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Review

Signaling through C2 domains: More than one lipid target ☆

Senena Corbalan-Garcia *, Juan C. Gómez-Fernández *

Departamento de Bioquímica y Biología Molecular-A, Facultad de Veterinaria, Regional Campus of International Excellence "Campus Mare Nostrum", Universidad de Murcia, 30100 Murcia, Spain

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ABSTRACT

C2 domains are membrane-binding modules that share a common overall fold: a single compact Greek-key motif organized as an eight-stranded anti-parallel β-sandwich consisting of a pair of four-stranded β-sheets. A myriad of studies have demonstrated that in spite of sharing the common structural β-sandwich core, slight variations in the residues located in the interconnecting loops confer C2 domains with functional abilities to respond to different Ca^{2+} concentrations and lipids, and to signal through protein–protein interactions as well. This review summarizes the main structural and functional findings on Ca^{2+} and lipid interactions by C2 domains, including the discovery of the phosphoinositide-binding site located in the β3–β4 strands. The wide variety of functions, together with the different Ca^{2+} and lipid affinities of these domains, converts this superfamily into a crucial player in many functions in the cell and more to be discovered. This Article is Part of a Special Issue Entitled: Membrane Structure and Function: Relevance in the Cell's Physiology, Pathology and Therapy.

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Contents

1. Introduction

C2-domains are independently folded modules, of about 130 residues, found in a large and diverse set of eukaryotic proteins [1–3]. They were discovered as the second of the four conserved domains in classical PKCs (α, βI, βII, γ) responsible for Ca^{2+}-dependent membrane binding [4–6]. Novel PKCs (ε, η, δ, θ) lack the Ca^{2+}-dependency of the classical isoforms but soon it was described that they contain a V0/C2 region at their N-terminal [7] that interacted with negatively charged phospholipids [8–13]. A wide variety of proteins containing C2-domains have been identified from their discovery, most of them are involved in membrane trafficking and fusion, and in signal transduction (Fig. 1).

These domains are structurally defined as all-beta protein members of the C2-domain superfamily of Ca^{2+}/lipid-binding domains (CaLB) (Structural Classification of Proteins, SCOP: http://scop.mrc-lmb.cam.ac.uk/scop/ and Class Architecture Topology Homology, CATH: http://www.cathdb.info/). SCOP classification is based on two circularly permuted topologies that render a different orientation of the eight β-strands to each group of domains [14]. Having one or the other topology is not a determinant factor for the domain's function, including the Ca^{2+}-binding properties (Fig. 2). The superfamily includes two families: (i) the PLC-like variants, also known as the P-family or the type II topology and (ii) the synaptotagmin-like variants also referred to as the S-family or the type I topology (Table 1).

Recent update of the CATH database collects 127 domains in this superfamily, with 102 unique PDB entries classified in 3 structural and 80 functional family clusters [15]. Additional bioinformatics analysis, based on sequence profile searches, phylogenetic and phyletic-pattern and structure-prediction, have implemented the long list of proteins containing C2 domains. This information has been included in the PFAM (Protein Families) database (http://pfam.sanger.ac.uk) and

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* Corresponding authors.
E-mail addresses: senena@um.es (S. Corbalan-Garcia), jcgomez@um.es (J.C. Gómez-Fernández).

