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Chapter 2

CREB: STRUCTURE, FUNCTIONS, AND ROLE IN DISEASE

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ABSTRACT

The cyclic AMP (cAMP) response element binding protein (CREB) is a member of the leucine zipper superfamily of transcription factors. CREB is activated by protein kinases in response to various stimuli and stresses, including cyclin AMP, calcium, and mitogenic signals. Activated CREB promotes target gene transcription through recruiting coactivator CREB-binding protein (CBP) and binding to the DNA cAMP response elements (CRE). More than 4,000 genes have CREB binding sites in their promoter regions; CREB has pleiotropic activities and is associated with various intracellular biological processes, including cell growth, proliferation, differentiation and survival. In this chapter, we will provide an overview of CREB structure and functions, and review the molecular mechanisms and role of CREB in disease processes, including neural diseases, diabetes and cancer. Additionally, we will review the potential for using CREB as a prognostic biomarker and therapeutic target.

INTRODUCTION

Cyclic AMP (cAMP) response element binding protein (CREB) is an intracellular protein that regulates the transcription of genes with cAMP responsive elements in their promoter (Gonzalez et al. 1989). CREB belongs to the CREB family, which also includes the activating transcription factor 1 (ATF1) and the cAMP response element modulator (CREM). In the last few decades, numerous studies have revealed that CREB is a critical transcription factor that mediates diverse cellular responses. Multiple protein kinases may activate CREB by phosphorylating Ser133 of CREB at the N-terminal transactivation domain (Shaywitz and Greenberg 1999). Hence, the activity of protein kinases in response to various stimuli, including the intracellular levels of cAMP and Ca^{+2}, growth factors and cellular stress, triggers the phosphorylation of CREB. The phosphorylated CREB affects gene transcription by recruiting co-activator CBP/p300 and binding to CRE on the promoters of the genes (Carlezon, Duman, and Nestler 2005). CREB plays an important role in cell survival, growth and proliferation by binding to the CRE to regulate downstream gene transcription. CREB-null mice died quickly after birth (Rudolph et al. 1998). In addition, CREB protein has been found to be involved in the formation of long-term memories (Kandel 2012, Bourtchuladze et al. 1994), drug addiction, psychological dependence (Nazarian et al. 2009, DiRocco et al. 2009, Wang et al. 2009), cancer (Steven and Seliger 2016), diabetes (He et al. 2009), and cardiovascular diseases (Schauer et al. 2010). In this chapter, we provide an overview of CREB molecular structure, biological function and its role in diseases.

MOLECULAR STRUCTURE

CREB is a member of the leucine-zipper superfamily of transcription factors. It is a 43-kDa nuclear protein. The CREB gene locates at chromosome 2 (2q33.3) and consists of 11 exons. The CREB gene

produces three different protein isoforms through alternative splicing (CREB1, CREB2, and CREB3). The CREB protein contains four functional domains (Figure 1), including the N-terminal glutamine rich domain referred to as the Q1 basal transcriptional activity domain, the kinase inducible domain (KID), a glutamine-rich constitutive activation domain (CAD, also referred to as the Q2 domain) (Mayr, Guzman, and Montminy 2005), and a basic motif region/leucine zipper domain (bZIP) at the C-terminal (Xu et al. 2007). The Q1 domain interacts with the TATA binding protein and promotes gene transcription (Quinn 1993). Functional mapping assays revealed that the KID and CAD are two distinct activation domains. Both are necessary and sufficient for stable binding of CREB to the CRE site (Mayr, Guzman, and Montminy 2005). Ser133 is a critical functional amino-acid residue of the CREB protein and is located at KID. Multiple protein kinases have been reported to initiate CREB activation via phosphorylation at Ser133 (Shaywitz and Greenberg 1999). The CAD is critical for promoter occupancy and interacts with a specific TATA binding protein-associated factor (TAF), $dTAF_{II}110$/ $hTAF_{II}135$, that promotes polymerase complex assembly and activates transcription (Felinski and Quinn 2001, Mayr, Guzman, and Montminy 2005). The bZIP domain localizes at the C-terminus of CREB. Upon phosphorylation at Ser133 of CREB, two bZIP domains self-associate, forming an active homodimer via the leucine zipper motif. The homodimer then interacts with the co-activators CBP/p300 and binds to the CRE site in the promoter of the target genes (Radhakrishnan et al. 1997). CRE sequences typically appear as either palindromic (TGACGTCA) or half-site (TGACG or CGTCA) sequences. CBP and p300 share extensive sequence similarity, though both of them perform similar actions in binding with CREB and perform numerous common biochemical functions, p300 is not required for CREB-dependent gene activity in every cell type (Yao et al. 1998). In addition, a family of cytoplasmic co-activators called cAMP-regulated transcriptional co-activators (CRTCs) has been identified as transcriptional coactivator for the CREB(Altarejos and Montminy 2011).The CRTC family consists of three members (CRTC1, CRTC2 and CRTC3) that have similar modular structures (Altarejos and Montminy 2011). In response to

increase in cytoplasmic cAMP and Ca^{2+} levels, CRTCs can be dephosphorylated, enter the nucleus and bind to the CREB (Bittinger et al. 2004). CBP, p300 and CRTCs may provide alternative, rather than cooperative, pathways for target gene induction in response to diverse stimuli in different cell types (Esvald et al. 2020, Kasper et al. 2010). More than 4000 genes contain CREs, mostly localized to promoter-proximal regions within 250 base pairs of the transcription start site. CREB interacts with these CREs and mediate gene activation through CREB-dependent pathways (Impey et al. 2004, Zhang et al. 2005).

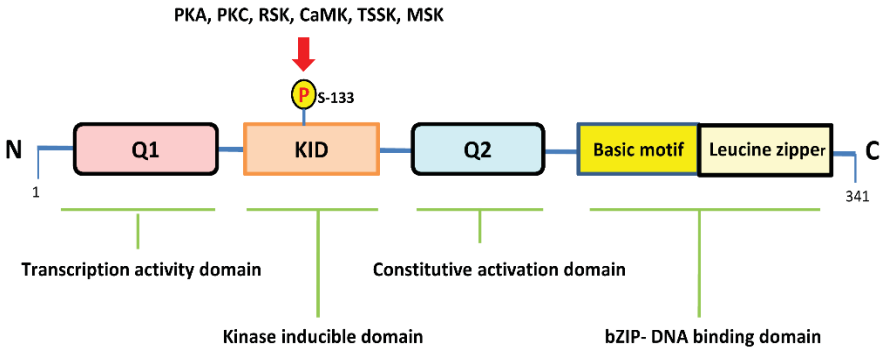

Figure 1. The schematic description of CREB domains. CREB has four domains, Q1, KID, Q2 and bZIP domains. bZIP domain contains basic motif and leucine-zipper region. Serine 133 in KID is a crucial amino-acid residue. Multiple protein kinases phosphorylate serine 133 and induce CREB activation.

