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Role of cAMP and its Effectors towards Maintaining the Integrity of the Endothelial Cell Junction. A review

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ABSTRACT

Cyclic adenosine monophosphate (cAMP) is a pleiotropic second messenger that plays crucial role in many biological processes. cAMP is a product of adenosine triphosphate and is employed for intracellular signal transduction in different organisms, via the cAMP-dependent pathway. The major intracellular functions of cAMP are transduced by protein kinase A (PKA), exchange proteins directly activated by cAMP (EPACs), families of universally expressed cAMP effector proteins and by Cyclic Nucleotide-gated (CNG) ion channels,. Cyclic AMP is an intracellular signalling molecule well-known in improving the barrier function in vascular endothelial cells. The focus of this review is to discuss the role of cAMP and its sensors on maintenance of endothelial cell (EC) junctions as well as the control of permeability and vascular integrity EC junctions. Current knowledge regarding the molecular role of PKA, CNG as well as EPAC were discussed. Proper understanding of the role played by each of these effectors will provide an attractive therapeutic targets for the treatment various disease conditions which interfere with the integrity of the EC barrier including inflammation and cancers.

Keywords: Cyclic adenosine 3',5' monophosphate (cAMP), Protein Kinase A (PKA), Exchange protein directly activated by cAMP (Epac), Cyclic Nucleotide-gated (CNG), Endothelial cell junctions.

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INTRODUCTION

Cyclic adenosine 3',5' monophosphate (cAMP), a nucleotide discovered in 1957 by Earl Sutherland and colleagues, is a ubiquitous intracellular second messenger capable of modulating a wide range of biological processes including differentiation, secretion, gene transcription, regulation of cell shape, cytoskeletal remodelling, proliferation, apoptosis, adhesion, and migration (1). The cellular functions of cAMP are mediated by two families of ubiquitously expressed cAMP effector proteins, namely: Protein kinase A (PKA), also known as cAMP-dependent protein kinase, and exchange protein directly activated by cAMP (EPAC), also known as cAMP-regulated guanine nucleotide exchange factor (cAMP-GEF), as well as tissue-restricted cyclic nucleotide-gated (CNG) ion channels and hyperpolarization-activated cyclic nucleotide –modulated (HCN) channels. This review describes the role played by the cAMP effectors towards the enhancement of the EC barrier as well as the therapeutic importance of Epac1 agonist / antagonist.

An overview of Cyclic adenosine monophosphate synthesis and degradation

The cAMP is synthesised via the activity of a family of ubiquitous enzymes called adenylyl cyclases, also initially referred to as adenylate cyclases (ACs), upon ligand binding to a G-protein-coupled receptor (GPCR). A GPCR is a 7 transmembrane protein present in the plasma membrane. Extracellular signals including hormones, neurotransmitters, and growth factors, amongst others, bind to the cognate GPCR to cause conformational changes in the associated heterotrimeric G-proteins (2), which are coupled to the intracellular surface of GPCRs. The G-proteins on the intracellular surface during the resting state (inactive) are made up of a Gα and Gβγ guanine nucleotide-binding subunits bound together as one unit. At the inactive state, the complex is bound to guanidine diphosphate (GDP) on the Gα subunit. Upon GPCR activation, the Gαβγ complex subsequently induces GDP/guanidine triphosphate (GTP) exchange thereby, leading to subsequent Gα-GTP and Gβγ dissociation (2) followed by downstream events. This subsequently leads to the activation of ACs. The Gα subunit exists either as stimulatory G-protein (Gs) where it is coupled positively to AC or as inhibitory G-protein (Gi) form which is negatively coupled to AC. The AC then converts adenosine triphosphate (ATP) into cAMP (3). Typically, during the resting state, the intracellular concentration of cAMP is less than 10 nM, however, this concentration can rise to 20-fold upon ligand binding to GPCR as shown in ECs (Figure 1) (4). In mammals there exists 10 ACs, nine of which are membrane-bound thus forming the transmembrane adenylyl cyclases (tmACs) i.e., AC1-AC9 (3). Of the nine tmACs, AC6 is the predominant isoform found to be expressed in ECs (5). AC6, as well as AC5, are the two members belonging to the calcium-inhibitable ACs group (6). In addition to tmACs there exist a soluble adenylyl cyclase (sAC), which is not membrane-bound and is largely found in the testis (7-9). These ACs are also capable of synthesizing cAMP in a cytosolic pool (9). sAC exhibit a variety of functions that are distinct from those of tmACs (7, 9).

