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PKA and Apicomplexan Parasite Diseases

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Abstract

The cAMP-dependent protein kinase PKA is a well-characterized member of the serine-threonine protein AGC kinase family and is the effector kinase of cAMP signaling. As such, PKA is involved in the control of a wide variety of cellular processes including metabolism, cell growth, gene expression and apoptosis. cAMP-dependent PKA signaling pathways play important roles during infection and virulence of various pathogens. Since fluxes in cAMP are involved in multiple intracellular functions, a variety of different pathological infectious processes can be affected by PKA signaling pathways. Here, we highlight some features of cAMP-PKA signaling that are relevant to Plasmodium falciparum-infection of erythrocytes and present an update on AKAP targeting of PKA in PGE2 signaling via EP4 in Theileria annulata-infection of leukocytes and discuss cAMP-PKA signling in Toxoplasma.

Keywords

cAMP; red blood cells; leukocytes; *Theileria*; *Plasmodium*; Merozoites; gametocytes

Introduction

cAMP-dependent protein kinase A (PKA) is a cytosolic holoenzyme playing key roles in a number of cellular process. In higher eukaryotes, it is composed of 2 regulatory subunits bound to 2 catalytic subunits in its inactive form [1]. There are 4 regulatory subunits (RIα, RIβ, RIIα, RIIβ) that are differentially expressed in different cell types [2]. The biochemical/biological functions of PKA are mainly different biochemical properties of the respective reflectedinthe isoforms, in particular acting as substrates/pseudosubstrates and docking platforms for other proteins [3]. Three catalytic subunits (Cα, Cβ, Cγ) may be

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Conflict of Interest

The authors declare no conflict of interest.

combined to the different regulatory subunits to generate holoenzymes with different properties. During both physiological and pathological conditions, the composition of the PKA holoenzymes, as well as their intracellular localization may change, inducing different effects [4]. In addition, kinase activity is inhibited when Protein Kinase Inhibitor (PKI) binds to the catalytic subunits [5]. The specificity of PKA signaling is determined by the cell type-specific expression of the different regulatory and catalytic PKA isoforms, the wide range of PKA substrates and also by the subcellular localization of PKA. Targeting of PKA to specific sites within the cell is largely achieved by binding of R subunits to A Kinase Anchoring Proteins (AKAPs) to specific locales within the cell [6, 7]. The PKA complex, however, is notably reduced in medically important Apicomplexa parasites like Plasmodium and Theileria that have just individual R and C subunits and no gene coding for PKI [8]. Toxoplasma parasites, however, encode 3 different C subunits like yeast, where TgPKAc1 and TgPKAc2 encode C subunits closely related to the C subunits of Plasmodium and Theileria [9]. Moreover, even though P. falciparum appears to have no functional AKAPs [10] both PfRab5A and PfRab7 can bind PfPKA and likely act as pseudo AKAPs [11].

Intracellular cAMP levels are regulated by the balanced action of adenylate cyclases (ACs) that generate cAMP and cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze cAMP to AMP so as to diminish or terminate cAMP-mediated PKA signaling [12, 13]. PKA signaling has been shown to regulate a variety of cellular responses in most eukaryotic cells, such as DNA replication [14, 15], cell growth and metabolism [16], cell division and rearrangement of the actin cytoskeleton [17, 18]. It can also regulate gene transcription by phosphorylating transcription factors such as the cAMP Response Element-Binding Protein (CREB) [19] that induces an array of transcriptional cascades involved in immune response, cellular metabolism and mitochondrial biogenesis [20–22]. Besides its role in transcriptional regulation, PKA phosphorylation regulates many other signaling proteins, such as phospholipase C (PLC) [23], protein kinase C (PKC) [24], phosphoinositide 3-kinase (PI3-K) [25, 26] and inositol trisphosphate (IP_3) receptors [27]. However, PKA can also be activated independently of cAMP, as for example, where certain pools of C subunits exist in a complex with IκBα and IκBβ, and degradation of IκB can lead to kinase activation [28]. Another cAMP-independent pathway of PKA regulation is via TGF-β, as it has been shown that the Smad3/Smad4 complex can directly activate PKA [29].

PKA and Theileria-Infected Leukocytes

Theileria annulata is a tick-borne apicomplexan parasite and causative agent of the cattle disease tropical theileriosis, which is of major economic importance in countries in Northern Africa and Asia. T. annulata infects and transforms B cells and monocytes/macrophages and transformed leukocytes display many characteristics of cancer cells, such as heightened migratory and invasive capacities [30, 31]. T. annulata-infection of its B cell host activates a PKA survival pathway via phosphorylation of S155 and inactivation of the pro-apoptotic protein Bad by mitochondria-localized PKA [32]. Part of the augmented Theileria-transformed B cell PKA activity comes from parasite-dependent increased expression of the PKA-Cβ subunit, a likely c-Myc target gene, as c-Myc is also induced by infection [32, 33].

