-b* are the major transcripts found in *Drosophila* (Yin and Tully, 1996). In contrast, dCREBB and mammalian CREB zipper domains show noticeable differences from dCREBA zippers in both length and composition. The potential DNA binding domains found in these proteins are highly conserved, whereas the dCREBB activation domain is entirely distinct from dCREBA and mammalian CREB. In 1994 and 1995, both Yin and his colleagues showed that multiple CREBB protein isoforms play a critical role in the formation of long-term memory (LTM) in fruit flies. During an olfactory avoidance conditioning experiment (space training) overexpression of the "dCREBB-b" repressor isoform showed significant impairment of the LTM (Yin et al., 1994). Additionally, overexpression of dCREBB-a, considered to be an activator isoform, enhances LTM (Yin et al., 1995), and consequently, neurogenesis and neuronal plasticity may depend on the balance between activators and repressors (Yin et al., 1995).

This claim was also supported by experiments involving avoidance conditioning and spatial escape learning in rodents. Numerous *in vivo* and *in vitro* genetic manipulation research indicated that CREB is essential for neuronal survival and plasticity (Josselyn and Nguyen, 2005). In the mice model, hypomorphic *CREB* mice exhibited deficits in both spatial memories, and hippocampal long-term potentiation (LTP) (Bianchi et al., 1996). Meanwhile, targeted deletion or targeted disruption of the $\alpha$ and $\delta$ isoforms of CREB in mice is profoundly deficient in LTM (Blendy et al., 1996). Even an experiment on the disruption of CREB in the dorsal hippocampus demonstrated impairment in water maze performance (Pittenger et al., 2002). In *CREB* null mice, there are aberrant axonal projections in the anterior commissure and corpus callosum, and more interestingly, homozygous null mutation in all CREB isoforms resulted in perinatal death (Rudolph et al., 1998). An interesting characteristic of CREB is that it exhibits LTM formation through interacting with its coactivators, such as CBP and cAMP responsive element modulator (CREM), which regulate the expression of genes that are essential for memory consolidation and neuronal survival (Cameron and Glover, 2015; Sekeres et al., 2010). During neural development, mice lacking

both *CREM* and *CREB1* in brain exhibit significant neuronal apoptosis (Mantamadiotis et al., 2002). Additionally, *in vitro* expression of the CREB family members' dominant-negative form impairs the dendritic development of cortical neurons (Pignataro et al., 2015). Numerous studies indicate that other members of the CREB family are also involved in embryonic development, neuroplasticity, and spatial memory. In experiments on deficient mice for both CREB and ATF1 (*ATF1*$^{-/-}$ *CREB1*$^{-/-}$ or *ATF1*$^{+/-}$ *CREB1*$^{-/-}$), the mutant embryos experience developmental arrest prior to implantation and exhibit a fatal phenotype by embryonic day 9.5 as a result of widespread apoptosis (Bleckmann et al., 2002). The overall findings suggest that CREB family-mediated signals are also crucial for maintaining cell viability in initial embryonic development. Nevertheless, the necessity of CREB1 in hippocampal plasticity is not absolute, but beyond dispute, and several studies have suggested the loss of CREB1 could be compensated by other molecular components (Kogan et al., 1997).

## Neurodegenerative diseases

The evidence clearly suggests that CREB is a neuroprotectant. Since CREB-mediated neuroprotection requires the expression of CREB target genes, like the pro-survival gene *Bcl-2*, CREB dysfunction is associated with multiple neuronal diseases (Meller et al., 2005). In particular, the CREB pathway participates in the pathogenesis of several neurodegenerative diseases, such as HD, RTS, AD, and CLS (Table 1) (Hallam and Bourtchouladze, 2006; Harum et al., 2001; Saura and Valero, 2011). In addition to neurodegenerative diseases and polygenic disorders, CREB is considered one of many genes that contribute to improper mood regulation, or other polygenic diseases. Therefore, many CREB-regulated genes are implicated in the pathogenesis of mood disorders, depression, and psychomotor retardation (Dragunow, 2004).

