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REVIEW

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Cyclic adenosine monophosphate (cAMP) signaling in melanocyte pigmentation and melanomagenesis

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Abstract

The second messenger cyclic adenosine monophosphate (cAMP) regulates numerous functions in both benign melanocytes and melanoma cells. cAMP is generated from two distinct sources, transmembrane and soluble adenylyl cyclases (tmAC and sAC, respectively), and is degraded by a family of proteins called phosphodiesterases (PDEs). cAMP signaling can be regulated in many different ways and can lead to varied effects in melanocytes. It was recently revealed that distinct cAMP signaling pathways regulate pigmentation by either altering pigment gene expression or the pH of melanosomes. In the context of melanoma, many studies report seemingly contradictory roles for cAMP in tumorigenesis. For example, cAMP signaling has been implicated in both cancer promotion and suppression, as well as both therapy resistance and sensitization. This conundrum in the field may be explained by the fact that cAMP signals in discrete microdomains and each microdomain can mediate differential cellular functions. Here, we review the role of cAMP signaling microdomains in benign melanocyte biology, focusing on pigmentation, and in melanomagenesis.

1 | cAMP SIGNALING PATHWAY

Cyclic adenosine monophosphate (cAMP) is a second messenger that regulates a wide variety of cellular functions, including cellular growth, differentiation, proliferation, migration, ion transport, pH regulation, and gene expression (Desman, Waintraub, & Zippin, 2014; Levin & Buck, 2015; Levy & Zhou, 2015; Pastor-Soler et al., 2003; Rahman, Buck, & Levin, 2013; Rodriguez & Setaluri, 2014; Sutherland, 1972). cAMP signaling is initiated in response to diverse stimuli and affects the aforementioned functions through its effector proteins: protein kinase A (PKA), exchange protein activated by cAMP (EPAC), and cyclic nucleotide-gated ion channels (Kaupp et al., 1989; Kawasaki et al., 1998; Kopperud, Krakstad, Selheim, & Døskeland, 2003; Walsh, Perkins, & Krebs, 1968). In mammalian cells, cAMP is produced from ATP by two distinct types of adenylyl cyclases (ACs): a family of transmembrane adenylyl cyclases (tmACs), comprised of nine members (ADCY1-9), and the more recently discovered soluble adenylyl cyclase (sAC), which is encoded by a single gene (ADCY10) (Buck, Sinclair, Schapal, Cann, & Levin, 1999; Taussig & Gilman, 1995). All members of the tmAC family are localized strictly to the plasma membrane and classically mediate cAMP responses to extracellular hormonal signals via G protein-coupled receptor (GPCR) activation of Gsα (Sassone-Corsi, 2012; Sunahara & Taussig, 2002). sAC, on the other hand, is found throughout the cytoplasm associated with protein structures such as centrioles, and inside organelles, including the nucleus and the mitochondria (Ladilov & Appukuttan, 2014; Valsecchi, Konrad, & Manfredi, 2014; Valsecchi, Ramos-Espiritu, Buck, Levin, & Manfredi, 2013; Zippin et al., 2002, 2004). Unlike tmACs, sAC is insensitive to stimulation by Gsα, but is instead uniquely regulated by bicarbonate and calcium ions and physiological fluctuations in intracellular ATP levels (Chen et al., 2000; Kleinboelting et al., 2014; Litvin, Kamenetsky, Zarifyan, Buck, & Levin, 2003; Steegborn, 2014; Zippin et al., 2013).

As early as 2000, it was well known that the activation of cAMP signaling via different receptors elicits different and, in many cases, non-overlapping functional responses (Barnes et al., 2005; Rich et al., 2000; Warrier et al., 2007). This suggested a model in which intracellular diffusion of cAMP does not occur but instead cAMP is

confined within a microdomain that includes the source of cAMP (AC), the catabolizer of cAMP (PDE), different effector proteins (e.g., PKA), and target proteins. Studies using fluorescence resonance energy transfer (FRET) to measure cAMP concentrations demonstrated that cAMP is produced in subcellular compartments, suggesting that cAMP does not just freely diffuse across the cell (Bacskai et al., 1993; Rich et al., 2000; Surdo et al., 2017; Zaccolo & Pozzan, 2002). It is now accepted that cAMP signaling does occur in distinct, highly localized intracellular microdomains. Once generated, cAMP is degraded readily by PDEs, ensuring that cAMP only activates spatially associated cAMP effectors (Baillie, 2009; Houslay, Baillie, & Maurice, 2007). cAMP microdomains are dependent upon anchoring proteins which tether cAMP signaling proteins to specific areas of the cell. PKA, the best characterized cAMP effector, is tethered to various intracellular sites by A-kinase-anchoring proteins or AKAPs (Papa, Sardanelli, Scacco, & Technikova-Dobrova, 1999; Pawson & Scott, 1997; Taylor et al., 2005; Terrin et al., 2012). EPAC is also known to be distributed throughout cells and can be associated with membranes and structural proteins (Bos, 2006; Breckler et al., 2011; De Rooij et al., 2000; Schmidt, Dekker, & Maarsingh, 2013). Given that activation of cAMP signaling is not due to a uniform increase in cAMP levels throughout the cell, different subsets of anchored cAMP effectors are exposed to different microdomains of cAMP (Bundey & Insel, 2004; Zaccolo & Pozzan, 2002). This allows for only the appropriate subset of targets to be selectively activated. These models help explain how a single second messenger is able to carry out a plethora of functions simultaneously.

Proteins called phosphodiesterases are essential in establishing cAMP microdomains, as they create a diffusional barrier for cAMP (Baillie, 2009; Barnes et al., 2005; Mika, Leroy, Vandecasteele, & Fischmeister, 2012; Oliveira et al., 2010; Zaccolo & Pozzan, 2002). Among its eleven isoforms, eight (cAMP-specific PDE4, PDE7, and PDE8, and both cAMP- and cGMP-selective PDE1, PDE2, PDE3, PDE10, and PDE11) hydrolyze cAMP (Conti & Beavo, 2007). Pivotal to the tight spatio-temporal control of cAMP signaling dynamics is the compartmentalization of PDEs. It is well known that specific PDE isoforms are localized to distinct subcellular compartments and regulate differential cAMP signaling pathways (Acin-Perez et al., 2011; Liu et al., 2019; Maurice et al., 2014; Miller et al., 2011; Rinaldi et al., 2019; Terrin et al., 2012). PDEs are also reported to form protein–protein interaction with various cAMP effector proteins, membrane-bound proteins, and scaffolding proteins (Baillie, Scott, & Houslay, 2005; Blair & Baillie, 2019; Dodge et al., 2001; Dodge-Kafka et al., 2005; Houslay et al., 2007; Kritzer, Li, Dodge-Kafka, & Kapiloff, 2012). One well-established example is the tethering of PDE4D3 isoform along with PKA to the scaffolding protein mAKAP at perinuclear sites and the positive regulation of PDE4 by PKA-mediated phosphorylation (Dodge et al., 2001; Oliveira et al., 2010). Increased cAMP signaling at these mAKAP-associated perinuclear sites, therefore, increases the activity of the local pool of PDE4D3, creating a diffusional barrier with a strength proportional to the intensity of cAMP signaling (Dodge et al., 2001; Oliveira et al., 2010). These examples of how specific PDE isoforms are integrated into unique cAMP signaling microdomains highlight their essential role in maintaining the specificity of functions carried out by different cAMP signaling microdomains.