MECHANISM OF ACTION

CREB is phosphorylated by a number of kinases in response to diverse cellular signals and stimuli that increase the production of second messengers, cAMP and Ca^{+2} (Dash et al. 1991, Sheng, Thompson, and Greenberg 1991). In addition, some stimuli including growth factors, hormones and neuronal activity can also induce CREB activation in a cAMP- and Ca^{+2}-independent manner (Tan et al. 1996, Yan et al. 2013, Bonni et al. 1995) (Figure 2). CREB activation is generally mediated through the phosphorylation of the critical serine 133 residue within its

kinase-inducible domain. We previously found that IGF-I treatment markedly increased the abundance of phosphorylated CREB at serine 133, promoted CREB recruitment to the *cyclin D1* promoter region and cell proliferation in rat oligodendroglial cells (Yan et al. 2013). A number of protein kinases can activate CREB, including protein kinase A (PKA), protein kinase C (PKC), pp90 ribosomal S6 kinase (RSK), Ca^{+2}/calmodulin-dependent protein kinase (CaMK), testis-specific serine/threonine kinase (TSSK), and mitogen and stress activated protein kinase (MSK) (Chen et al. 2005, Ahn, Ginty, and Linden 1999, Kawasaki et al. 2004, Mayr and Montminy 2001, Shaywitz and Greenberg 1999). Upon phosphorylation, CREB forms an active homodimer, interacts with KIX domain of CBP/p300 and binds to the CRE in the promoters of target genes, resulting in transcription (Lundblad et al. 1995). In parallel, cAMP and calcium signals, but not other signals, stimulate the interaction of CREB with the family of CREB regulated transcriptional coactivators (CRTCs) to bind with CRE sites (Sonntag et al. 2019). Co-activators CBP/p300 and CRTCs are critical for CREB-mediated transcriptional induction in response to second messages (Sonntag et al. 2019). CRTC2 overexpression increases its recruitment to CREB target promoters and rescues the expression of certain genes in the absence of CBP/p300; CRTC2 knockdown reduces the CBP/p300-independent expression of CREB target genes. The impact on the level of CREB activation depends on the stimuli, signaling pathway and cell. CREB coactivator CRTCs are also distinctly regulated by protein phosphatases (Sonntag et al. 2019). CREB phosphorylation induced by cAMP is dynamic and reaches peak quickly; thereafter, the transcription rate decreases progressively following dephosphorylating of CREB (Hagiwara et al. 1993). In oligodendroglia cells, we found that stimulation with IGF-I resulted in a rapid induction of CREB phosphorylation, which peaked at 10 min after stimulation, and lasted more than 2 hours (Yan et al. 2013).

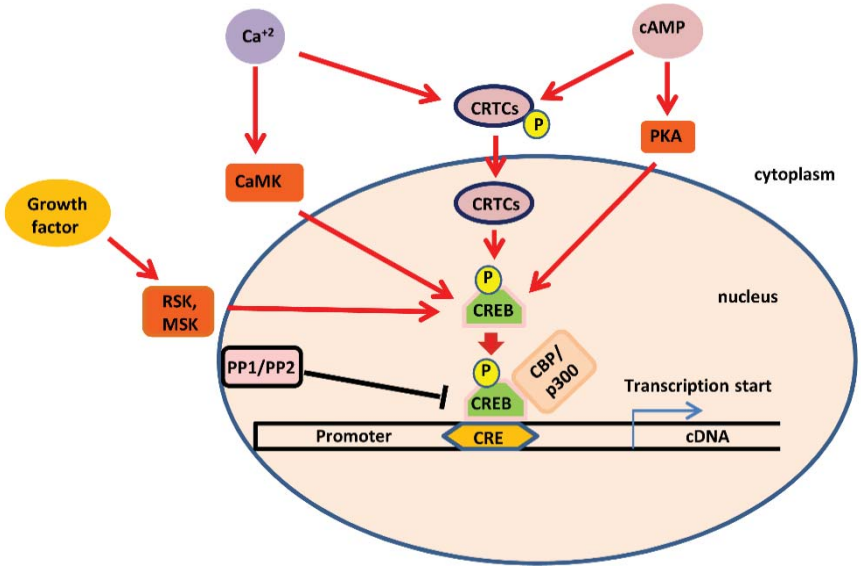

Figure 2. The schematic description of the CAMP/CREB signaling pathway. The cAMP and Ca^{+2} activate protein kinases (PKA, CaMK, etc) to induce CREB phosphorylation. The phosphorylated CREB binds to CRE on the promoter of target gene, CREB recruits co-activator proteins (CBP/p300) and initiates target gene transcription. cAMP and calcium signals may promote CRTCs dephosphorylation. Dephosporylated CRTCs enter the nucleus, bind to CREB and promote transcription. Phosphatases, PP1 and PP2, dephosphorylate CREB and inhibit the transcription.

The transcription activity depends on the level of phosphorylated CREB in the nucleus. Attenuation of CREB activity is determined by the opposing action of dephosphorylating CREB. The dephosphorization is mediated by Ser/Thr protein phosphatases (PP), including PP-1 and PP2. PP2 has been classified into A, B, C based on metal-ion requirement (PP2A, no metal-ion; PP2B, Ca^{2+}dependent; PP2C, Mg^{2+} dependent) (Moorhead, Trinkle-Mulcahy, and Ulke-Lemee 2007). PP-1 and PP2A are major CREB phosphatases. PP1 specifically dephosphorylates CREB at Ser-133 and was reported to be a major down-regulator of CREB transcription following cAMP stimulation (Hagiwara et al. 1992). PP2B plays an important role in numerous calcium-dependent biological processes. In rat live cell, it was reported that PP2A is most effective to dephosphorylate PKA-phosphorylated CREB and inhibited PKA-

stimulated transcription activity (Wadzinski et al. 1993). CREB induced-gene transcription depends on the balance kinase responsible for phosphorylating CREB and phosphatase capable of dephosphorylating CREB (Hagiwara et al. 1992).