Degradation of the intracellular cAMP level is known to be catalysed through the action of phosphodiesterases (PDEs) (10). PDEs are an enzyme superfamily that is capable of converting cAMP to AMP through the hydrolysis of the phosphodiester bond of intracellular second messenger molecules including both cAMP and cGMP (11, 12). In mammals, the PDEs are made up of 11 distinct enzyme families with more than 50 distinct isoforms (13-15). PDE expression varies between the various cell types, with different cells expressing a subset of PDEs from the 11 families (16, 17). Of the 11 PDEs, only eight members possess the ability to hydrolyse cAMP (16, 18). Netherton and colleagues demonstrated that human vascular endothelial cells primarily express the cGMP-stimulated PDE2, the cGMP-inhibited PDE3, the cAMP-specific PDE4 and the cGMP-specific PDE5 and that the levels of these enzymes vary within the endothelial cells along the vascular network (19). This is in cognisance with the earlier

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report by Lugnier and colleagues where they showed PDE3 and PDE4 to be the primary enzymes for the hydrolysis of cAMP within the ECs (20). Additionally, the pattern of PDE expression has been found to vary depending on the passaging number in bovine aortic endothelial cells (BAECs), with PDE2 and PDE4 expressed in cells with of between 4-6 passages and cells at passage 10 predominantly expressing PDE4 (21, 22). The spatial distributions of PDEs act to simultaneously regulate the cAMP gradients, on one hand preventing cAMP diffusion, on the other ensuring specific activation of nearby signalling complexes (13). Furthermore, evidence has pointed to the partial role played by PDEs towards the compartmentalisation of cAMP (23), where PDE4D4, a splice variant of the PDE4 expressed in pulmonary microvascular endothelial cells, was demonstrated to interact with α-II spectrin within the membrane to subsequently limits the diffusion of cAMP to the cytosol (23). Taken together the PDEs through their hydrolytic action play an important regulatory role in controlling cAMP availability and curtailing unwanted downstream effects that could result for high intracellular levels of cAMP.

The cAMP pathway and endothelial cells

cAMP as earlier stated is a derivative of ATP, that controls a wide range of biological processes (22). The cAMP signalling pathways operate in a stimulation specific manner as evident by the compartmentalization of proteins that produce, degrade as well as activate the cAMP effectors in the cell (18). In the vascular endothelial cell cAMP via the activation of EPAC 1 acts to enhance endothelial barrier (22) (Figure 2).

cAMP sensors in Endothelial Cells

cAMP exerts its effects via three main effectors namely Protein kinase A (PKA) (22), Exchange protein directly activated by cAMP (Epac) (24, 25) and Cyclic-nucleotide-gated ion channels (26).

Protein Kinase A (PKA)