Within a cell exists a number of spatially restricted cAMP microdomains. Plasma membrane-localized cAMP microdomains are usually initiated by a GPCR, which is activated by ligand binding, followed by release of Gsα leading to adenylyl cyclase activation and upregulation of cAMP at sites near the plasma membrane (Sassone-Corsi, 2012; Sunahara & Taussig, 2002). Different GPCRs have distinct localizations at the plasma membrane (i.e., caveolar or non-caveolar) and initiate different target responses of cAMP signaling, suggesting that this near-plasma membrane compartment can be further subdivided into distinct cAMP microdomains (Bhogal, Hasan, & Gorelik, 2018; Warrier et al., 2007). Furthermore, recent evidence shows that internalized GPCRs on endosomes maintain their ability to activate cAMP production, defining an additional GPCR-mediated cAMP microdomain that is further away from the plasma membrane (Calebiro & Maiellaro, 2014; Calebiro et al., 2009). Even though GPCR-mediated cAMP microdomains were thought to be solely dependent on tmACs, a recent study suggests the potential involvement of sAC (Inda et al., 2016). In most cases, sAC regulates intracellular cAMP microdomains found in the cytoplasm, nucleus, and the mitochondrial matrix (Acin-Perez et al., 2009; Appukuttan et al., 2012; Sample et al., 2012; Tresguerres, Levin, & Buck, 2011). In contrast to tmACs, Gsα does not directly regulate sAC, and instead, sAC is stimulated by intracellular signals such as pH, bicarbonate ions, calcium ions, and ATP (Chen et al., 2000; Kleinboelting et al., 2014; Litvin et al., 2003; Steegborn, 2014; Zippin et al., 2013). cAMP signaling in each microdomain leads to disparate effects in cells. For example, tmAC-generated cAMP is known to regulate gene expression that can affect metabolism whereas mitochondrial sAC-generated cAMP leads to post-translational modification of electron transport complex proteins and direct modulation of oxidative phosphorylation (Acin-Perez et al., 2009; Di Benedetto, Scalzotto, Mongillo, & Pozzan, 2013; Valsecchi et al., 2013, 2017; Valsecchi et al., 2014). tmACs and sAC can be activated by both similar and different paracrine factors important for neuronal cell activation and migration (Martinez et al., 2014; Stessin et al., 2006; Wu et al., 2006). tmACs are known to regulate gene expression by activating PKA in the cytoplasm and inducing its translocation into the nucleus (Mayr & Montminy, 2001; Sassone-Corsi, 2012). sAC isoforms are already present in the nucleus and activate nuclear PKA presumably to also regulate gene expression but the mechanism is not established (Zippin, Chadwick, Levin, Buck, & Magro, 2010; Zippin et al., 2004).

2 | cAMP SIGNALING IN PIGMENTATION BY BENIGN MELANOCYTES

Pigmentation of the skin is a critical protective mechanism against UV radiation, and deficiency of pigmentation is a major risk factor for melanoma and other skin cancers (Gilchrest, Eller, Geller, & Yaar, 1999; Kondo & Hearing, 2011; Miller & Mihm Jr, 2006).

Melanocytes make the pigment melanin in lysosome-like organelles known as melanosomes (Dell'Angelica, Mullins, Caplan, & Bonifacino, 2000; Marks & Seabra, 2001). Melanin consists of two main types: brown/black eumelanin and red/yellow pheomelanin (Ito & Wakamatsu, 2003; Prota, 1980). Eumelanin provides effective protection from UV radiation, whereas pheomelanin increases susceptibility to cytotoxic effects of UV radiation and reactive oxygen species (ROS) (Costin & Hearing, 2007; García-Borrón, Abdel-Malek, & Jiménez-Cervantes, 2014; Kondo & Hearing, 2011). The rate-limiting step in both eumelanin and pheomelanin synthesis is the hydroxylation of tyrosine to levodopa (L-DOPA) and then to dopaquinone by tyrosinase (*TYR*) (Hearing, Ekel, Montague, & Nicholson, 1980). The pathways for eumelanin and pheomelanin synthesis start to diverge from dopaquinone. Tyrosinase-related-protein-1 (*TYRP1*) and tyrosinase-related-protein-2 (*TYRP2*) become main drivers of eumelanogenesis, whereas conjugation by glutathione or thiol-containing cysteine yields pheomelanin (Prota, 1980; Slominski, Tobin, Shibahara, & Wortsman, 2004). These melanin species then accumulate within the melanosome, which is then exported to adjacent keratinocytes to provide UV protection (Hearing, 2005; Lin & Fisher, 2007).

The canonical regulatory mechanism of melanin production is driven by melanocortin 1 receptor (MC1R)-induced changes in pigment gene expression. MC1R is a seven-transmembrane GPCR expressed on the plasma membrane of melanocytes (Mountjoy, Robbins, Mortrud, & Cone, 1992). Upon binding to its agonists, α-melanocyte-stimulating hormone (α-MSH), and adrenocorticotropic hormone (ACTH), MC1R activates tmAC-dependent cAMP production (Sassone-Corsi, 2012; Sunahara & Taussig, 2002; Suzuki, Cone, Im, Nordlund, & Abdel-Malek, 1996). The increased cAMP level activates PKA, which phosphorylates cAMP response element-binding protein (CREB) (Sassone-Corsi, 1995). CREB activation leads to the expression of many genes, one of which is microphthalmia transcription factor (*MITF*) (Bertolotto et al., 1998). MITF is a "master regulator" of survival and proliferation of melanocyte precursors as well as pigment production by melanocytes (Levy, Khaled, & Fisher, 2006). MITF upregulates the expression of *TYR*, *TYRP1*, and *TYRP2*, thereby increasing eumelanin synthesis (Fang, Kute, & Setaluri, 2001; Fang, Tsuji, & Setaluri, 2002; García-Borrón et al., 2014). In addition to the agonists of MC1R, α-MSH, and ACTH (Suzuki et al., 1996), there are multiple antagonists including agouti-signaling protein (ASIP) and human β-defensin 3 (HBD3), which increase pheomelanin synthesis (Candille et al., 2007; Swope et al., 2012; Walker & Gunn, 2010).