CREB is a ubiquitous transcription factor. CREB can be activated, affects multiple signaling pathways and has various biological functions. CREB has been shown to perform a pivotal role in cell survival and cell proliferation in many organs and systems. Recent studies have revealed specific functions of CREB in immune responses and inflammation, including inhibiting NF-κB activation, inducing cytokine production and promoting monocytes and macrophage survival (Park et al. 2005, Wen, Sakamoto, and Miller 2010). CREB is found to be involved in learning, both short-term and long-term memory and Alzheimer's disease (Yang and Calakos 2013, Chen et al. 2010). CREB has been found to be involved in cancer, diabetes and cardiovascular diseases.

INFLAMMATION AND IMMUNITY

CREB has a dual role in inflammation and immune response. CREB may play protective role by inhibiting immune response, inflammation and autoimmune response. Conversely, CREB can be pathogenic due to its anti-inflammatory response (Wen, Sakamoto, and Miller 2010).

The NF-κB signaling pathway is a central regulator in inflammatory responses. CREB has been shown to inhibit NF-κB activity through competition for co-activators CBP/p300 in mice lungs after hemorrhage or endotoxemia (Shenkar et al. 2001). CREB binding to CBP may lead to displacement of NF-κB from the same interaction domain on CBP and induce expression of anti-inflammatory cytokines (such as IL10 and IL6), IL10 represses the expression of proinflammatory cytokines and prevents tissue damage caused by infections and inflammation (Parry and Mackman 1997, Zhong et al. 2002, Ouyang et al. 2011). CREB contributes to cAMP-induced expression of IL-10 and IL-6 (Larabee, Hauck, and Ballard 2018). CREB plays an anti-inflammatory role by blocking NF-κB binding to

CBP. Several different factors may inhibit NF-κB activity by inducing CREB signaling. PKA mediated CREB signaling negatively regulates NF-κB p65-mediated gene transcription in cultured human monocytes (Ollivier et al. 1996). On the other hand, enhancing NF-κB binding to the promoter of IL-6 appears to dissolve the binding of CREB-CBP (Zhang et al. 2019).

CREB is required for B and T cell activation in response to stimulation. CREB mediates the transcription of immune-related genes that have CRE sites on their promoters, including interleukin, tumor necrosis factor alpha (TNF-α), cyclooxygenase-2, and macrophage migration-inhibitory factor. CREB regulates the transcription of TCRα, TCR Vβ, CD3δ, CD8α, IL-2, CD25/IL-2Rα, and IL-2Rγ in T cells (Wen, Sakamoto, and Miller 2010). CREB also governs the cytokines produced by Th1 (IL-2 and IFN-γ) and Th2 cells (IL-4 and IL-13) through the regulation of IFN-γ production (Yano et al. 2003). T helper (Th) 17 cells play a key role in immune responses and inflammatory and autoimmune diseases. One recent study suggested that CREB is a critical regulator of autoimmune diseases by promoting Th17 differentiation and inhibiting regulatory T cell differentiation (Wang et al. 2017). IL17 is involved in many autoimmune diseases (Adami et al. 2014, Hashimoto 2017). The CREB/CRTC2 pathway promotes Th17 differentiation and regulates expression of IL-17 (Hernandez et al. 2015).

CREB signaling promotes dendritic cell activation and maturation (Armbruster et al. 2016, Al-Huseini et al. 2014). CREB expression in dendritic cells is important for antigen-specific B cell differentiation in the germinal centers. CREB deficiency also affects innate dendritic cell function and reduces adaptive immune responses (Ohl, Schippers, and Tenbrock 2018). The deletion of CREB in mice impaired dendritic cell immune function, and specifically reduced spontaneous B cell activation and germinal center response (Ohl, Schippers, and Tenbrock 2018). In macrophages, CREB is a p38 MAPK-regulated transcription factor. CREB can be activated by lipopolysaccharides (LPS) and plays a role in the LPS/toll-like receptor 4 (TLR4) pathway that mediates an anti-apoptotic response. CREB is required for macrophages survival and host immune

responses (Park et al. 2005). In microglia of the brain, the CREB pathway has anti-neuroinflammatory effects (Zhao et al. 2017).

CENTRAL NERVOUS SYSTEM

CREB has emerged as a central transcription factor in neuronal function, neuronal survival, and brain development. Abundant evidence to date indicates that CREB is involved in learning and memory formation (Kim et al. 2014), Alzheimer's disease(Bartolotti, Bennett, and Lazarov 2016), recovery after stroke (Caracciolo et al. 2018), schizophrenia (Wang et al. 2018), depression and drug addiction (Krasnova, Justinova, and Cadet 2016, Rexach et al. 2012). CREB can be directly or indirectly activated by different protein kinases in neurons. PKA and CaMKIV can directly phosphorylate CREB, but ERK and p38 MAPK indirectly phosphorylate CREB. The neurotrophins nerve growth factor (NGF) is involved in differentiation, survival, and proliferation of neurons (Lewin and Barde 1996). NGF was found to indirectly activate CREB via two distinct MAPK pathways; NGF can activate ERK and MAPK, which in turn activate the pp90 ribosomal S6 kinase (RSK) family of Ser/Thr kinases, resulting in CREB Ser-133 phosphorylation. NGF can also phosphorylate CREB at Ser-133 by activating p38 MAPK and its downstream effector MAPK-activated protein kinase 2 (Xing et al. 1998).

Brain Development

In the developing brain, CREB knockout in neurons elicits apoptosis. Postnatal ablation of CREB results in progressive neuronal degeneration in the brain in mice (Mayr and Montminy 2001, Lonze et al. 2002). High levels of endogenous cAMP in neurons promoted neurite outgrowth and regeneration during development of the central nervous system (Cai et al. 2001, Batty, Fenrich, and Fouad 2017), and elevating endogenous levels of cAMP that effectively block the inhibition of axonal regeneration by

myelin (Cai et al. 1999). cAMP directly activated PKA to phosphorylate CREB, resulting in axon growth and regeneration in neurons (Murray and Shewan 2008, Bos 2006). We previously reported that insulin growth like factor I (IGF-I) supports neuronal cells growth by inducing CREB-dependent gene expression (Yan et al. 2013). Retinoic acid (RA) is abundant in the mammalian nervous system, and it induces neurite outgrowth and neuronal differentiation from various sources, including embryonic stem cells (Maden 2001). RA has been demonstrated to induce ERK1/2 activation in neuronal cells, which is required both for CREB phosphorylation and for transcription activity in pheochromocytoma PC12 cells and primary neuronal cells via a PKA-independent pathway (Canon et al. 2004).