Protein kinase A was among the first of the protein kinase families discovered by Walsh and colleagues in rabbit in 1968 (27). PKA holoenzyme exists as a tetrameric complex (R2C2) consisting of two catalytic subunits and two regulatory subunits. The C subunit bears the active site and has to be phosphorylated at Threonine 197 (T197) by phosphoinositide-dependent protein kinase (PDK1) (28) for the proper maturation and optimal biological activity of the enzyme (29). PKA holoenzyme is identified based on the R subunits as PKA (I), with RI and RII for each of the designated classes. Activation of the dormant PKA requires binding of four cAMP molecules to the two regulatory subunits. (22, 29). This cooperative cAMP binding results in a conformational change of the PKA enzyme complex, which subsequently leads to the release of the catalytic subunit and further ensuing phosphorylation of substrates (30, 31). To activate PKA, the local cAMP levels must exceed the basal cellular threshold, however simultaneously cAMP molecules are constantly being degraded by PDEs to adenosine monophosphate (AMP) resulting in re-binding of the R subunit to the activated catalytic subunits. Normally R and C subunits exist in a ratio of 1:1 in tissues, however the relative amount of RI and RII varies and depends on various conditions such as hormonal and physiological changes (32). Treatment of rat hepatocytes with dibutyryl cyclic AMP (db-cAMP) specifically activates Type I PKA, while to 10 μM it triggers activation of Type II PKA (33). PKA has been reported to retain its kinase activity sequel to its being compartmentalized to discrete intracellular locations via the association with anchoring proteins (34). The RII subunit of PKA is responsible for compartmentalisation through being tethered by A-kinase anchoring proteins (AKAPs) to specific subcellular structures (34). Additionally, RI and RII specific AKAPs have also been identified (35). There are close to 50 human AKAPs (52 and all possess a conserved RII-binding site which is made up of amphipathic helices through which it anchors PKA (36). These complexes are subsequently guided to particular subcellular sites by protein-protein or protein-lipid interaction (37). The phosphorylation of the target proteins and the AKAP itself have both been attributed to the AKAP/PKA complexes (38). PKA is a kinase which is concerned with phosphorylation of various proteins which subsequently lead to activation or deactivation of the target protein. Phosphorylation cascades eventually lead to changes in the structure of the endothelial barrier to finally result in the opening of the paracellular pathways (39). As earlier stated, barrier structure in the endothelium is closely maintained through an important interaction/balance between endothelial cytoskeleton (actin and myosin) (40) and the adheren junctional complex (41). Within the endothelial barrier, PKA acts to inhibit EC contraction. In vascular endothelial cells, phosphorylation of myosin light chain (MLC) is carried out by the MLC kinase (MLCK) enzyme. MLCK is a calcium/calmodulin-dependent enzyme required for actinomyosin generated contraction (22, 42). The MLCK in human ECs, a protein with a molecular mass of 214 kDa, is derived from a single gene on chromosome 3 (22, 43). MLC phosphorylation occurs as mono-phosphorylation at Ser19 or di-phosphorylation at Ser19/Thr18, which results in actinomyosin contraction (22, 44). PKA is capable of phosphorylating, and consequently inactivating, MLCK (22, 44). At the ECs adherens junctions, intracellular (VE)-cadherin domain interacts with the actin cytoskeleton via α-catenin, β-catenin, γ-catenin and p120 to maintain junctional strength and paracellular permeability (22, 45). Previous studies have shown that separation of the VE-cadherin–catenin complex from the cytoskeleton eventually results in the dysfunction endothelial barrier (46). Phosphorylation of β-catenin ultimately enhances the separation of junctional proteins from their cytoskeletal attachments (22, 47). This junctional disorganization is directly as a result of actin stress fibres formation, which is eventually inhibited by PKA (22, 48). PKA phosphorylates RhoA on Ser188, thus inactivating the GTPase, and as such causing cell contraction (22, 49, 50) . In ECs, RhoA regulates actin-myosin-induced endothelial cell contraction (22). ROCK (Rho-kinase) an effector of RhoA, induces phosphorylation of myosin light chain phosphatase regulatory subunit to consequently lower phosphatase activity, and as such causes cell contraction (51, 52). In addition to the PKA direct effect in inhibition of endothelial contraction, it also acts through RAC activation, a member of the Rho family of small guanosine triphosphatases (GTPases) to produce a similar inhibitory effect on endothelial cell contraction (22, 53). Activation of Rap1, a small GTPases, mediated activation of RAC1 to thereby lead to inhibition of RhoA, stabilizing the EC barrier (54, 55). All these findings above suggest promising targets for the possible therapeutic control of cancer metastasis when fully explored (Figure 1).

Cyclic nucleotide-gated ion channels (CNG)

Cyclic nucleotide-gated (CNG) ion channels were first discovered in 1985 by Fesenko and colleagues in the plasma membrane of the outer segment of rod cells in the retina (56). CNG channels have also been found to exist in olfactory neurons (57). The CNG channels are non-selective cation channels permeable to both monovalent and divalent cations, through the binding of either cAMP or cGMP (26). Previous studies have fully determined the

