Journal of Bioenergetics and Biomembranes, Vol. 32, No. 3, 2000

MINIREVIEW SERIES
Nucleoside Diphosphate Kinases: Structure, Mechanism, Genetics, and Roles in Cell Metabolism, Signal Transduction, Development and Disease

Series Editor: Ioan Lascu

0145-479X/00/0600-0211$18.00/0

Journal of Bioenergetics and Biomembranes, Vol. 32, No. 3, 2000

The Nucleoside Diphosphate Kinases 1973–2000

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Received April 25, 2000; accepted May 12, 2000

The nucleoside diphosphate (NDP) kinases are classic metabolic enzymes, responsible for the synthesis of nonadenine nucleoside triphosphates from the corresponding diphosphates, with ATP as phosphoryl donor. As such, they are the link between oxidative phosphorylation and functions, such as nucleic acid, sugar, and complex lipid biosynthesis, but also protein synthesis and signal transduction. Given their multiple functions and high levels of activity in cells, NDP kinases were thought to be unlikely sites of metabolic regulation. This is probably why, after a decade of enthusiastic work (1963–1973), summarized in the classic review written by Parks and Agarwal in 1973, NDP kinase studies entered a 15-year period of dormancy. In 1989, Patricia Steeg and Allen Shearn discovered the *nm23* and *awd* genes, involved in human cancer and *Drosophila* development, respectively. At the time, the two genes had no homologs in databases and the functions of the encoded proteins were unknown (Rosengard *et al.*, 1898). It soon became clear that they were NDP kinases (Biggs *et al.*, 1990; Wallet *et al.*, 1990; Gilles *et al.*, 1991). This revived interest in NDP kinases in cell biology and human pathology. The number of publications about NDP kinases grew exponentially. Only 4 years after the cloning of the *nm23* and *awd* genes and 2 years after their identification as NDP kinases, the first crystal structure of an NDP kinase was solved (Dumas *et al.*, 1992). Over 30 NDP kinase crystal structures have been solved, including, in particular, those of point mutants and of NDP kinases complexed with nucleotides. Determination of the enzyme's structure greatly contributed to the establishment of a sound basis for elucidating their catalytic mechanism and stability to denaturation. We hope that the knowledge obtained will extend in future years to regulatory functions, such as cell proliferation and differentiation, metastasis of tumors, regulation of gene expression, and apoptosis.

This series of minireviews is intended to summarize current knowledge about the classic function of NDP kinases in nucleotide biosynthesis, as well as newly discovered regulatory functions. Rather than cataloguing the results published since the Parks and Agarwal review, we chose to concentrate on a few aspects in which a substantial body of knowledge has accumulated. The various aspects will be presented in a critical way, based on the structural data. This may make clearer the conflicting reports that have appeared on several topics. We hope that this series will be a valuable working instrument in the interim period before new data makes it necessary to write new review articles. For the easy dissemination of new results and methods, author's contributions to meetings, Ph.D. dissertations, and unpublished results will also be quoted in the minireviews. In addition, a web site dedicated to NDP kinases will be set-up *(http://www.ibgc.u-bordeaux2.fr/).*

I would like to highlight here two recent findings of primary interest. The systematic sequencing of bacterial genomes has led to the identification of three organisms, *Mycoplasma genitalium*, *Mycoplasma tuberculosis*, and *Thermotoga maritima*, which have no gene encoding an NDP kinase. The disruption of the unique NDP kinase gene in *E. coli* (Hama *et al.*, 1991) and *S. cerevisiae* (Fukuchi *et al.*, 1993) has no major effect on cell growth. If non-adenine nucleoside triphosphate content were entirely dependent on NDP kinase activity, a major effect on growth, and possibly on survival, would be expected. Two interesting questions arise. How are nucleoside triphosphates made? If nucleoside triphosphates can be synthesized via other enzymic pathways, what is the true function of NDP kinases? Studies of nucleotide metabolism in microorganisms should generate answers to these two very fundamental questions.

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0145-479X/00/0600-0213$18.00/0

A second exciting discovery was the existence of "new" NDP kinaselike proteins. They have a much lower level of sequence similarity to classic NDP kinases and generally have insertions and longer termini. However, it is clear that they are related to NDP kinases. Several key residues are conserved, including most of the residues known to be essential for catalysis. Their sequences are compatible with NDP kinases fold since insertions are in loops (but the quaternary structure is probably different). The first such protein to be characterized, nm23-H5, has no NDP kinase activity. A great surprise was the discovery of as many as three tandem NDP kinaselike modules in the intermediate chain of dynein in *Chlamydomonas* sperm axoneme (Ogawa *et al.*, 1996). This is reminiscent of the membrane-associated guanylate kinase family of proteins that assemble protein complexes at synapses and other cell junctions (Tsukita *et al.*, 1999). It is possible that the "new" nm23 proteins, such as the NDP kinaselike modules of dynein, have lost their catalytic function and are used as modules for interaction with other proteins. Biochemical and "two-hybrid" demonstrations of this function could open up new and exciting areas of research in the field.

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