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Review

The Role of the CREB Signaling Pathway in Tumor Development and Therapeutic Potential

Qunlong Jin [1,2,†], Youheng Jiang [1,2,†], Zhiheng Zhang [1,3,†], Yanming Yang [1], Zhang Fu [1], Yunfeng Gao [1,4], Ningning Li [1,5], Yulong He [2,*], and Changxue Li [1,2,*]

[1] Tomas Lindahl Nobel Laureate Laboratory, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, 518107, China
[2] Digestive Diseases Center, Guangdong Provincial Key Laboratory of Digestive Cancer Research, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, 518107, China
[3] The Affiliated High School of Shenzhen University, Shenzhen, 518066, China
[4] Department of Otolaryngology, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, 518107, China
[5] China-UK Institute for Frontier Science, Shenzhen, 518107, China
† These authors contributed equally to this work.
* Correspondence: heyulong@mail.sysu.edu.cn (Y.L.H.); lichx59@mail2.sysu.edu.cn (C.X.L.)

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Abstract: The cAMP response element-binding protein (CREB) is a multifunctional transcription factor belonging to the basic leucine zipper (bZIP) family of proteins. It regulates the expression of target genes by binding to the cAMP response element (CRE) on DNA. The activation of CREB in cells typically depends on its phosphorylation, mediated by kinases activated by various signaling pathways, such as the cAMP-dependent protein kinase A (PKA) pathway and the PI3K-AKT pathway. CREB regulates genes involved in various cellular functions, including cell growth, differentiation, survival, as well as the development and plasticity of the nervous system. Therefore, CREB plays a key role in the development of neurological diseases, oncology, and other diseases. This review aims to systematically elucidate the structure and regulatory mechanisms of CREB, its biological function in tumors, and the potential of targeting the CREB signaling pathway in anti-tumor therapy, with the hope of providing new strategies and targets for cancer treatment.

Keywords: transcription factor; CREB; tumor development; signaling pathway

1. Introduction

The global incidence and mortality rates of cancer are rapidly increasing. According to the World Health Organization (WHO) estimates in 2019, cancer has become one of the top two causes of death in the under-70 population in 112 countries [1]. Drug therapy is a crucial treatment modality for cancer. Despite the explosive growth in cancer drug research from conventional cytotoxic drugs to targeted therapies over the past few decades [2], very few drugs have successfully entered clinical use [3]. Additionally, drug resistance and toxicity to normal tissues pose significant challenges to drug application. Therefore, there is an urgent need for new therapeutic targets to provide more clues for cancer drug therapy [4].

Cancer is a heterogeneous disease with multiple pathogenic mechanisms, including somatic mutations, genomic instability, and epigenetic alterations [5–7]. Transcription factors regulate chromatin transcription by recognizing specific DNA sequences, forming a complex system to guide genome expression [8], and playing a significant role in cancer initiation and progression [9]. cAMP response element-binding protein (CREB) belongs to the basic leucine zipper (bZIP) family [10]. Genome-wide screening for CREB binding sites has identified over 4000 genes potentially controlled by CREB, highlighting its importance as a transcription

factor [11]. CREB regulates a wide range of biological processes, coordinating cell differentiation and growth [12]. Moreover, studies have shown that CREB activation is a critical driver of tumorigenesis. Its overexpression is closely associated with poor prognosis, and targeting CREB therapy can effectively reduce tumor burden [13]. Therefore, CREB has the potential to serve as a biomarker and therapeutic target for cancer. This review summarizes the structural characteristics of CREB, its functions in different types of cancer, and the potential mechanisms by which various factors regulate CREB. Additionally, it outlines the utility of CREB as a therapeutic target to aid in the development of new treatment strategies.

2. The Main Structural Features of CREB

CREB is a 43kDa basic leucine zipper (bZIP) transcription factor that can recognize and bind to the full-length 5'-TGACGTCA-3' palindromic cAMP response element (CRE) sequence and the half-site 5'-TGACG-3' [10]. Its C-terminus contains a leucine zipper structure, which serves as the DNA binding site. The N-terminus serves as the transcription activation domain, which includes a kinase-inducible domain (KID) with multiple phosphorylation sites that can be phosphorylated by various protein kinases. Surrounding the KID are regions rich in glutamine residues, which may be associated with RNA polymerase binding [14–16].