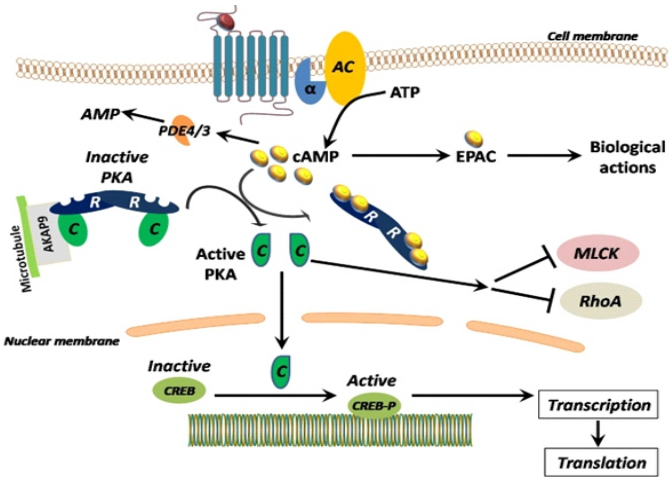


Figure 1. Summary of PKA activation pathway. The figure illustrates the mechanisms of PKA pathway activation in endothelial cells. Initial activation of adenylate cyclase (AC) induces the formation of cAMP (yellow) from ATP, thereby raising the level of intracellular cAMP. Four cAMP molecules bind to the two regulatory domains (blue) of the inactive PKA holoenzyme complex. cAMP binding causes conformational change which then leads to the release of the two catalytic subunits (green) from the regulatory subunit dimer of the inactive PKA. The catalytic subunit can then act on its effectors within the cytosol or could be carried into the nucleus where it phosphorylates the inactive CREB. Within the cytoplasm, PKA can phosphorylate both MLCK and RhoA, inhibiting endothelial cell contraction as well as the disruption of the endothelial barrier. The intracellular cAMP gradient is maintained through the hydrolytic action of PDEs (3 and 4) (brown) on cAMP, producing AMP. Intracellular compartmentalisation of PKA is provided by the A Kinase anchoring proteins (AKAP9).

Cyclic nucleotide-gated ion channels (CNG)

functional role of CNG channels in both retinal photoreceptors (58) and also in olfactory sensory neurons (59). In similar related studies, retinal degeneration and colour blindness were found to be associated with a mutation in CNG channel genes. Furthermore, CNG channels are found to be expressed in vascular endothelial cells and as well as in vascular smooth muscle cells and are concerned with Ca^{2+} influx (61). Vascular endothelial cells have high expression of CNGA1, in contrast to vascular smooth muscle cells in which expression is much lower (61). In another study, CNGA2 was found to be strongly expressed in both vascular endothelial cells and vascular smooth muscle cells of human arteries (62). Recently Almke and colleagues reported cAMP activation of cyclic nucleotide-gated (CNG) channels in human cerebral microvascular endothelial cells induced Ca2+influx, which results in an increase in gap junction coupling (63). Overall these studies demonstrated the important role played by CNG channels in endothelium-dependent vascular dilatation (63-65).

Exchange proteins directly activated by cAMP (Epac)

Exchange protein directly activated by cAMP (Epac), also referred to as cAMP-GEF (cAMP-regulated guanine exchange factor) is the most recently identified amongst the three cAMP sensors. The Epac proteins were discovered in 1998 by two independent research groups (25, 66). Two isoforms of Epac (Epac1 and Epac2) were revealed (66). The two isoforms exhibit their functions as guanine-nucleotide exchange factors (GEFs) for the small GTPases Rap1 and Rap2 (67). Rap is a member of the Ras family of small G-proteins. During signalling, Rap hydrolyses GTP from an on (active) state to an inactive (off) state. GEFs are found to be catalysed by this exchange of GDP for GTP (25). However, the intrinsic activity of GTPase-activating proteins (GAPs) was found to enhance the hydrolysis of GTP (68). Epac1 is found to be universally expressed at high levels in the heart, blood vessels, uterus, kidney, and central nervous system , while Epac2 distribution is limited to adrenal gland, and pancreas respectively (25, 66). Epac1 and Epac2 are multi-domain proteins, and share extensive sequence homology. The C-terminal catalytic region of Epac1 contains the CDC25-homology domain (CDC25-HD) (25). This domain is responsible for exchange activity and is