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Diacylglycerol Kinases: Emerging Downstream Regulators in Cell Signaling Systems

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Diacylglycerol kinase (DGK) regulates signal transduction by modulating the balance between the two signaling lipids, diacylglycerol and phosphatidic acid. DGK and its homologs occur in a wide range of multicellular organisms and the mammalian DGK is known to consist of nine members with a considerable incidence of alternative splicing. Recent work has established that DGK serves as a key attenuator of diacylglycerol of signaling functions and that the mammalian isozymes are equipped with molecular machineries which enable them to act in specific intracellular sites and/or in signaling protein complexes.

Key words: alternative splicing, diacylglycerol, diacylglycerol kinase, phosphatidic acid, signal transduction.

Diacylglycerol kinase (DGK) phosphorylates diacylglycerol (DG) to yield phosphatidic acid (PA). This enzyme initiates resynthesis of phosphoinositides consumed by phospholipase C during cellular signal transduction. The discovery of protein kinase C (PKC) that is allosterically activated by DG (*1*) has accelerated DGK investigation, since this enzyme has been generally thought to act as an attenuator of PKC by terminating the DG signal generated in response to cell surface receptor stimulation. In mammalian cells it is difficult to define the contribution of DGK to the regulation of steady-state levels of DG, since DG, a common precursor for synthesis of glycerolipids, can be metabolized potentially by a number of enzymes including, for example, DG lipase. It is believed that DGK acts at the early phase of phosphoinositide signaling and that the contribution of DGK to metabolic processing of cellular DG is quantitatively minor when compared to other enzymes. However, in view of recent understanding of the regulatory roles of DGK, it becomes clear that the cellular DG pool is spatially and functionally segregated and that DGK is critically involved in depleting DG generated in a signaling complex containing DGK itself or at certain restricted intracellular sites such as plasma membranes and nuclei.

DGK and its homologs in different organisms

It is now well established that mammalian DGK consists of nine isozymes encoded by separate genes (*2, 3*). In addition to PKC-like zinc fingers and catalytic regions commonly conserved in all DGKs, these isozymes contain a variety of regulatory domains of known and/or predicted functions. The mammalian isozymes are named according to the order of their cDNA cloning and are subdivided into five groups based on their characteristic structural features (*2–5*). Figure 1 summarizes schematic structures of DGKs in mammalian and other organisms to show the extended occurrence of evolutionally conserved enzymes. Although DGKs depicted for organisms other than mammals contain putative enzymes collected from available data bases and the naming system has not been established, it is amazing to see that not only the basic catalytic regions but also a considerable part of regulatory domains detected for mammalian enzymes are conserved in diverse organisms. This suggests the fundamental importance of DGKs in the regulation of basic cellular functions. It is also of note that no DGK gene has yet been detected in yeast. This may suggest that DGK is needed to control functions unique to multicellular organisms. Figure 1 also includes the occurrence of alternative splicing recently detected for several mammalian DGK genes. The splice variants may be potentially present in DGKs other than those presented, adding further complication to the attempts to define the physiological functions of many isozymes.

Genetic evidence of physiological implication

It is difficult to interpret the implication of DGK action, because both the substrate DG and the reaction product, PA, act as lipid mediators. Phospholipase D rather than DGK has been regarded as being primarily responsible for generating signaling PA (*6*). Indeed, PA generated by phospholipase D associated with the Golgi membranes is implicated in the control of membrane traffic at the distal stage of the secretory pathway (*7*). Recently, PA generated by phospholipase D was shown to bind to and regulate mTOR, which is a critical component of a mitogen-dependent signaling pathway (*8*). It is not known to what extent the quantitatively minor PA formed by DGK contributes to cellular signaling. The importance of DGK in the control of cellular function has been well documented in non-mammalian animals like *Drosophila* and *Caenorhabditis elegans*, both of which were subjected to straightforward gene manipulation. *Drosophila rdgA* encodes DGK (dmDGK2 in

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Abbreviations: DG, diacylglycerol; DGK, diacylglycerol kinase; GRP, guanyl nucleotide-releasing protein; PA, phosphatidic acid; PKC, protein kinase C.

