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An intimate connection between ubiquitination and compartmentalized cAMP signaling

Luca Lignitto, Maria Sepe, Annalisa Carlucci and Antonio Feliciello*

Department of Biology and Cellular and Molecular Pathology L. Califano; University of Naples Federico II; Naples, Italy

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The cAMP is an evolutionary conserved second messenger that plays an essential role in development, survival, differentiation, growth and metabolism. The biological effects of the cAMP are mostly mediated by protein kinase A (PKA). Binding of cAMP to the regulatory subunit (R) of PKA dissociates the holoenzyme and releases the catalytic moiety (PKAc), which phosphorylates a wide array of cellular substrates, controlling fundamental aspects of cell physiology.[1]

Specificity of PKA signaling can be achieved by localizing the kinase in close proximity to its targets, avoiding occurrence of widespread and uncontrolled phosphorylation at other sites. Compartmentalization of PKA within intracellular pools is mediated by A-Kinase Anchoring Proteins (AKAPs). These belong to a growing family of proteins that assemble multivalent "transduceosomes" which include not only PKA, but also cAMP-generating systems (receptors and adenylate cyclase), PKA effectors and attenuating enzymes, cAMP phosphodiesterase (PDE) and phosphatases (PPs).[2-5] Clustering signaling components within the same AKAP complex allows space-restricted and time-monitored activation of the pathway, optimally coupling signals generated at cell membrane to specific biological responses. Disassembly of AKAP scaffolds in the course of cAMP stimulation provides a control mechanism to dampen overstimulation by a given ligand and to attenuate downstream signaling events.[6]

Modulating the levels of AKAPs and PKA may profoundly alter the sensitivity of cells to hormone stimulation. Thus, transcriptional induction of some AKAPs and PKA isoforms by cAMP-elevating agents shifts the focus of cAMP signaling from membrane to intracellular compartments, accounting for differential cellular responses to discrete extracellular signals that activate adenylate cyclase.[5] The levels of AKAPs and PKA can also be regulated at the post-translational level by the ubiquitin-proteasome pathway (UPS). This is emerging as important mechanism that finely modulates the extent and duration of the activation cascade. As an example, degradation of mitochondrial AKAP121/149 by the hypoxia-UPS pathway rapidly reduces mitochondrial respiration and oxidative ATP synthesis, providing a mechanism of attenuation of the cAMP/PKA cascade that occurs at sites distal of signal generation.[7,8] Regulated proteolysis of free R subunits has been recently described as positive signal amplification loop during the course of cAMP stimulation. The RING ligase praja2 forms a complex with PKA, optimally decoding cAMP signals traveling from cell membrane to the downstream effector kinase (**Fig. 1**). Under basal conditions, praja2 controls the bulk levels of compartmentalized PKA holoenzyme. cAMP stimulation increases praja2:PKA complex formation, favouring efficient and synchronized local activation of the kinase. Phosphorylation of praja2 by PKAc stimulates R subunit proteolysis, reducing the R/PKAc ratio and sustaining substrate phosphorylation by the activated kinase. By attenuating the inhibitory constraints of R subunits on active PKAc, praja2 positively impacts on CREB phosphorylation and gene transcription, translating cAMP signals into efficient biological responses (i.e., synaptic plasticity and long-term memory).[9] Prolonged activation of PKAc by praja2 may also provide a negative control mechanism to locally attenuate the signal. Thus, by reducing total amount of PKA holoenzyme, praja2-mediated degradation of R subunits desensitizes the kinase to the prolonged wave of cAMP stimulation, avoiding unwanted prolonged PKAc activation. Based on these findings, we would expect that other PKA-dependent events related to differentiation, metabolism, growth and survival are likewise under the control of praja2 activity. Regulation of praja2 activity by PKA also predicts that a number of as yet unidentified praja2 substrates can be regulated by the UPS in a cAMP-dependent manner, pointing to a more general role of the ligase in cell physiology.

Collectively, these findings indicate that ubiquitination and regulated proteolysis of kinases, regulators and scaffolds represent important mechanisms that control the rate and magnitude of downstream kinase signaling. Dysregulation of any component of this circuitry may lead to cell disfunction and human disease. Thus, dissecting the mechanism(s) controlling the cAMP and the ubiquitin-proteasome system provides a molecular map for the design of drugs that selectively restore a disturbed cAMP cascade.