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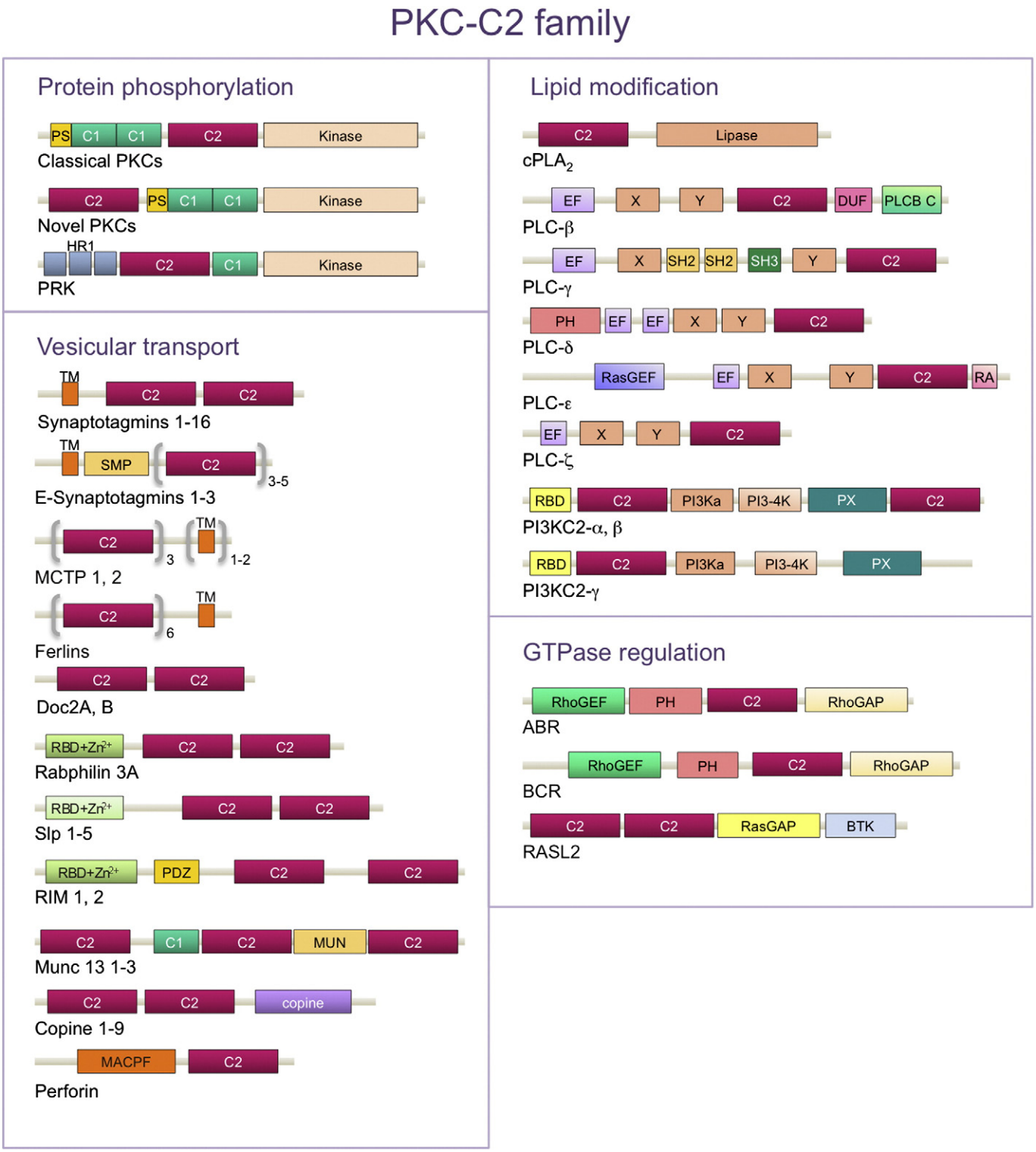

Fig. 1. Domain structures of proteins included in the PFAM/PKC-C2 family. The proteins have been classified into four groups depending on their functions: protein phosphorylation, vesicular transport, lipid modification and GTPase regulation. Parentheses in the diagram are associated with the number of C2 domains in a protein. Abbreviations: PS, pseudosubstrate; PKC, protein kinase C; HR1, protein kinase C-related kinase homology region 1; TM, transmembrane region; SMP, synaptotagmin-like-mitochondrial-lipid binding protein; MCTP, multiple C2 domain and transmembrane region proteins; DOC2, double C2-like domain-containing protein; Slp, synaptotagmin-like protein; RIM, Rab3-interacting molecule; cPLA2, cytosolic phospholipase A2; PLC, phospholipase C; EF, EF-hand motif; DUF, domain of unknown function; SH2, Src homology 2; SH3, Src homology 3; PH, pleckstrin homology domain; GEF, guanine nucleotide exchange factor; RA, ras association domain; RBD, ras binding domain; PX, P40/47phox homology domain; GAP, GTPase-activating protein; BTK, Bruton's tyrosine kinase.

provides a wider view about the evolution, structure and function of the members of this superfamily (Table 2) [16–18]. Interestingly, these studies show evidences that the last eukaryotic common ancestor contains about 9 families that participate in many functions related to membranes like repair and vesicular trafficking, actin and tubulin anchoring to the plasma and vesicular membranes, localization of small GTPases to membranes, lipid-based signal transduction and ciliogenesis [17,19]. This classification also shows that the calcium-dependent membrane interaction is a derived feature restricted to the PKC-C2 family, an ability that was acquired by its last common ancestor.

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