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# Cyclic AMP-regulatory element-binding protein: a novel UV-targeted transcription factor in skin cancer

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REVIEWS

# Cyclic AMP-regulatory element-binding protein: a novel UV-targeted transcription factor in skin cancer

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## 1 Background

Understanding the behaviour of cancer cells is crucial to developing novel therapies. In melanoma, the mitogen-activated protein kinase (MAPK) signalling pathway is activated in more than half of melanoma patients. This activation is driven by the mutation on v-Raf murine sarcoma viral oncogene homolog B1 ($BRAF^{V600}$) [1]. Accordingly, the current approved form of therapy is through monotherapy of BRAF inhibitors or in combination with mitogen-activated protein kinase kinase (MEK) inhibitors which ultimately act on kinases in the pathway [2]. Despite treatment, however, 50% of patients develop resistance to these inhibitors, resulting in disease progression within 6 to 7 months [3]. Similarly, in advanced squamous cell carcinoma (SCC), epidermal growth factor receptor (EGFR) activation results in further tumour progression. EGFR is overexpressed in 35–100% cases. Treatment options are limited but clinical trials using an EGFR inhibitor, Gefitinib, have only provided partial benefit [4].

An alternative therapeutic approach is to focus on transcription factors, which are key regulators of gene expression in cancer cells via their control over critical processes such as cell survival, invasion and proliferation [5]. Moreover, in cancer cells, transcription factors are mediators of oncogenic events that occur upstream in the signalling pathway, and their altered expression levels can be critical to tumorigenesis.

cAMP-regulatory element-binding protein (CREB) is a basic leucine zipper (bZIP) transcription factor that is located in the nucleus. Activated CREB is able to bind to cAMP-response elements (CREs) within the promoter region of target genes. The CREB–CRE interaction results in the recruitment of CREB-binding protein (CBP) which initiates transcription. This sequence of events is essential for critical processes such as cell proliferation and survival [6]. Overactivation of CREB, however, results in enhanced proliferation and survival of cancer cells, emphasising the critical role of CREB in cancer [7, 8]. This relationship has been observed in many cancers including glioblastoma, non-small-cell lung carcinoma, breast carcinoma and even melanoma [9]. Therefore, it is evident that CREB plays a significant role in cancer progression and is worthy of investigation to develop novel prophylactic agents and therapeutics for skin cancers.

## 2 Skin cancer

Herein, we focus on the role of CREB in skin carcinogenesis. Skin cancer consists of both non-melanoma and melanoma skin cancers. Non-melanoma skin cancers (NMSC), derived from keratinocytes, include basal cell carcinoma (BCC) and SCC. NMSC is the most commonly diagnosed cancer in Australia with over one million paid Medicare services for patients requiring NMSC treatment [10]. The incidence for NMSC was reported to be 49 per 100,000 in 2016 [11]. Indeed, NMSC cases are often not recorded by cancer registries due to the large number of people affected.[11]. Melanoma on the other hand is the second most commonly diagnosed cancer in men and the third most commonly

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diagnosed cancer in women in Australia. Melanoma incidence has steadily increased from 54 cases per 100,000 people recorded in 2000 to 69 cases per 100,000 people in 2023 [12]. With the significant amount of NMSC cases and the increasing number of melanoma cases, it is crucial to identify more successful therapeutic targets for skin cancer.

## 3 UV activates CREB in normal skin cells

One of the main causes of skin cancer is exposure of skin to ultraviolet radiation (UVR) which causes DNA photolesions and immunosuppression, both of which have been associated with skin carcinogenesis [13, 14]. UVR is also capable of modulating CREB levels. In both melanocytes and keratinocytes, ultraviolet B radiation (UVB) induces the stress-signalling pathway which results in the phosphorylation of p38 MAPK and thereafter CREB at the serine133 residue [15]. In addition, in keratinocytes, ultraviolet A radiation (UVA) is capable of activating p38.

