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Introduction

Nucleoside Diphosphate Kinases: Genes and Protein Functions

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The 5′-diphosphates and 5′-triphosphates of ribonucleosides and 2-deoxyribonucleosides, including ADP and ATP, participate in cellular energy transfers and play important roles in nucleic acids syntheses and other biosynthetic reactions such as proteins, polysaccharides, and lipids. These various nucleoside diphosphates, synthesized via their independent metabolic pathways, are funneled through nucleoside diphosphate (NDP) kinase to produce corresponding nucleoside triphosphates at the expense of ATP. On the basis of the biochemical characteristics, NDP kinase has long been regarded as a nonregulatory housekeeping enzyme. During the last decade, however, our understanding of this enzyme has innovated dramatically since NDP kinases were found to possess multiple functions, such as transcription regulatory activity, differentiation inhibitory activity, and protein kinase activity, in addition to the conventional NDP kinase enzyme activity. Furthermore, to our surprise was the finding that their quantitative and/or qualitative alterations were associated with serious deterioration in cells and tissues as exemplified in morphological abnormality in flies and metastasis and tumorigenesis in certain types of mammalian cells. These recent advances raise the question as to the true role of NDP kinases in cells and inevitably force researchers in the NDP kinase field to reconstruct the whole picture of the "well-known" enzyme. To this goal, this issue is organized to focus on recent advances in the NDP kinase researches, particularly on the genes and the protein functions under physiological and pathological conditions.

The NDP kinase genes are highly conserved from prokaryotes to eukaryotes. Despite the seemingly indispensable nature of this protein, disruption of the gene results in, except *Myxococcus xanthus*, no apparent phenotypic changes in *E. coli* and the yeasts, *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*, although the latter bacterial gene was later found to function as a mutator. Ishikawa *et al.* investigate the NDP kinase genes structures and their regulatory mechanisms from a viewpoint of evolution and analyze phylogenetically the orthologs and paralogs. Multiplication of the gene and acquisition of "multiple-layered" regulatory mechanisms would be a hint to figure out the role of this important protein. Arnaud-Dabernat *et al.* report on a knockout mouse in which *nm23-M1* gene is disrupted. Very interestingly, these knockout mice can grow without major health problems but their potential usefulness is discussed. Postel describes a novel function of nm23-H2/NDP kinase B, in terms of DNA binding and transcription, and a recently discovered DNA-cleavage reaction.

A number of literatures demonstrate that NDP kinases appear to exert their effects through protein–protein interactions under certain conditions. One of the intriguing examples is the interaction of NDP kinases with a variety of GTP binding proteins, especially, those in signal transduction systems. Kimura *et al.* trace this framework from the beginning to the latest, evaluate recent developments carefully, and extend this view from the G-protein-coupled signal transduction systems to the receptor tyrosine kinase signal transduction systems. Narayanan and Ramaswami, making full use of genetics, describe the functional interaction of NDP kinase with dynamin, a GTPase essential for endocytosis, and suggest that NDP kinase may play a role as a guanine nucleotide exchange factor (GEF) for dynamin. Hasunuma *et al.* mention the NDP kinases in plants and fungi, and demonstrate an intriguing property in the light signal transduction system coupled to morphogenesis of *Neurospora crassa*. Lombardi and Mileo summarize recent literatures on the interaction between NDP kinases and other proteins.

The discovery of *nm23*, the tumor metastasis suppressor gene, and its identity to NDP kinase brought about enthusiasm in the NDP kinase/nm23 research field. The anti-metastatic action of *nm23* has been established in a number of tumor cells by using animal model systems.

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Ouatas *et al*. collectively depict the state of the art on the role of nm23/NDP kinase during metastasis and potential approaches for the suppression of metastasis. On the basis of our realization that the metastatic potential and cell migration may be closely associated, Fournier *et al.* postulate the crucial role of the complex between NDP kinase B/nm23-H2 and a regulator of $\beta 1$ integrin mediated cell adhesion, ICAP-1, in the regulation of cell migration. Okabe-Kado and Kasukabe point out the increased serum level of NDP kinase A/nm23-H1 and discuss its relationship with a poor prognosis in patients with hematological malignancies.

Our attempt to reconstruct a novel picture of NDP kinase/nm23 is still under way. We do not really know why NDP kinases can interact with so many different kinds of proteins nor how such interactions are regulated under physiological and pathological conditions. Obviously, it is an important task to establish a better and coherent view on the NDP kinases with housekeeping as well as regulatory properties. The elucidation of the NDP kinase functions should provide an invaluable clue to understand a link between fundamental biological processes, such as energy metabolism, cell growth, differentiation, and signal transduction, in cells.