### *Huntington's disease*

HD is the most prevalent hereditary neurodegenerative condition, an autosomal dominant disease characterized by irreversible motor impairments, cognitive decline, and psychiatric difficulties, which progresses to dementia and mortality 15-20 years after onset (Eggert et al., 2022). In HD, mutations resulting in expanded CAG repeats are responsible for long segments of polyglutamine (polyQ) in the HD protein Huntingtin (Htt) (*IT15* gene encodes the Htt; normal repeats range [6 to 35]; repeats of 36 or more are synonymous with HD) (Kay et al., 2016). Mutant Htt protein and expanded polyQ tracts form nuclear aggregates that contain CREB-binding protein CBP (Table 1) (McCampbell et al., 2000). However, the CBP correlation with HD or Htt toxicity has been controversial. Surprisingly, experimental evidence demonstrates that transfection with mutant Htt induced endogenous CBP to be depleted from Neuro2a cells' nucleus (Jiang et al., 2003). Also, it has been recommended that mutant Htt expression may exert an impact on histone acetyltransferases (HATs) like CBP to decrease histone acetylation levels, which is associated with polyQ toxicity (Steffan et al., 2001). Numerous studies have demonstrated that, in addition to CBP, altered CREB function also plays a role in the HD pathogenesis (Landles and Bates, 2004). In mice lacking both *CREB1* and *CREM* in the postnatal forebrain HD-like progressive neurodegeneration was observed in the dorsolateral striatum and hippocampal region (Mantamadiotis et al., 2002). Consistent with this, some of CRE-regulated genes have been downregulated in the HD patients. Furthermore, transgenic A-CREB, which expresses a dominant negative form of CREB, showed increased 3-nitropropionic acid-induced striatal lesion size and motor impairment, and also robustly deteriorated motor dysfunction observed in genetic mouse model of HD. In summary, these observations demonstrate that loss of CREB activity and the resulting disruption of CREB-mediated gene expression contributes to the pathogenesis of HD (Landles and Bates, 2004).

### *Rubinstein–Taybi syndrome*

RTS is a rare congenital condition that is marked by mental and physical impairment, mood instability, behavioral stereotypes, and abnormalities of the thumbs, big toes, and face (Hallam and Bourtchouladze, 2006). Many chromosomal breakpoints observed in patients with RTS have been shown to be associated with the *CBP* locus (Table 1) (Petrij et al., 1995). Biochemical and genetic studies using RTS-associated HAT domain mutants uncovered that these mutations led to loss of *in vitro* acetyltransferase activity and also reduced CREB-mediated transcription (Kalkhoven et al., 2003).

### *Alzheimer's disease*

Accumulation of Aβ and mutations in two *presenilin* (*PS*) genes are considered as the familial cause of AD pathogenesis (Jeong, 2017). Preceding genetic investigations have demonstrated that PSs play indispensable roles in synaptic function, memory, and neuronal survival (Zhang et al., 2009). Amyloid beta 42 (Aβ42) peptides, which are produced through sequential proteolysis of the APP (amyloid precursor protein) by β-secretase and γ-secretase, and are major insoluble components of neuritic plaques found in patients of AD, lowered the PKA activity, as well as the levels of phosphorylated CREB (Table 1) (Vitolo et al., 2002). Even the most hazardous Aβ species, Aβ oligomers, also block CREB phosphorylation in primary neurons through a mechanism necessitating NMDA receptor degradation (Ma et al., 2007). It is evident that the expression of CREB-target genes and CBP is reduced in the absence of wild-type PSs, which implies a direct pathophysiological correlation of AD. Calcium influx and CREB phosphorylation mediate the effect of neuronal activity on *PS1* expression, whereas the CREB with a mutated Ser-133 residue (S133A) lowers expression levels of *PS1* (Mitsuda et al., 2001). CREB also regulates the transcription of *PEN-2*, that is a critical component of the γ-secretase complex (Wang et al., 2006). In conclusion, these findings show that PS/γ-secretase and CREB signaling may be regulated in a reciprocal manner during activity-dependent synaptic function.

### *Coffin–Lowry syndrome*

CLS is a rare X-linked condition that is characterized by severe mental retardation and physical anomalies, such as facial characteristics, large hands and fingers, and short stature in both males and females (Harum et al., 2001). Cognitive impairments in CSL may be caused by deregulation of CREB sig-

naling induced by deficiency or mutations in the RSK2 (Table 1) (Trivier et al., 1996). Lack of functional RSK2 in CSL patient fibroblasts, as well as reduction in CREB phosphorylation and c-Fos expression in response to epidermal growth factor are correlated with cognitive impairment in patients of CSL (Cesare et al., 1998; Harum et al., 2001).

A strong correlation exists between CREB and age-dependent cognitive impairment (Table 1). A study on rodents has demonstrated that CREB signaling contributes to age-related memory deficits by cross-linking age-dependent cognitive decline. Reduced levels of CREB, CBP, and phosphorylated CREB in the hippocampus of old rats are associated with deficits in spatial memory (Morris and Gold, 2012). Genome-wide analysis of gene expression has revealed that CaMKIV expression is reduced in the cortex of mice, rhesus macaques, and humans as they age (Loerch et al., 2008). In very old rats, clindamycin, a cyclic nucleotide phosphodiesterase 4 inhibitor, increased CREB activity and restored aging-related memory and LTP deficiencies, supporting the idea of CREB-mediated memory enhancement (Morris and Gold, 2012). All these findings back up the theory that as people age, there is a link between CREB malfunction, synaptic plasticity, and memory loss. CREB plays a role in mental disorders, retardation, and depression through different pathways. There is evidence from several sources that symptoms such as depression, schizophrenia, drug addiction, and psychological dependence can be directly related to CREB activity (Table 1).

