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Diacylglycerol kinase ζ: At the crossroads of lipid signaling and protein complex organization

Esther Rincón [a,1], Severine I. Gharbi [a], Teresa Santos-Mendoza [b], Isabel Mérida [a,*]

[a] Department of Immunology and Oncology, Centro Nacional de Biotecnología/CSIC, E-28049 Madrid, Spain
[b] Laboratory of Immunobiology and Genetics, National Institute of Respiratory Diseases (INER), Mexico City, Mexico

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ABSTRACT

Diacylglycerol (DAG) and phosphatidic acid (PA) are lipids with unique functions as metabolic intermediates, basic membrane constituents, and second-signal components. Diacylglycerol kinases (DGK) regulate the levels of these two lipids, catalyzing the interconversion of one to the other. The DGK family of enzymes is composed of 10 isoforms, grouped into five subfamilies based on the presence of distinct regulatory domains. From its initial characterization as a type IV DGK to the generation of mouse models showing its importance in cardiac dysfunction and immune pathologies, diacylglycerol kinase ζ (DGKζ) has proved an excellent example of the critical role of lipid-metabolizing enzymes in the control of cell responses. Although the mechanism that regulates this enzyme is not well known, many studies demonstrate its subtle regulation and its strategic function in specific signaling and as part of adaptor protein complexes. These data suggest that DGKζ offers new opportunities for therapeutic manipulation of lipid metabolism.

Contents

Abbreviations: APC, antigen-presenting cell; DAG, diacylglycerol; DGK, diacylglycerol kinase; GFP, green fluorescent protein; GPCR, G protein-coupled receptor; LTP, long-term potentiation; MARCKS, myristoylated alanine-rich C kinase substrate protein; PDZ-bm, PDZ binding motif; PA, phosphatidic acid; PI, phosphatidylinositol; PtdIns(4,5)P_2, phosphatidylinositol 4,5 bisphosphate; PI4P5K, phosphatidylinositol-4-phosphate 5-kinase; PLC, phospholipase C; PLD, phospholipase D; PH, pleckstrin homology domain; C1, protein kinase C conserved type I domain; PKC, protein kinase C; SNX, sorting nexin; TCR, T cell receptor.

* Corresponding author. Address: Department of Immunology and Oncology, Centro Nacional de Biotecnología/CSIC, Darwin, 3, UAM Campus de Cantoblanco, E-28049 Madrid, Spain. Tel.: +34 915854702; fax: +34 913720493.
E-mail address: imerida@cnb.csic.es (I. Mérida).
[1] Present address: Departamento de Biología Celular y del Desarrollo, Centro Nacional de Microbiología, Instituto de Salud Carlos III, E-28220 Madrid, Spain.

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1. Introduction

The diacylglycerol kinases (DGK) are a family of lipid kinases that catalyze conversion of diacylglycerol (DAG) into phosphatidic acid (PA) (Fig. 1A). This highly conserved family of enzymes is present in all multicellular organisms including *Dictyostelium discoideum*, *Drosophila melanogaster*, *Caenorhabditis elegans*, plants and mammals [1–4].

DGK activity was first described in 1959 [5], and it was soon identified as a component of the phosphatidylinositol (PI) cycle [6–8]. For several decades, it was thought that PA synthesized by DGK channeled rapidly into the PI cycle, with no obvious signaling function. The DGK were also proposed to metabolize only the DAG generated in response to receptor-stimulated PLC activation, with no contribution to the regulation of steady-state DAG then thought to be metabolized by other mechanisms [9,10]. It is now clear that DGK functions are much more complex, with multiple DGK isoforms that can act both as DAG and PA signal regulators and participate in different aspects of the lipid metabolic cycle [11,12]. As a result, DGK take part in numerous cell processes, and their precise regulation is essential for maintaining appropriate cell homeostasis [13–17]. The presence of specific motifs involved in protein–protein and protein–lipid interaction suggests that DGK modulate lipid levels in the context of supramolecular complexes [4,14]. This mechanism of action provides a means to modulate the activity of interacting partners, ensuring restricted spatial tuning of lipid levels wherever it is required.

