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Sommario/riassunto

Diacylglycerol kinases (DGKs) phosphorylate diacylglycerol (DG), catalyzing its conversion into phosphatidic acid (PA). This reaction attenuates membrane DG levels, limiting the localization/activation of signaling proteins that bind this lipid. Initially recognized as modulators of classical and novel PKC family members, the function of the DGK has further expanded with the identification of novel DG effectors including Ras Guanyl nucleotide-releasing proteins (RasGRP) and chimaerin Rac GTPases. The product of the DGK reaction, PA, is also a signaling lipid that mediates activation of multiple proteins including the mammalian target of rapamycin (mTOR). The DGK pathway thus modulates two lipids with important signaling properties that are also key intermediates in lipid metabolism and membrane trafficking. The DGK family in eukaryotes comprises 10 different members grouped into five different subfamilies characterized by the presence of particular regulatory motifs. These regions allow the different DGK isoforms to establish specific complexes and/or to be recruited to specific subcellular compartments. The subtle regulation of DG and PA catalyzed byspecific DGKs is sensed by a restricted set of molecules, providing the means for spatio-temporal regulation of signals in highly specialized cell systems. In the recent years, multiple studies have unveiled the functions of specific isoforms, their mechanisms of regulation and their participation in different pathways leading to and from DG and PA. Animal models have greatly helped to

understand the specialized contribution of DGK mediated signals, particularly in the immune and central nervous systems. Mice deficient for individual DGK isoforms show defects in T and B cell functions, dendritic spine maintenance, osteoclast and mechanical-induced skeletal muscle formation. Studies in flies and worms link DGK mediated DAG metabolism with mTOR- mediated regulation of lifespan and stress responses. In plants DGK mediated PA formation contributes to plant responses to environmental signals. Aberrant DGK function has been recently associated with pathological states, an expected consequence of the essential role of these enzymes in the regulation of multiple tissue and systemic functions. DGK mutations/deletions have been related to human diseases including diabetes, atypical hemolytic-uremic syndrome, Parkinson disease and bipolar disorders. On the contrary DGK upregulation emerges as a non-oncogenic addition of certain tumors and represents one of the main mechanism by which cancer evades the immune attack. As a result, the DGK field emerges an exciting new area of research with important therapeutic potential.