Postmortem examinations have shown that the cortices of CLS patients contain reduced concentrations of CREB, compared with patients treated with anti-depressants. A growing number of studies has shown that decreased levels of total or phosphorylated CREB are detected in the hippocampus of elderly mice or rats (Kudo et al., 2005). Interestingly, overexpression of the CREB gene in the dentate gyrus (all sensory modalities merge and play a critical role in learning and memory) exhibits anti-depressive behavior that is quite similar to that observed when anti-depressant drugs are used (Blendy, 2006). More recent researches have revealed that CREB activity modulates the behavioral phenotypes of mice in response to emotional stimuli (Barrot et al., 2002). In addition, prolonged anti-depressant treatment increases CREB expression in the hippocampus, indicating the role of CREB in the pathogenic process and therapy of depression (Gass and Riva, 2007). CREB activity is associated with upregulation of neural circuit excitability that improves motor performance after stroke. Therefore, motor recovery following a stroke is improved by raising CREB levels, whereas stroke recovery is inhibited by limiting CREB signaling (Caracciolo et al., 2018).

## CREB FUNCTIONS IN THE IMMUNE SYSTEM

Interestingly, CREB is also involved in the control of diverse

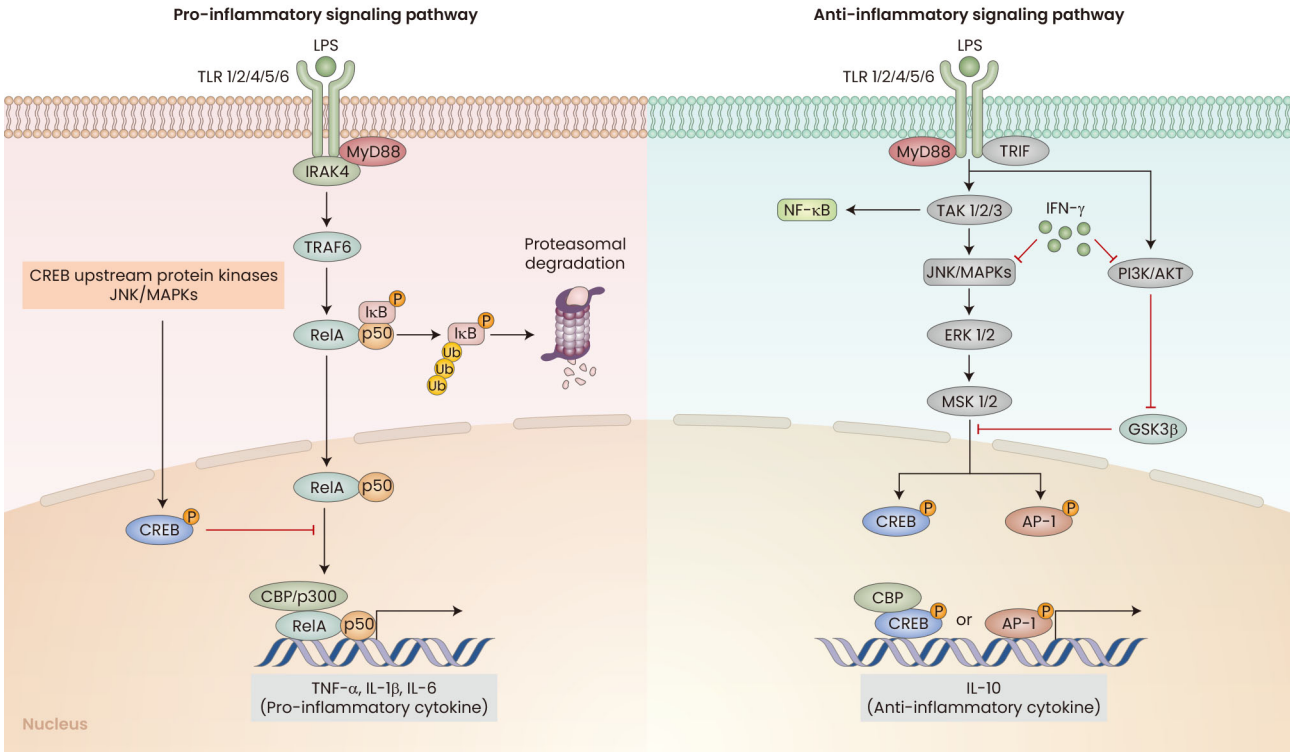


**Fig. 3. CREB-induced immune response.** CREB plays crucial roles in the innate immune system that involves Toll-like receptors (TLRs) and their activation. As part of NF-κB signaling pathway that induces production of pro-inflammatory cytokines, such as interleukin (IL)-6, IL-1β, and tumor necrosis factor α (TNF-α), phosphorylated CREB directly inhibit NF-κB activation by interfering with the binding of CREB-binding protein (CBP) to the RelA/p50 complex. On the other hand, TLR signaling leads to the activation of MSK1/2, which induces phosphorylation of CREB and then production of anti-inflammatory cytokine IL-10. This CREB-induced IL-10 production can be negatively regulated by interferon-γ (IFN-γ). CREB, cAMP responsive element-binding protein; LPS, lipopolysaccharide.