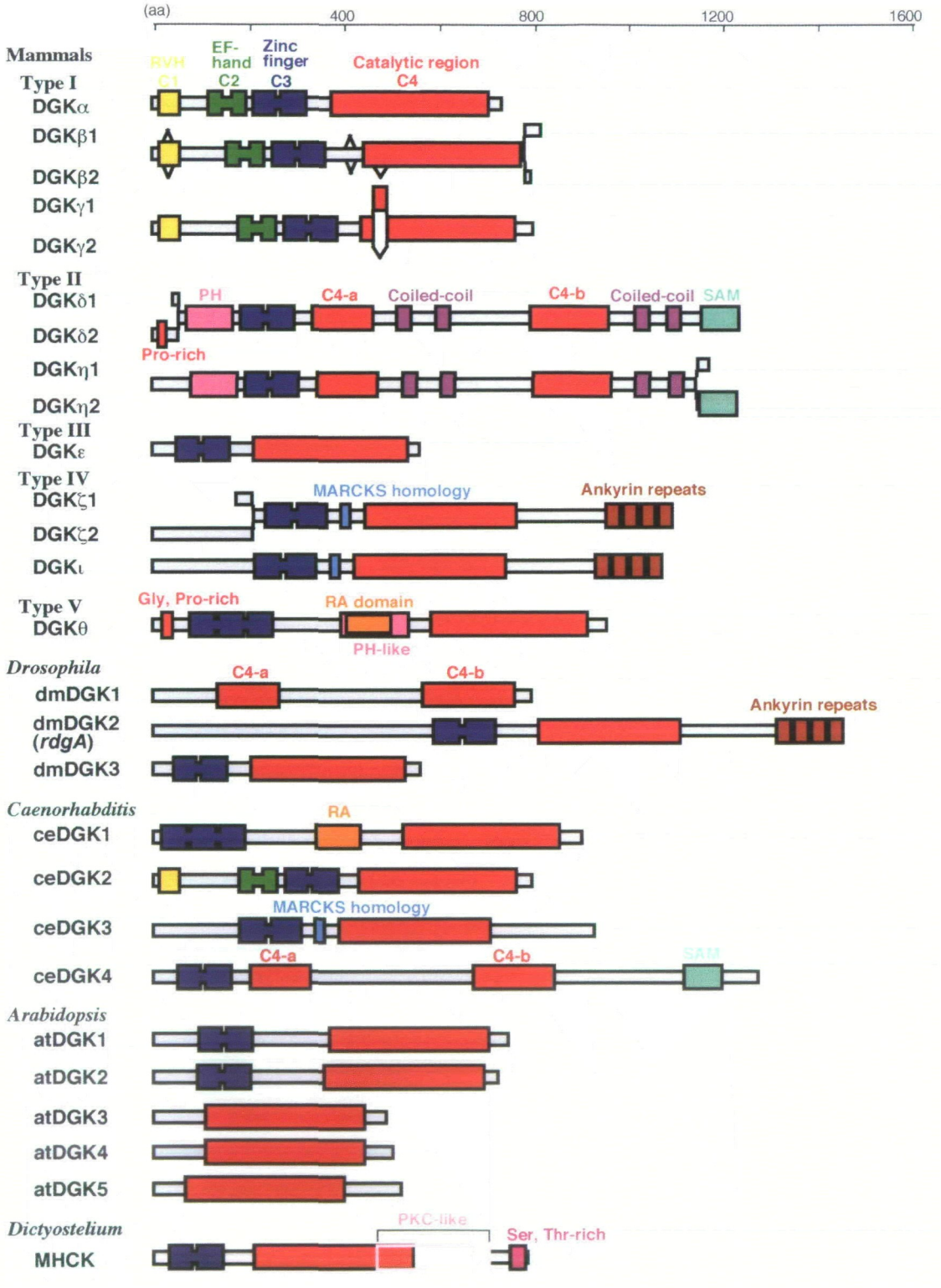

Fig. 1), which is 49% identical to mammalian DGKι (*9, 10*). The loss-of-function mutation of *rdgA* causes the most severe form of retinal degeneration (*9, 10*). Recent work shows that the depletion of phospholipase C-derived DG by *rdgA* gene product is closely linked to the regulation of Ca^{2+}-channels and that DGK represents the major mechanism of light response termination (*10*). In the case of *C. elegans*, DGK1 (ceDGK1 in Fig. 1) is 38% identical to human DGKθ (*11, 12*). The *dgk*1 mutation causes impairment of serotonin inhibition of synaptic transmission, resulting in abnormality of animal locomotion and egg-laying behavior (*11, 12*). The DG signal in this case is mediated by presynaptic DG-binding UNC13. The results obtained for the two non-mammalian animals further strengthen the im-