Learning and Memory

Synaptic plasticity is a key step in memory storage and is widely considered a primary mechanism for learning and memory (Kandel 2012, Bourtchuladze et al. 1994). The CREB signaling plays a crucial role in this process (Sakamoto, Karelina, and Obrietan 2011, Pulimood et al. 2017). In neurons, elevated CREB is associated with memory traces and behavioral recall (Kim et al. 2014). Mice with a targeted disruption of CREB exhibit impairments in long-term memory and in memory-based behavior tests, such as fear conditioning and water maze (Bourtchuladze et al. 1994). Overexpression of CREB in the rodent hippocampus has been shown to ameliorate long-time memory and improved performance in a water maze test (Yu et al. 2017). Increasing the level of CREB with a viral vector in a small pool of motor neurons has been shown to enhance motor recovery after stroke, while blocking CREB signaling prevented stroke recovery, indicating that CREB plays a role in functional recovery after stroke (Caracciolo et al. 2018). CaMKIV can phosphorylate CREB in neurons and is involved in long-term synaptic plasticity (Yang and Calakos 2013). CaMKIV-CREB signaling plays an important role in the hippocampus-

dependent long-term memory and in the late phase of cerebellar long-term depression (Kang et al. 2001, Ahn, Ginty, and Linden 1999).

CREB is also a major target of ERK1/2 signaling in neuronal cells. Increasing evidence indicates that ERK is involved in neural plasticity and pain hypersensitivity, ERK-CREB signaling contributes to the acute phase of central sensitization, leading to long-lasting changes in sensory processing (Kawasaki et al. 2004).

Alzheimer's Disease

The role of CREB signaling in neural synaptic plasticity and memory suggests a link between dysfunctional CREB and Alzheimer's disease (AD). Cognitive function and memory, episodic memory, and semantic memory in particular, are disrupted in AD. Age is one of the primary risk factors for AD. CREB level decreases with age in the hippocampus of human and rat (Yamamoto-Sasaki et al. 1999, Asanuma et al. 1996). The chronic downregulation of CREB-mediated transcription is implicated in the exacerbation of AD. The prefrontal cortex and hippocampus have been thought to be the most important brain regions for episodic and semantic memory. The levels of total and phosphorylated CREB in the prefrontal cortex and hippocampus from postmortem AD have been shown to be diminished (Bartolotti, Bennett, and Lazarov 2016, Pugazhenthi et al. 2011, Yamamoto-Sasaki et al. 1999). Protein kinases related to phosphorylate of CREB, including PKA and CaMKII have also been found to show decreased activity in the AD brain (Kim et al. 2001, Reese et al. 2011). Single-nucleotide polymorphisms (SNPs) in CREB have been found to contribute to individual difference in the level of memory and executive function performance and are associated with impaired memory and executive function in human (Wolf et al. 2017). CREB genetic variants are associated with episodic memory performance and accelerated cognitive decline in elderly people (Barral et al. 2014). The aging-related decrease in long-term memory could be prevented by hippocampal CREB gene transfer in rats (Mouravlev et al. 2006). Overexpression of CREB

protected rat hippocampal neurons from amyloid-beta induced apoptosis and rescued the memory deficits in a mouse model of AD (Yiu, Rashid, and Josselyn 2011). These studies indicate that the CREB dysfunction plays an important role in AD progression. Increasing the expression of CREB is being considered as a possible therapeutic target for AD (Pugazhenthi et al. 2011, Yiu, Rashid, and Josselyn 2011).

Nitric oxide (NO) signaling is involved in synaptic plasticity and long-term potentiation (LTP), essential for learning and memory (Schuman and Madison 1991, Mutlu, Ulak, and Belzung 2011). NO signaling leads to CREB activity by stimulating the production of second messenger cyclic guanosine monophosphate (cGMP; collectively called NO/cGMP/CREB signaling). NO/cGMP/CREB signaling ameliorates altered neuroplasticity and memory deficits in AD animal models. Aberrant NO signaling in AD suggests an association altered NO signaling and AD (de la Monte and Bloch 1997, de la Monte et al. 2000). Given the evidence of decreased phosphorylated CREB in the brain with AD (Bartolotti, Bennett, and Lazarov 2016, Yamamoto-Sasaki et al. 1999, Pugazhenthi et al. 2011), several pharmacological agents enhancing NO/cGMP/CREB signaling have been considered as therapy for AD, including NO donors and phosphodiesterase (PDE) inhibitors. Furoxan is a NO mimetic drug that has been used as a NO donor and has exhibited neuroprotection and LTP restoration in rat neuronal cells (Schiefer et al. 2012). PDE degrades the cAMP and cGMP levels by hydrolyzing their phosphodiester bond (Francis, Blount, and Corbin 2011). Changes in PDE expression may alter the activation of CREB; therefore, the important role of PDE in NO/cGMP/CREB has led to growing interest in exploring PDE inhibitors as preventive therapies for AD (Omori and Kotera 2007). The PDE family includes 11 splice variants; most of them have been found in the human brain. PDE5 inhibitors have been used to activate the NO/cGMP/CREB pathway for the treatment of AD in preclinical studies (Zuccarello et al. 2020), since the PDE5 protein is highly expressed in the human neurons, specifically in the cortex and hippocampus (Teich et al. 2016). In animal models, PDE5 inhibitors increased cGMP levels in the hippocampal neurons, restored cognitive function and improved learning and memory

(Cuadrado-Tejedor et al. 2011, Palmeri et al. 2013, Rutten et al. 2005). These results show that the PDE5 inhibitor may improve cognitive function and counter AD progression by enhancing the NO/cGMP/CREB pathway (Rutten et al. 2005, Jin et al. 2014).