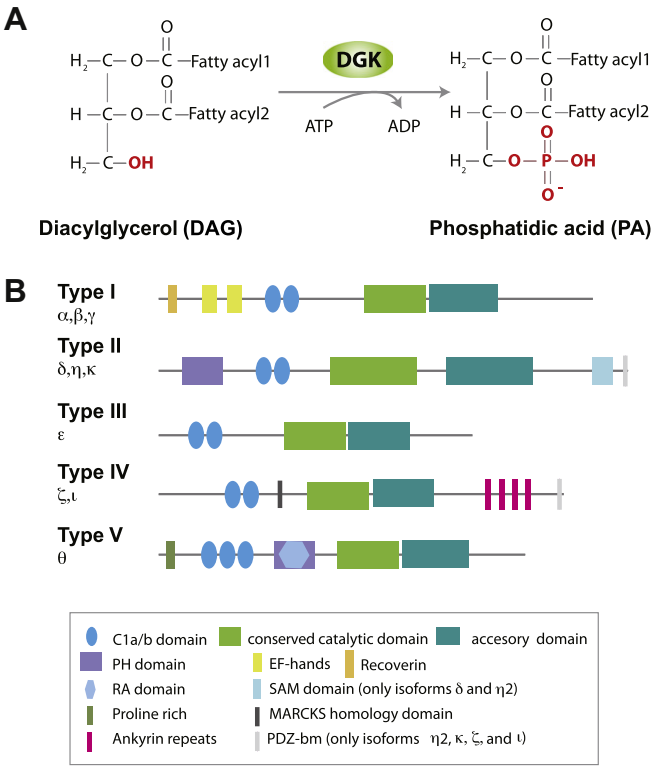

Fig. 1. Catalytic function of the DGK family and classification of mammalian DGK. (A) DGK phosphorylate diacylglycerol (DAG) into phosphatidic acid (PA). (B) DGK are grouped into five types, based on the presence of conserved domains. Type I DGK (α, β, γ) have two EF-hand calcium-binding domains and a recoverin homology-like domain (RVH) with different calcium affinities [103]. The type II DGK (η, κ, δ) have a pleckstrin homology (PH) domain [104]; in DGKδ, this domain binds PI [105]. In addition, DGKδ and the alternative transcript DGKη2 have sterile alpha motifs (SAM domain). Finally, in the C terminus (C-term), DGKη2 and DGKκ have a PDZ-binding motif (PDZ-bm), and DGKκ has a domain with 33 EPAP repeats (Glu-Pro-Ala-Pro) [106]. DGKε is the only member of the DGK type III group; no regulatory domain characteristics have so far been described for this DGK. Type IV DGK (ζ,ι) have a MARCKS-like region, as well as four ankyrin repeats and a PDZ-bm [28–30]. The type V DGK (DGKθ) has an additional C1 domain, a PH domain that overlaps a Ras association domain (RA), and a Pro-rich domain (PR) [107].

In addition to these shared regions, specific domains in the DGK sequence are used to classify them into five subtypes (I–V) (Fig. 1B). Each domain confers specific characteristics, including calcium regulation (EF hands, recoverin domain), lipid binding (PH domain), protein/protein interactions (RA, PDZ-bm, MARCKS), and subcellular localization (NLS, ankyrin repeats) and, for all, precise three-dimensional conformation. There are several excellent reviews that have summarized the latest studies of the DGK enzyme family. Here we have specifically focused on those that characterize DGKζ regulation and functions.

From its initial description as a nuclear enzyme to the most recent characterization of DGKζ transgenic and -deficient mice, this isoform is probably the best-studied of the entire DGK family. To date, however, there is no clear correlation between the studies in different systems and, more importantly, it is difficult to discern which functions can be attributed to this isoform. Here we review the literature in light of new advances regarding the identification of novel DGKζ partners. These studies support the growing concept that DGKζ acts as a component of large protein complexes that bring together lipid-metabolizing enzymes and lipid effectors near the membrane. This mechanism of action reveals the importance of local modulation of lipid second messengers at specific sites and helps to understand the contribution of this isoform in the control of neuronal and immune responses.

The DGK belong to a superfamily that also includes the sphingosine kinases (SPK) and ceramide kinases (CEK) [18]. Mammals express 10 DGK isoforms (see Fig. 1B), with a large number of alternative transcripts [3]; they share a common catalytic domain that is subdivided into a conserved motif (DGKc) and an accessory domain (DGKa). All DGK are soluble enzymes that act at the membrane interface, catalyzing conversion of lypophilic substrates. As a result, they are subject to strict regulation to permit movement to and interaction with their substrates at the membrane. The mechanism by which DGK target to specific membranes is not clear, but the protein kinase C (PKC) type 1 conserved (C1) domains found in all isoforms appear to be critical for adequate DGK membrane and protein–protein interaction [19–21]. The two DGK C1 domains lack the residues needed for DAG and phorbol ester binding [22], except those of DGKγ and DGKβ [23,24] and (Fig. 1B). The two DGKζ C1 domains and the second DGKθ C1 domain are essential for their catalytic action [19,25], whereas the DGKα C1 domains are dispensable for enzyme activity *in vitro* [26]. The existence of DGK orthologs in plants that lack C1 domains suggests that these regions are not necessary for catalytic function [27].