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Introduction

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Nucleoside diphosphate kinase (NDPK) discovered more than 50 years ago is widely recognized as a house-keeping enzyme involved in the bioenergetics of all cell types. The remarkable capacity of NDPK to catalyze transphosphorylation reactions between nucleoside triphosphates and nucleoside diphosphates underscores the importance of this enzyme and related isozymes to cell metabolism in general and bioenergetics more specifically. More recently, the discoveries of other important roles of NDPK have come to the forefront of work in this field. In particular, the identification in 1990 of NDPK with nm23, a metastasis suppressor, had a significant impact and prompted researchers to establish a novel feature of NDPK/nm23. Since then, there have been a number of publications that characterize NDPK/nm23 from distinct aspects. In fact, today NDPK/nm23, constituting a relatively large family, is accepted as a pivotal, regulatory protein that possesses multiple functions in addition to its well-known phosphotransferase activity. It seems to play an important role not only in tumor metastasis but in cell growth, differentiation, development and apoptosis. Nevertheless, to date no one has succeeded in unveiling the whole picture of NDPK/nm23 as it relates to its multiple functions and the significance of these to normal and pathological states.

Specifically, this special topic issue summarizes some recent advances in research on NDPK/nm23 that I believe will help the readers understand this very interesting and important, but still enigmatic biological molecule. The papers, grouped into two sections, minireviews followed by original contributions, are focusing on the following major topics: cancer and metastasis, other diseases, development and biochemical properties. The first minireview by Palmieri et al. summarizes metastasis suppressors that cause reduction of metastasis with no apparent effect on tumorigenicity. A translational strategy is proposed for limiting metastasis by manipulating nm23/NDPK gene expression. Kaetzel et al. describe a role of 3′-5′ exonuclease activity of nm23-H1 in relation to DNA repair and cancer progression. Boissan and Lacombe interrogate whether nm23/NDPK is qualified as a diagnostic and/or prognostic marker in hepatocellular carcinoma and denote the metastasis suppressive ability of nm23 using an nm23-invalidated mouse model for hepatocarcinoma. Lombardi overviews the physiological and pathological behavior of nm23 and proposes its possible novel function as a tumor suppressor. Possible involvement of NDPK/nm23 in other diseases has been challenged by a couple of research groups. Muimo et al. analyze the role of NDPK-A in airway epithelia and suggest an interaction with AMP-activated protein kinase and possibly with the cystic fibrosis transmembrane conductance regulator. The latter may provide an insight into understanding the role of NDPK in cystic fibrosis. *Killer of prune*(*Kpn*) is a mutant Awd(NDPK) whose Pro97 is mutated to Ser. Provost and Shearn, in search of a suppressor of *Kpn*, give details of the identification of a gene that suppresses the lethal interaction between *prune* and *Killer of prune*. The translated product contains four zinc-finger domains and a C-terminal glutathione S transferase domain. Its physiological function is discussed. Hippe and Wieland propose an alternative activation pathway for G proteins in which a complex between NDPK(-B) and G protein $\beta\gamma$ subunits leads to phosphorylation of His266 of the Gβ subunit. The phosphate is then transferred to GDP on Gα resulting in activation of the G protein.

Garzia et al. in their original contribution demonstrate the biochemical nature of h-prune as a phosphodiesterase

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and postulate the crucial role of the h-prune-nm23 complex during tumor progression and metastasis. Mileo *et al*. report the interaction of human papillomavirus-16 E7 oncoprotein with nm23-H1 and speculate about its pathological consequence in terms of invasion and apoptosis. Kowluru et al. investigate a regulatory role for NDPK/nm23-like activity in insulin secretion and its defects in islets from the Goto-Kakizaki rat, a model for type 2 diabetes. Carotenuto et al., perform histological and biochemical approaches to demonstrate the interaction between *prune* and *nm23*/*NDPK* in relation to mammalian brain development and adult brain function. Jeudy et al. for the first time report on an NDPK of virus origin from Mimivirus, the largest known virus. It has a shorter Kpn-loop and shows unique property with preferential affinity for deoxypyrimidine nucleotides. Shen et al. delineate the behavior of NDPK of bacterial origin upon bacteriophage T4 infection. Here, the bacterial NDPK is shown to form specific contacts with phage-coded proteins involved in dNTP and DNA synthesis. Upon presenting the crystal structures of an NDPK(S120G) mutant found in aggressive neuroblastomas, Giraud et al. detect no major difference between the mutant and the wild type NDPK in the overall structure as well as the structure within the neighborhood of the mutation. Last, Lascu, comparing structures of NDPKs of various origins during denaturation and renaturation processes, hypothesizes that folding intermediates of wild type NDPK(-A) may play an important role in the enzyme's capacity to exhibit its regulatory properties. Such intermediates are also discussed in relation to cancer.

Finally, I refer the readers to the Appendix of this issue where titles of papers are listed that were presented in a recent international meeting entitled "Genetics, Biochemistry and Physiology of NDP Kinase/NM23/AWD" in Naples (organizers: Zollo, M. and Lombardi, D.).

The next NDPK meeting will be in Dundee, Scotland from September 2nd to September 6th, 2007. A preliminary program is available at www.dundee.ac.uk/mchs/ndpk.