The importance of the canonical MC1R-tmAC-MITF pathway in pigment production and melanocyte biology is well established (Holcomb et al., 2019; Rouzaud, Kadekaro, Abdel-Malek, & Hearing, 2005; Scott et al., 2002). In humans, single nucleotide polymorphisms in MC1R impair downstream cAMP signaling and result in impaired eumelanogenesis leading to red hair color and fair skin phenotype (Bastiaens et al., 2001; Box, Wyeth, O'Gorman, Martin, & Sturm, 1997; Smith et al., 1998; Valverde, Healy, Jackson, Rees, & Thody, 1995). Without the ability to appropriately synthesize eumelanin, people who harbor these MC1R variants are highly susceptible to the cytotoxic effects of UV radiation and carry a high risk of skin cancer (Abdel-Malek et al., 2000; Abdel-Malek, Suzuki, Tada, Im, & Akcali, 1999; Nasti & Timares, 2015; Palmer et al., 2000; Scott et al., 2002). Similarly, in non-functional MC1R mice models, UV radiation fails to induce pigmentary changes, while leading to a proper tanning response in the control mice with intact MSH-MC1R pathway (D'Orazio et al., 2006). Mice with non-functional MC1R are also more susceptible to developing melanoma (Mitra et al., 2012). Susceptible to melanoma and DNA damage is a result of deficiencies in cAMP signaling since topical application of forskolin (FSK), an inducer of cAMP signaling via tmAC activation, rescues eumelanin synthesis and enhances UV resistance (Amaro-Ortiz, Yan, & D'Orazio, 2014; Bautista et al., 2020; D'Orazio & Fisher, 2011; Kadekaro et al., 2010; Spry et al., 2009). Forskolin is also reported to protect skin from UV-induced damage, independent of pigmentation, by promoting epidermal thickening and inhibiting UVB-induced apoptosis (Passeron, Namiki, Passeron, Le Pape, & Hearing, 2009; Scott et al., 2012). Thus, MC1R-induced, tmAC-dependent cAMP signaling plays a crucial role in the regulation of pigmentation and response to UV.

More recently, sex steroids such as estrogen and progesterone have also been shown to regulate melanin synthesis by altering cAMP signaling (Natale et al., 2016; Sun et al., 2017). The classical nuclear estrogen and progesterone receptors (ER and PR) appear absent in normal human melanocytes; however, estrogen stimulates the membrane-bound G protein-coupled estrogen receptor (GPER) in melanocytes to increase melanin synthesis (Natale et al., 2016). Upon activation, GPER induces cAMP signaling via Gsα (Filardo & Thomas, 2012). In contrast, progesterone acts on a different member of the GPCR family found in melanocytes, progestin and adipoQ receptor 7 (PAQR7), to decrease cAMP and melanin synthesis (Natale et al., 2016). Interestingly, induction of cAMP signaling by GPER stimulation activates the aforementioned components of the canonical pigment production pathway, such as PKA and CREB, leading to an increase in MITF and TYR expression (Natale et al., 2016; Sun et al., 2017). Thus, GPER stimulation by estrogen activates a distinct plasma membrane-localized cAMP microdomain that provides an alternative route of stimulation for the tmAC-dependent cAMP signaling pathway.

However, less well understood is the role of sAC-dependent cAMP signaling in pigmentation. Recent evidence suggests that sAC regulates pigmentation by altering the pH of melanosomes (Ota, Zhou, & Zippin, 2017; Zhou et al., 2018). Tyrosinase, the rate-limiting enzyme of melanin synthesis, is highly sensitive to pH (Ancans et al., 2001; Ito, Suzuki, Takebayashi, Commo, & Wakamatsu, 2013); thus, alteration in melanosome pH is predicted to affect tyrosinase activity. In fact, the pH of melanosomes is reported to be higher in darker-skinned individuals compared to lighter-skinned individuals, and this difference in pH is thought to contribute to the variations in skin and hair color (Fuller, Spaulding, & Smith, 2001; Schallreuter, Kothari, Chavan, & Spencer, 2008). Zhou et al. demonstrated that inhibition of sAC enhances eumelanin synthesis by increasing melanosomal pH and tyrosinase activity (2018). sAC-dependent alteration

of melanosomal pH occurred rather quickly, suggesting that melanosomal pH is dynamically regulated (Zhou et al., 2018). In contrast to tmAC-dependent regulation of gene expression, sAC regulation of melanosomal pH did not involve PKA signaling, but signaled via EPAC. Furthermore, sAC-dependent cAMP signaling did not affect *TYR* gene expression levels, further distinguishing sAC- from tmAC-generated cAMP. Thus, MC1R-induced, tmAC-generated cAMP enhances eumelanogenesis by increasing the expression of the *TYR* and other pigment genes, whereas inhibition of sAC-generated cAMP enhances eumelanin synthesis by alkalinizing melanosomal pH and increasing tyrosinase activity. Hence, in melanocytes, there are two cAMP signaling pathways mediating the same cellular function, melanin synthesis, but via distinct mechanisms; this reinforces the model that cAMP signaling occurs in distinct, independently regulated microdomains (Figure 1).

Some studies have also examined the role of PDEs in melanocyte biology. In melanocytes, the PDE4D3 isoform is reported to be a direct target of the MC1R-cAMP-MITF pathway, as MITF transcriptionally activates *PDE4D3* (Khaled, Levy, & Fisher, 2010). This creates a negative feedback loop, in which increased levels of *MITF* expression attenuate cAMP signaling by upregulating *PDE4D3* expression. The pivotal role of PDE4 in regulating cAMP signaling in melanocytes is further reinforced by a study demonstrating that topical application of PDE4 inhibitor synergizes with FSK to increase mouse skin pigmentation (Khaled et al., 2010). However, the roles of other PDE isoforms in melanocyte biology and pigmentation have not been described. Viable PDE knockout mouse models exist for all eleven PDE isoforms, but no pigment phenotype has been reported (Jin, Latour, & Conti, 2005; Maurice et al., 2014). However, it is noteworthy that published images reveal that PDE4 knockout mice appear darker than wild-type controls, even though a pigment change was not noted in the study (Figure 2) (Jin, Richard, Kuo, D'Ercole, & Conti, 1999; Rodriguez & Setaluri, 2014).

