Cyclic AMP signalling

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Cyclic adenosine 3′,5′-monophosphate (cAMP) was the first identified second messenger. A large number of studies during the past 30 years have elucidated the fundamental role of cAMP in the cellular response to many hormones and neurotransmitters. Although the main components in the cAMP-mediated signalling pathway are well known, recently new important players have been identified, which have further elucidated its complex regulation and the extensive crosstalk between this and other known signalling pathways.

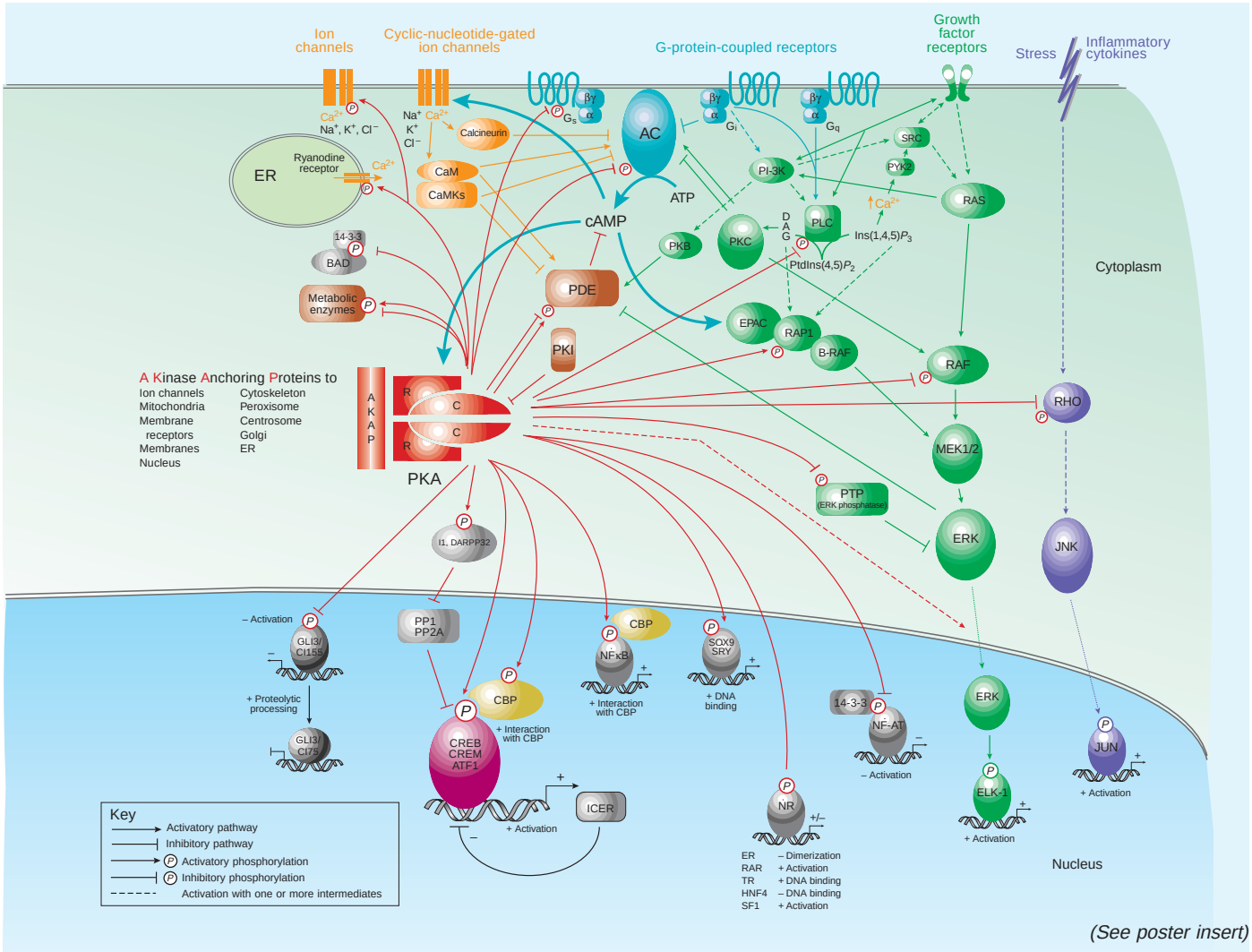
The level of intracellular cAMP is regulated by the balance between the activity of two types of enzyme: adenylyl cyclase (AC) and the cyclic nucleotide phosphodiesterase (PDE). Both enzymes are encoded by a large number of genes, which differ in their expression patterns and mechanisms of regulation.