3. The Regulation of CREB

The regulation of CREB involves multiple forms, with genetic mutations reported in various tumors and cell lines, including amplifications, deletions, missense mutations, truncation mutations, and fusions. However, the impact of these mutations on CREB function requires further investigation [17–20]. Therefore, this review will focus on the post-transcriptional and post-translational regulation of CREB (Figure 1).

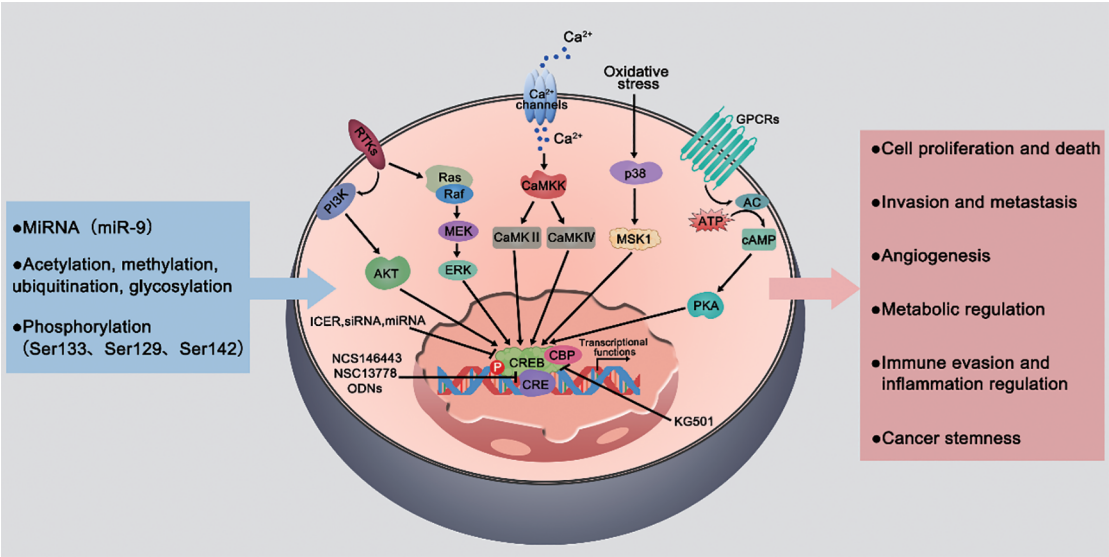

Figure 1. The intricate regulatory network of the CREB signaling pathway and its consequential impact on tumor development. The activation of CREB is facilitated through phosphorylation by various kinases, notably AKT, RSK, MSK, PKA, CAMKII, and CAMKIV. Additionally, the functionality of CREB signaling pathway is subject to modulation by miRNAs, phosphorylation, and a myriad of other post-translational modifications, encompassing acetylation, methylation, ubiquitination, glycosylation, and more. The tumorigenic effects of the CREB signaling pathway on tumor development involves various factors such as ICER, siRNA, miRNA, KG501, NSC13778, NSC146443, and ODNs, suppressing the function of CREB signaling pathway.

3.1. The Interaction between miRNA and CREB

MicroRNAs (miRNAs) are a class of non-coding RNAs that post-transcriptionally regulate gene expression by inducing mRNA translation repression or degradation, typically through imperfect base pairing with the 3'-UTR of target mRNAs [21]. In recent years, a large number of miRNAs have been found to be regulated by CREB or to target CREB. Research suggests that the regulation between miRNAs and CREB

may be bidirectional. For example, miR-9 suppresses the migration and proliferation of glioma cells by targeting CREB, while miR-9 is also transcriptionally activated by CREB, forming a negative feedback loop. The balance between CREB and miR-9 determines the "go or grow" state of glioma cells, contributing to a better understanding of the transition from proliferation to migration phenotype during glioma progression [22]. Hopefully, more miRNAs like miR-9 will be discovered in the future to help us better understand the mechanisms underlying tumor initiation and development.

