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Infection-Induced cAMP-Independent Regulation of Protein Kinase A (PKA)

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Abstract

The regulation of cellular signaling pathways is crucial for maintaining cellular equilibrium and coordinating responses to parasite infections. Protein Kinase A (PKA) is a key player in cellular signaling involved in regulating these processes. *Apicomplexa* parasites, including *Plasmodium falciparum* and *Theileria annulata*, exploit PKA to promote infection-induced pathogenesis. In this commentary, we describe two alternative mechanisms employed by these medically important parasites to regulate Protein Kinase A (PKA) activity independent of fluxes in cyclic Adenosine Monophosphate (cAMP). Epigenetic regulation of PRKAR2B expression not only bypasses traditional cAMP-dependent regulation of PKA activity, but in doing so also provides new therapeutic targets for the potential treatment of malaria and tropical theileriosis.

Keywords: miR-34c; PRKAR2B; cAMP; *Theileria*; *Plasmodium*

Description

The regulation of cellular signaling pathways is vital for maintaining cellular equilibrium and coordinating appropriate responses to environmental stresses, including parasite infection. Protein Kinase A (PKA) plays a key role in modulating cellular signaling by controlling various cellular processes such as metabolism, gene expression, cell growth, and differentiation [1]. *Apicomplexa* parasites, which include species like *Plasmodium falciparum* (causative agent of pernicious human malaria), *Toxoplasma gondii* (causing toxoplasmosis), and *Theileria annulata* (causing tropical theileriosis), employ PKA to promote infection-induced pathogenesis [2].

PKA is a cytosolic holoenzyme composed of two catalytic subunits and two regulatory subunits that are classically regulated by fluxes in cAMP [3]. Under basal conditions, regulatory subunits are bound to catalytic subunits, maintaining PKA activity in an inactive state. Upon cAMP binding to regulatory subunits, a conformational change occurs leading to the release and activation of catalytic subunits. However, *T. annulata* exploits a unique strategy to bypass the cAMP-dependent regulation of PKA activity. In this commentary, we provide a brief description of the mechanism employed by *Theileria* and *Plasmodium* to regulate PKA activity independently of changes in cAMP fluxes and discuss its implications in the pathophysiology of tropical theileriosis and malaria [4].

Infection-induced cAMP-independent regulation of PKA

miRNAs are small, non-coding RNA molecules that regulate gene expression by binding to the target messenger RNAs (mRNAs) inhibiting their translation or promoting their degradation. They exhibit a wide range of functions in various physiological and pathological conditions [5]. miR-34c-3p is a specific member of a microRNA family known as miR-34c and infection of bovine leukocytes by *T. annulata* induces upregulation of miR-34c-3p levels [4]. miR-34c-3p directly targets and degrades the type II-beta regulatory subunit (*prkar2b*) leading to reduced expression of the inhibitory subunit and increased PKA activity in *T. annulata*-infected leukocytes. As a result, the disseminating tumor-like phenotype of *T. annulata*-transformed macrophages is enhanced. Similarly, *P. falciparum* infection of red blood cells induces augmentation in miR-34c-3p levels, provoking degradation of residual red blood cell *prkar2b* and enhancing PKA activity [4]. Infection-induced increase in miR-34c-3p levels, therefore, provides a novel epigenetic mechanism for regulating host cell PKA activity independent of cAMP fluxes to aggravate tumor dissemination and improve parasite fitness.

Theileria infection also regulates leukocyte PKA activity in second way independent of cAMP. PKI γ is a member of the Protein Kinase A Inhibitor (PKIs) family that regulates PKA activity by acting as a pseudo-substrate that binds to and deactivates C-subunits. In *Theileria*-infected and transformed disseminating macrophages PKI γ levels are typically low, and associated with tumor virulence [5,6]. However, long-term culture of *Theileria*-transformed macrophages leads to dampening of their dissemination potential and these cell lines are used as attenuated vaccines against tropical theileriosis [7]. Attenuation of virulence results in elevated PKI γ expression, reduced PKA activity, and diminished infected macrophage dissemination [6]. This again highlights a non-cAMP mechanism employed by *Theileria annulata* to manipulate host PKA activity to promote infected leukocyte pathogenicity.

Significance and implications

The important role that PKA plays in the pathogenesis of *Plasmodium*, due to its regulation of red blood cell and parasite protein phosphorylation, as well as intra-erythrocyte development, is

well known; reviewed in [8]. Moreover, the contribution of PKA to the survival and tumorigenic phenotype of *T. annulata*-infected leukocytes is well documented; reviewed in [2]. The recent identification of *prkar2b* as a target gene of miR-34c-3p uncovered a novel mechanism for regulating mammalian PKA activity, and provides a new and potential therapeutic target for the treatment of malaria and tropical theileriosis [4].

Conclusion

By shedding light on a cAMP-independent pathway for PKA activation and revealing a novel mechanism for parasite manipulation of host cell signaling, epigenetic regulation of PKA activity opens up new avenues for therapeutic intervention and calls for a deeper understanding of the different mechanisms underlying alternative modes of PKA activation and their functional implications in cellular physiology and disease pathogenesis.

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