In Theileria-infected macrophages, TGF-β2-signaling regulates the expression of PTGS2 (COX2), PTGER4 (EP4) and PKIG that collectively modulate cAMP levels and consequently both PKA and EPAC activities [34]. Protein kinase inhibitor gamma (PKIG) is a specific and potent inhibitor of PKA [35]. Prostaglandin-endoperoxide synthase 2 (PTGS2), also known as cyclooxygenase-2 (COX-2), is an enzyme that plays a pivotal role in the synthesis of prostaglandin E2 (PGE2) from arachidonic acid following its release from the plasma membrane by the action of phospholipase-A2 [36]. PGE2 can act in both an autocrine and paracrine manner via a family of 4 membrane-spanning G protein-coupled receptors (GPCRs) termed EP1, EP2, EP3, and EP4 [37]. EPs are linked to different transduction pathways that may induce altered cellular responses. For example, EP2 and EP4 are coupled to stimulatory (Gs) G-proteins that activate ACs and lead to increased levels of cAMP, whereas EP3 signals through inhibitory (Gi) proteins that activate potassium channels and inhibit cAMP production [33]. On the other hand, EP1 is coupled to Gαq and its activation results in an increase in intracellular calcium levels [37]. cAMP is the main intracellular second messenger of PGE2 signaling in macrophages, playing a crucial role in the modulation of several biological activities. EP2 is reported to signal primarily via PKA leading to the phosphorylation of numerous proteins, including cAMP-responsive element binding protein (CREB), which is known to regulate anti-apoptotic gene products such as Bcl-2 and IAP [22]. PKA also inactivates glycogen synthase kinase (GSK) [38] and the pro-apoptotic protein Bad by phosphorylation [38, 39]. As stated above, subcellular distribution of the PKA holoenzyme is derived from R-subunit binding to a range of specific AKAPs, each with a particular subcellular localization. Stapled AKAP Disruptor 2 (STAD-2) can inhibit the interaction between PKA-RII and AKAPs [40, 41].

Importantly, it has been shown that elevated cAMP-PKA signaling slows down the import of mitochondrial proteins, and fosters the metabolic switch from oxidative phosphorylation to glycolysis in conditions of increased glucose, or reduced oxygen availability [42]. Moreover, PKA can phosphorylate BAD and has a well-established role in the regulation of the glucose metabolism that is distinct from its role in apoptosis. In hepatocytes, the impact of BAD on cellular metabolism depends on its ability to bind glucokinase (GK) [43, 44], where GK binding to BAD also requires S155 phosphorylation by a range of kinases such including PKA [45]. We recall that in T. annulata-infected B cells, PKA-mediated phosphorylation of S155 of BAD occurs as part of an anti-apoptotic response [32]. The intriguing involvement of S155 phosphorylation by PKA on glucose metabolism of Theileria-infected leukocytes will stimulate our future studies.

cAMP-Dependent PKA in Red Blood Cells and Plasmodium falciparum

P. falciparum infection causes the most prevalent form of human malaria in sub-Saharan Africa. Severe malaria in African children often presents diverse clinical symptoms, ranging from mild infections to life-threatening complications such as severe anemia, cerebral malaria, acute renal failure, hypoglycemia, and acidosis/respiratory distress [46, 47]. In P. falciparum-infected erythrocytes, both host and parasite PKA appears to play important roles in pathogenesis due to its regulation of both red blood cell [48] and parasite protein phosphorylation [49, 50] and transport of molecules across the red blood cell (RBC) plasma membrane via activation of new permeability pathways [51, 52]. Moreover, ATP is released

from RBCs in response to infection with Plasmodium parasites, which after conversion into adenosine by the ectonucleoside triphosphate diphosphohydrolase-1 (CD39), activates extracellular beta-adrenergic receptors to activate ACs and increase intracellular cAMP concentrations, thereby activating PKA (reviewed in [53]). ATP-dependent adenosine signaling can lead to deformations in the plasma membrane of both uninfected and infected RBCs [46].