Depression

There is evidence to suggest that under-function of CREB is associated with major depressive disorder (Belmaker and Agam 2008). Postmortem studies have shown that the level of CREB is reduced in the cortexes of individuals who had a major depressive disorder and had not taken antidepressants, whereas those who had taken an antidepressant showed an increased level of CREB (Dowlatshahi et al. 1998). In a rat model of depression, the CREB level was upregulated by chronic antidepressant treatment. Increasing the CREB level by viral vector in the dentate gyrus of the rat hippocampus resulted in antidepressant-like behaviors, but overexpression of CREB did not produce these effects in either the CA1 pyramidal cell layer of hippocampus or the prefrontal cortex (Chen, Shirayama, et al. 2001). Instead, CREB overexpression produces the opposite effects in the basolateral amygdala or in the nucleus accumbens (Wallace et al. 2004, Pliakas et al. 2001). These data indicate that the activity of CREB in the hippocampus is involved in the pathogenesis of depression. In addition, CREB-mediated synaptogenesis and neurogenesis are crucial for the role of 5-HT1, a receptor implicated in modulating anxiety-related behaviors (Zhang et al. 2016).

Drug Addiction

Accumulated evidence suggests that the CREB signaling pathway is involved in the acquisition of addictive behaviors. CREB signaling plays an important role in drug-induced neural synaptic plasticity and drug addiction development (Krasnova, Justinova, and Cadet 2016, Krasnova et

al. 2013). A recent study has shown that the CREB pathway is activated in animals undergoing a self-administration paradigm and that it facilitates the formation of morphine addiction in the rat nucleus accumbens (Ma et al. 2018).

The research reveals that c-fos, FosB and brain-derived neurotrophic factor (BDNF) are involved in forming substrates for methamphetamine addiction and are associated with drug relapse after withdrawal from methamphetamine administration (Krasnova et al. 2013, Li et al. 2015, Ru et al. 2019). CREB plays an important role in the regulation the expression of c-fos, FosB and BDNF caused by drug administration. One study has demonstrated that drug cessation increases the phosphorylated CREB in an animal model of methamphetamine self-adminstration, pCREB bound to the promoters of c-fos, fosb and BDNF increased their transcription, followed by a decrease after 1 month of abstinence (Krasnova et al. 2013). Changes in levels of BDNF have been found in multiple brain regions after administration of several models of addictive drugs (Russo et al. 2009). The BDNF signaling pathway regulates structural and behavioral plasticity in drug addiction (Russo et al. 2009).

Drugs abuse induced changes in serum concentration of BDNF have been reported in human addiction to several drugs, including cocaine, amphetamine, ecstasy and heroin (Angelucci et al. 2007, Kim et al. 2005, Rovis et al. 2018, Angelucci et al. 2010). Male mice with a conditional knockout of BDNF exhibit locomotor activity behaviors (Monteggia et al. 2007). BDNF overexpression increases relapse to cocaine–seeking in an animal model of depression (Zilkha et al. 2019). One recent study found that CREB directly binds to the CRE site on the promoter of BDNF and induces BDNF expression. CREB is a major mediators of BDNF transcriptional autoregulation in rat and human cortical neurons (Esvald et al. 2020). Aberrant change of the BDNF-CREB pathway is associated with anxiety and depression-like behavior following abstinence (Ru et al. 2019).

In addition, several studies have revealed that hypocretin receptors (HCRTR) are also involved in behavioral aspects of addiction and in relapse to drug seeking after periods of abstinence (Harris, Wimmer, and Aston-Jones 2005, Aston-Jones et al. 2009). HCRTR are peptides that are

produced from a prepro-orexin molecule made solely in hypothalamic neurons. HCRTR2 induces CREB phosphorylation via a PKC-dependent pathway (Guo and Feng 2012).

CANCER

Role of CREB in Tumorigenesis

CREB functions in a variety of cell types and contributes to the progression of tumorigenesis.Current evidence indicates that cAMP/CREB signaling is a key regulator of tumorigenesis, tumor progression, chemotherapy resistance, and survival in patient with cancer (Steven and Seliger 2016).

Abnormal cell-cycle is a pervasive finding in human cancers. The formation of new cells and programmed cell death are regulated by cyclin-dependent kinase (CDK). Cyclin D1 is a regulatory subunit for CDK; its overexpression presents in many human cancers and is correlated with cancer progression and metastasis (Thomas, Nadiminti, and Regalado 2005, Ikeguchi et al. 2001, Gansauge et al. 1997). Cyclin D1 is thought to be an oncogene and is recognized as a therapeutic target in human cancers (Lapenna and Giordano 2009). The inhibition of cyclin D1 expression leads to cell cycle arrest, whereas overexpression of cyclin D1 promotes cell cycle progression from the G1 to S phase (Jiang et al. 1993, Quelle et al. 1993). Overexpression of cyclin D1 is sufficient for the induction of mammary tumorigenesis (Casimiro et al. 2012, Wang et al. 1994). The expression of cyclin D1 is highly CREB-dependent (Yan et al. 2013). CREB knockdown significantly inhibits the expression of Cyclin D1 (Daniel et al. 2014). Our own previous study found that CREB participates in IGF-I-stimulated cyclin D 1 transcription through the ERK/MAP kinase pathway (Yan et al. 2013).

Pharmacology and Clinical Trials

CREB is overexpressed and constitutively phosphorylated in a number of human cancers, which indicates that CREB may act as a proto-oncogene in the pathogenesis and development of tumors. CREB is thought to be a potential target for cancer therapy (Sakamoto and Frank 2009).

Selective CREB inhibitors have been evaluated in several clinical trials. One trial has evaluated the role of BAY 43-9006, one of a new class of anticancer agents known as bi-aryl ureas (clinicaltrials.gov/NCT00098254). This clinical trial has investigated the efficacy of BAY43-9006 in persons with advanced, recurrent, or refractory non-small-cell lung carcinoma. CREB is involved in the BAY 43-9006-induced the inhibition of cancer cell proliferation, migration and invasion (Huang et al. 2018). Another clinical trial assessed the safety and efficacy of PRI-724 in persons with advanced or metastatic pancreatic cancer (NCT01764477). PRI-724 is a small molecule antagonist. PRI-724 may stop cancer cells from growing by affecting an interaction between CREB and β-catenin (Osawa et al. 2019).

