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Review

Cyclic AMP-mediated immune regulation — Overview of mechanisms of action in T cells

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ABSTRACT

The canonical second messenger cAMP is well established as a potent negative regulator of T cell immune function. Through protein kinase A (PKA) it regulates T cell function at the level of transcription factors, members of the mitogen-activated protein kinase pathway, phospholipases (PLs), Ras homolog (Rho)A and proteins involved in the control of cell cycle progression. Type I PKA is the predominant PKA isoform in T cells. Furthermore, whereas type II PKA is located at the centrosome, type I PKA is anchored close to the T cell receptor (TCR) in lipid rafts by the Ezrin–ERM-binding phosphoprotein of 50 kDa (EBP50)-phosphoprotein associated with glycosphingolipid-enriched microdomains (PAG) scaffold complex. The most TCR-proximal target for type I PKA is C-terminal Src kinase (Csk), which upon activation by raft recruitment and phosphorylation inhibits the Src family tyrosine kinases Lck and Fyn and thus functions to maintain T cell homeostasis. Recently, induction of cAMP levels in responder T cells has emerged as one of the mechanisms by which regulatory T (T_R) cells execute their suppressive action. Thus, the cAMP-type I PKA–Csk pathway emerges as a putative target for therapeutic intervention in autoimmune disorders as well as in cancer, where T_R cell-mediated suppression contributes to suboptimal local immune responses.

Contents

Abbreviations: AC, Adenylyl cyclase; AKAP, A-kinase anchoring protein; AKAP-KL, AKAP-kidney lung; AKB, A-kinase binding domain; AP-1, Activator protein 1; ATF, Activation transcription factor; C, Catalytic (subunit of PKA); CBP, CREB-binding protein; CNG, Cyclic nucleotide-gated; CRE, cAMP response element; CREB, CRE-binding protein; CREM, CRE modulator; Csk, C-terminal Src kinase; D-AKAP, Dual-specificity AKAP; EBP50, ERM-binding phosphoprotein of 50 kDa; Epac, Exchange protein activated by cAMP; ERK, Extracellular signal-regulated kinase; ERM, Ezrin/Radixin/Moesin; FERM, N-terminal band 4.1 ERM; FOXP3, Forkhead box protein-3; Gα, G protein α; GPR83, G protein-coupled receptor 83; GPCR, G protein-coupled receptors; HePTP, Hematopoietic protein tyrosine phosphatase; ICER, Inducible cAMP early repressor; IKK, IκB kinase; ITAM, Immunoreceptor tyrosine-based activation motif; IκB, Inhibitor of κB; LAT, Linker for activation of T cells; mAKAP, Muscle AKAP; MHC, Major histocompatibility complex; MTG, Myeloid translocation gene; NFκB, Nuclear factor κB; NFAT, Nuclear factor of activated T cells; PAG, Phosphoprotein associated with glycosphingolipid-enriched micro-domains; PAP7, Peripheral benzodiazepine receptor-associated AKAP protein; PDE, Phosphodiesterase; PG, Prostaglandin; PKA, Protein kinase A; PL, Phospholipase; R, Regulatory (subunit of PKA); Rap, Ras-proximate; Rho, Ras homolog; RIAD, RI anchoring disruptor; RISR, RI specifier region; SHP, SH2 domain containing tyrosine phosphatase; STAT, Signal transducer and activator of transcription; TCR, T cell receptor; T_R, Regulatory T (cell); UCR, Upstream conserved region; WAVE, Wiskott-Aldrich syndrome protein verprolin homologous protein; Zap-70, ζ-chain-associated protein of 70 kDa.

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1. Introduction

Cyclic AMP was identified in 1957 [1] as the first intracellular second messenger of extracellular ligand action [2]. In T cells, cAMP mediates the effects of prostaglandins (PGs) [3], adenosine [4], histamine [5], β-adrenergic agonists [6], neuropeptide hormones [7] and β-endorphin [8]. When these agents engage G protein-coupled receptors (GPCRs), conformational changes are induced in the receptors and the associated heterotrimeric G proteins, leading to release of activated stimulatory G protein α (Gα) subunits from G protein βγ dimers and subsequent activation of adenylyl cyclases (ACs), which hydrolyze ATP to cAMP. In mammals, nine membrane-bound isoforms of AC (ACs 1–9) as well as one soluble AC isoform have been identified [9]. In mouse T cells, AC7 is expressed together with lower levels of AC3, 6 and 9, and appears to be the major AC isoform for regulating cAMP synthesis [10]. AC3 and 6, but not AC7 and 9, localize to cholesterol and sphingolipid-enriched membrane domains important for the assembly of signaling proteins termed lipid rafts [9,11,12]. Chimeric mice carrying AC7-deficient immune systems display compromised antibody responses toward T cell dependent antigens. The generation of memory T cells is also impaired [10]. Cyclic AMP is produced in lipid rafts of both Jurkat T cells and primary human T cells upon T cell receptor (TCR) engagement [13,14]. This local cAMP generation seems to be induced by concurrent recruitment of additional stimulatory Gα subunits to lipid rafts and dissociation of inhibitory Gα subunits away from lipid rafts [13].

