The Cyclic AMP Pathway

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Cyclic adenosine 3′,5′-monophosphate (cAMP) was the first second messenger to be identified and plays fundamental roles in cellular responses to many hormones and neurotransmitters (Sutherland and Rall 1958). The intracellular levels of cAMP are regulated by the balance between the activities of two enzymes (see Fig. 1): adenylyl cyclase (AC) and cyclic nucleotide phosphodiesterase (PDE). Different isoforms of these enzymes are encoded by a large

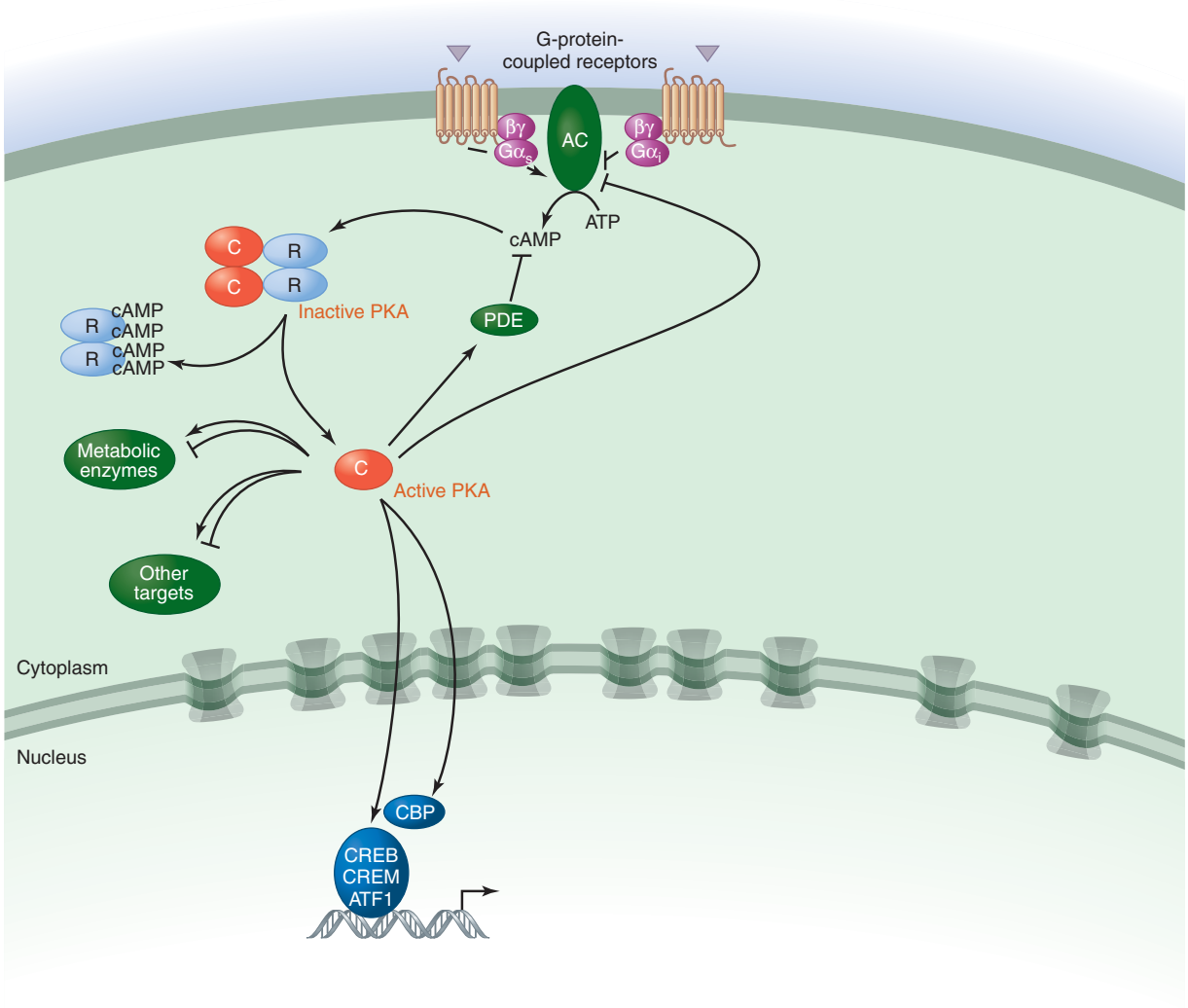

Figure 1. PKA regulation.

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number of genes, which differ in their expression patterns and mechanisms of regulation, generating cell-type and stimulus-specific responses (McKnight 1991).