Nine different adenylyl cyclases exist in mammals. Their activities are stimulated by interaction with the α subunit of G_s proteins. G_s α subunits are coupled with different types of membrane receptor in heterotrimeric complexes together with the β and γ subunits, from which they dissociate after the binding of specific ligands. Degradation of cAMP is regulated by at least 12 different members of a large family of PDEs. The activities of ACs and PDEs are regulated positively and negatively by other signalling systems, such as calcium signalling (through calmodulin (CaM), CamKII, CamKIV and calcineurin), subunits of other G proteins (e.g. G_i, G_o and G_q proteins), inositol lipids (by PKC) and receptor tyrosine kinases (through ERK and PKB).

Three main targets of cAMP have been identified: protein kinase A (PKA), the GTP-exchange protein EPAC and the cyclic-nucleotide-gated ion channels.

PKA consists of a complex of two regulatory (R) subunits and two catalytic (C) subunits. Four genes encode the R subunits (RIα, RIβ, RIIα and RIIβ), and three encode the C subunits (Cα, Cβ and Cγ). PKA is activated by the binding of cAMP to the R subunits, which induces their dissociation from the C subunits.

Apart from the R subunits, PKA activity is downregulated by protein kinase inhibitors (PKIs). Three known isoforms



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of PKI (α, β and γ) are encoded by different genes, which each have specific expression patterns. Interestingly, PKI could act as a chaperone for nuclear export of the C subunit and thereby influence the extent of PKA activity in the nucleus. An important breakthrough in our understanding of the action of PKA has been the identification of PKA-anchoring proteins (AKAPs). These proteins allow specificity in cAMP signal transduction by placing PKA close to specific effectors and substrates.

A large number of proteins have been identified as substrates for PKA. In this poster, we have focused our attention mainly on targets that are involved in control of transcription. To achieve a more complete view of transcriptional modulation by cAMP, we include a detailed description of PKA targets present both in its own pathway and in other signal transduction pathways, which regulate the activity of distinct transcription factors.

PKA modulates the cAMP response by phosphorylating other components of the cAMP pathway, such as receptors, ACs and PDEs. Phosphorylation of these proteins results, depending on the cellular system, in an enhancement of the cAMP signal (for example repressing the activity of PDE1) or in a rapid downregulation of the pathway to obtain a transient effect (for example, by repressing the activity of AC V and AC VI, or the β2 adrenergic receptor).

PKA interferes at different levels with other signalling pathways. Interesting examples are represented by the inactivation of phospholipase C (PLC) β2, the phosphorylation of a tyrosine phosphatase (PTP), which results in dissociation from and consequent activation of mitogen-activated protein kinases (MAPKs), the downregulation of Raf and Rho activities, and the modulation of ion channel permeability.