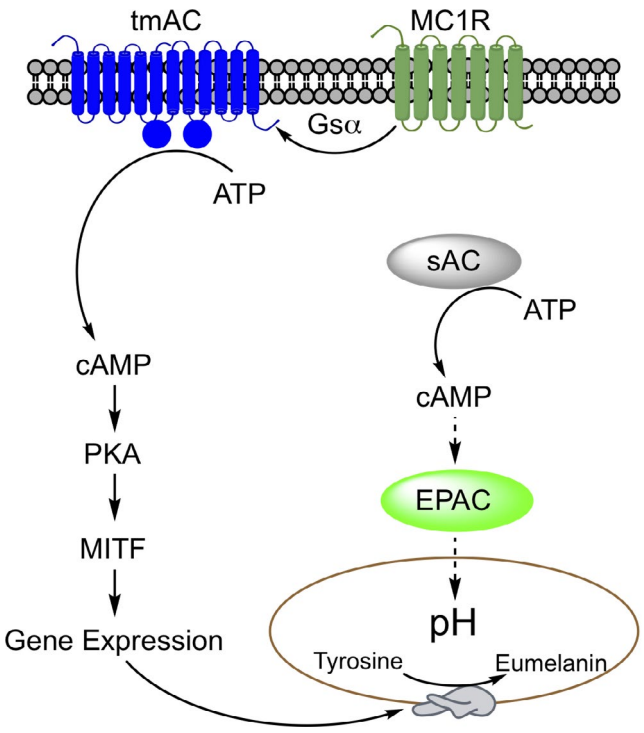

FIGURE 1 Melanin synthesis in melanocytes by tmAC- and sAC-dependent pathways. MC1R-induced, tmAC-generated cAMP enhances eumelanin synthesis by upregulating the expression of pigment genes, including TYR, via PKA-dependent signaling. sAC-generated cAMP enhances eumelanin synthesis by alkalinizing melanosomal pH and increasing tyrosinase activity via EPAC-dependent signaling. MC1R, melanocortin 1 receptor; Gsα, Gs protein α subunit; tmAC, transmembrane adenylyl cyclase; PKA, protein kinase A; MITF, microphthalmia transcription factor; sAC, soluble adenylyl cyclase; EPAC, exchange protein activated by cAMP

3 | cAMP SIGNALING IN MELANOMA

The majority of cutaneous melanomas harbor driver mutations that activate the mitogen-activated protein kinase (MAPK) pathway (Colombino et al., 2012; Hayward et al., 2017). The classical MAPK pathway is comprised of the signaling proteins RAS, RAF, MEK, and ERK, which sequentially transduce proliferative signals from the cell surface receptor tyrosine kinase (RTK) (Lopez-Bergami, Fitchman, & Ronai, 2008). c-KIT is one RTK found in melanocytes, and it activates the small GTPase RAS upon binding to its ligand, the stem cell factor (SCF) (Katz, Amit, & Yarden, 2007). RAS, in turn, activates the RAF kinase (MAP3K) family. Members of the RAF kinase family, including BRAF and CRAF, activate MEK (MAP2K), which subsequently activates ERK (Wellbrock, Karasarides, & Marais, 2004). ERK phosphorylates and activates multiple downstream targets, including MITF, and contributes to the regulation of numerous cellular functions in melanocytes.

FIGURE 2 Comparison of a PDE4D−/− mouse (lower) and a control littermate (upper) at D34. This image, reproduced from the original Figure by Jin et al., suggests that PDE4 knockout mice have darker hair and skin color as compared to littermate controls (1999). This phenotype supports a role for PDE4 in pigmentation and is consistent with more recent data, demonstrating that topical application of PDE4 inhibitor synergizes with forskolin to increase skin pigmentation (Khaled et al., 2010). PDE, phosphodiesterase. Copyright (1999) National Academy of Sciences, USA