3.2. Post-Translational Modifications of CREB

Post-translational modification is an important mechanism for transcription factor regulation, and phosphorylation is one of the most extensively studied and diverse types of modifications [23]. The transcriptional activity of CREB involves phosphorylation of various serine residues, but primarily at Ser133. Phosphorylation of Ser133 requires induction by various upstream kinases, such as protein kinase A (PKA), protein kinase B (PKB/AKT), protein kinase C (PKC), calcium/calmodulin-dependent kinase (CaMK), and mitogen-activated protein kinase (MAPK) [24]. Phosphorylated CREB (pCREB) can interact with various transcriptional co-activators, such as CREB-binding protein (CBP) and p300, through its kinase-inducible domain (KID) and the CREB interaction domain (KIX) in CBP/P300, thereby enhancing its transcriptional activity [25, 26]. The CREB/CBP complex promotes the expression of nuclear genes by targeting various promoter regions containing CREs [27]. In addition to Ser133, phosphorylation of other serine residues has been shown to affect CREB's transcriptional activity. However, not all phosphorylation events have a positive effect. For example, while phosphorylation of Ser129 and Ser142 promotes CREB transcriptional activity, phosphorylation of Ser111, Ser117 [28,29], and Ser121 inhibits CREB function [30,31]. In addition to phosphorylation, other post-translational modifications such as acetylation, methylation, ubiquitination, glycosylation, etc., also play important roles in tumor progression, and these modifications have been detected in CREB as well [32, 33]. For example, SIRT1 can deacetylate CREB at Lys136, reducing the phosphorylation level of Ser133 in CREB and thereby decreasing its function [34]. Conversely, downregulation of CUE domain-containing protein 2 (CUEDC2), a ubiquitination regulatory protein, can increase CREB stability by reducing CREB ubiquitination [35]. Additionally, although numerous studies have shown that the function of CREB and its transcriptional co-activators can be regulated by different forms of glycosylation such as O-GlcNAcylation and N-glycosylation, their roles in tumors still require further investigation [36].

4. The Role of CREB in Cancer

In 2000, Professor Hanahan summarized the characteristics of cancer as six biological capabilities acquired by human tumors during the multi-stage development process. These characteristics constitute the organizing principles that explain the complexity of cancer disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [37]. Twenty years later, these features have been expanded to fourteen [38]. CREB, as an important growth factor, naturally plays a significant role in the process of tumors acquiring these biological capabilities (Figure 1).

4.1. Cell Proliferation and Death

In normal tissues, growth factor signaling is tightly regulated, while cancer cells can acquire these signals through various means [39], subsequently activating downstream CREB-related pathways to promote proliferation. For instance, prostaglandin E2 (PGE2) activates the epidermal growth factor receptor (EGFR) and its downstream signaling pathways to increase cAMP production and activate CREB, promoting tumor proliferation [40]. Additionally, EGFR can promote the expression of the proto-oncogene c-Fos, facilitating the proliferation of oncogenic osteoblasts, through activation of the RSK2/CREB signaling pathway [41]. Besides facilitating the increase in proliferative signals, CREB also participates in the proliferation process due to the weakening of inhibitory signals. For example, the loss of the tumor suppressor gene PTEN can activate the AKT1-CREB pathway, enhancing the expression of platelet-derived growth factor receptor alpha (PDGFRα) and promoting tumor proliferation [42].

Programmed cell death serves as a natural barrier to cancer development [43], and CREB plays a significant role in limiting or preventing apoptosis in tumor cells. There are many factors that can trigger cell apoptosis, with P53 being an important pro-apoptotic gene. Walia M.K. et al. found that in osteoblasts lacking p53, parathyroid hormone-related protein (PTHrP) can activate the cAMP-CREB1-dependent signaling pathway, promoting tumor cell proliferation [44]. Subsequently, the team demonstrated that the restoration of p53 function can directly inhibit CREB expression, thereby resisting CREB-induced cell proliferation [45]. Additionally, the regulation of apoptosis is related to the balance of pro-apoptotic and anti-apoptotic members of the Bcl-2 protein family. High collagen XI/αI (COL11A1) can change the balance between the pro-apoptotic protein BCL-2 and the anti-apoptotic protein BAX through the Akt/CREB pathway, mediating their mitochondrial translocation in pancreatic cancer cells, thereby inhibiting cancer cell apoptosis [46].