Most ACs (soluble bicarbonate-regulated ACs are the exception) are activated downstream from G-protein-coupled receptors (GPCRs) such as the β adrenoceptor by interactions with the α subunit of the G_s protein (α_s). α_s is released from heterotrimeric αβγ G-protein complexes following binding of agonist ligands to GPCRs (e.g., epinephrine in the case of β adrenoceptors) and binds to and activates AC. The βγ subunits can also stimulate some AC isoforms. cAMP generated as a consequence of AC activation can activate several effectors, the most well studied of which is cAMP-dependent protein kinase (PKA) (Pierce et al. 2002).

Alternatively, AC activity can be inhibited by ligands that stimulate GPCRs coupled to G_i and/or cAMP can be degraded by PDEs. Indeed both ACs and PDEs are regulated positively and negatively by numerous other signaling pathways (see Fig. 2), such as calcium signaling (through calmodulin [CaM], CamKII, CamKIV, and calcineurin [also know as PP2B]), subunits of other G proteins (e.g., α_i, α_o, and α_q proteins, and the βγ subunits in some cases), inositol lipids (by PKC), and receptor tyrosine kinases (through the ERK MAP kinase and PKB) (Yoshimasa et al. 1987; Bruce et al. 2003; Goraya and Cooper 2005).

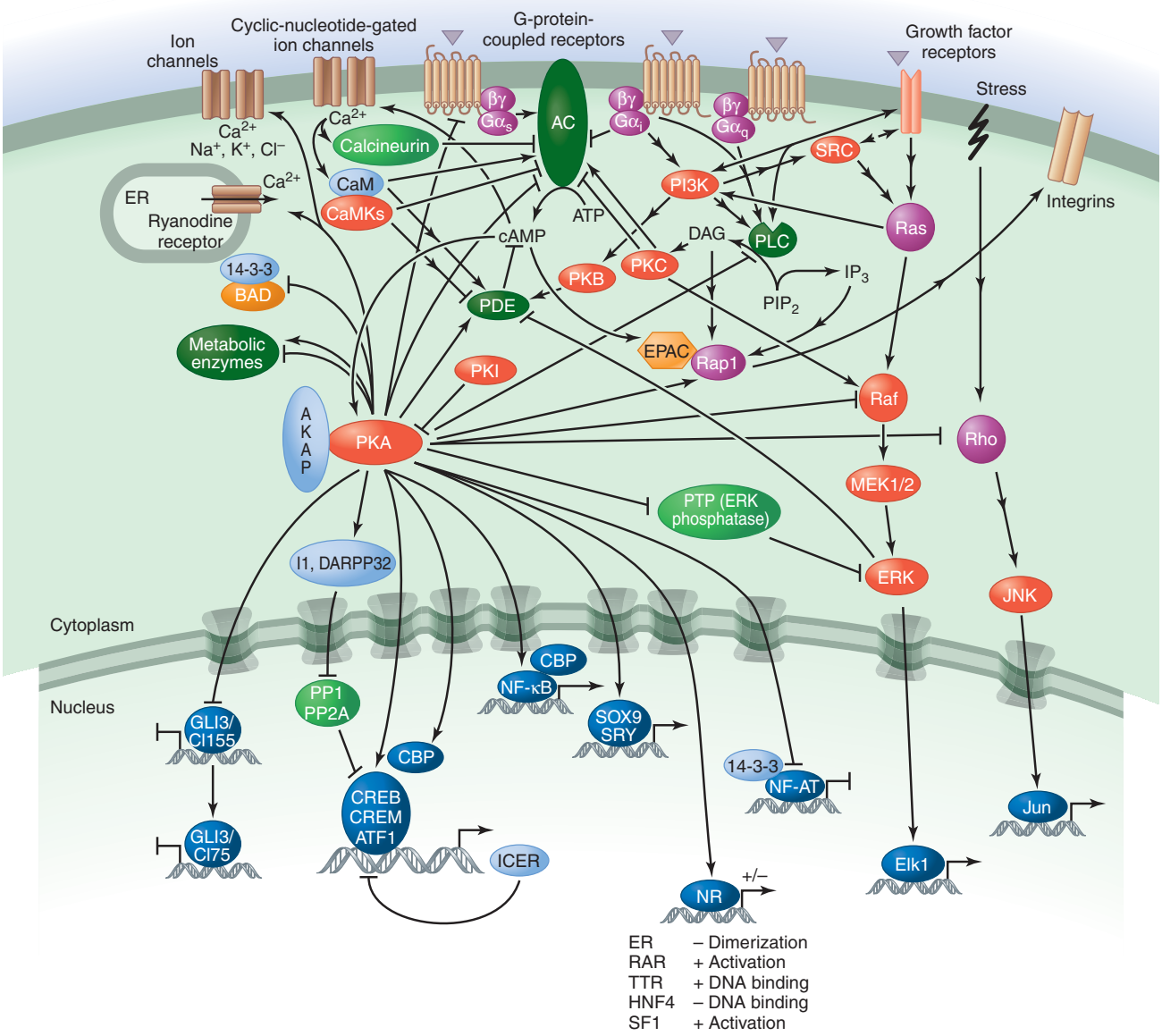

Figure 2. The cAMP/PKA pathway.

Crosstalk with other pathways provides further modulation of the signal strength and cell-type specificity, and feedforward signaling by PKA itself stimulates PDE4.

There are three main effectors of cAMP: PKA, the guanine-nucleotide-exchange factor (GEF) EPAC and cyclic-nucleotide-gated ion channels. Protein kinase (PKA), the best-understood target, is a symmetrical complex of two regulatory (R) subunits and two catalytic (C) subunits (there are several isoforms of both subunits). It is activated by the binding of cAMP to two sites on each of the R subunits, which causes their dissociation from the C subunits (Taylor et al. 1992). The catalytic activity of the C subunit is decreased by a protein kinase inhibitor (PKI), which can also act as a chaperone and promote nuclear export of the C subunit, thereby decreasing nuclear functions of PKA. PKA-anchoring proteins (AKAPs) provide specificity in cAMP signal transduction by placing PKA close to specific effectors and substrates. They can also target it to particular subcellular locations and anchor it to ACs (for immediate local activation of PKA) or PDEs (to create local negative feedback loops for signal termination) (Wong and Scott 2004).