Cyclic nucleotide phosphodiesterases (PDEs) hydrolyze cyclic nucleotides and are therefore important regulators of intracellular cAMP homeostasis. The PDEs comprise a superfamily of more than 100 enzyme variants divided into 11 families (PDEs 1–11) [15]. Several enzyme variants from the families PDE1, 2, 3, 4, 5, 7 and 8 have been identified in T cells [16]. CD3 and CD28 costimulation induce expression of the high affinity cAMP specific PDEs 7 [17] and 8 [18] in T cells [15,19,20]. However, PDE7A knockout mice display normal T cell function [21]. Moreover, the PDE4 family, which is also cAMP specific, seems to account for the majority of the cAMP-hydrolyzing activity in T cells [22,23]. The PDE4 genes are linked to schizophrenia, stroke and asthma [24], thus indicating a therapeutic potential for selective PDE4 inhibitors [25]. Four genes (*PDE4A/B/C/D*) encode more than 20 distinct PDE4 isoforms as a result of mRNA splicing and the use of distinct promoters. The PDE4 family has unique and highly conserved regulatory regions termed upstream conserved region 1 (UCR1) and upstream conserved region 2 (UCR2). PDE4 isoforms are subcategorized into four groups based on their UCR1/UCR2 content. Thus, "long" isoforms have UCR1 and UCR2, "short" isoforms lack UCR1, and "super-short" isoforms have just a truncated UCR2, whereas "dead-short" isoforms lack UCR1 and UCR2 and have an inactive catalytic unit that is both N- and C-terminally truncated [26]. PDE4A4 (long), PDE4B2 (short) and PDE4D1/2 (short) have all been detected in T cell lipid rafts. Their recruitment to lipid rafts upon CD3 and CD28 costimulation involves association with β-arrestin and protein kinase B and is thought to counteract TCR-induced cAMP production in lipid rafts sufficiently to allow T cell activation to occur [13,27]. Furthermore, PDE4-β-arrestin complexes have been shown to affect β-adrenergic receptor function [28]. Although cAMP has been demonstrated to also exert its effects through cyclic nucleotide-gated (CNG) ion channels [29] and exchange protein activated by cAMP (Epac), a guanine nucleotide exchange factor for the small GTPase Ras-proximate (Rap)-1 [30,31], the principal cAMP effector is protein kinase A (PKA) [32,33]. Epac has been shown to be expressed in Jurkat T cells. However, PKA appears to be the main cAMP effector in T cells [13,34,35]. Fig. 1 illustrates canonical cAMP signaling.

2. Protein kinase A (PKA)

The PKA holoenzyme is composed of two catalytic (C) subunits maintained in an inactive conformation by association with a regulatory (R) subunit dimer. Consecutive binding of two cAMP molecules to paired binding pockets on each of the R subunits [36] induces a conformational change, leading to release of active C subunit monomers able to phosphorylate nearby substrates with the target sequences RRXS/T, RKXS/T, KRXS/T and KKXS/T [37].

Specificity in PKA signaling is ensured by the differential expression of distinct isoforms and splice variants of both the R subunit and the C subunit in various tissues and cell types. Four different R subunit isoforms, RIα, RIβ, RIIα and RIIβ, and three different C subunit isoforms, Cα, Cβ and PrKX/PKARE are expressed in humans and mice. Several splice variants of the Cα and the Cβ genes add further heterogeneity [38]. In T cells, 80% of the total PKA activity is associated with the type I PKA isoform ($RI\alpha_2C_2$), whereas approximately 10–20% is accounted for by type II PKA ($RII\alpha_2C_2$) [39]. Moreover, studies of RIIα knockout mice show that type II PKA is dispensable for normal immune function [40]. RIα knockout mice are embryonically lethal [41]. However, Griffin et al., generated a mouse containing an antisense transgene targeted to the RIα gene [42,43]. This was placed under the control of a doxycycline-suppressible promoter to circumvent problems with embryonic lethality. The RIα-antisense mice exhibited normal development, but as they aged they developed a variety of neoplastic lesions, including lymphomas. The main C subunits expressed in T cells are splice variants Cα1 and Cβ2 [44–46]. Ablation of Cα but not Cβ in mice augmented the expression of the activation marker CD69 on lymphocytes, coinciding with immune cell hyperresponsiveness and reduced sensitivity to cAMP-mediated inhibition of anti-CD3-induced T cell proliferation. These effects were however not reflected in the systemic immune response after antigen immunization or by development of spontaneous autoimmunity [47].

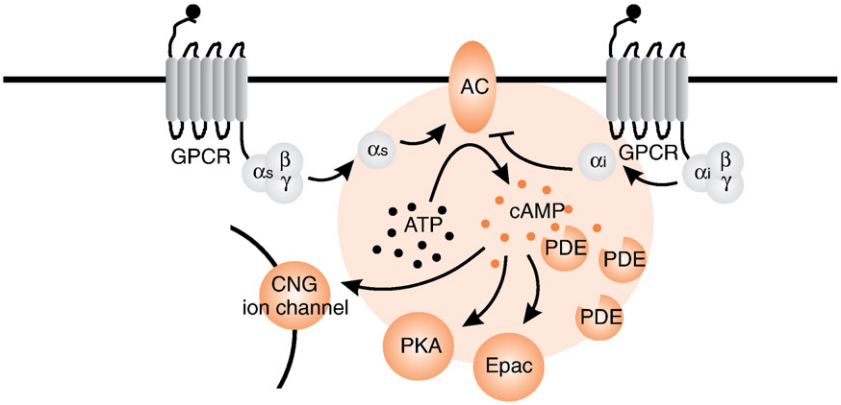

Fig. 1. Canonical cAMP signaling. Ligand binding to GPCRs is coupled to regulation of AC activity and cAMP generation through activation of stimulatory Gα subunits (α_s) and inhibitory Gα subunits (α_i). Intracellular cAMP homeostasis is maintained by PDEs, and the second messenger exerts its functions through activation of PKA, CNG ion channels and Epac. β — G protein β subunit, γ — G protein γ subunit.