*Correspondence to: Antonio Feliciello; Email: feliciel@unina.it
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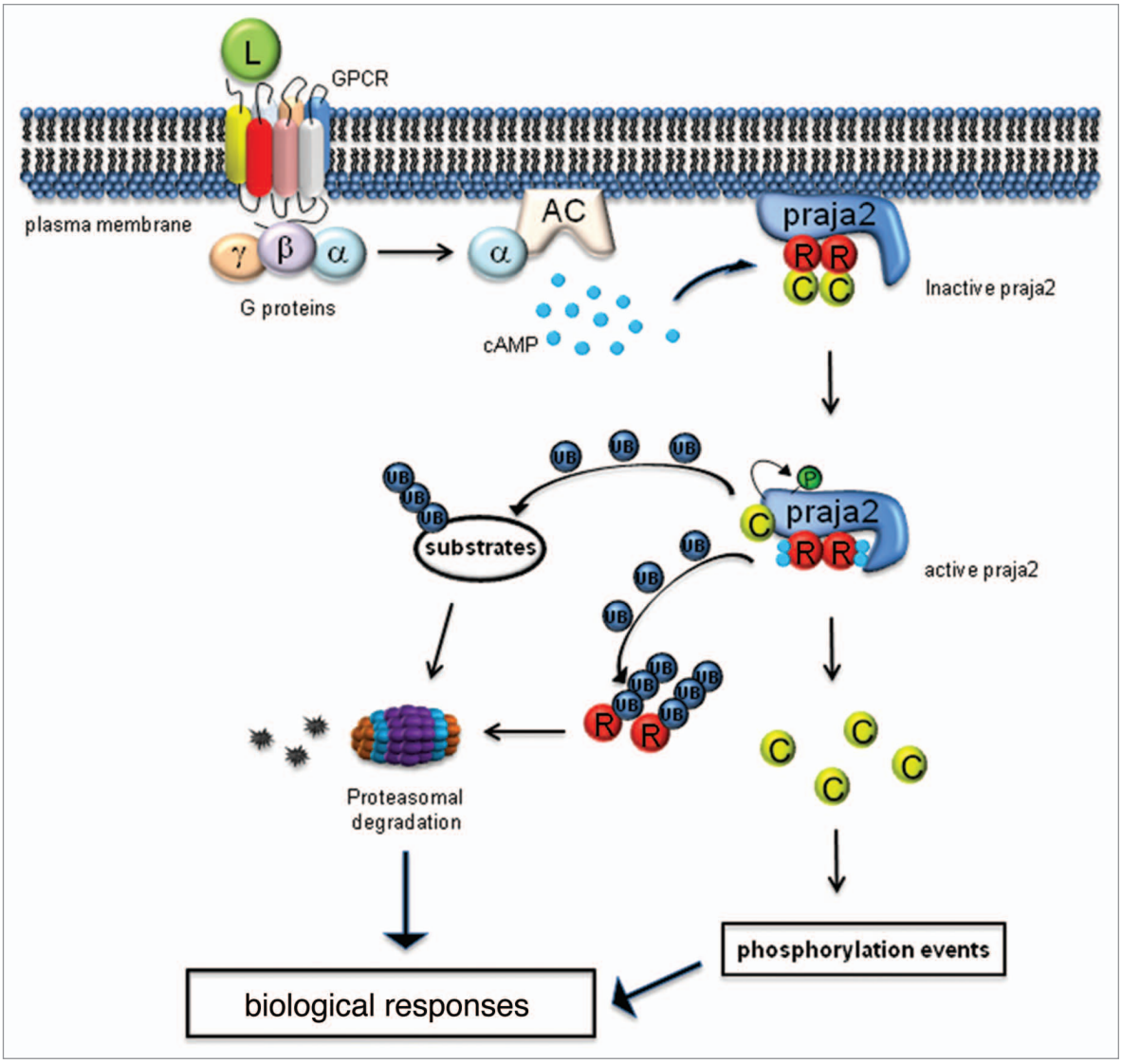

Figure 1. Proposed role of praja2 in PKA signaling. Ligand (L) binding to its G-protein coupled receptor (GPCR) at plasma membrane stimulates adenylate cyclase (AC) and elevates intracellular cAMP levels. cAMP binding to R subunits of PKA holoenzyme releases the catalytic mojety of PKA (C), which in turn phosphorylates praja2. Phosphorylated praja2 ubiquitylates and degrades R subunits through the proteasome pathway. Accumulation of free, active PKAc (C) sustains substrate phosphorylation, positively impacting on the rate and magnitude of cAMP signaling. Proteolysis of other praja2 substrates may also contribute to the hormone responses.

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