Creatine kinases: a cornerstone for structural research in the phosphagen kinase family

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In their recently published manuscript, Wu *et al.* (1) solved a 1.75 Å structure of a dimeric arginine kinase (AK) and propose a mechanism for negative cooperativity in dimeric phosphagen kinases (PK) in general. The authors correctly cite that such AK dimers probably evolved from another PK family member, a dimeric creatine kinase (CK)-like ancestor (2), that CKs are the most studied family members for their multiple implications in human pathologies, and that their results have repercussions for the understanding of CK function. Unfortunately, some fundamental results concerning the structure/function relationship of CKs have been omitted. Pertinent to this work is the historically first X-ray structure of a PK proper, that is the large cuboidal octamer of sarcomeric mitochondrial CK with bound ADP (3), whose coordinates have been used to solve many subsequent PK structures by molecular replacement, as well as the first X-ray structures of two other CK isoforms. These include octameric ubiquitous mitochondrial CK (4) and dimeric human brain BB-CK (5), solved at 1.41 Å, the highest resolution obtained so far within the PK family. These structures allowed already 13 years ago to conclude on separated active sites within the CK homooligomers and to examine the monomer/monomer interface. Even before, in 1994, the importance of the N-termini in CK protomer communication has been shown by mutational analysis (6), similar to what is presented by Wu *et al.* (1). Cooperativity between CK monomers within a functional CK dimer was demonstrated (7) and the conformational change in CK upon substrate (TSAC) binding from an open to a closed conformation elaborated by in-solution X-ray scattering (8). Recent reviews on these results are available (9–11). FJ

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