Acute Myeloid Leukemia

CREB appears to be a critical regulator of the growth and survival of acute myeloid leukemia (AML) cells. CREB overexpressed in leukemic cells is associated with worse prognosis in persons with AML (Shankar et al. 2005). Studies of bone marrow show that the level of phosphorylated CREB was increased in patients with AML. CREB activation in AML cells augments the growth rate of AML cells and confers resistance to apoptosis in vitro (Pigazzi et al. 2007). Transgenic mice with CREB overexpression in the myeloid lineage were found to develop myeloproliferative disease (Shankar et al. 2005, Pigazzi et al. 2007).

A number of studies have indicated that granulocyte macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) can stimulate the proliferation and differentiation of

myeloid cells and enhance granulocyte function via the CREB pathway. Autocrine production of G-CSF and interleukin-3 (IL-3) may trigger binding to their cognate receptors and activate signaling pathways to promote leukemia cell growth and survival (Jiang et al. 1999). GM-CSF and IL-3 stimulation result in CREB phosphorylation and activation (Kwon et al. 2000, Chen, Yu, et al. 2001). Activated CREB promotes pleiotropic effects, including cell proliferation, differentiation, and survival of hematopoietic cells. CREB has been identified as a proto-oncogene involved in transformation by promoting abnormal proliferation and survival of myeloid cells (Shankar et al. 2005). CREB has been shown to directly regulate replication factor C3 to promote neoplastic myelopoiesis (Chae et al. 2015). CREB-overexpression also leads to persistent expression of Meis1 and thus blocks differentiation of primitive hematopoietic progenitor cells, contributing to transformation and the development of acute leukemia (Esparza et al. 2008).

CREB knockdown has been found to inhibit AML cell proliferation and delayed leukemia cell progression (Cheng et al. 2008). CREB antisense oligonucleotides induce non-apoptotic cell death in proliferating leukemia cells, but no toxicity to normal hematopoietic cells. Blocking the interaction between CREB and CBP using small molecules induces cell-cycle arrest and apoptosis in AML cells (Mitton et al. 2016). These studies strongly support the CREB as a potential therapeutic target in AML therapy (Saeki et al. 2001, Mitton et al. 2016).

Lung Cancer

CREB and phosphorylated CREB (p-CREB) are over-expressed in individuals with non-small-cell lung cancer (NSCLC). The overexpression is associated with a negative prognosis in never-smokers with NSCLC. CREB and p-CREB are expressed at significantly higher levels in most of the NSCLC cell lines and tumor specimens than in the normal human tracheobronchial epithelial (NHTBE) cells and adjacent normal lung tissue, respectively (Seo et al. 2008). P21-activated kinase 4 (PAK4), a member of

the PAK family, promotes lung cancer progression through the CREB pathway (Cai et al. 2015). Serine/Threonine kinase II (STK-II) (also known as liver kinase B1, LKB1) is a tumor suppressor. STKII is often inactivation in individuals with NSCLC (Davies et al. 2005, Ding et al. 2008). Genetic analysis found that loss of heterozygosity and homozygous deletion of the STK-II gene jointly occurs in nearly 90% of persons with NSCLC (Gill et al. 2011). Loss of STK-II function has been shown to increases the expression of CREB target genes (Komiya et al. 2010, Shaw et al. 2005). CREB coactivator CRTC2 is dephosphorylated and constitutively activated to stimulate expression of oncogene inhibitor of DNA binding I in STK-II mutant NSCLC. CTRC2 is a critical factor to promote oncogenesis in STK-II-deficient-lung cancers, suggesting that the CREB/CRTC pathway plays an important role in lung cancer development in loss of STK-II activity (Rodon et al. 2019). Administrating recombinant insulin-like growth factor II (IGF-II) to the cultured human lung cancer cell lines has been shown to induce CREB phosphorylation, and activated CREB has been shown to enhance the lung cancer cell survival and tumorigenicity of normal bronchial epithelial cells (Linnerth et al. 2005, Moorehead et al. 2003). In addition, transfected dominant-negative CREB vectors have been reported to significantly inhibit the growth of lung cancer cells (Linnerth et al. 2005).

Prostate Cancer

Elevation of cAMP promotes neuroendocrine differentiation and growth of prostate cancer cells through CREB activation (Deeble et al. 2001, Chen et al. 1999). Huang et al. has identified CREB as a critical effector in prostate cancer bone metastasis (Huang et al. 2006). P21-activated kinase 4 (PAK4), a member of the PAK family, promotes prostate cancer progression (Cai et al. 2015) and is thought to be as a novel regulator of CREB in prostate cancer (Park et al. 2013). PAK4 has been found to promote prostate cancer progression by regulating the transcriptional activity of CREB (Park et al. 2013). G protein-coupled

receptor kinase 3 (GRK3) is up-regulated in prostate cancer and is essential for prostate tumor progression and metastasis (Li et al. 2014). One recent study reveals that GRK3 is a direct transcriptional target of CREB. GRK3 regulates neuroendocrine differentiation of prostate cancer cells and promotes prostate cancer progression through CREB activation (Sang et al. 2016). In addition, over expression of vascular endothelial growth factor (VEGF) is associated with human prostate cancer metastasis and poor prognosis. The activation of CREB signaling is involved in prostate cancer bone metastasis by inducing VEGF expression in prostate cancer cells (Wu et al. 2007). These results reveal the role of CREB in prostate cancer cells and may help to establish CREB as a therapeutics target in the treatment of prostate for prostate cancer.

Breast Cancer

CREB is involved in brain metastasis by the breast cancer cell via directly regulating glucose transporter 3 expression to promote breast cancer cell survival in the brain microenvironment (Kuo et al. 2019). Microenvironmental IL1β has long been proposed as an important cytokine in cancer metastasis (Tulotta et al. 2019, Bani et al. 1991). In mouse models, IL1β has been shown to promote breast cancer growth and metastasis, and inhibition of IL1 prevents bone metastasis (Coffelt et al. 2015, Holen et al. 2016, Tulotta et al. 2019). A most recent study has found that IL1 promotes the metastases in the bone by activating the intracellular NF-κB/CREB-Wnt signaling pathway in breast cancer cells, and that the drugs targeting the IL1β-NFκB/CREB-Wnt pathway prevent both bone metastases in vivo and colony formation of breast cancer cells in vitro (Eyre et al. 2019). Inhibiting IL1β-NFκB/CREB-Wnt signaling could be considered as an adjuvant therapeutic strategy in breast cancer to prevent bone metastasis (Eyre et al. 2019).