immune responses. The innate immune system uses various types of pattern recognition receptors, including Toll-like receptors (TLRs), to initiate various signaling cascades in innate immune cells, including macrophages, neutrophils, and dendritic cells (Fig. 3) (Suresh and Mosser, 2013). Remarkably, CREB activation, which appears to be induced through the activation of T-cells and monocytic cells, has been shown to upregulate the expression of a large number of immune-related genes including tumor necrosis factor (TNF), interleukin (IL)-2, IL-10, and chemokine ligands via the CRE promoter (Hughes-Fulford et al., 2005). These cytokines play crucial roles in mediating pro-inflammatory and anti-inflammatory immune responses.

### Pro-inflammatory signaling

Bacterial lipopolysaccharide (LPS) can initiate pro-inflammatory signaling through the activation of TLRs (Fig. 3, left). Subsequently, the activation of the NF-κB family members via the adaptor molecules, such as MyD88, IRAK4, and TRAF6, are required for the production of pro-inflammatory cytokines. The nuclear factor-κB (NF-κB) family transcription factors serve as evolutionarily conserved regulators of the innate immune responses. Five members of the NF-κB family are NF-κB1, NF-κB2, RelA, RelB, and c-Rel, and have a conserved Rel homology domain (RHD) in the amino-terminal region (Ghosh et al., 1998). Functionally, they combine to create homo- and heterodimeric complexes that are transcriptionally active, whereas the RHD contains sequences necessary for dimerization, DNA binding, interacting with IκBs, and nuclear translocation. The formation of the active RelA/p50 complex requires proteasomal degradation of phosphorylated IκB that is also induced by LPS (Fig. 3). The CREB coactivator CBP needs to directly interact with the RelA Ser-276 for optimal RelA/p50 activity, whereas acetylation of CBP further increases RelA activity. Interestingly, since RelA competes with phospho-CREB for CBP, the NF-κB activity can be inhibited by increased CREB activation or enhanced by overexpression of CBP (Fig. 3) (Ollivier et al., 1996).

### Anti-inflammatory signaling

In macrophages, several TLR signals (TLRs 2, 3, 4, 7, and 9) induce the expression of IL-10, which is a potent anti-inflammatory cytokine that limits overactivation of inflammatory signaling, and minimize undesirable tissue damage (Saraiva and O'Garra, 2010). Upon TLR ligation by LPS, NF-κB/MAPKs-dependent signaling cascades produce anti-inflammatory cytokine IL-10 together with pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6. MSK1 and MSK2 are required for the phosphorylation of CREB and AP-1, their binding to the promotor of *IL-10*, and transcriptional activation (Fig. 3) (Saraiva and O'Garra, 2010). Interferon-γ (IFN-γ), which is predominantly generated by natural killer cells and T cells, suppresses the production of IL-10 through two different mechanisms. First, IFN-γ inhibits the TLR-mediated activation of PI3K-AKT and the resulting derepression of GSK3β interferes with CREB activation. Second, IFN-γ also directly downregulates MAPK pathway (Fig. 3) (Hu et al., 2006).

## CREB FUNCTIONS IN CANCER DEVELOPMENT

The CREB transcription factor drives expression of numerous target genes that are involved in proliferation, self-renewal, differentiation, and apoptosis (Steven et al., 2020). However, there is no concrete proof that mutated CREB protein is directly associated with cancer development. Rather, the mutation of diverse upstream regulators appear to mediate the constitutive activation of CREB target genes, such as early growth response protein 1, cyclins A1 & D1, and Bcl-2, contributing to tumorigenesis (Sakamoto and Frank, 2009).

The discovery of a chromosomal t (12; 22) (q13; q12) translocation that resulted in the production of a fusion protein EWS-ATF1 in soft tissue clear cell sarcomas provided the first evidence of CREB-associated cancer (Schaefer et al., 2004). As of now, CREB is linked to a wide range of cancer types, including hematopoietic and solid tumors, acute myeloid leukemia, prostate and lung cancers, as well as gastric, melanoma, pancreatic, and breast carcinomas, since CREB has been shown to act either as a direct mediator or as a proto-oncogene (Table 2) (Sakamoto and Frank, 2009; Shankar et al., 2005). In most of the case hyperphosphorylated and overexpressed CREB are identified in both nonhematologic and hematological cancers. In fact, elevated CREB expression and activation are linked to cancer initiation and progression, increased chemo-resistance (cisplatin resistance), and lower survival rate of cancer patients (Steven et al., 2020; Zhang et al., 2017). In the most common subtype of lung cancer, CREB was overexpressed, and inhibited ferroptosis to enhance the rapid growth of cancer (Xiao et al., 2010).