A large number of cytosolic and nuclear proteins have been identified as substrates for PKA (Tasken et al. 1997). PKA phosphorylates numerous metabolic enzymes, including glycogen synthase and phosphorylase kinase, which inhibits glycogen synthesis and promotes glycogen breakdown, respectively, and acetyl CoA carboxylase, which inhibits lipid synthesis. PKA also regulates other signaling pathways. For example, it phosphorylates and thereby inactivates phospholipase C (PLC) β2. In contrast, it activates MAP kinases; in this case, PKA promotes phosphorylation and dissociation of an inhibitory tyrosine phosphatase (PTP). PKA also decreases the activities of Raf and Rho and modulates ion channel permeability. In addition, it regulates the expression and activity of various ACs and PDEs.

Regulation of transcription by PKA is mainly achieved by direct phosphorylation of the transcription factors cAMP-response element-binding protein (CREB), cAMP-responsive modulator (CREM), and ATF1. Phosphorylation is a crucial event because it allows these proteins to interact with the transcriptional coactivators CREB-binding protein (CBP) and p300 when bound to cAMP-response elements (CREs) in target genes (Mayr and Montminy 2001). The *CREM* gene also encodes the powerful repressor ICER, which negatively feeds back on cAMP-induced transcription (Sassone-Corsi 1995). Note, however, that the picture is more complex, because CREB, CREM, and ATF1 can all be phosphorylated by many different kinases, and PKA can also influence the activity of other transcription factors, including some nuclear receptors.

In addition to the negative regulation by signals that inhibit AC or stimulate PDE activity, the action of PKA is counterbalanced by specific protein phosphatases, including PP1 and PP2A. PKA in turn can negatively regulate phosphatase activity by phosphorylating and activating specific PP1 inhibitors, such as I1 and DARPP32. PKA-promoted phosphorylation can also increase the activity of PP2A as part of a negative feedback mechanism.

Another important effector for cAMP is EPAC, a GEF that promotes activation of certain small GTPases (e.g., Rap1). A major function of Rap1 is to increase cell adhesion via integrin receptors (how this occurs is unclear) (Bos 2003).

Finally, cAMP can bind to and modulate the function of a family of cyclic-nucleotide-gated ion channels. These are relatively nonselective cation channels that conduct calcium. Calcium stimulates CaM and CaM-dependent kinases and, in turn, modulates cAMP production by regulating the activity of ACs and PDEs (Zaccolo and Pozzan 2003). The channels are also permeable to sodium and potassium, which can alter the membrane potential in electrically active cells.

Figure 2 adapted from Fimia and Sassone-Corsi (2001).

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