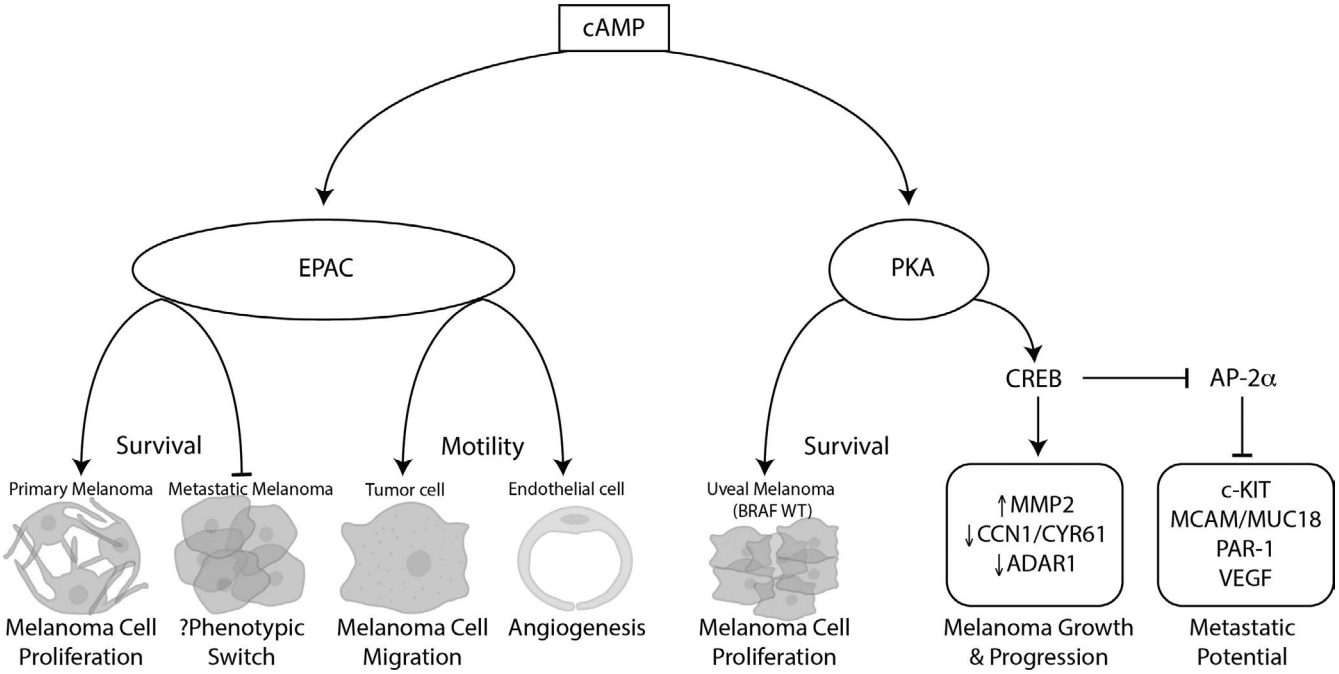

FIGURE 3 Evidence for the tumorigenic effect of cAMP in melanoma. cAMP-EPAC pathway promotes cell proliferation in primary melanoma, while mediating the anti-proliferative response to cAMP signaling in metastatic melanoma, which may be indicative of a phenotypic switch from a proliferative to an invasive state. EPAC also promotes melanoma cell migration and angiogenesis. cAMP-PKA pathway in BRAF wild-type uveal melanoma promotes cell proliferation. CREB, downstream of the cAMP-PKA pathway, inhibits AP-2α and regulates multiple genes linked to melanoma progression and metastatic potential. EPAC, exchange protein activated by cAMP; PKA, protein kinase A; CREB, cAMP response element-binding protein; AP-2α, activator protein-2α; MMP2, matrix metalloproteinase 2; CCN1/CYR61, cysteine-rich protein 61; ADAR1, adenosine deaminase acting on RNA 1; MCAM/MUC18, melanoma cell adhesion molecule; PAR-1, protease-activated receptor-1; VEGF, vascular endothelial growth factor

Multiple levels of interconnection between cAMP signaling and the MAPK pathway have been described. PKA-dependent cAMP signaling inhibits CRAF (Cook & McCormick, 1993; Dhillon et al., 2002; J. Wu et al., 1993), while EPAC-dependent cAMP signaling activates BRAF (Laroche-Joubert, Marsy, Michelet, Imbert-Teboul, & Doucet, 2002; Vossler et al., 1997). In addition, cAMP signaling can activate RAS through PDZ-GEF1, also referred to as RapGEF2 or CNrasGEF, which is a RAS guanine nucleotide exchange factor that possesses a cAMP/cGMP-binding domain (Li, Dillon, Takahashi, Earley, & Stork, 2016; Pak, Pham, & Rotin, 2002). Moreover, CREB is reported to induce the expression of the RAF kinase inhibitory protein (RKIP), a well-established inhibitor of RAF kinase (Zhang et al., 2013). RAF kinase inhibitory protein is reported to be downregulated in several types of cancers, including melanoma, leading to overactivation of downstream MAPK signaling (Hagan et al., 2005; Lee, Tian, Sedivy, Wands, & Kim, 2006; Park, Yeung, Beach, Shields, & Yeung, 2005). It is also well established that constitutive activation of the MAPK pathway, most commonly by mutations in BRAF and RAS, promotes melanoma development, invasion, metastasis, and angiogenesis (Michaloglou, Vredeveld, Mooi, & Peeper, 2008; Panka, Atkins, & Mier, 2006). Cross talk between the MAPK pathway and cAMP signaling suggests a possible role of cAMP signaling in melanomagenesis. However, the role of cAMP in melanoma is not well understood, and studies that examine the effect of cAMP signaling in the context of melanoma often report contradictory results.

3.1 | Evidence for the tumorigenic effect of cAMP

Many studies support a role for cAMP signaling in the promotion of melanomagenesis. Rodriguez et al. demonstrated that in the BRAF(V600E)/PTEN-null mouse model, topical application of FSK accelerates melanoma development and that treatment with an adenylyl cyclase inhibitor delays tumor growth (,2017, 2018). Similarly, in vitro treatment with FSK stimulated proliferation in mouse and human primary melanoma cell lines (Rodriguez et al., 2017). This group also demonstrated that the pro-tumorigenic effect of cAMP in melanoma was not dependent on PKA activation, but instead functioned via the EPAC-RAP1 axis (Rodriguez et al., 2017). EPAC is a cAMP effector protein that also functions as a guanine nucleotide exchange factor for Ras-related protein 1 (RAP1). EPAC1 is reported to be upregulated in metastatic melanoma compared to primary tumors (Baljinnyam et al., 2010), and its role has been associated with tumor progression in the context of melanoma (Figure 3). For example, Baljinnyam et al. showed that EPAC1 in melanoma cells increases their migration and somehow induces the migration of neighboring lower expressing EPAC1 melanoma cells (2014). This is consistent with this group's previous discovery that EPAC1 activates Ca(2+) release from endoplasmic reticulum to increase actin assembly and cell migration (Baljinnyam et al., 2010), and that EPAC1-rich melanoma cells promote angiogenesis by increasing migration of neighboring endothelial cells via fibroblast growth factor 2 (FGF2)-mediated

signaling (Baljinnyam et al., 2014). The EPAC1 effect on FGF2 signaling is likely because EPAC1 increases the N-sulfation of heparan sulfate, which is required for FGF2 to bind its receptor (Baljinnyam et al., 2011).

However, in contrast to above, an increase in cAMP signaling by FSK can also inhibit cell proliferation of metastatic melanoma cells in vitro (Rodriguez et al., 2017). Interestingly, the EPAC-RAP1 axis is also required for the anti-proliferative effect of FSK on metastatic melanoma. These seemingly opposing effects of the cAMP-EPAC-RAP1 pathway in melanoma (pro-proliferative in primary tumor, but anti-proliferative in metastatic tumor) may be explained by the opposing effects of proliferation and invasion (Rodriguez & Setaluri, 2019). In melanoma, phenotypic switch from a proliferative to an invasive state is accompanied by slower growth rate and greater motility (Hoek et al., 2008). Anti-proliferative effects of the EPAC-RAP1 axis, therefore, may be a sign of this phenotypic switch and be interpreted as pro-tumorigenic, especially when also considering the positive role of EPAC1 on cell migration and angiogenesis, which increase metastatic potential (Figure 3). However, it should be noted that these results rely on the use of FSK, which strongly stimulates cAMP synthesis, can overwhelm PDEs, and can lead to the simultaneous activation of multiple microdomains; thus, these data may not be reflective of physiological cAMP effects but instead are reflective of the supra-physiological cAMP effects only seen with FSK (Bacskai et al., 1993).

Another study reports a tumorigenic effect of cAMP signaling in melanoma via PKA-dependent activation of the MAPK pathway. Calipel et al. examined the effect of PKA-dependent cAMP signaling in BRAF wild-type and BRAF mutant uveal melanoma cells (2006). Inhibition or deletion of PKA decreased cell proliferation and reduced BRAF and ERK1/2 activity in BRAF wild-type cells, but the same modulation of PKA did not affect BRAF mutant cells. This suggests that PKA-dependent cAMP signaling is crucial in promoting the proliferation of BRAF wild-type uveal melanoma cells (Figure 3). Interestingly, this group also demonstrated that RAP1 activity is not affected by PKA inactivation and that RAP1 depletion does not affect BRAF or ERK1/2 activity (Calipel et al., 2006). Taken together, these findings suggest that the tumorigenic effect of cAMP signaling in BRAF wild-type uveal melanoma cells is mediated by PKA-dependent but not EPAC/RAP1-dependent pathways (Figure 3).