Fig. 1. **Schematic representation of DGK isozymes and their homologs.** The mammalian DGKs except for splice variants have been reviewed previously (*2–5*). DGKβ1 and DGKβ2 are referred to as DGKβSTD and DGKβSV3′, respectively, in Ref. *18*, and triangles on DGKβ indicate potential deletion sites by alternative splicing (*18*). DGK homologs are also shown for insect (*Drosophila melanogaster*), nematode (*Caenorhabditis elegans*), plant (*Arabidopsis thaliana*), and slime mold (*Dictyostelium discoideum*). We number these homologs following the extents of sequence similarities to the N-terminal half (C4-a) of mammalian DGKα, although those with already published designations are given priority. To save space, only accession numbers are given for the DGK family members as listed below.
Mammals: pig DGKα [X53256]; rat DGKβ1 [D16100]; human DGKβ2 [AX032745]; human DGKγ1 and γ2 [D26135]; human DGKδ1 [D73409]; human DGKδ2 [AB078966]; hamster DGKη1 [U49379]; human DGKη2 [AB078968]; human DGKε [U49379]; human DGKζ1 [U51477]; human DGKζ2 [U94905]; human DGKι [AF061936]; human DGKθ [L38707]. *Drosophila*: DGK1 [D11120]; DGK2 [U49946]; DGK3 [U23449-6]; DGK4 [U61952-8]. *Arabidopsis*: DGK1 [D63787]; DGK2 [AB005234-23]; DGK3 [AC005724-11]; DGK4 [G85354]; DGK5 [AF360300-1]. *Dictyostelium*: MHCK (myosin-heavy chain kinase) [A46136]. MARCKS, myristoylated, alanine-rich C-kinase substrate; PH, pleckstrin homology; RA, Ras-associating; rdgA, retinal degeneration A; RVH, recoverin homology; SAM, sterile α motif.

portance of the DG-signal in cellular function and also indicate that reduction of the DG-signal rather than PA formation is important for considering the implication of DGK action.

In mammalian systems, a variety of functions have been recently defined for DGK isozymes, in particular for α- and ζ-isozymes. It has become increasingly clear that each DGK isozyme is a critical downstream component of the DG-dependent signaling system. This paper deals with the structure and function of mammalian DGKs and aims, by incorporating recent progress, to supplement the reviews already available for this enzyme family (*2–5*).

Novel aspects of type I DGKs

DGKα and tyrosine phosphorylation. Regulatory functions of DGKα in the downstream signaling pathways linked to cell-surface tyrosine kinase receptors have recently been described for T-lymphocytes (T-cell receptor, Ref. *13*), and epithelial and endothelial cells (hepatocyte growth factor receptor, Ref. *14*). In these studies, the use of kinase-dead, dominant-negative as well as constitutively active, dominant-positive forms of DGKα contributed to pinpoint the action of this particular isozyme. In hepatocyte growth factor-stimulated cells, DGKα positively acts in inducing cell motility, scattering and proliferation (*14*). In lymphocytes, this isozyme is a negative regulator of lymphocyte activation as evidenced by down-regulation of the T cell activation marker (*13*). In both cases, tyrosine kinase activity of the receptors is required for DGK action, but the molecular mechanisms underlying DGKα activation appear to be distinct from each other. In the case of hepatocyte growth factor-stimulated cells, DGKα forms a complex with Src and is activated presumably by tyrosine phosphorylation, at least in *in vitro* assays (*14*). Upon T cell activation, on the other hand, DGKα translocates from the cytoplasm to the plasma membrane, where subsequent phosphorylation of DG causes a rapid release of the enzyme back to the cytoplasm (*13*). Translocation of DGKα was also observed in CHO-K1 cells stimulated by ATP or arachidonic acid (*15*). Common to all experimental systems, covalent modification of DGKα protein such as tyrosine phosphorylation could not be detected or failed to correlate with its activation. It thus seems that the molecular mechanisms of DGK translocation and activation remain to be elucidated.