Triple negative breast cancers (TNBCs) are an aggressive breast cancer subtype with high rates of drug resistance and poor survival rates. CBP/β-catenin/FOXM1 signaling is thought to be an important driver of drug

resistance in TNBCs (Ring et al. 2018). A recent study reported that small molecule naphthol AS-E (nAS-E), a specific inhibitor targeting the interaction between CREB and CBP, inhibits human breast cancer cell proliferation, migration survival and metastasis (Jiang et al. 2019). These studies have proposed that inhibiting CREB signaling could be considered as an adjuvant therapeutic strategy in breast cancer (Eyre et al. 2019, Jiang et al. 2019, Kuo et al. 2019, Ring et al. 2018).

Brain Tumor

CREB is highly expressed and constitutively activated in human glioblastoma cell lines and human brain tumors. CREB modulates the expression of three key cycle factors, cyclin B, cyclin D and proliferating cell nuclear antigen (PCNA), to support glioblastoma cell proliferation (Daniel et al. 2014). Normal brain tissue and tissue adjacent to tumors from patients with glioblastoma show little to no CREB activation. By contrast, tumor tissue exhibits grade-dependent levels of p-CREB expression (Daniel et al. 2014). In addition, one study has revealed that a specific small molecule, CG500354, alters the phenotypes of human primary glioblastoma cells from an oncogenic state into a less oncogenic and more differential state through upgrading cAMP/CREB signaling (Kang et al. 2014). These results indicate that the homeostasis of CREB in the brain is important for brain tumor development.

Other Tumors

The activation of CREB has been seen in a number of other tumors (Siu and Jin 2007), including gastrointestinal tumors (Sampurno et al. 2013), cervical cancer (Lv et al. 2019), colon cancer (Nishihara et al. 2004), thyroid tumors(Ayroldi et al. 2018), melanoma(Xie et al. 1997, Shoshan et al. 2015), pancreatic cancer (Zhang et al. 2013), and hepatocellular carcinoma(Cougot et al. 2007). Current evidence has shown

that constitutive activation of CREB signaling may be one contributory factor in oncogenesis, while dominant-negative CREB inhibits tumor growth and metastasis (Xie et al. 1997, Linnerth et al. 2005). Taken together, these studies suggest that the CREB signaling pathway might service as a potential therapeutic target to prevent cancer progression and metastasis (Eyre et al. 2019, Wu et al. 2007, Jiang et al. 2019).

DIABETES

Blood Glucose Levels

CREB function is required in glucose homeostasis and pancreatic β-cell survival (Jhala et al. 2003). Hepatic gluconeogenesis plays an important role in maintaining normal blood glucose levels. Glucagon promotes hepatic glucose production by the CREB-CBP-TORC2 signaling pathway. CREB-CBP-TORC2 signaling induces transcription of gluconeogenic genes, including peroxisome proliferator-activated receptor coactivator (PGC-1) (Lee et al. 2018), phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) (Herzig et al. 2001). PGC-1 is a key regulator of hepatic gluconeogenesis and is involved in obesity and diabetes (Liang and Ward 2006, Yoon et al. 2001). Overexpression of PGC-1 rescued expression of gluconeogenic genes and restored glucose homeostasis in CREB-knockout mice. The activation of PGC-1 by CREB in liver may contribute to the pathogenesis of type 2 diabetes (Herzig et al. 2001).

Consistent with an important role for CREB in mediating gluconeogenesis, overexpression of hepatic CRTC2 in mice leads to fasting hyperglycemia (Koo et al. 2005), whereas the knockdown of CRTC2 reduces hepatic gluconeogenesis and blood glucose level (Saberi et al. 2009). During fasting, glucagon induces CREB phosphorylation by activating cAMP-PKA signaling or by inducing activation of CRTC2. CREB/CRTC2 activity is increased during hyperglycemia and is a key regulator in fasting glucose metabolism (Koo et al. 2005). Metformin and

insulin suppress hepatic gluconeogenesis by phosphorylating CBP at Ser436 via PKC1/λ to disrupt cAMP-CREB-CBP-CRTC2 signaling (Zhou et al. 2004, He et al. 2009).

Pancreatic Beta Cell

In type 1 diabetes, pancreatic β-cell function progressively declines; this decline is partly mediated via β -cell death (Rojas et al. 2018). β-cell death occurs mainly through apoptosis in type 1 diabetes. The apoptosis of β-cell is induced by cytokines, including IL-1β, TNF-α and IFN-γ. Studies have shown that adenoviral transfer of a dominant-negative form of CREB results in the exaggeration of cytokine-induced the apoptosis of β-cell, while overexpression of CREB in cultured pancreatic β-cells protects the β-cells from cytokine-induced apoptosis. These results indicated that CREB function is required for β-cell survival (Jambal et al. 2003). Transgenic mice expressing dominant-negative CREB in β-cells developed to hyperglycemia with decreased islet mass owing to a decreased β-cell proliferation and increased β-cell apoptosis (Jhala et al. 2003). Insulin receptor substrate 2 (IRS2) is a critical factor for β-cell survival. IRS2 mediates phosphorylation of Akt at Thr 308 in response to insulin and IGF1 signaling (Tuttle et al. 2001, Withers et al. 1999, Withers et al. 1998). CREB promotes β-cell survival by stimulating the expression of IRS2, disrupting CREB activity induced apoptosis in β-cell and caused diabetes in animal model (Jhala et al. 2003).

Treatment

Metformin lowers blood glucose levels via multiple mechanisms (Rena, Hardie, and Pearson 2017). One study revealed that liver STK-II is required to lower blood glucose levels in metformin treatment; metformin treatment could not reduce blood glucose levels in the mice in which STK-II had been deleted in the liver (Shaw et al. 2005). The CREB coactivator,

CRTC2 is a critical downstream target of STK-II-dependent kinase in the control of gluconeogenesis (Shaw et al. 2005). Glucagon activates cAMP-PKA signaling to phosphorylate CREB. Activated CREB recruits CBP and CRTC2 to form a complex on CRE sites of target gene promoters. Serine 436 of CBP is adjacent to the CREB-binding domain. Mutant CBP (S436A) is aberrantly recruited to form a complex with CREB, resulting in increased hepatic glucose production (Zhou et al. 2004). Metformin and insulin phosphorylate the CBP at Ser 436 via PKC1/γ, leading to disassembly of the CREB-CBP-TORC2 transcription complex and reduction of hepatic gluconeogenesis (He et al. 2009, Zhou et al. 2004). High glucose reduces p-CREB in human endothelial cells(Han et al. 2018). Metformin significantly improves human endothelial cell proliferation and inhibits apoptosis under high glucose conditions through the CREB/BDNF pathway (Han et al. 2018).