In melanocytes, the process of melanogenesis results in the upregulation of CREB. UVR-induced DNA damage in keratinocytes results in the formation of α-melanocyte stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH) which are agonists of melanocortin 1 receptors (MC1R) located on melanocytes. Once bound, MC1R-induced signalling results in the activation of the cAMP–PKA–CREB pathway [16, 17]. Activation of CREB results in the expression of proteins associated with melanin synthesis [18]. In addition, through the activation of this pathway, elevated cAMP levels are capable of activating Mitogen-activated protein kinases (MAPK) such as extracellular signal-regulated kinase (ERK) [19]. Studies have shown that phosphorylated ERK 1/2 can activate mitogen- and stress-activated protein kinase 1 (MSK1). MSK1 is a kinase that is ultimately capable of phosphorylating CREB during melanogenesis. [20, 21] Studies have emphasised the importance of cAMP/PKA and the ERK signalling pathway in regulating CREB in the melanogenesis pathway through the introduction of inhibitors and promoters [22, 23].

Alternatively, melanin synthesis regulated by CREB can be stimulated upon stem cell factor (SCF) binding to tyrosine- protein kinase (c-kit). Binding results in p38 MAPK pathway activation which then results in CREB phosphorylation [24, 25]. Studies have shown that UVB increases protein levels of c-kit and SCF in cultured keratinocytes and melanocytes (Fig. 1) [26].

In keratinocytes, UVR results in the activation of the p38 MAPK pathway, p38α and p38β, and ultimately CREB at the serine133 residue [27, 28]. UVR-induced DNA damage or reactive oxygen species (ROS) are also capable of activating the p38 signalling pathway [27]. UVR also activates the extracellular signal-regulated kinase (ERK 1/2) pathway in keratinocytes resulting in CREB activation [29]. Specifically, UVB irradiation leads to the generation of ROS which in turn mediates EGFR phosphorylation [30]. EGFR phosphorylation causes activation of ERK 1/2 via the activation of upstream substrates such as ras [31]. Once activated, ERK1/2 can activate CREB (Fig. 2).

ERK activation in a delayed and sustained manner. Specifically, UVA activates ERK via PKCα which is then able to activate Ras and then ERK. This pathway also involves phospholipase C (PLC) and calcium (Fig. 2) [32].

## 4 The effects of UVR-activated CREB

The presence of melanin might be necessary for the malignant transformation of melanocytes. Studies have shown the ability of UVA to induce melanoma in the presence of melanin whereas UVB-induced melanoma is independent of melanin [33, 34]. Indeed, the presence of melanin suggests the ongoing activation of melanogenesis in contributing to melanoma. CREB plays an integral role in melanogenesis. Upstream events include common mutagenetic events that occur in melanoma such as $BRAF^{V600}$ mutation and NRAS mutation which can result in the overstimulation of CREB. Downstream events include the ability of CREB to activate MITF that induces various proteins associated with melanin synthesis [35]. Though CREB is not directly activated by UVR, the secondary effects of UVR can activate CREB and result in melanoma progression.

Similarly, UVR-activated CREB occurs in keratinocytes and is involved in the transcriptional activity of c-Fos. Studies have demonstrated a clear relationship between UVB phosphorylated CREB and c-Fos in the human keratinocyte cell line, HaCaT. Moreover, studies in c-Fos deficient mice have demonstrated that expression of c-FOS is necessary for benign to malignant progression in skin tumours [36]. UVB induction appears to mediate CRE and FAP1 cis elements to a greater extent as compared to the other elements in the promoter region resulting in c-Fos transcription.