Autophagy is an important cellular physiological response where cellular material is delivered to lysosomes for degradation, leading to the renewal of cellular components and providing energy and macromolecular precursors. Autophagy typically occurs at a low basal level in cells but can be strongly induced under certain cellular stress conditions [47]. However, the role of autophagy in the process of tumor formation may be conflicting. In acute myeloid leukemia (AML), depletion of the transient receptor potential melastatin 2 (TRPM2) ion channel can decrease the expression levels of CREB and ATF4, thereby inhibiting cellular autophagy, resulting in mitochondrial damage and cell death, whereas the restoration of CREB and ATF4 expression can restore autophagy, promoting cell survival and proliferation [48]. Conversely, purple sweet potato delfinidin-3-rutinoside (PSPD3R) induces autophagy and apoptosis in glioblastoma through the Akt/CREB/miR-20b-5p/Atg7 pathway [49]. Therefore, autophagy acts as a double-edged sword, and it is hoped that future research will elucidate the conditions and mechanisms by which CREB and autophagy play different roles in tumor progression, making autophagy a powerful weapon in cancer therapy.

4.2. Invasion and Metastasis

Scholars unanimously agree that the metastasis of malignant tumors is dynamic and continuous, involving invasion, intravasation, circulation, extravasation, and colonization throughout the entire process [50]. Many factors influence tumor invasion and metastasis, with CREB primarily regulating these processes through involvement in epithelial-mesenchymal transition (EMT) and changes in the extracellular matrix (ECM).

EMT is a process of cellular transformation that endows epithelial cells with the ability to invade, resist stress, and spread, being transiently or stably activated to varying degrees in various cancer cells [51]. In bladder cancer, CREB1 can affect EMT by indirectly regulating the c-Met/Akt/GSK-3β/Snail signaling pathway [52]. Furthermore, activated CREB can recruit HIF-1α and promote its binding to the VEGF promoter region, increasing VEGF secretion to induce EMT in prostate cancer cells, thereby promoting bone metastasis in prostate cancer [53].

The ECM is a dynamic three-dimensional macromolecular network that provides structural support for cells and tissues and is also an important tissue barrier for tumor metastasis [54]. Tumor cells can promote local invasion by providing matrix-degrading enzymes such as matrix metalloproteinases (MMPs) and cysteine cathepsins [55]. For example, intercellular adhesion molecule-3 (ICAM-3) increases the expression of MMP-2 and MMP-9 through the Akt/CREB pathway, thereby promoting the invasion and metastasis of non-small cell lung cancer cells [56]. Additionally, the relationship between CREB and MMP-2 and MMP-9 has been verified in other tumors as well [57,58]. However, whether other proteins in the MMP family are also regulated by CREB requires further high-quality research for confirmation.

Invasion and metastasis, as hallmark capabilities of malignant tumors, involve highly complex regulatory mechanisms. In addition to the pathways mentioned earlier, CREB can also promote tumor invasion and metastasis through other mechanisms such as autophagy [59] and maintaining cancer stemness [60]. As research progresses, it is believed that more related mechanisms will continue to be discovered in the future.

4.3. Angiogenesis

Angiogenesis is a complex process wherein new capillaries are formed from existing blood vessels.

Under normal adult physiological conditions, the balance between pro-angiogenic and anti-angiogenic factors maintains the vascular system in a quiescent state, with few new branches forming. However, tumor cells secrete various substances to disrupt this balance and induce pathological angiogenesis, ultimately leading to the development of a complex, mature vascular system [61]. The most classical pro-angiogenic and anti-angiogenic factors are vascular endothelial growth factor (VEGF) and thrombospondin-1 (TSP-1), respectively. VEGF, secreted by tumor cells and the surrounding stroma, stimulates endothelial cell proliferation and survival, leading to neovascularization, which is overexpressed in most human tumors and is associated with aggressiveness, metastasis, recurrence, and prognosis [62]. Previous studies have shown that VEGF can activate CREB through the PKC-dependent PKD pathway, and activated CREB binds to the promoter region of Nurr1, stimulating Nurr1 expression in cultured endothelial cells, further promoting angiogenesis [63]. On the other hand, TSP-1, known for its ability to inhibit endothelial cell migration and proliferation, induce endothelial cell apoptosis, and suppress angiogenesis, has attracted interest in its role in cancer biology and its potential as a therapeutic target [64]. In advanced cancer, TSP-1 expression is often downregulated. For instance, in prostate cancer, activated CREB can inhibit TSP-1 expression through pathways such as HDAC2/TSP-1 and CREB-EZH2-TSP-1, promoting angiogenesis and tumor progression [65,66]. Besides VEGF and TSP-1, CREB can regulate angiogenesis through other molecules such as CCN1 (CYR61), but its function in different research findings is contradictory [67, 68], necessitating further exploration. With a deeper understanding of CREB's regulation of angiogenesis, CREB-targeted therapy may emerge as a novel anti-angiogenic treatment strategy for late-stage tumors.