Consistent with the fact that elevated CREB expression correlates with tumorigenesis, a large number of previous studies have shown that downregulation of CREB is closely related to suppression of tumorigenesis in many different cells. The knockdown of CREB downregulates anti-apoptotic Bcl-2 and IAP family members, such as Bcl-2, Bcl-xL, Mcl-1, XIAP and survivin, validating the connection between CREB and these prosurvival oncogenes (Xiang et al., 2006). Ro-31-8220 (a synthetic S6 kinases inhibitor) mediated CREB inactivation arrests the cell cycle at the G2-M phase, and also mediates the inhibitory action to anti-apoptotic factors Bcl-2 and Bcl-xL, signifying that CREB could be a potential therapeutic target in non-small cell lung carcinoma (NSCLC) (Xiang et al., 2006). Interestingly, the treatment of lung adenocarcinoma cells with AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) antagonists reduced phosphorylation of CREB, suppressed the expression of cyclin D1, upregulated the tumor suppressor proteins p21 and p53, and decreased the number of metastatic cells (Stepulak et al., 2007). Furthermore, a dominant-negative form of CREB and siRNA-mediated knockdown of CREB suppressed the proliferation and induced apoptosis of NSCLC (Xiao et al., 2010). In a same manner, decoy oligonucleotides and RNA interference both suppress CREB-mediated gene transcription thereby negatively impacting tumor growth, increased apoptosis, become sensitive to antiproliferative signals and inhibition of anchorage-independent proliferation (Sakamoto and Frank, 2009; Xie et al., 2015). The metastatic potential of tumor cells is also inhibited by the overexpression of dominant negative

**Table 2**. CREB-associated cancers

| Type of cancer | Altered expression and function of CREB | Reference |
|---|---|---|
| Prostate cancer | Increased levels of CREB mRNA and phosphorylated CREB proteins were consistently observed in prostate cancer tissues. Overexpression and hyperphosphorylated CREB induce tumor differentiation, overall proliferation, and metastasis condition. | (Zhang et al., 2018) |
| Breast cancer | Overexpression and overactivation of CREB were observed in breast cancer tissues. CREB overexpression resulted rapid cell proliferation. | (Xiao et al., 2010) |
| Non-small cell lung carcinoma | Expression of IGF-III or IGF-II induced overexpression of phosphorylated CREB or even CREB level that are clearly upregulated in tumor tissues compared to the control tissues. Overexpression of CREB is responsible for dedifferentiation, fast proliferation and even metastasis. | (Xia et al., 2018) |
| Lung adenocarcinoma | Level of phosphorylated CREB gradually elevated, as this lung adenocarcinoma developed. CREB hyperactivity along with the low level of NF-κB promotes tumorigenesis and tumor progression. | (Zhang et al., 2021) |
| Bone marrow neoplasms | Higher expression levels of CREB and phospho-CREB were observed in the bone marrow of patients. Overactivation of CREB is responsible for myeloproliferative disorder as well as aberrant myelopoiesis. | (Sandoval et al., 2009) |
| Adult T-cell leukemia | Intact CREB signaling is required for oncogenesis by the oncoprotein Tax derived from human T-cell lymphotropic virus type 1. | (Cho et al., 2011) |
| Acute lymphoid leukemia | CREB activation promotes cell cycle progression and growth through aberrant expression of cyclin A1 and D2. | (Cho et al., 2011) |
| Acute myeloid leukemia | Upregulated CREB, which stimulates the expression of survival-related genes (Bcl-2, Mcl-1, Bcl-xL, survivin and XIAP), is responsible for uncontrolled cell growth and apoptosis repression in hematopoietic cell lineage. Collectively hyperactivity of CREB alters the proliferation and survival functions of hematopoietic cells and finally induces defective differentiation or aberrant monocytosis or loss of apoptosis in cells. | (Cho et al., 2011) |
| Renal cell carcinoma (RCC) | Phosphorylated CREB was upregulated in these cancer cells. In addition, CREB has been shown to induce metastatic RCC through the expression of MMP2/9 and EMT-associated proteins. Mechanistically, CREB is associated with angiogenesis through the CREB-PGC-1-VEGF pathway and promotes the migration and invasion of the proliferated cells, and overall metastasis. | (Friedrich et al., 2020) |
| Glioblastoma | CREB is upregulated in glioma tissues. CREB promotes glioma genesis through the expression of oncogenic microRNA-23a (miR-23a) that silences the tumor suppressor PTEN. CREB enhances tumor cell growth, survival, and overall tumorigenesis. | (Tan et al., 2012) |
| Pancreatic cancer | The zinc importer ZIP4 activates CREB, resulting in CREB-dependent induction of oncogenic miR-373. ZIP4-CREB-miR-373 signaling facilitates pancreatic cancer progression by enhancing uncontrolled cell proliferation, invasion, and tumor growth. | (Zhang et al., 2013) |
| Gastric cancer | The expression of carbonic anhydrase IX, which is negatively regulated in cancer cells, can be robustly suppressed by CREB overexpression in gastric cancer. Overexpression of CREB promotes tumor progression, aberrant proliferation, and overall metastasis. | (Wang et al., 2015a) |