Moreover, several studies support the role of CREB as a "master switch" in melanoma progression (Braeuer, Zigler, Villares, Dobroff, & Bar-Eli, 2011). In melanoma, overexpression of CREB is associated with transition from radial to vertical growth phase (Braeuer et al., 2011; Mobley, Braeuer, Kamiya, Shoshan, & Bar-Eli, 2012; Poser & Bosserhoff, 2004), while inhibition of CREB by its dominant-negative form KCREB decreases metastatic potential in vivo (Xie et al., 1997). Melnikova et al. elucidated one possible mechanism of CREB-mediated oncogenesis by demonstrating that CREB inhibits the transcription factor activator protein-2α (AP-2α) (2010). Loss of AP-2α is one of the hallmarks of melanoma progression, as it regulates a number of genes associated with metastatic potential including *c-KIT*, melanoma cell adhesion molecule (*MCAM/MUC18*), protease-activated receptor-1 (*PAR-1*), and vascular endothelial growth factor (*VEGF*) (Bar-Eli, 1997; Braeuer et al., 2011; Huang, Jean, Luca, Tainsky, & Bar-Eli, 1998; Jean et al., 1998; Melnikova et al., 2010; Ruiz et al., 2004; Tellez et al., 2007; Tellez, McCarty, Ruiz, & Bar-Eli, 2003). CREB is also reported to stimulate matrix metalloproteinase (MMP) 2, which is thought to contribute to melanoma progression and metastasis (Melnikova, Mourad-Zeidan, Lev, & Bar-Eli, 2006), and negatively regulate cysteine-rich protein 61 (CCN1/CYR61), a melanoma tumor suppressor gene (Dobroff et al., 2009). More recently, Shoshan et al. identified a novel target for CREB: RNA-editing enzyme adenosine deaminase acting on RNA 1 (ADAR1) (2015). This group found that CREB negatively regulates ADAR1 and that ADAR1 inhibits tumor growth and metastasis in vivo (Shoshan et al., 2015). Taken together, cAMP signaling can exert tumorigenic effects in melanoma by activating CREB, which regulates multiple genes linked to melanoma progression (Figure 3).

3.2 | Evidence for the anti-tumorigenic effect of cAMP

In contrast to above, other studies have shown that impairment in cAMP signaling promotes melanomagenesis. As described in the previous section, the MC1R-cAMP-MITF pathway is crucial for the synthesis of eumelanin, which protects cells from UV-induced cytotoxicity and reduces the risk of melanoma (Hauser et al., 2006; Kadekaro, Kanto, Kavanagh, & Abdel-Malek, 2003; Nasti & Timares, 2015; Palmer et al., 2000; Rouzaud et al., 2005; Scott et al., 2002). This protective role of cAMP in melanoma is further reinforced by a study showing that in mouse models lacking functional MC1R, topical application of FSK not only rescues pigmentation but also reduces tumor formation (D'Orazio et al., 2006). Moreover, Mitra et al. (2012) demonstrated that MC1R inactivation can promote melanoma formation via a UV-independent mechanism that is driven by pheomelanin-induced oxidative damage (Mitra et al., 2012). Therefore, current evidence suggests that impairment of MC1R-induced cAMP signaling increases both the UV-dependent and UV-independent risks of melanoma development (Figure 4).

The anti-tumorigenic effect of MC1R-induced cAMP signaling is mediated by mechanisms beyond pigmentation. MC1R stimulation enhances the repair of UV-induced DNA photolesions by improving nucleotide excision repair (NER) and reduces the accumulation of ROS-induced DNA damage and double-strand breaks (Bautista et al., 2020; Castejón-Griñán, Herraiz, Olivares, Jiménez-Cervantes, & García-Borrón, 2018; Holcomb et al., 2019; Jarrett & D'Orazio, 2017; Jarrett, Wolf Horrell, Boulanger, & D'Orazio, 2015; Jarrett et al., 2014; Kadekaro et al., 2012; Maresca et al., 2010; Song et al., 2009; Swope, Starner, Rauck, & Abdel-Malek, 2020). MC1R-induced cAMP signaling improves NER via PKA-mediated phosphorylation of ataxia telangiectasia and Rad3-related protein (ATR), which recruits a key NER protein, xeroderma pigmentosum complementation group A (XPA), to sites of nuclear UV photodamage (Jarrett et al., 2014, 2015; Swope et al., 2020). AKAP12 is