4.4. Metabolic Regulation

To meet the needs of cell growth and division, tumor cells often undergo corresponding adjustments in energy metabolism. Therefore, abnormal cancer metabolism, such as increased aerobic glycolysis and synthetic metabolic pathways, plays an important role in tumor initiation, metastasis, drug resistance, and cancer stem cells [69]. In the 1920s, Warburg and colleagues observed that tumors absorb large amounts of glucose compared to surrounding tissues. Additionally, even in the presence of oxygen, glucose is fermented to produce lactate, hence termed aerobic glycolysis [70]. Currently, a large body of research indicates that glycolysis is not only a characteristic of tumors but can even directly lead to tumor initiation [71, 72]. Moreover, in addition to activating oncogenes, CREB can also promote tumor progression by activating aerobic glycolysis to maintain cancer cell stemness [73]. However, compared to oxidative phosphorylation in mitochondria, glycolysis is less efficient in producing ATP. Therefore, to address this issue, tumor cells must increase the efficiency of glucose uptake and utilization, such as upregulating glucose transporter proteins (GLUT). Studies have shown that CREB can upregulate the expression of glucose transporter 3 (GLUT3) in breast cancer cells, greatly enhancing the cells' ability to absorb glucose and increasing the malignancy of tumors [74]. Interestingly, not only tumor cells but also cancer-associated fibroblasts (CAFs) in the tumor microenvironment can trigger aerobic glycolysis under estrogen stimulation through the G protein-coupled estrogen receptor (GPER)/cAMP/PKA/CREB pathway, providing "fuel" for cancer cell energy metabolism, increasing cancer cell mitochondrial activity, and ultimately endowing cancer cells with multidrug resistance [75].

In summary, aerobic glycolysis is a significant driving factor in tumorigenesis, and reprogramming tumor energy metabolism may become a strategy for cancer therapy. Currently, researchers have successfully induced a metabolic transition from glycolysis to oxidative phosphorylation in glioblastoma stem-like cells through the dbcAMP-CREB-PGC1α pathway, driving the differentiation of glioblastoma stem cells into astrocytes [76]. This study suggests that the anti-Warburg effect holds great promise for application in cancer therapy.

4.5. Immune Evasion and Inflammation Regulation

The immune system plays a crucial role in tumor development. Firstly, it effectively protects the host from microbial pathogens, preventing virus-induced tumor formation and establishing an inflammatory environment conducive to tumor growth. Secondly, it identifies and eliminates tumor cells based on their specific antigens or molecules, a process known as immune surveillance [77, 78]. Therefore, tumors must

somehow evade immune system surveillance or limit immune cytotoxicity to avoid eradication. Numerous studies have shown that tumor cells can achieve immune evasion by suppressing components of the immune system through CREB. Macrophages, derived from monocytes, can differentiate into M1 macrophages under the stimulation of factors such as TLR, TNF-α, IFN-γ, and CSF2, exerting pro-inflammatory, antimicrobial, and anti-tumor effects. However, under the stimulation of cytokines such as IL4, IL-10, IL-13, TGF-β, and PGE2, macrophages differentiate into the M2 subtype. Although M2 macrophages can suppress inflammation and promote wound healing, they also facilitate tumor proliferation and metastasis [79]. For instance, in hypoxic environments, the transcription factor ZEB-1 enhances glycolysis to produce lactate, which stimulates PKA/CREB to induce macrophage polarization into tumor-associated macrophages (TAMs) of the M2 phenotype, thereby promoting breast cancer progression [80]. Conversely, protein kinase N2 (PKN2) inhibits M2 polarization by suppressing CREB and thereby reducing the transcription of IL4 and IL-10 [81].

The A2A receptor (A2AR) is a typical G protein-coupled receptor (GPCR) with high affinity for adenosine, expressed in many immune cells such as T cells, NK cells, and macrophages. The binding of adenosine to the A2AR receptor triggers the cAMP/PKA/CREB pathway, inhibiting the immune response of immune cells, thereby promoting immune evasion of tumor cells [82]. For example, adenosine can reduce TCR-dependent mTORC1 activation by triggering A2AR/PKA/CREB, thereby impairing the metabolic function of CD8+ T cells and suppressing immunity [83]. Conversely, inhibiting A2AR through the PKA/CREB pathway can restore the anti-tumor activity of T cells [84]. Therefore, the use of PKA/CREB inhibitors or adenosine receptor antagonists to release lymphocytes from adenosine immunosuppression, restoring their cytotoxic potential, may be a powerful approach in anti-tumor immunotherapy [84,85].