## 5 CREB and melanoma

In melanoma, CREB overexpression has been reported to promote tumour growth and metastasis. One study showed that CREB negatively regulates cellular communication network factor 1/ cysteine-rich angiogenic inducer 61 (CCN1/CYR61) expression [37]. Unlike its ability to usually act as a transactivator, in the case of CCN1/CYR61, CREB acts as a repressor. Indeed, the overexpression of CREB hinders the role of CCN1/CYR61 as a suppressor of tumour progression and metastasis in melanoma. In melanoma cell lines A375SM and C8161-c9, the overexpression of CCN1/CYR61 resulted in a significant

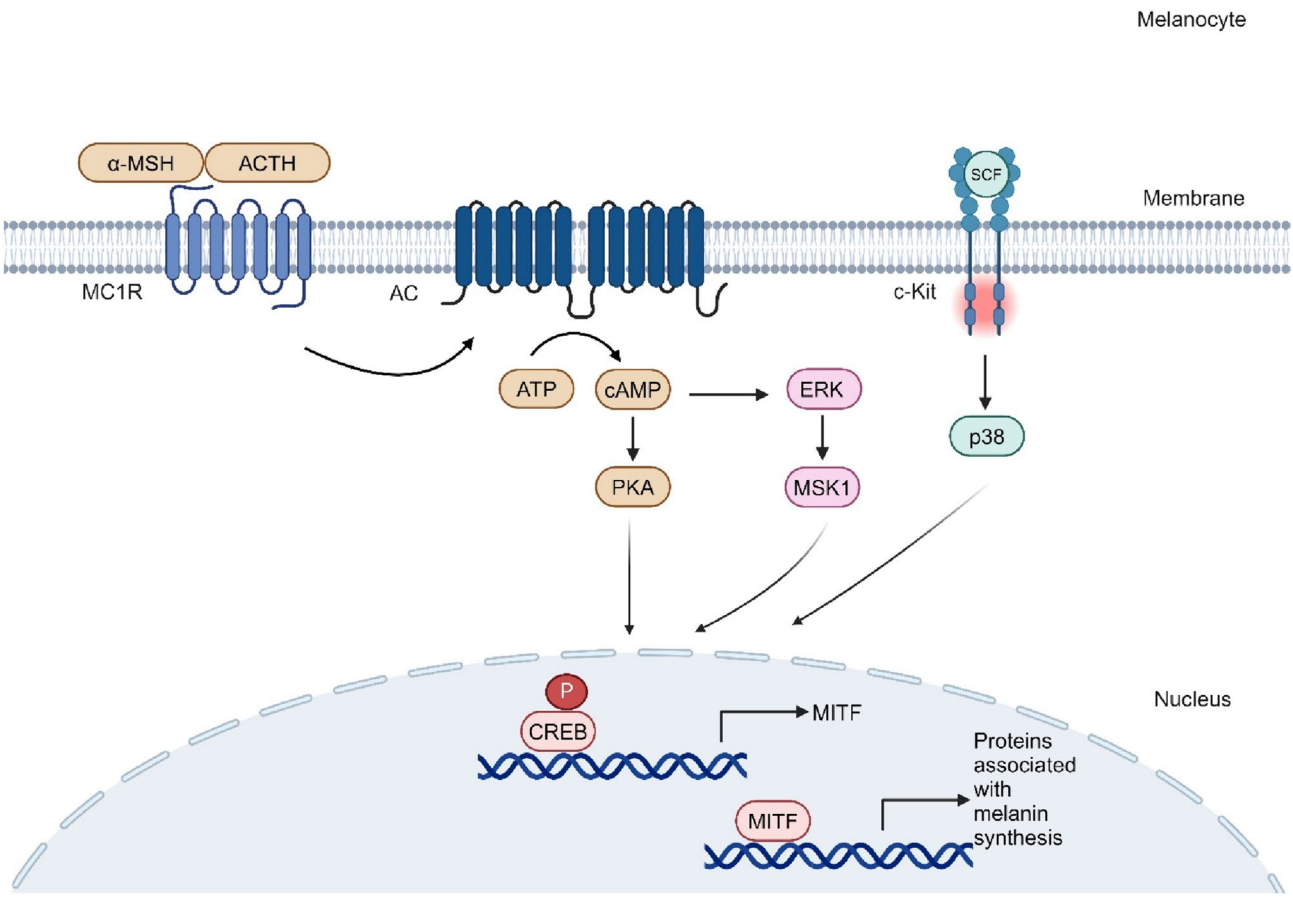


**Fig.1** Melanogenesis involves the phosphorylation of CREB (activated CREB). Upon UVR exposure, keratinocytes release α-melanocyte stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH) which are agonists of melanocortin 1 receptors (MC1R) located on melanocytes. Once bound, the cAMP–PKA pathway is activated resulting in the phosphorylation of CREB. Elevated cAMP levels, upon the activation of the cAMP-PKA pathway, are capable of activating extracellular signal-regulated kinase (ERK). Activated ERK is capable of activating mitogen-and stress-activated protein kinase 1 (MSK1) that phosphorylates CREB. Alternatively, CREB can be stimulated upon SCF binding to tyrosine- protein kinase (c-kit). Binding results in the activation of the p38 MAPK pathway which then results in CREB phosphorylation. pCREB results in the sequential activation of MITF. MITF is capable of increasing the expression of proteins associated with melanin synthesis. Created using BioRender

decrease in melanoma tumour growth [37]. Furthermore, the overexpression of CCN1/CYR61 reduces MMP-2 expression. The reduction of MMP-2 expression decreases cell motility and invasion of melanoma cells, angiogenesis and increases apoptosis. The study shows that in melanoma, where CREB is overexpressed, CCN1/CYR61 is downregulated which in turn upregulates MMP-2 expression [37]. This highlights the critical role of CREB as a transcription factor that is responsible for interacting with genes associated with tumour growth and metastasis in melanoma.

## 6 CREB and non-melanoma cancers

It has been demonstrated in mice that CREB is essential to initiate papilloma formation, the precursor lesion to SCC in this model [38]. One study showed that a transcription factor complex, made of CREB and regulatory factor X1 (RFX1), is stabilised by cell cycle and apoptosis regulator 2 (CCAR2). The study suggested a role for this complex in maintaining cell cycle progression and promoting SCC tumorigenesis [39]. The importance of each individual component of the complex was further shown by introducing shRNA-mediated knockdown of CREB which then resulted in a significant increase in G2 phase cell cycle arrest and as such a reduction in tumorigenic activity. The role of CREB in SCC is further highlighted in another study that showed that CREB is a downstream modulator of β-catenin ensuring the development and preservation of the human squamous carcinoma cell line (SCC13). This study suggested potential crosstalk between protein kinase A (PKA) signalling and the β-catenin pathway [40]. These studies collectively highlight the importance of CREB in promoting and maintaining tumorigenesis in SCC.

