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Comments on the Nomenclature of Nucleoside Diphosphate Kinase

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There have been some important subjects in issue regarding the nomenclature of nucleoside diphosphate kinase that was discovered about 50 years ago. For many years some people have insisted that the presently adopted recommended name, nucleoside diphosphate kinase, does not represent its catalytic reaction properly and thus must be replaced by nucleoside-triphosphate:nucleoside-diphosphate phosphotransferase because many ribo- and deoxyribonucleoside triphosphates besides ATP can act as phosphate donors. Nevertheless, the designation, nucleoside diphosphate kinase, has long been accepted probably because it at least represents the essential part of this enzyme.

Apart from this old argument, I would like to make some comments here about related problems in the context of recent advances in this research field. As readers may realize while reading this issue or related articles in other journals, nucleoside diphosphate kinase is named in alternative ways according to the finding that genes or proteins named such as nm23, awd, PuF, or I-factor were found to be identical or similar to nucleoside diphosphate kinase upon their cDNA cloning and/or protein sequencing. Moreover, identification of homologous genes or proteins has revealed that nucleoside diphosphate kinase consists of a relatively large family with different properties in terms of its function, and intracellular and tissue localization; some of these homologous proteins exert their functions independent of the conventional enzyme activity. Presently, we still feel difficulty to predict exactly how many homologous proteins exist in this family and how many functions are born by the family proteins. Even under such a fluid situation, it is an important task to find a way toward establishing an appropriate nomenclature for this intriguing protein (family). For the sake of stimulating discussion on this issue, I would like to provide some viewpoints that should be taken into consideration.

General Concepts

1. By definition, orthologs are genes that are related by vertical descent from a common ancestor and encode proteins with the same function in different species. By contrast, paralogs are homologous genes that have evolved by duplication and code for proteins with similar but not identical functions. The nomenclature of a gene or protein (family) should be derived from orthologs and represent their properties.
2. Recommendations (1984) of the Nomenclature Committee of IUB published in “Enzyme Nomenclature 1992” (1992, Academic Press) describe that (a) names should be used only for single enzymes, i.e., single catalytic entities; designations given based on a natural substrate responsible for a physiological phenomenon that cannot be described in terms of a definite chemical reaction are discouraged; (b) enzymes are to be classified and named in principle according to the reaction they catalyze; (c) a systematic name cannot be given to an enzyme until it is known what chemical reaction it catalyzes; (d) a certain name designates not a single enzyme protein but a group of proteins with the same catalytic property. Enzymes from different sources (various bacterial, plant, or animal species) are classified as one entry; (e) when an enzyme catalyzes more than one type of reaction, the name should normally refer to one reaction only.

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Facts Obtained for Nucleoside Diphosphate Kinase

1. A study on nucleoside diphosphate kinase from an aspect of molecular evolution done by Ishikawa *et al.* (in this issue) revealed that (a) highly conserved orthologous genes for nucleoside diphosphate kinase are present in every organism in the major domains, eubacteria, archaea, and eucarya; (b) unicellular organisms in principle possess only one gene encoding nucleoside diphosphate kinase, whereas multicellular organisms possess paralogous genes besides an orthologous one and, therefore, the common ancestor might have a single ancestral nucleoside diphosphate kinase gene; (c) comparison between the genes coding for the highly homologous two major isoforms (rat nucleoside diphosphate kinase alpha (human nucleoside diphosphate kinase B/nm23-H2) vs. rat nucleoside diphosphate kinase beta (human nucleoside diphosphate kinase A/nm23-H1)) revealed that the former is the ortholog and thus the latter is the paralog.
2. The protein products of the orthologous genes from procaryotes to eucaryotes consistently exhibit the conventional nucleoside diphosphate kinase enzyme activity.
3. There exist several additional functions reported for nucleoside diphosphate kinase. However, these functions are neither extensively delineated nor found for the gene products from various species.

A Proposal

Available data strongly imply that the common ancestral nucleoside diphosphate kinase gene and its orthologs encode proteins that show the well-known conventional enzyme activity, and thus nucleoside diphosphate kinase may be appropriate as the designation of this gene and protein family . Further, they provide a hint to rationalize that an ortholog, the direct descendant among homologous genes in a given species, should take priority over paralogs in their numbering. According to this rule, nucleoside diphosphate kinase B (nm23-H2), a human homolog of rat nucleoside diphosphate kinase alpha, should be positioned in the first place.