Although most studies have confirmed the role of CREB in promoting immune evasion of tumor cells, some scholars have enhanced the in vitro cytotoxicity of NK cells by inducing the expression of NKG2D ligands on the surface of tumor cells through the recruitment of CBP/p300 to CREB. Since NKG2D is a major cytotoxic receptor for NK cell recognition and killing of tumor cells and is only expressed on the surface of malignant cells [86].

When innate immune cells detect infection or tissue damage, inflammation is triggered. While inflammation plays a role in resolving infection and damage, mounting evidence suggests that chronic inflammation is a risk factor for cancer [87]. CREB plays an important regulatory role in the inflammatory response [88]. As mentioned earlier, CREB can promote tumor progression by providing biologically active molecules such as growth factors to the tumor microenvironment [40] or by promoting tumor immune evasion [81]. In addition, CREB can accelerate cancer progression by regulating pro-inflammatory cytokines. For example, CREB can mediate the expression of inflammatory cytokines IL-1β and IL-18, promoting the growth of malignant mesothelioma [89]. Loss of FFAR2 in colorectal cancer leads to upregulation of cAMP/CREB, dysregulation of anti-inflammatory factor expression, increased expression of inflammatory factors, and consequently tumor progression [90]. Conversely, studies have shown that inflammatory factors can also promote CREB activation and increase cancer cell survival, providing strong evidence for preventing tumors by controlling inflammation [91].

In summary, CREB plays diverse roles in immunity and inflammation. Further understanding of its activation and mechanisms in different contexts may lead to better strategies for anti-tumor immunotherapy.

4.6. Cancer Stemness

In tumor cells, there exists a population of cells called cancer stem cells (CSCs), which share similar transcriptional profiles and possess unlimited self-renewal and differentiation capabilities with certain normal tissue stem cell populations. CSCs are considered one of the primary reasons for cancer initiation, metastasis, and drug resistance. Initially identified in acute myeloid leukemia, CSCs have been confirmed to exist in an increasing number of solid tumors [92,93]. The exact origin of CSCs in solid tumors is not fully elucidated at present. However, it is speculated that stem/progenitor cells from normal tissues may transform cancer stem cells under the influence of carcinogenic factors. For example, when the tumor suppressor gene PTEN is lost, CREB transcriptional activity is enhanced, leading to the appearance of glioblastoma stem cell-like phenotypes in neural stem/progenitor cells [94,95]. In various types of tumors, CREB regulates tumor cell stemness in different ways. CD44, a transmembrane glycoprotein, is recognized, isolated, and enriched in

cancer stem cells in many different types of cancers. Its intracellular domain (CD44ICD) acts as a co-transcription factor, binding to the promoter of PFKFB4 along with CREB, promoting its transcription. PFKFB4-mediated glycolysis can enhance the stemness of breast cancer [73].

Metastasis is often the primary cause of mortality in cancer patients. In a recent study, researchers utilized a novel spontaneous CRC liver metastasis mouse model to investigate the mechanisms underlying CRC metastasis. This model was generated by introducing mutations in four CRC-associated genes (Ctnnb1, Kras, Trp53, and Smad) into mouse intestinal epithelial cells. Analysis of this model revealed the critical role of CRC stem cell markers ALCAM (CD166) and PROM1 (CD133), upregulated by the cAMP/PKA/CREB pathway, in maintaining the plasticity and metastatic activity of CRC stem cells [60]. In addition to directly maintaining cancer cell stemness, studies suggest that CREB can also promote tumor metastasis by inducing distant colonization of CSCs [96]. These findings imply that inhibiting CREB may represent a potential therapeutic strategy for metastatic CRC.

Chemoresistance poses a significant obstacle to effective cancer treatment, and increasing evidence suggests that cells with CSC characteristics exhibit greater resistance to chemotherapy. In breast cancer, overexpression of the low molecular weight glycoprotein Serglycin (SRGN) can enhance the expression of YES-associated protein (YAP) by activating the ITGα5/FAK/CREB signaling pathway. YAP interacts with RUNX1 to upregulate HDAC2, maintaining the stemness of breast cancer cells and thereby mediating their chemoresistance. Additionally, YAP promotes the transcription of SRGN, forming a positive feedback loop that further exacerbates chemoresistance in breast cancer [97]. Scholars have successfully prevented tumor recurrence by blocking the EGFR/CREB/GRβ/IL6 axis in paclitaxel-resistant cancer stem cells in MUC1-positive cervical cancer using erlotinib. However, the clinical efficacy of this approach requires further investigation [98].