DGKγ as phorbol ester receptor. Important observations concerning DGKγ have been made on the role of its zinc finger in the translocation occurring in cells treated with tumor-promoting phorbol esters. Saito's group (*15*) first discovered that DGKγ but not DGKα was irreversibly translocated to plasma membranes in cells treated with phorbol ester. This translocation depends on the first zinc finger of the C3 region (Fig. 1), corresponding to the C1a zinc finger of PKC, thus suggesting that the zinc finger of DGKγ is capable of binding diacylglycerol and its analogs, phorbol esters. Indeed, it was subsequently demonstrated that the C1a zinc finger of this isozyme is a high-affinity phorbol dibutyrate receptor (*16*). This observation established that DGKγ and possibly several other DGKs serve as receptors of tumor-promoting phorbol esters. It is of interest to delineate functions of other DGK zinc fingers, which show sequence homology to PKC C1a region to highly variable extents (*16*). Ambiguity remains concerning the functions of zinc fingers present in DGKs, since DGKα does not respond to phorbol esters (*15*), while the zinc finger-deleted, C-terminal part of DGKα can catalyze the enzyme reaction (*5*). Is it possible that DGKγ possesses two sets of DG-binding or -recognition sites, one for sensing DG-generation at the plasma membrane and the other acting as a catalytic site? What is the function of non-DG-binding DGK zinc fingers? Further investigation of DGK zinc fingers is expected to provide key insights into the mechanisms of catalysis and activation of DGKs.

Other aspects of type I DGKs. Besides intracellular translocation, there are two additional findings potentially important for understanding the implication of the type I DGKs. Firstly, these enzymes are known to contain a conserved N-terminal region (C1 in Fig. 1), the function of which has remained unknown until recently. Walsh's group (*17*) noted a significant sequence homology between this region and the N-termini of the recoverin family of neuronal calcium sensors. This region is thus designated RVH (recoverin homology) domain and is shown to act together with Ca^{2+}-binding EF-hands as an autoinhibitory domain. The RVH domain, though itself incapable of binding Ca^{2+}, also participates in concert with EF-hands in the enzyme activation and conformational changes induced by Ca^{2+}. This finding suggests the importance of the Ca^{2+} signal in the regulation of DGK activity, although the activation of DGKα by Ca^{2+} has so far been detected only *in vitro* (*5*). Secondly, the occurrence of alternative splicing was first suggested by the finding of an internally truncated and catalytically inactive form of DGKγ (*5*). Recently, human DGKβ gene was proposed to yield potentially as many as 16 splice variants, 8 of which were confirmed to be expressed in human tissues, albeit to an extremely limited extent (*18*). One of the variants with a deletion of the C-terminal 35 amino acid residues (DGKβ SV3′ in Ref. *18*, DGKβ2 in Fig. 1) was confirmed to possess DGK activity and was shown to respond to phorbol ester treatment differently from the full-length (DGKβSTD in Ref. *18*) enzyme.

The type I DGKs are the prototypes of the extended fam-

ily members, but their physiological implication has long remained unsettled. The repeated use of commercially available DGK inhibitors such as R59022 and R59949 has suggested that DGK acts as a PKC attenuator. These inhibitors were shown to be relatively specific to the EF-hand–containing type I DGKs (*19*), and indeed, the effects of negative-dominant DGKα could be reproduced using these inhibitors (*13, 14*). Although the molecular mechanisms of translocation and/or activation of these DGKs need to be further explored, this class of DGK now appears to be established as a critical regulator of DG-dependent signaling pathways.

DGKζ with diverse functions

DGKζ in nuclear functions. Among DGK isozymes, the physiological implication of DGKζ was first elucidated at the molecular level (*20*). This enzyme is localized in cell nuclei through the action of its MARCKS domain as a nuclear localization signal and is shown to regulate the amount of nuclear DG accumulated in growth factor-stimulated cells. The nuclear DG promotes cell growth and differentiation through PKC activation, and overexpression of this enzyme results in an increased cell cycle duration. Interestingly, phosphorylation of the MARCKS domain by PKC causes relocation of the nuclear DGKζ to the cytoplasm, suggesting the existence of a feed-back mechanism of cell growth regulation. Surprisingly, DGKζ was later found to recruit γ1-syntrophin, a member of dystrophin-associated protein complex, into the nuclei by forming a stable complex (*21*). In this case the C-terminus of this DGK isozyme contains a consensus PDZ-binding motif that interacts with the PDZ domain of syntrophins. It thus seems possible that, in addition to the MARCKS domain, the modes of nuclear localization and subcellular distribution of DGKζ can be controlled by interaction with the cytoplasmic PDZ domain–containing proteins.