further stabilized by a Ras exchange motif (REM) (25). This REM domain is found in all Ras- and Rap1-specific GEFs and is important in the stabilisation of the GEF structure (67, 69). The regulatory region of Epac1 and Epac2 contains a Dishevelled/Egl-10/pleckstrin (DEP) domain, followed by a cyclic nucleotide-binding domain-B (CNBD-B) that is evolutionally conserved to the CNBD of PKA. Between these domains lies a Ras-association (RA) domain (25, 67). Epac acts as an auto-inhibitory domain, blocking the interaction between the catalytic region of Epac and Rap1 in the absence of cAMP (67, 70). The CNBD-A of Epac2 binds cAMP with low affinity and is not essential for auto-inhibition (67, 71). The regulatory and catalytic regions are connected through a linker region which contains both the hinge and the lid (72). In the absence of cAMP, Epac assumes an inactive conformation with the CNBD-B becoming bound to the CDC25-HD via an ionic interaction. This interaction further prevents binding of the Rap effector (67). Rap GTPase then ultimately catalyzes the exchange of GDP for GTP. Epac proteins are involved in a host of cellular functions including; cell adhesion (73, 74), cell-cell junctions (75, 76), exocytosis/secretion (77-80), cell differentiation and proliferation (81), and cardiovascular functions and diseases (22). Concerning ECs, stable contacts between cells are essential for the barrier function. In this context, the integrity of EC junctional complex is important in control of vascular permeability. Dysfunction of the endothelial barrier could eventually result in an increase in vascular permeability which is often encountered in oedema, inflammation, or cancer metastasis (82). It has been fully established that cAMP enhances the endothelial barrier through the inhibition of actin dynamics and actin-myosin-based contractility in a PKA dependent manner (39, 83). Epac1 is the main isoform expressed in vascular endothelial cells (107, 115) and several studies have reported that activation of Epac1–Rap1 signalling pathway by means of 8-pCPT was found to enhanced the barrier function in human umbilical vein endothelium (75, 76, 84). In the same vein, Epac1 activation has been shown to counteract the effect of thrombin-induced permeability in the ECs (75, 76, 85). The stability of the endothelial cell-cell junction was shown to involve an accumulation of junctional proteins at cell contacts, increased VE-cadherin-dependent cell adhesion, and linearization following Epac1 activation (75, 76, 84). Additionally, PDE4D enzyme acts to tether Epac1 into the VE-cadherin–based complex as such promoting interactions between PDE4D-and EPAC1. This interaction plays also an essential role in vascular permeability (86). Epac1 also promotes endothelial barrier function via the modulation of actin cytoskeleton dynamics in human pulmonary artery ECs (75, 76). This involves Rac activation in an Epac-dependent manner together with RAC specific GEFs, Tiam1 and Vav2 to cause actin rearrangements and barrier strengthening (87, 88). Similarly Epac1–Rap1 through a protein complex containing the Rap1 effectors, Radil and Rasip1 and the Rho GTPase–activating protein 29 (ArhGAP29) has been shown to down-regulate RhoA activity, thus resulting in decreased cellular contractility and further stabilization of VE-cadherin–induced cell-cell adhesion (89-91). Lastly, the actin linking protein Ezrin which upon binding to Epac1 in response to an increase in intracellular cAMP level has been suggested to also