5. Targeting CREB in Tumor Therapy

Due to the significant role of CREB in the initiation and progression of tumors, the inhibition of CREB has garnered increasing attention as a therapeutic approach for malignant tumors. Currently, based on different target sites, compounds targeting CREB can be categorized as CREB inhibitors, CREB-CBP inhibitors, CREB-DNA inhibitors, and inhibitors of CREB-related pathways (Figure 1).

5.1. Targeting CREB

Currently, there are various methods to inhibit CREB. For instance: (1) Inhibitors capable of forming dimers with CREB. The cAMP early repressor (ICER) is a unique cAMP response element modulator (CREM) isoform that can homodimerize or heterodimerize with CREB, counteracting CREB activity. Research on ICER has demonstrated the effectiveness and feasibility of targeting CREB as a cancer therapy [99,100]. Dominant-negative CREB mutants (KCREB) can also inhibit CREB's transcriptional function by heterodimerizing with wild-type CREB. The expression of KCREB in MeWo human melanoma cells reduced their tumorigenic and metastatic potential in nude mice [101]. (2) Using siRNA or shRNA to directly downregulate or inhibit CREB expression has become a common approach for investigating CREB function [68,102]. (3) miRNAs directly target the 3'UTR of CREB mRNA, thereby downregulating or inhibiting CREB expression [103]. (4) As mentioned earlier, inhibiting CREB phosphorylation and other post-translational modifications can affect CREB function [24,35,104].

5.2. Targeting CREB-CBP

To investigate the significance of the CREB-CBP complex in activating target genes in response to various stimuli, the Best team screened a preselected library containing 762 compounds for compounds capable of binding to KIX. Ultimately, Naphthol AS-E Phosphate (KG501) was determined as an inhibitor of CREB-CBP because KG501 specifically targets the KIX site responsible for binding to KID [105]. This site can also bind to other proteins such as c-myc and p53, with reports indicating that p53 competitively binds to CBP to inhibit CREB function [45,106,107]. Although KG501 can inhibit the binding between CREB and CBP, this action is not entirely specific; for example, in non-small cell lung cancer cell lines, KG501 can simultaneously inhibit the interaction between CREB and NF-κB with CBP, thereby suppressing IL-1β-induced

angiogenesis [108]. Additionally, the effects of KG501 on CREB may vary under different experimental conditions; for instance, in HER-2/neu-overexpressing cell lines, 5 μmol/L of KG-501 did not affect CREB expression and phosphorylation, whereas in hepatocellular carcinoma, 10 μmol/L of KG-501 downregulated CREB phosphorylation [109, 110]. To find a better inhibitor of CREB-CBP, the Best team tested several molecules with a similar naphthol-AS structure, such as naphthol-AS, naphthol-AS-TR, naphthol-AS-phenylacetate, naphthol-AS-MX-butyrate, and naphthol-AS-MX-acetate. However, most of them had low solubility in water, and their binding and activation results from NMR were not satisfactory [105]. However, Lee's team later found that the phosphate of naphthol-AS-TR appeared to be highly effective (IC_{50} = 3.701 μmol/L), inhibiting lung cancer development by inducing cell cycle arrest, inhibiting carcinogenic autophagy, etc [111].

Compared to KG501, Xiao's team found that its dephosphorylated product could disrupt the structure of CREB-CBP at lower concentrations [112]. Additionally, nAS-E exhibited no toxicity to normal human cells while inhibiting CREB-induced cancer cell growth. This selective cytotoxicity suggests that nAS-E is a feasible cancer therapeutic agent [113]. In a recent study by the team, it was shown that nAS-E inhibits breast cancer cell proliferation, migration, survival, as well as osteoclast differentiation and bone resorption by inhibiting the interaction between CREB and CBP. Moreover, nAS-E can reverse breast cancer tumor cell-induced bone loss, indicating its potential as a treatment for breast cancer bone metastasis [114]. Subsequently, Xiao's team designed a series of improved molecules based on the structure of nAS-E, among which a molecule named 666-15 exhibited the best efficacy, showing good cancer cell inhibitory effects both in vitro and in vivo, and demonstrating good tolerance in C57BL/6 mice [115, 116]. To further improve the solubility of 666-15, the team designed a synergistic inhibitor, 653-47. Although 653-47 alone had no effect, it could act as an active enhancer when combined with 666-15, inhibiting CREB-mediated gene transcription and breast cancer cell growth [117]. Unfortunately, the bioavailability of the combination of 653-47 and 666-15 was not high. To address this issue, Xiao and colleagues have recently utilized a phenolic group to design, synthesize, and evaluate a series of prodrugs of 666-15 [118], further enhancing its bioavailability.