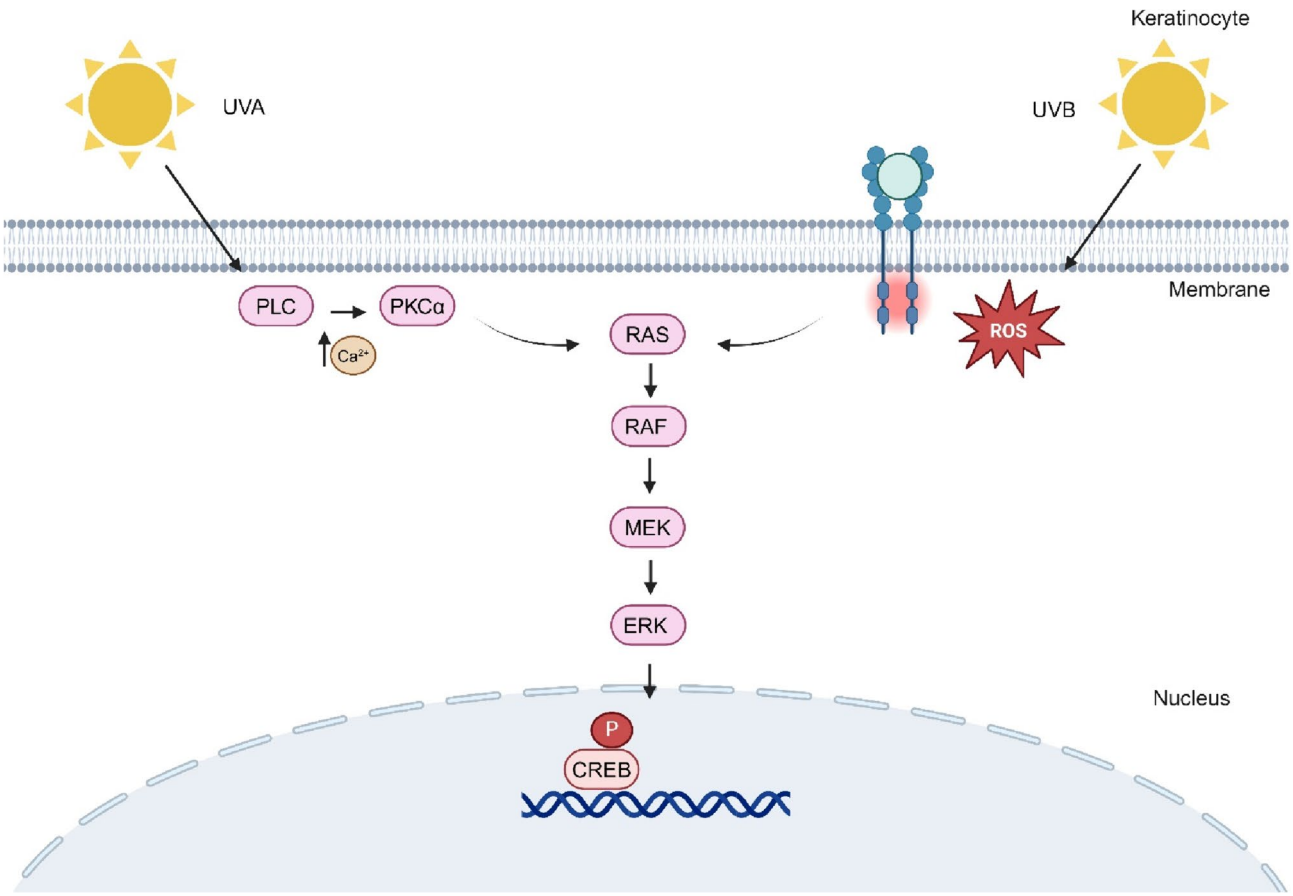


**Fig. 2** UVA and UVB induce the RAF-MEK-ERK pathway that phosphorylates CREB (activated CREB). UVA activates the pathway via phospholipase C (PLC) and calcium. UVB activates the pathway by producing ROS in the skin which then results in the phosphorylation of EGFR. Activated EGFR then activates the pathway. Activation of the pathway results in the formation of phosphorylated CREB. Created using BioRender

## 7 Diagnostic or prognostic role for pCREB

Studies have shown that nuclear pCREB levels correlate with the proliferative status of human melanoma tissue. Specifically, Rodriguez and colleagues (2018) have shown that pCREB expression has a moderate positive correlation with the proliferative status in early stages of melanoma. The same study showed that later stages of melanoma have low proliferative status and low pCREB levels. This aligns with the fact that melanoma cells undergo a phenotypic switch from a proliferative status to an invasive status in vivo. Interestingly, the same study showed that low pCREB levels in patients with melanoma have been associated with tumour aggressiveness and metastasis recurrence. Overall, this suggests that pCREB can be a valuable prognostic tool to predict the aggressiveness of melanoma [41]. However, there is a lack of information available on pCREB levels in relation to patients with non-melanoma skin cancers. Nevertheless, studies have shown the importance of CREB in the development, especially in the early stages, and maintenance of SCC suggesting a possible role for pCREB as a diagnostic marker [36, 42].

## 8 Future therapies to reduce CREB levels

From this review, it is evident that the overactivation/overexpression of CREB in skin cancer represents a potential target for future therapies. A possible therapeutic approach would be to inhibit the biological function of CREB as a transcription factor.