play a significant role on EC barrier function (92, 93).
Collectively, these pieces of evidence suggest that Epac/Rap1 signalling plays an essential role for the maintenance of both integrity and function of the endothelial barrier, as such it could serve as a therapeutic target for the control of metastasis when fully explored (Figure 2).

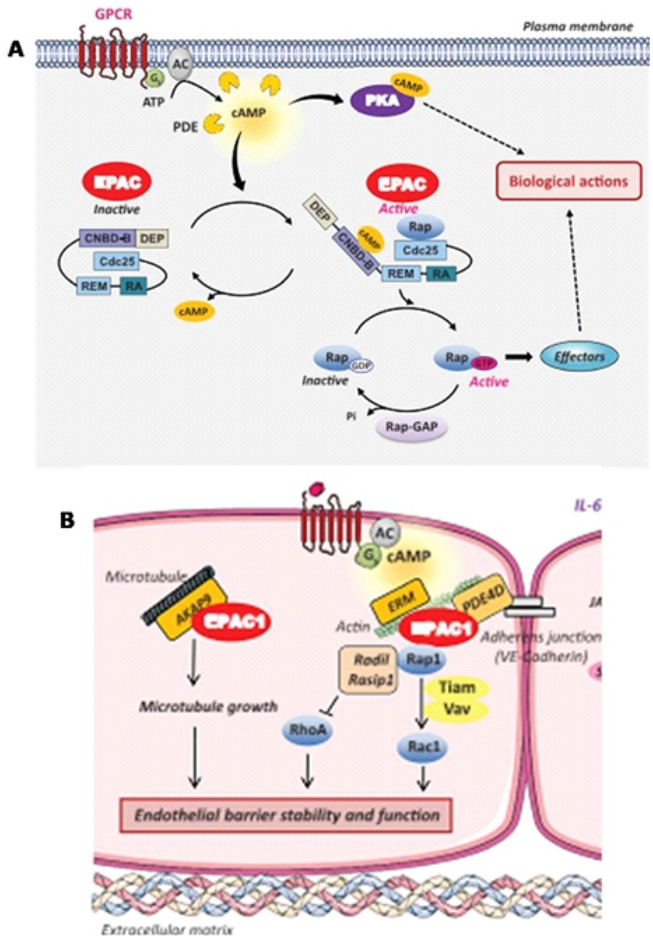


Figure 2. Summary of exchange protein directly activated by cAMP (Epac) activation pathway (A) and Epac function on the vascular endothelial barrier (B). Production cAMP is produced as illustrated in (figure above). The function of Epac is PKA-independent. Unlike PKA, Epac requires binding of a single cAMP molecule for activation. Binding of cAMP to the inactive Epac protein onto the cyclic nucleotide-binding domain (CNBD-B) evoke conformational changes in the Epac protein as shown in (**A**), which then opens up the protein, making the catalytic site available for binding of Rap GTPase. This then leads to the exchange of GDP for GTP. On the other hand, intrinsic hydrolysis of GTP is carried out by the Rap-GTPase–activating proteins (Rap-GAPs) to inactive the GTPase. (**B**) Epac1 maintains the endothelial barrier via interaction with A-kinase anchoring protein 9 (AKAP9) promoting the growth of microtubule as shown. It also acts to modulate RhoA (via Radil and Rasip1) and RAC1 (via the Rac-GEFs, Tiam and Vav) activity as such enhancing the stability of the endothelial barrier. Also, Epac1 forms a complex with PDE4D at the region of vascular adherens junctions (VE-cadherin), which subsequently interacts with Ezrin/radixin/moesin (ERM) molecules forming a complex to further strengthen the endothelial barrier. Adapted with permission from Wolters Kluwer Health, Inc., Circulation Research, Cyclic AMP Sensor EPAC Proteins and Their Role in Cardiovascular Function and Disease, Frank Lezoualc'h, Loubina Fazal, Marion Laudette, et al, 2016.

Therapeutic role of Epac 1 agonist and antagonists

Several form of pharmacological agents that target the cAMP system have been in use as therapeutic agents for conditions including asthma (94, 95), chronic obstructive pulmonary (96) disorder among others. Since the discovery Epac proteins in 1998, efforts have been geared towards developing agents for a more specific targeted cAMP-based therapies with the aim of limiting the off-target effects which could have result from a broad treatment. These unwanted effects include nausea, vomiting, cardiac inotropy as well as chronotropy (97). As earlier stated in the previous section Epac 1 isoform found to be universally expressed in the heart, blood vessels, uterus, kidney, and central nervous system (25, 66). As several reports in the literature have demonstrated the essential role of Epac 1 in the regulation of diverse cAMP-dependent biological processes, specific regulation of Epac 1 via pharmacological modulators in form of agonist / antagonist may play a role as an attractive therapeutic target in several medical conditions.
Within the vascular system Epac 1 in addition to playing a role in the stabilisation of vascular endothelial cadherin (VE-cadherin) junctional complexes between adjacent cells (75, 76), it also induces suppressor of cytokine signalling (SOCS3) gene expression in vascular endothelial cells. This further results in suppression of the JAK–STAT activation evoked by the sIL-6Rα/IL-6 trans-signalling complex (98), which subsequently inhibit proinflammatory IL-6 signalling in vascular endothelial cells which could lead to the development of neointimal thickening (99), hypertension (100), vascular dysfunction (101) as well as myocardial infarction (102). In another study inhibition of Epac 1 via the application of its antagonist was reported to block the adhesion as well as the invasion of has bacteria and rickettsia to the vascular endothelial cells (103).
Furthermore, in a recent review Muayad and colleagues described the pleiotropic role of exchange protein directly activated by cAMP 1 in various cancers (104). Numerous studies have reported the critical role played by Epac 1 during the process of invasion and metastasis of quite a lot of cancers, chiefly those of epithelial origin (73, 105-111). Epac 1 has been reported to enhance invasion and metastasis in melanoma and similarly also promotes metastasis and cellular proliferation in prostate cancer (104, 112-114). Additionally in ovarian cancer, Epac 1 has been reported to exert a pro-migratory effect in some cell lines (Ovcar3) (73, 104) as well as anti-migratory effects in others (104, 106).
By and large the above findings together with the recent this successful development of Epac 1 agonist as well as it antagonists may prove to be a promising therapeutic target in the treatments of several medical conditions including vascular inflammation, as well as cancers amongst others. treatments.

CONCLUSION

The role of cAMP as well as its effectors in maintaining the integrity of the endothelial cell junctions are complex. Adequate and proper understanding of the role played by the cAMP and its effectors at both molecular and cellular level will invariably lead to the expansion in developing agents that could be utilised for the treatment of wide range of disease conditions including inflammations, cancer, cardiovascular diseases amongst others. In recent times pharmacological agents in form agonists as well as antagonists to the cAMP effectors which modulates the integrity and function of endothelial junctions are emerging. These presents a potential therapeutic means of targeting diseases where cAMP effectors are implicated.

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