XX-650-23 (*N*-(4-cyanophenyl)-3-hydroxy-2-naphthamide) is another compound developed based on KG501, with higher CREB-CBP inhibitory efficiency than KG501. It selectively disrupts CREB transcription in AML cells, prolonging the lifespan of AML mice with minimal toxicity, and induces apoptosis and cell cycle arrest by reducing the expression of Bcl-2 and RFC3 [119]. Despite this, the small molecule still lacks sufficient physicochemical properties or clinical efficacy. Therefore, researchers further explored the structure-activity relationship of XX-650-23 and similar compounds, not only discovering various ways to further improve the effectiveness of XX-650-23 [120], but also identifying a harmless oral anthelmintic, chloroquine amide, which can inhibit AML proliferation by blocking the CREB-CBP pathway.

5.3. Targeting CREB-DNA

Compared to CREB-CBP inhibitors, research on CREB-DNA inhibitors is relatively scarce. B-ZIP transcription factors constitute a group of 63 genes in the human genome [121]. They mediate various signaling pathways by forming homodimers or heterodimers and binding to DNA to regulate gene expression. Some researchers have developed a high-throughput screening method to identify small molecules that disrupt the binding of b-ZIP proteins to DNA [122]. Two active aromatic antimony acids, NSC13778 and NSC146443, were ultimately identified, both of which bind to the basic region of the b-ZIP motif. However, their roles in cancer are still awaiting further investigation. Nonetheless, the derivative of NSC13778, P6981, has been proven to be a more effective inhibitor, significantly inhibiting the growth of CCS-1 cells, a clear cell sarcoma cell line containing the EWS-ATF1 fusion [123].

Enhancer DNA decoy oligodeoxynucleotides (ODNs) can inhibit transcription by competing with transcription factors. Decoy ODNs composed of CRE (CRE-decoy) act by blocking the ability of transcription factors to bind to CRE enhancers, thereby inhibiting CRE-directed gene transcription and tumor growth without affecting normal cell growth [124]. For example, studies have shown that CRE-decoy can increase the sensitivity of various human cancer cell lines (including TP53- and/or RB-mutant cells) to γ-irradiation-induced cytotoxic stress by inhibiting CREB [125]. Beyond the field of oncology, there have been reports in recent years indicating significant effects of CRE decoy ODNs in other areas, such as

inhibiting intimal hyperplasia in injured vascular walls in animal models [126].

However, while CREB is widely expressed throughout the human body and plays a crucial role in various normal physiological and pathological processes [127], its potential as a therapeutic target must be approached with caution. When designing drugs that target CREB, it is essential to consider the possibility of off-target effects [128] that could result in unintended consequences. For instance, inhibiting CREB phosphorylation in the brain, while potentially beneficial in certain contexts such as cancer treatment, could lead to cognitive impairment and memory loss [129]. Therefore, the development of CREB-targeted therapies must carefully balance the benefits of targeting CREB in specific disease contexts with the potential risks to normal physiological function.

6. Conclusion

The high metastatic rate and recurrence of cancer make it a highly complex disease, and the emergence of acquired drug resistance further increases the difficulty of treatment. Despite the emergence of numerous targeted therapies, the prognosis for patients remains suboptimal, especially for those in advanced stages. Therefore, it is imperative to discover more therapeutic targets and drugs to improve the treatment outcomes of cancer. To date, extensive research suggests that CREB may be a potential target for therapy, as it plays crucial roles in the occurrence, invasion, metastasis, and angiogenesis of various tumors. Although its clinical application value is currently very limited, with advancements in research and further exploration of the regulatory role of CREB in tumors, it is believed that CREB-targeted therapy will bring more hope to cancer patients in the future.

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