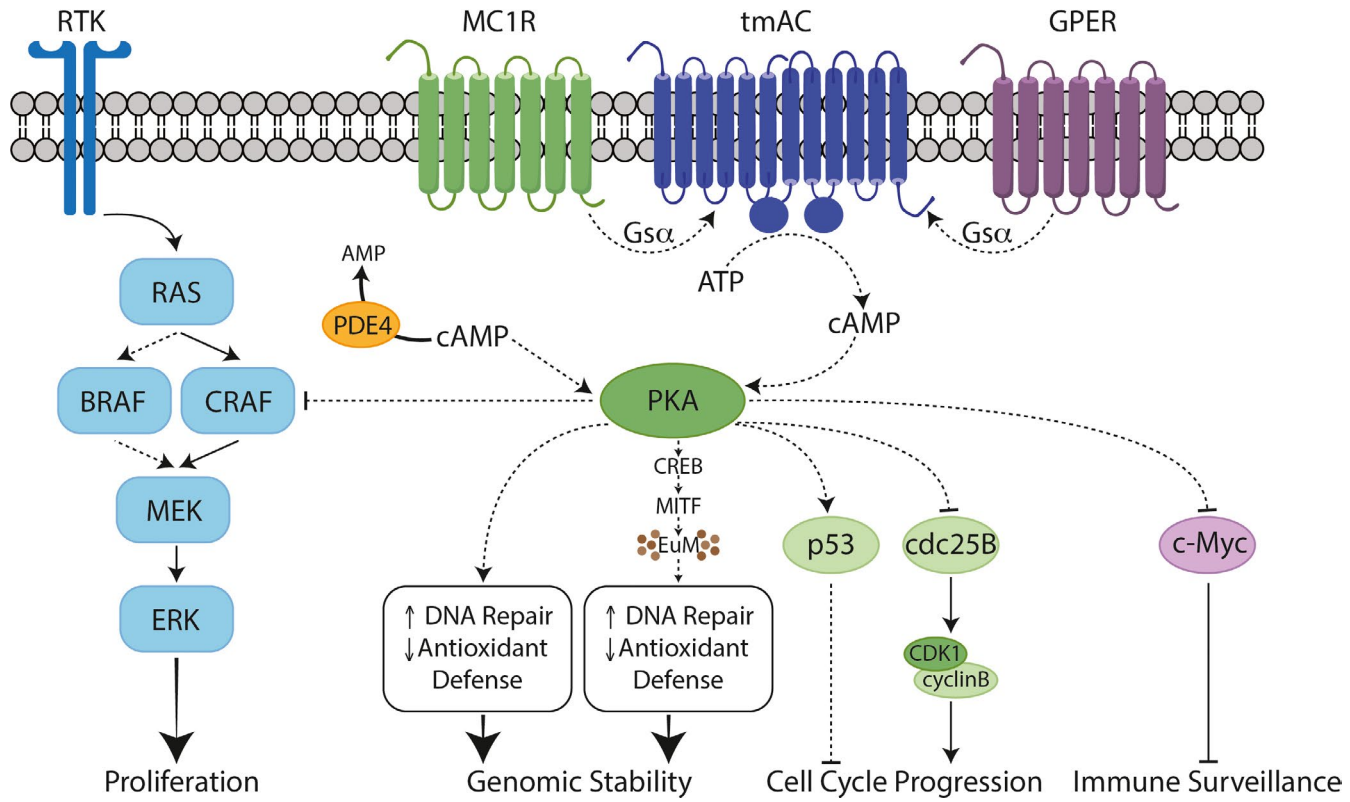

FIGURE 4 Mechanisms of the anti-tumorigenic effect of cAMP in melanoma. Upregulation of PDE4 degrades cAMP and attenuates the PKA-dependent suppression of CRAF. This allows for the switch from relying on BRAF to CRAF to activate the MAPK pathway downstream of RAS, which occur during the malignant transformation of RAS-mutated melanoma. MC1R-induced, tmAC-generated cAMP exerts anti-tumorigenic effect in melanoma by inducing pigmentation, improving DNA repair, and reducing oxidative stress. MC1R activation also regulates the cell cycle by stabilizing p53 and inhibiting cdc25B. GPER-induced, tmAC-generated cAMP leads to loss of c-Myc, a transcription factor associated with enhanced escape from immune surveillance. RTK, receptor tyrosine kinase; PDE, phosphodiesterase; MC1R, melanocortin 1 receptor; GPER, G protein-coupled estrogen receptor; Gsα, Gs protein α subunit; PKA, protein kinase A; CREB, cAMP response element-binding protein; MITF, microphthalmia transcription factor; EuM, eumelanin; CDK1, cyclin-dependent kinase 1

also a required participant of this repair complex that mediates cAMP-enhanced NER (Jarrett, Wolf Horrell, & D'Orazio, 2016). It is important to note that this cAMP-enhanced NER is independent of MITF activation, and MC1R-mediated pigmentation is independent of ATR, implicating that MC1R-induced cAMP signaling mediates DNA repair and pigment synthesis via distinct mechanisms or cAMP microdomains (Wolf Horrell, Jarrett, Carter, & D'Orazio, 2017). MC1R activation is also reported to increase the expression of DNA damage response proteins such as XPC and γH2AX, upregulate the expression of base excision repair enzymes, and activate antioxidant enzymes such as catalase via PKA-dependent phosphorylation (Kadekaro et al., 2010, 2012; Maresca et al., 2010; Song et al., 2009; Swope et al., 2014). Similarly, studies examining the effects of FSK reported that FSK-induced cAMP signaling protects against oxidative stress by decreasing nitric oxide levels and enhancing antioxidant enzyme copper/zinc superoxide dismutase (Cu/ZnSOD) (Al-Ayadhi, Korish, & Al-Tuwaijri, 2006; Mishima, Baba, Matsuo, Itoh, & Oishi, 2006). Taken together, MC1R-induced cAMP signaling exerts its anti-tumorigenic effect in melanoma, not only by increasing eumelanin, but also by improving DNA repair and reducing oxidative stress (Figure 4).

Similarly, GPER-induced cAMP signaling induces pigmentation and exerts an anti-tumorigenic effect in melanoma. GPER activation by either estrogen or the specific GPER agonist, G-1, induces differentiation and decreases the proliferative capacity of mouse and human melanoma cells (Natale et al., 2018). G-1 treatment in melanoma-bearing mice also increases the infiltration of T cells and NK cells within the tumors, suggesting a more robust immune response (Natale et al., 2018). This is because GPER signaling induces the loss of c-Myc, a well-established onco-driver known to antagonize differentiation, promote proliferation, and enhance escape from immune surveillance (Casey, Baylot, & Felsher, 2017; Natale et al., 2018; Schlagbauer-Wadl et al., 1999) (Figure 4). Natale et al. reinforce the importance of c-Myc loss for the anti-proliferative effects of GPER signaling by demonstrating that protein degradation of c-Myc is PKA-dependent and that melanoma cells engineered to maintain c-Myc protein levels are resistant to G-1 (2018). These anti-melanoma effects of GPER signaling are particularly interesting in light of the fact that female sex is

associated with a decreased incidence and favorable melanoma prognosis (Joosse et al., 2013).

Moreover, other studies have reported that MC1R-induced cAMP signaling regulates the cell cycle. Lyons et al. showed that MC1R activation in melanoma cell lines caused delayed progression from G2 into mitosis by inhibiting cdc25B, a cyclin-dependent kinase 1-activating phosphatase (2013). Another study demonstrated that stimulation of MC1R by α-MSH contributes to the phosphorylation and stabilization of p53, a major tumor suppressor protein that plays a critical role in regulating both the G1/S and G2/M checkpoint (Kadekaro et al., 2012).