CREB, cAMP responsive element-binding protein.

form of CREB (KCREB), which loses its ability to bind to CRE elements, but can form a nonfunctional heterodimer with wild-type CREB (Linnerth-Petrik et al., 2012).

Apart from CREB, there are a number of regulatory loops involved in migration, invasion, and metastasis formation, including CBP, CREM, and CRTCs (Iourgenko et al., 2003). In mutagen analysis of CRTCs, the expression of dominant-negative mutant specifically inhibits the oncogenic transcriptional program of CREB (Ostojić et al., 2021). Other than the functional component, processes like dimerization, CRE-dependent regulation of CREB target gene expression, posttranslational modifications (PTMs), circumstantial excessive phosphorylation, and the ratio of repressor or ICER are also involved in cancer progression and overall pathogenesis (Voropaev et al., 2019). The qualitative control of CREB, through different combinations of dimerization and PTMs, such as phosphorylation, ubiquitination, methylation, glycosylation, and SUMOylation, seems more important than

the quantitative regulation of CREB expression levels during tumorigenesis. Number of experimental models indicate that PTM affects the overall stability and activation. For example, multiple site phosphorylation of CREB at Ser129 and Ser133 enhances transcription activity, whereas the phosphorylation of Ser111 and Ser121 totally abolishes the CREB-dependent gene expression (Sapio et al., 2020). Furthermore, previous studies demonstrate that hyperphosphorylation of CREB is correlated with its ubiquitination and increased proteasomal degradation (Steven et al., 2020).

CREB activity can be also regulated by several miRNAs at the transcriptional level. In certain conditions, miRNAs may function as either tumor suppressors or oncogenes. In a contextual manner, CREB either regulates miRNAs or miRNAs regulate CREB expression in different types of cancer proliferative signaling (Pigazzi et al., 2009). A recent investigation in acute myeloid leukemia revealed that the 3′-UTR of CREB contains a miR-34b regulatory element, providing a negative feedback regulation of CREB activity (Pigazzi et al., 2009). Extensive studies demonstrate that miR-200b and miR-203 have been shown to target CREB, suggesting their tumor-suppressing mechanism (Noguchi et al., 2016). Consistent with this, low miR-200b expression coupled with high levels of CREB expression can serve as a significant factor of prognosis in astrocytoma (Zhang et al., 2014).

Unexpectedly, high CREB expression also possess benefit in some cancer types, such as clear cell renal cell carcinoma, breast cancer, and esophageal squamous cell carcinoma. For example, overexpression of CREB in breast cancer (HER-2/neu-positive or basal-like or luminal-type A) collectively improves the survival of patient as well as recurrence-free survival (Steven et al., 2020). In order to get deeper knowledge of the fundamental processes of CREB regulation and function, it is essential to further examine CREB as "friend or foe" due to its dual and opposing roles that confound various cancer entities. Nevertheless, it seems clear that CREB is regarded as a promising biomarker and an ideal therapeutic target gene for a wide range of cancers due to its essential role in the development, maintenance, and proliferation of many different types of cancer (Table 2) (Sakamoto and Frank, 2009).

## CREB FUNCTIONS IN HEPATIC PHYSIOLOGY AND DISEASES

CREB plays a vital role in liver to respond to various metabolic demands responsible for normal physiological functions of major body organs (Table 3) (Wang et al., 2015a). Glucose homeostasis is controlled by two antagonistic hormones glucagon and insulin. During fasting time glucagon enhances the CREB transcriptional activity, resulting in the expression of gluconeogenic genes, such as pyruvate carboxylase (PC), glucose-6-phosphatase (G6Pase), and phosphoenolpyruvate carboxykinase 1 (PEPCK1), and an increase in overall glucose output (Oh et al., 2022; Zhang et al., 2016). However, feeding conditions enhance the secretion of insulin and sequentially activates AKT and SIK2. Both kinases phosphorylate CBP/P300 and CRTC2 in an inhibitory manner for forming active complex with CREB, leading to inhibition of gluconeogenic program and decreased glucose output (Oh et al., 2013).