Other aspects of DGKζ. An important function of DGKζ in the regulation of cell proliferation and transformation has recently been disclosed by the finding that this enzyme specifically regulates Ras through attenuating the DG signal targeted to the activation of Ras-GRP (guanyl nucleotide–releasing protein, Ref. *22*). Ras-GRP is known to be activated by binding DG or phorbol esters to its C1 domain. DGKζ and Ras-GRP form a complex in response to the DG signal, thus showing that DGKζ is involved in DG metabolism occurring in a signaling protein complex. Furthermore, the kinase-dead DGKζ mutant potentiates Ras action, presumably by suppressing the endogenous enzyme activity. The Ras regulation by DGKζ is highly specific to this isozyme, because other DGKs including even the ζ2 (Fig. 1), the product of alternative splicing differing only in the N-terminal sequence, failed to regulate Ras-GRP. The region of the DGKζ molecule responsible for the interaction with Ras-GRP remains unclear, but appears to reside in the C-terminal portion of its catalytic domain.

Extending the repertoire of DGKζ actions is the finding that this isozyme interacts through its ankyrin repeats with the cytoplasmic portion of leptin receptor (*23*). The DGKζ mRNA level in rat hypothalamic nuclei is linked to the level of circulating leptin or the consumption of high-fat diet. This unexpected role of DGKζ in energy homeostasis represents a unique aspect of DGK action, and may suggest that in certain cells DGK is involved in a classical pathway of glycerolipid biosynthesis. A common feature of all of the DGKζ actions is that this enzyme can be spatially segregated within the cells through protein–protein interactions, thus enabling the enzyme to act as an off-mechanism in highly restricted sites. It still remains to be seen whether DGKζ still possesses more hidden functions and whether such a diversity of functions ascribed to a single isozyme can be also applicable to other DGKs.

Other DGKs

DGKε in neuronal functions. DGKε is known to possess a unique substrate selectivity to arachidonoyl DG, which is the major molecular species of DG liberated from phosphoinositides by phospholipase C (*2–5*). Gene targeting of DGK has been first achieved for this enzyme (*24*). The depletion of DGKε affected neuronal responses including long-term potentiation (LTP) and susceptibility to electroconvulsive shock. Although the neuronal phosphoinositide signaling was significantly attenuated in the knock-out mice, the observed phenotypes were not dramatically altered, possibly because of adaptive responses and compensation by other DGKs.

DGKθ and RhoA. DGKθ was recently shown to bind specifically to active RhoA (*25*). This interaction is highly specific, because neither inactive RhoA nor other RhoA family members (Rac and Cdc42) can bind to DGKθ. Remarkably, the activity of DGKθ bound to RhoA is strongly suppressed. Because RhoA is known to activate phospholipase D, thereby generating PA (*6*), it is difficult to reconcile the implication of DGK inhibition by RhoA. It is possible that phospholipase D and DGK operate in a temporally and spatially separated manner, yielding PA of distinct functional roles. It would be interesting to further explore the role of RhoA in lipid signaling systems. The nuclei of IIC9 fibroblasts contain both DGKθ and DGKδ (*26*). The increase of the nuclear DGK activity in cells stimulated with α-thrombin is accounted for by a rapid and transient translocation of DGKθ (*26*). Similar redistribution of DGKθ was also noted in rat small arteries stimulated with noradrenaline, and in these tissues this isozyme was activated in a phosphoinositide-3-kinase dependent manner (*27*).

DGKδ and membrane traffic. A moderate overexpression of DGKδ was recently observed to elicit redistribution of the Golgi membrane proteins to the endoplasmic reticulum, similarly to brefeldin A treatment (*28*). In this case, DGKδ associates with the endoplasmic reticulum through its SAM domain and suppresses the anterograde transport from the endoplasmic reticulum to the Golgi by specifically inhibiting the formation of COPII-coated structure on the membranes. Puzzlingly, the kinase-dead DGKδ mutants also inhibit the anterograde transport, and the mechanisms of this interesting observation remain unclear. It was also noted that the intracellular distribution patterns of DGKδ expressed in various cells were quite heterogeneous, suggesting multiple functions of this isozyme acting in different intracellular compartments.

Perspective

More than a decade has elapsed since the first cDNA cloning of a DGK isozyme (α), and research on DGK family members has established the importance of the DG signal in a wide range of cellular functions. As typically represented by numerous functions described for a single

isozyme, DGKζ, future studies are expected to add to the list of functions of DGK isozymes. There remain a number of regulatory domains whose functions need to be characterized in order to specify the functions of individual DGK isozymes. There is no shortage of materials to deal with in further research on DGKs.

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