More evidence supporting the anti-tumorigenic effect of cAMP comes from studies that investigated the cross talk between cAMP signaling and the MAPK pathway. It has been shown that CRAF expression is increased in both primary and metastatic melanomas compared to benign nevi (Jilaveanu et al., 2009). This could be explained by Dumaz et al.'s study demonstrating that melanomas harboring RAS mutations rely on CRAF to activate the MAPK pathway, whereas benign melanocytes rely on BRAF (2006). CRAF is inhibited by PKA-mediated cAMP signaling (Cook & McCormick, 1993; Dhillon et al., 2002; Wu et al., 1993); therefore, a switch from relying on BRAF to CRAF in RAS-mutated melanoma requires an inhibition of cAMP signaling (Figure 4). One mechanism of decreasing cAMP signaling is an increase in PDE4 activity. In mouse melanocytes with RAS mutations, cAMP levels are reportedly inhibited by the overexpression of PDE4 (Dumaz, 2011). PDE4 overexpression occurs during malignant transformation, thereby allowing CRAF to become activated (Dumaz, 2011). Furthermore, treatment of melanoma cells with a PDE4 inhibitor in combination with FSK suppresses CRAF activity, decreases cell proliferation, and induces apoptosis (Drees, Zimmermann, & Eisenbrand, 1993; Marquette, André, Bagot, Bensussan, & Dumaz, 2011), while ectopic expression of PDE4D2 promotes melanoma proliferation both in vitro and in vivo (Lin et al., 2013). Interestingly, the PDE4D isoforms were recently shown to be overexpressed in numerous types of cancers, including melanoma, suggesting that disruption of the cAMP pathway may be a more general phenomenon in cancer (Delyon et al., 2017; Lin et al., 2013). In the context of melanoma, PDE4D expression was increased in patients with advanced melanomas and was negatively associated with survival (Bogunovic et al., 2009; Delyon et al., 2017). Several studies have revealed other possible mechanisms by which increased PDE4 activity promotes tumor progression in melanoma. Delyon et al. showed that in BRAF-mutated melanoma cells, PDE4D promotes melanoma invasion by interacting with focal adhesion kinase (FAK) and that inhibiting the interaction between PDE4D and FAK reduces invasion (2017). PDE4 activity can also play an important role in migration via inhibition of PKA-dependent cAMP signaling (Watanabe et al., 2012). Taken together, inhibition of cAMP signaling by increased PDE4 activity may be critical for the proliferation, invasion, and migration of BRAF- and RAS-driven melanomas (Figure 4).

Several studies also suggest a role of PDE8 in CRAF activation, as PDE8A directly interacts with CRAF to protect CRAF from PKA-mediated inhibition (Brown et al., 2013; Maurice, 2013). Pharmacological disruption of this PDE8A-CRAF complex with PPL-008 attenuates downstream MAPK signaling and decreases cell proliferation in vitro (Blair, Walsh, Littman, Marcoux, & Baillie, 2019). This reinforces the concept that impairment in cAMP signaling by increased PDE activity is associated with CRAF activation and oncogenic progression, while restoration of cAMP signaling is protective. Studies examining the role of PDE2 in melanoma also support a protective role of cAMP signaling in melanoma. In human malignant melanoma PMP cell lines, elevation of cAMP levels by PDE2 inhibition increases the number of cells arrested at the G2/M checkpoint and decreases growth and invasion (Hiramoto et al., 2014; Morita et al., 2013).

The effect of differential adenylyl cyclase activity on tumorigenesis, specifically melanoma, is less well understood. Little is known about the expression levels of various tmAC isoforms (ADCY1-9) in melanoma. Expression of sAC (ADCY10), on the other hand, is reported to be diminished in a number of human cancers, including melanoma (Ramos-Espiritu et al., 2016). We also demonstrated that loss of sAC increases cellular transformation in vitro and malignant transformation in vivo, suggesting a role of sAC as a tumor suppressor; however, the mechanism of tumor suppression is not known. Multiple studies have reported that sAC localization is not static but changes upon cellular transformation (Magro, Crowson, Desman, & Zippin, 2012; Magro, Yang, Zippin, & Zembowicz, 2012; Zippin et al., 2004, 2010). Whereas sAC is cytoplasmic in benign melanocytes, it is nuclear during malignant transformation (Magro, Crowson, et al., 2012). This suggests that nuclear expression of sAC may have an important role during early melanoma transformation.

3.3 | Evidence for the role of cAMP in therapy response

Several studies have also examined the role of cAMP in the response of melanoma to therapeutic interventions. Johannessen et al. performed a systematic gain-of-function resistance study where they expressed more than 15,500 genes individually in a BRAF V600E melanoma cell line to examine the effect of each gene on the sensitivity of melanoma to MAPK pathway inhibition (2013). This study revealed a set of genes whose overexpression was associated with resistance: those encoding for the key components of plasma membrane cAMP signaling microdomains, including GPCRs, tmACs, PKA, and CREB (Johannessen et al., 2013). In addition, increased expression of adipocyte enhancer-binding protein 1 (*AEBP1*) was also reported to confer resistance to BRAF inhibition in vivo, and increased activation of CREB was critical for *AEBP1* upregulation in resistant melanoma cells (Hu et al., 2013). These studies suggest a role for cAMP signaling in therapy resistance.

However, another study suggests that loss of cAMP signaling is associated with resistance to BRAF inhibitors. Krayem et al. showed that in BRAF wild-type and NRAS wild-type melanoma cells, resistance to BRAF inhibitor is associated with lower cAMP levels, and restoring cAMP levels with FSK and IBMX, a global

inhibitor of PDEs, sensitizes melanoma to BRAF inhibitor (2014). In addition, recent evidence suggests that cAMP signaling downstream of GPER renders melanoma cells more vulnerable to immunotherapy. Natale et al. demonstrated that pretreatment of melanoma cells with G-1 synergized with systemic administration of anti-programmed cell death 1 (αPD-1) antibody to inhibit tumor growth and extend survival (2018).

As discussed above, it is important to note that many of these studies above examine cAMP signaling using pharmacological agents such as FSK. FSK is a molecule that binds to the allosteric regulatory site of tmACs and stimulates its activity (Tesmer et al., 1999); however, FSK does not stimulate sAC (Buck et al., 1999; Kleinboelting et al., 2014). Therefore, the role of sAC in cAMP-dependent effects in melanoma has not been explored. Given that distinct intracellular cAMP microdomains contribute to differential cellular processes, examination of cAMP at the level of individual microdomains will be important to better understand how this single second messenger has such a disparate effect on melanoma biology.

4 | CONCLUSION

Cyclic adenosine monophosphate has diverse effects on benign and malignant melanocyte biology suggesting the existence of numerous independent cAMP signaling pathways in this cell. Our general understanding of cAMP signaling in benign and malignant melanocytes is largely based on studies which were not designed to study cAMP at the level of microdomains. Whereas the role of cAMP signaling in melanocytes via the canonical MC1R/tmAC signaling pathway at the plasma membrane is well established, the role of non-canonical sAC cAMP signaling pathways within the cytoplasm and organelles has only recently been appreciated. Expanding our understanding of the differential role of spatially distinct cAMP microdomains will help elucidate mechanisms that mediate the different functions of cAMP signaling in melanocyte biology.

CONFLICT OF INTEREST

J.H.Z. owns equity interest in CEP Biotech which has licensed commercialization of a panel of monoclonal antibodies directed against sAC. J.H.Z. is a paid consultant and on the medical advisory board of Hoth Therapeutics. J.H.Z. is on the medical advisory board of SHADE, Inc. J.H.Z. is an inventor on a US patent 8,859,213 on the use of antibodies directed against soluble adenylyl cyclase for the diagnosis of melanocytic proliferations.

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