CARDIOVASCULAR SYSTEM

CREB has emerged as an important transcription factor in the cardiovascular system due to its ability to regulate the expression of the genes that contribute to maintaining normal cardiac and vascular function. CREB can be activated by elevated cAMP in response to various stimuli and promotes the development of cardiovascular disease (CVD). Aberrant cAMP signaling has been reported to be involved in the pathogenesis of vascular diseases, including cardiac hypertrophy (Metrich et al. 2008), atherogenesis (Schauer et al. 2010), chronic stable angina (Punchard et al. 2007) and pulmonary hypertension (Murray et al. 2007).

In mice, overexpression of dominant-negative CREB in the heart leads to dysfunction and increased mortality (Watson et al. 2010). In rodent models of insulin-resistant and diabetic animals, the levels of CREB and p-CREB were decreased in the vascular stroma. In persons with diabetes, decreased vascular CREB content associated with increased the risk of atherosclerosis (Watson et al. 2001).

Exaggerated growth and proliferation of vascular smooth muscle cell (VSMC) may be major contributors to the development of CVD, such as hypertension, atherosclerosis and restenosis (Dickinson et al. 2014, Jackson and Schwartz 1992). Accumulated evidence has suggested that CREB pathway plays an important role in the regulation of VSMC phenotype and proliferation (Yu et al. 2019, Hudson et al. 2018). In a rat model of pulmonary hypertension, the CREB protein level in aortic VSMC was significantly diminished (Schauer et al. 2010). The loss of the CREB protein renders VSMC more susceptible to vascular injury and potentially contributes to plaque progression (Schauer et al. 2010).

Early growth response protein-1 (Egr-1) is an important regulator of multiple genes implicated in the pathophysiology of cardiovascular diseases (McCaffrey et al. 2000, Khachigian 2016). Egr-1 has been reported to be elevated in human atherosclerotic carotid arteries. In an animal model of atherosclerosis, Egr-1 expression progressively increased in the aorta (McCaffrey et al. 2000). Egr-1 is a direct target of CREB. CREB has been shown to bind to the promoter of Egr-1 and regulate the expression of Egr-1 in VSMC (Cui et al. 2006). CREB knockdown by siRNA reduces the expression of Egr-1in VSMC (Simo-Cheyou et al. 2017). These data suggest that CREB regulates Egr-1 expression in VSMC.

Increased generation of reactive oxygen species (ROS) and vasoactive peptide have been implicated in the pathogenesis of vascular diseases. Angiotensin II (Ang-II) is a vasoactive peptide and has been demonstrated to contribute to vascular damage by promoting inflammation, oxidative stress and VSMC proliferation (Montezano et al. 2014). ROS are important signaling molecules in cardiovascular cells. ROS have been found to participate in the regulation of endothelial function, in the growth and migration of VSMC, and in the development of cardiovascular diseases by activating multiple intracellular proteins and enzymes (Brown and Griendling 2015, Griendling et al. 2000). Recent studies have shown that hydrogen peroxide (H_2O_2, a ROS) and Ang-II increase Egr-1 expression in VSMC. The CREB signaling pathway play an essential role in the Egr-1 expression induced by vasoactive peptide or ROS in VSMC, indicating

CREB is involved in the pathophysiology of cardiovascular diseases (Simo-Cheyou et al. 2017, Rondeau et al. 2019).

Many studies have demonstrated that the level of CREB is downregulated in response to cardiovascular risk factors (Schauer et al. 2010, Watson et al. 2001, Klemm et al. 2001), and that elevated CREB inhibits VSMC proliferation (Kothapalli et al. 2003). Nevertheless, some authors have reported that CREB activity increases in response to stimuli in VSMC, and that activated CREB enhances VSMC proliferation (Molnar et al. 2014, Tokunou et al. 2001). The role of CREB in VSMC proliferation is in contradiction and has been debated for a long time. It is possibly because CREB plays a dual role in regulating proliferation of VSMC with the mode of activation determining its pro-or anti-mitogenic function (Hudson et al. 2018). Activation of CREB by CRTC2/3 in response to cAMP-elevating stimuli is anti-mitogenic and inhibits VSMC proliferation, however, activation of CREB by mitogenic growth factors is pro-mitogenic and enhances VSMC proliferation, suggesting that CREB plays an important role in maintaining normal VSMC physiology and controlling VSMC proliferation (Hudson et al. 2018).

Cardiovascular disease is a major cause of mortality and morbidity among persons with diabetes. One report suggests that high glucose–induced ROS result in a decrease of CREB in the vasculature. Loss of CREB could be one of the molecular mechanisms leading to atherosclerosis in persons with diabetes (Watson et al. 2001). Metformin, a common oral antidiabetic agent, has a sustained protective role in reducing cardiovascular disease. Metformin improves vascular function and reduces cardiovascular disease mortality among persons with type 2 diabetes (Han et al. 2019, Rena and Lang 2018). One recent study reported that the CREB signaling pathway is involved in the role of metformin in attenuating human endothelial dysfunction under high glucose condition (Han et al. 2018). Overall, clarifying the role of CREB in maintaining normal cardiovascular function may suggest a new target for intervention to improve or prevent cardiovascular disease.

CONCLUSION

CREB is a key transcriptional regulator of more than 4000 genes. CREB is phosphorylated by multiple protein kinases in response to cAMP, Ca^{2+}, growth factor stimulation, and neuronal activation. CREB-mediated transcription regulates diverse cellular responses, including metabolism, immune function, neuronal signaling, cell proliferation, and apoptosis. Accordingly, CREB is found to be involved in the pathogenesis and development of various human diseases. The novel properties and effects of CREB continue to emerge. A more thorough understanding of CREB function and its effect in diseases will lead to more effective therapeutics targeting its function.

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