A promising compound that could inhibit the transcriptional activity of CREB is the vitamin D metabolite, 1,25-dihydroxyvitamin D (1,25D). This compound has been shown to reduce skin carcinogenesis in mice [14]. In addition, 1,25D has been shown to reduce UVR upregulated pCREB in human keratinocytes [43, 44]. It was suggested by De Silva and colleagues (2018) that decreased levels of pCREB induced by 1,25D could be due to its ability to suppress phosphorylation of ERK 1/2 after UVR exposure

[45]. Taking into account that ERK1/2 can activate CREB in keratinocytes, this suggests that 1,25D could inhibit CREB activity by targeting kinases upstream of CREB. Furthermore, 1,25D has been shown to increase phosphatase and tensin homolog (PTEN) levels after UVR exposure in melanocytes and in mouse epidermis [46]. This is likely due to the binding of 1,25D to the vitamin D receptor (VDR) which is thereafter able to bind to the promoter region of PTEN [47]. Indeed, PTEN dephosphorylates CREB at Ser133, regulating pCREB activity and ultimately preventing the over transcription of genes associated with CREB [48]. Although promising, 1,25D is not light stable and may cause hypercalcaemia [49]. However, studies have shown low calcaemic vitamin D analogue, 1α,25(OH)2-lumisterol has similar photoprotective functions to 1,25D in decreasing DNA damage, immunosuppression and photocarcinogenesis [14].

Another approach to inhibit the transcriptional activity of CREB is to introduce an inhibitor that prevents the pCREB- CBP/P300 interaction which is necessary to initiate CREB-dependent gene transcription. The binding involves kinase- inducible domain (KID) in pCREB and the KID interacting domain (KIX) in CBP/p300. A study in HEK293 cells identified that a potent CREB inhibitor, 666–15, at concentrations that provided CREB inhibition, did not inhibit other transcription factors that also required CBP recruitment, such as Gal4-MLL. In addition, in vivo studies in C57BL/6 mice injected intraperitoneally with 666–15 showed no alterations in blood chemistry profiles and no functional deterioration of vital organs. Interestingly, unlike other forms of CREB inhibitors which resulted in complete CREB inhibition, the administration of 666–15 resulted in a pulsatile inhibition system of CREB [50]. Moreover, 666–15 was shown to have anti-proliferative activity in breast cancer cell lines [51]. Whilst these studies were carried out in different models, they suggest that inhibition of CREB is viable and could be applicable to skin.

To the best of our knowledge, there are limited studies focussed on inhibiting CREB in skin cancer but extensive studies in other cancers including leukaemia. CREB is a potential target in leukaemia cells and has been a focus in a number of preclinical studies [52, 53]. An interesting study by Illiano and colleagues (2020) showed that a histone demethylase (KDM) inhibitor, GSKJ4, is capable of significantly decreasing CREB protein levels but not CREB mRNA expression levels. GSKJ4 is able to decrease CREB levels by altering the ubiquitin/proteasome system which affects the stability of CREB. Their studies have shown that PKA is required in GSKJ4-induced CREB phosphorylation and protein downregulation [54]. In relation to melanoma specifically, this inhibitor shows promise considering the importance of the overactivation of the cAMP/PKA signalling pathway in increasing CREB levels, and warrants further investigation in melanoma cells.

## 9 Conclusion and final remarks

It is evident that most studies of signalling pathways involved in UVR-induced CREB activation in skin cells utilised either UVA or UVB. Though insightful, exposure of skin to the combined effects of UVA and UVB in a ratio that mimics the solar spectrum would provide a more accurate representation of solar UVR and will account for the interactive effects of the different UV wavelengths [55].

This review highlights the significant role of CREB in cancer progression, warranting its investigation as a potential prognostic and diagnostic marker of skin cancer and a possible target for future therapeutic intervention.

**Author contribution** JCN, MA and KMD planned the topic and ideas for the manuscript. JCN prepared the first draft and revision of the manuscript. MA and KMD edited all drafts of the manuscript.

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## Declarations

**Conflict of interest** There are no conflicts of interest.

**Ethical approval** Not applicable.



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