Communally, CREB in the liver participates in the control of lipogenesis and lipolysis, in addition to glucose homeostasis, specifically gluconeogenesis, through PEPCK and G6Pase (Table 3) (Han et al., 2016; Rowe and Arany, 2014). Studies have demonstrated that peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1α (PGC-1α), which is activated by CREB activation, not only upregulates gluconeogenesis, but also enhances lipolysis via the oxidation of long-chain fatty acids (Huang et al., 2017; Lin et al., 2005). Since a nuclear hormone receptor PPAR-γ is one of key lipogenic mediators, CREB negatively regulates the lipid synthesis during fasting conditions through inhibition of PPAR-γ expression (Herzig et al., 2003).

It has been shown that dysregulation of the CREB-dependent gluconeogenic gene pathway can result in metabolic diseases (Han et al., 2020). In pathological conditions like obesity and T2DM, insulin fails to regulate hepatic metabolism, resulting in excess glucose and fat production, as well as hepatic insulin resistance (Petersen et al., 2017). Remarkably, genetic ablation or downregulation of the CREB gene resulted in profoundly fasting hypoglycemia and also reduced mRNA expression of gluconeogenic genes such as PC, G6Pase, and PEPCK (Herzig et al., 2001).

Studies have demonstrated that PGC-1α, which is associated with the pathogenesis of T2DM, induced expression of a number of transcription factors that drive the expression of key gluconeogenic genes (Liang and Ward, 2006).

There are several forms of liver disorders that can be caused by infections, hereditary abnormalities, obesity, and alcohol abuse (Li et al., 2019). The most common chronic liver illness, nonalcoholic fatty liver disease (NAFLD), which includes simple hepatic steatosis, nonalcoholic steatohepatitis, liver fibrosis, and liver cirrhosis, is characterized by abnormal accumulation of lipids, involving hepatic injury and inflammation (Awaad et al., 2020).

Additionally, a fatty liver symptom combined with increased expression of PPARγ, a key regulator of lipogenesis, were observed in CREB-deficient animals (Herzig et al., 2003). Based on the fact that during fasting CREB activation upregulates gluconeogenesis through the induction of PGC-1α, but suppresses lipogenesis by inhibition of PPARγ, the discovery and development of selective CREB antagonists may provide an effective treatment for diabetic patients by improving glucose control and/or insulin sensitivity (Herzig et al., 2001).

According to the proposed model, NAFLD is caused by lipid peroxidation-mediated liver injury owing to a “two-hit” pathogenesis. Early in the disease, the first hit involves excessive accumulation of hepatic triglyceride along with insulin resistance, while the second hit includes pro-inflammatory cytokines, mitochondrial dysfunction, and oxidative stress, leading to hepatic fibrosis and cirrhosis (Fang et al., 2018). When high fat diet was given to rats to drive the development of NAFLD, higher levels of both cAMP and CREB in the liver tissue were significantly detected in these NAFLD rats, compared to control animals (Awaad et al., 2020).

Additionally, CREB controls the expression of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG–CoA) synthase

**Table 3**. The functional role of CREB and its mediators in liver, heart, and kidney

| Organ | Function | Mechanisms | References |
|---|---|---|---|
| Liver | Lipogenesis | CRTC2 regulates compartmental transportation of SERBP1, which is a key component of lipogenesis. Also, SREBPs, NF-Y/CBF, and CREB complex enhance lipogenesis, and dysregulate the activation profile of FOXO. | (Petersen et al., 2017; Wang et al., 2015b) |
| | Fatty acid oxidation and lipolysis | CREB enhances the expression of PGC-1, as well as suppresses PPARγ, leading to an increase in fatty acid oxidation. | (Rui, 2014) |
| | Glucose metabolism | CREB transcriptionally regulates the expression of gluconeogenic genes, such as PEPCK1, G6Pase, while PGC-1α transcription is controlled by CREB or CREB-CRTC2 complex. And during prolonged fasting time PGC-1α has up-regulated the GLUT2 level. | (Rui, 2014) |
| Heart | Cardiac contraction | Overexpression of dominant negative CREB reduces cardiac contractility. | (Fentzke et al., 1998) |
| | Prevention of apoptosis | IGF-1 suppresses cardiac myocytes apoptosis via CREB and dominant negative CREB induces VSMC apoptosis. | (Mehrhof et al., 2001; Tokunou et al., 2003) |
| | Cardiac remodeling and heart failure | Restoration of Gsα increases CREB1 expression and enhances the Bmp10-mediated signaling pathway. | (Yin et al., 2021) |
| | Angiogenesis | VEGF induces activation of CREB. | (Mayo et al., 2001) |
| | Cardiac fibrosis | The prostacyclin/IP pathway suppresses cardiac fibrosis, in part by inducing CREB phosphorylation. | (Chan et al., 2010) |
| | Cardiac hypertrophy | Overexpression of PGC-1α and suppression of PPARγ in cardiomyocyte enhance the hypertrophy. | (Sano et al., 2004) |
| | Cardiac myocyte contractility. | Repression of CREB enhances the PPARγ expression, while PPARγ enhances cardiac contractile function and antagonizes the cardiac hypertrophy. | (Asakawa et al., 2002; Planavila et al., 2005; Yamamoto et al., 2001) |
| | Ischemic heart disease<br>Hypertensive heart disease | Overexpression of PGC-1α by estrogen and PPARγ agonists affects CREB expression levels involved in cardiac recovery. | (Garnier et al., 2003)<br>(Arany et al., 2006) |
| Kidney | Recovery from acute kidney injury due to systemic inflammation or cisplatin-induced acute renal injury | Overexpression of PGC-1α expression inhibit the tubulointerstitial inflammation by suppressing the expression of proinflammatory cytokines. | (Portilla et al., 2002; Tran et al., 2011) |
| | Survival of mouse renal tubular cells during oxidative stress | During oxidative-induced ischemia/reperfusion (I/R) injury in in renal proximal tubule, ERK-mediated CREB target gene activates the survival pathways. | (Arany et al., 2005) |

