Section «Bioengineering Bioinformatics»

Thiamin-binding motifs in proteins

Aleshin Vasily Alexeevich
Student
Lomonosov Moscow State University, Faculty of Bioengineering and Bioinformatics, Moscow, Russia
E-mail: Aleshin_ Vasily@mail.ru

Thiamin (vitamin B1) is involved in metabolism of all species as coenzyme thiamin diphosphate (ThDP), but this is not the only role of the molecule. Non-coenzyme derivatives of thiamin, such as thiamin triphosphate and adenylated thiamin phosphates, are synthesized under metabolic stress and may therefore be important regulators [1, 2]. Yet protein targets/producers of the derivatives are unknown. We aimed at identification of these proteins and associated pathways through definition of thiamin-binding motifs in proteins known to interact with thiamin, its natural derivatives or biosynthetic precursors, followed by scanning the protein/genome databases against the motifs with PROSITE. 21 motifs were created using resolved structures of relevant enzyme-ligand complexes and multiple sequence alignments of the enzymes. These motifs together with the known motif of ThDP-dependent enzymes were submitted to PROSITE. Presence in the PROSITE-generated list of known thiamin-dependent enzymes and total number of hits estimated the motif sensitivity and specificity. Co-occurrence of the motifs binding specific structural elements of thiamin and derivatives in one protein was considered to predict the thiamine compound to be bound.

Full list of potential thiamin-binding proteins found by PROSITE was subject to species-specific analysis by DAVID to find enrichment with certain functional annotation terms and clusters of functionally related proteins. High enrichment scores for the cluster including annotated ThDP-dependent enzymes indicated satisfactory specificity and sensitivity of our search. Top enrichment scores defined cluster of signal proteins. Interactome analysis of this cluster by STRING revealed a number of interactions, particularly those linking the acetylcholine and NMDA receptors. Receptor activity of thiamin-binding proteome was also favored by other highly enriched clusters (extracellular matrix, hydroxylation, kinase-related nucleotide binding, EGF-related calcium binding). Catalytic, binding, receptor and transporter activities were top molecular functions revealed by PANTHER. Thus, bioinformatics suggests involvement of thiamin in the calcium- and phosphorylation-dependent transduction of signals from cell membrane receptors. The finding is in accord with experimental studies [1, 3], and aids future research by indicating proteins potentially involved.

References

1. Bettendorff L, Wins P. Thiamin diphosphate in biological chemistry: new aspects of thiamin metabolism, especially triphosphate derivatives acting other than as cofactors // FEBS J 2009. № 276. p 2917-25.

2. Bettendorff L, Wirtzfeld B, Makarchikov AF, Mazzucchelli G, Frédérich M, Gigliobianco T, Gangolf M, De Pauw E, Angenot L, Wins P. Discovery of a natural thiamine adenine nucleotide // Nat Chem Biol 2007. № 3. p 211-2.

3. Parkhomenko IuM, Donchenko GV, Protasova ZS. The neural activity of thiamine: facts and hypotheses // Ukr Biokhim Zh 1996. № 68. p 3-14.

Words of gratitude

The author is very grateful to his tutor Dr. Bunik V.I. for her permanent assistance and support.