cAMP fluxes have been demonstrated to play important yet contrasting roles at 2 different points in P. falciparum intra-erythrocyte development. At the end of each intra-erythrocyte developmental cycle, invasive forms called merozoites are released to invade fresh red blood cells so as to initiate new rounds of development and in such a way the parasite population is amplified. Upon release, merozoites are subjected to a lower K^+ environment that is typical of blood plasma. In order to maintain homeostasis in this environment, they exchange protons (H^+) that could lead to acidification of the parasite cytosol. To mitigate this a carbonic anhydrase is activated and this increases bicarbonate levels that, in turn, activates a soluble AC to consequently increase cAMP levels and activate both PKA and EPAC [54]. Pharmacological inhibition of sAC by KH7 blocks merozoite invasion of erythrocytes, demonstrating that the rise in cAMP levels is crucial. However, at some point to complete their life cycle, parasites must be transmitted to Anopheles mosquitoes and this depends on gametocyte development. During development, gametocyte-infected red blood cells are sequestered in the bone marrow to avoid being cleared by the spleen, but this prevents them from being taken up in the blood meal of a feeding female mosquito. Therefore, mosquito-infective stage V gametocyte-infected red blood cells de-sequester and become deformable to facilitate their passage through the spleen [55]. This is triggered by a massive drop in cAMP levels and raising levels via pharmacological inhibition of PDEs and renders stage V gametocyte-infected red blood cells more rigid. This has led to the proposition that PDE inhibitors may have the potential to block transmission of malaria [55]. The importance of tightly regulating cAMP fluxes in malaria parasites is underscored by the antagonistic observation where, on one hand, merozoite cAMP levels must rise to successfully invade erythrocytes, while on the other hand cAMP levels must drop to successfully transmit stage V gametocytes to mosquitoes. Fine-tuning cAMP levels clearly underpins much of the biology of malaria parasites.

Prostaglandins are known to modulate cAMP concentrations and P. falciparum-infected red blood cells produce prostaglandins that contribute to many malaria symptoms [56]. For example, PGD2 may contribute to the pathogenesis of cerebral malaria by inducing HO-1 expression in malaria patients [57]. In addition, decreased COX-2-derived PGE2 levels are associated with enhanced clinical severity in cerebral malaria, malarial anemia, and malaria during pregnancy [58–60]. Furthermore, suppression of COX-2-derived PGE2 is associated with reduced erythropoiesis and worsening anemia in children with falciparum malaria [61]. This argues that a PGE2-cAMP-PKA signaling pathway may contribute to the pathogenesis of P. falciparum-infected RBC.

PKA and Toxoplasma

Toxoplasma gondii is an obligate intracellular apicomplexan parasite that infects warm-blooded vertebrates, including humans, where it causes toxoplasmosis. Toxoplasmosis in pregnant women can lead to the fetus being affected by encysted (bradyzoite) parasite formation in the brain and both congenital toxoplasmosis and toxoplasmic encephalitis is associated with severe neuropsychiatric symptoms [62]. Like Plasmodium, Toxoplasma also expresses cAMP-dependent PKA [63] and like Plasmodium, the gene coding for the regulatory subunit (TGGT1_242070) is essential for asexual tachyzoite growth [64]. However, unlike Plasmodium there are 3 genes coding for different catalytic subunits (TGGT1_226030; TGGT1_228420; TGGT1_286470) and TgPKAc2 (TGGT1_228420) does not appear to code for an essential function during tachyzoite growth [64]. TgPKAc2 is highly expressed in the cat intestine perhaps being essential in bradyzoite sexual reproduction [65]. Interestingly, knockout of TgPKAc3 (TGGT1_286470) affects the tackyzoite to bradyzoite transition [9]. In human neuroepithelioma cells, Toxoplasma infection raises cAMP levels, thereby inducing CREB to drive miR-132 expression that downregulates D1-like dopamine receptors and hence dopamine signaling [9, 62]. Moreover, increases in cytosolic cAMP levels activate PKA to trigger the developmental switch from proliferating tachyzoites to quiescent bradyzoites [9].

As described above for P. falciparum, pharmacological inhibition of PDE activity is a promising strategy for treatment of Toxplasmosis. PDE4 inhibitors such as rolipram interfere with the transition of Toxoplasma infection to a chronic phase and induce elevated levels of intracellular cAMP [66]. PDE4 inhibitors are also known to induce a potent shift toward a T-helper2 (Th2) type immune response [67] via a reduction in the activity of pro-inflammatory Th1 cytokines with specific inhibition of TNF-α [68, 69]; a major factor in parasitic conversion to the bradyzoite stage [70, 71]. Furthermore, treatment with rolipram prevented biochemical and histological signs of Toxoplasma-induced hepatitis in mice as well as the expected brain pathology of latent toxoplasmosis [72].

Importantly, elevated PGE2 levels contribute to T. gondii proliferation [73]. Furthermore, PGE2 and COX-2 contribute to the establishment and maintenance of the chronic phase of the T. gondii infection in muscle cells [74]. Serine/threonine kinases including cAMP-dependent PKA have been implicated in calcium-signal transduction, leading to regulated secretion [75]. Similarly in Plasmodium, cAMP plays a central role in regulating cytosolic Ca^{2+} levels and microneme secretion during merozoite invasion of RBCs [54]. Due to its significance in tachyzoite infection, cAMP fluxes likely activating TgPKAc1 (TGGT1_242070) stimulate microneme secretion and Toxoplasma tachyzoite egress for its host cells.

Conclusions

Apicomplexa parasite infection alters intracellular cAMP levels in both host and parasite and these cAMP fluxes impact the infected host cell phenotype. Therefore, pharmacological manipulation of cAMP levels and of PKA-mediated signaling holds much promise in the fight against apicomplexan parasite pathogenesis.

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