CREB, cAMP responsive element-binding protein.

gene which contains a consensus CRE and two binding sites for sterol regulatory element-binding proteins (SREBPs) in its promotor (Dooley et al., 1998). The HMG-CoA synthase, which converts acetoacetyl-CoA and acetyl-CoA into HMG-CoA, is the rate-limiting enzyme for cholesterol synthesis. The SREBPs collaborate with CREB to drive gene expression of HMG-CoA synthase, in response to low levels of cellular cholesterol (Dooley et al., 1999).

Liver fibrosis is caused by the extensive accumulation of extracellular matrix, and can lead to liver cirrhosis, portal hypertension, and even multi-organ dysfunction (Liu et al., 2017). Numerous researches conducted over the past several decades has advanced our understanding of the close correlation between hepatic fibrosis and CREB-dependent gene expression (Li et al., 2019). Investigations demonstrate that the upregulated activation of CREB1 antagonizes the development of liver fibrosis through the downregulation of transforming growth factor-β1 (TGF-β1) signaling pathway, which is thought to serve as a key fibrogenic driver (Li et al., 2019). TGF-β1-induced phospho-Smad2 and phosphor-ERK1/2 expression was significantly suppressed by CREB1 overexpression (Deng et al., 2016). As a consequence, acetylation and/or extended phosphorylation of CREB-1 inhibit TGF-β1-mediated fibrogenesis in hepatic stellate cells via Smad2-dependent and independent pathways (Deng et al., 2016).

## ROLES OF CREB IN CARDIOVASCULAR FUNCTION AND REMODELING

Numerous findings show that CREB is involved in both the positive and negative aspects of cardiovascular remodeling (Table 3). Other transcription factors that are activated at the same time as CREB by particular extracellular stimuli may influence whether CREB is beneficial or harmful to cardiovascular remodeling. Several important functions of CREB in the cardiovascular system have been identified. First, CREB activ-

ity is required for normal contractile response to extracellular stimuli, gene expression of voltage-gated $K^+$ channel $K_v4.3$ in the heart, and IGF-1-mediated suppression of apoptosis in cardiac myocytes (Schulte et al., 2012). Second, CREB in the endothelial cells appears to mediate the expression of angiogenesis-related genes and Cox-2, a key inflammatory response gene, suggesting an essential function for CREB in vascular remodeling (Scoditti et al., 2010). Lastly, angiotensin II- and thrombin-induced hypertrophy of vascular smooth muscle cells (VSMC) requires the CREB activity, emphasizing the importance of CREB function in VSMC proliferation/survival (Truong et al., 2021).

## CONCLUSION

It is clear that CREB acts as a phosphorylation-dependent transcription factor that is associated with a wide range of cellular processes that include cell proliferation, survival, differentiation, and physiology. These pleiotropic effects of CREB are mediated by distinct target gene expression in response to diverse physiological stimuli. A lot of evidence supports that several regulatory modes of CREB family transcription factors contribute to selective target gene expression, and thus the pleiotropic roles of CREB proteins in neuronal and non-neuronal cells. Despite more than three decades of intensive research, there are still a few crucial unanswered questions with regard to the molecular mechanisms underlying the activation of transcription by CREB. Therefore, better understanding of CREB-mediated transcriptional regulation should be essential for the development of therapeutics for CREB-related diseases.

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## AUTHOR CONTRIBUTIONS

M.A.R.C., J.A., and S.J. contributed to the literature search and the final manuscript. M.A.R.C. and S.J. discussed and designed the frame of the manuscript. M.A.R.C. wrote the first draft of this manuscript and also generated figures and tables. All authors reviewed, revised, and approved the final version of the manuscript.

## CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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