Regulation of transcription by PKA is mainly achieved by direct phosphorylation of transcription factors. CREB, CREM and ATF1 were originally identified as the activators that respond to the cAMP and are phosphorylated by PKA in their activation domains. Phosphorylation is a crucial event in transcriptional activation by CREB, CREM and ATF1, because it allows interaction with the transcriptional coactivators CBP and p300. A specific characteristic of the CREM gene is that it encodes many different isoforms, some of which have repressive functions. Particularly interesting is the repressor ICER, which is produced by use of an alternative cAMP-inducible promoter within the *CREM* gene and participates in the downregulation of cAMP-induced transcription by competing with the binding of CREB and CREM activators to their DNA binding sites. Several lines of evidence support the notion that CREB, CREM and ATF1 can be phosphorylated by many different kinases. Importantly, the phospho-acceptor sites (Ser133 in CREB, Ser117 in CREM and Ser63 in ATF1) are the same as those targeted by PKA. It is, therefore, evident that members of the CREB family play important roles in the nuclear responses to a variety of external stimuli. Similarly to CREB, phosphorylation of NF-κB by PKA is necessary for transcriptional activation, being required for the interaction with CBP. PKA also modulates the activity of other transcription factors, such as nuclear receptors and HMG-containing proteins, influencing their dimerization or DNA-binding properties. A peculiar example is the mechanism by which PKA regulates Cubitus Interruptus (CI) activity: in this case phosphorylation stimulates a specific cleavage of CI, which transforms the protein from an activator to a repressor.

The action of PKA, as with many other serine/threonine kinases, is counterbalanced by specific protein phosphatases. In some cases, it has been demonstrated that phosphatases belonging to the PP1 and PP2A families are responsible for dephosphorylation of PKA substrates. For the sake of simplicity, only the roles of PP1 and PP2A in the regulation of CREB activity are indicated, but note that these phosphatases could potentially be involved in the dephosphorylation of any PKA substrate, as well as of many other kinase targets. Interestingly, PKA can control phosphatase activity by phosphorylation of specific PP1 inhibitors, such as I-1 and DARPP32

Apart from PKA, cAMP can activate intracellular pathways by binding to and modulating the function of a family of cyclic-nucleotide-gated ion channels. These are relatively nonselective cation channels. They conduct Ca^{2+}, which stimulates CaM and CaM-dependent kinases and, in turn, modulates cAMP production by regulating the activity of ACs and PDEs. These channels are also permeable to Na^+ and K^+, which could alter the membrane potential in electrically active cells.

Finally, cAMP could directly modulate the mitogen-activated protein kinase (MAPK) pathway by binding to and activating EPAC, a specific GTP exchange-protein for the small GTPase Rap1. Although the role of Rap1 in the MAPK pathway is not completely understood, it seems to act by binding to and activating B-Raf and/or inhibiting the Ras-Raf pathway.

Abbreviations used: AC, adenylyl cyclase; AKAP, A-kinase anchoring protein; ATF1, activating transcription factor; cAMP, cyclic adenosine monophosphate; CaM, calmodulin; CaMK, calmodulin-dependent kinase; CBP, CREB-binding protein; CI, cubitus interruptus; CREB, cAMP-responsive-element-binding protein; CREM, cAMP-responsive-element-binding modulator; DAG, diacylglycerol; DARPP-32, dopamine and cAMP-regulated phosphoprotein of apparent M_r 32; EPAC, exchange protein directly activated by cAMP; ER, estrogen receptor; ERK, extracellular-signal-regulated kinase; Gli3, glioma-associated oncogene 3; HNF4, hepatocyte nuclear factor 4; JNK, Jun N-terminal protein kinase; ICER, inducible cAMP early repressor; Ins(1,4,5)P_3, inositol 1,4,5-trisphosphate; I-1, Inhibitor 1; MEK, MAPK/ERK kinase; MAPK, mitogen-activated protein kinase; NF-AT, nuclear factor of activated T cells; NFκB, nuclear factor κB; NR, nuclear receptor; PDE, cyclic nucleotide phosphodiesterase; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PKI, protein kinase inhibitor; PtdIns(4,5)P_2, phosphatidylinositol(4,5)-biphosphate; PI3-K, phosphoinositide 3-kinase; PLC, phospholipase C; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; PTP, protein tyrosine phosphatase; SR, sarcoplasmic reticulum; RAR, retinoic acid receptor; TR, thyroid hormone; SF1, steroidogenic factor 1; SRY, sex-determining region Y.

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