Evolution of enzyme regulation and the mechanistic drift hypothesis: The case of the activation by AMP in archaeal ADP-dependent sugar kinases

P-35-050

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Allosteric regulation of archaeal carbohydrate metabolism is a scarcely studied phenomenon. It has recently been demonstrated that AMP activates the bifunctional ADP-dependent phosphofructokinase/glucokinase from the methanogenic archaea Methanococcus maripaludis (MmPFK/GK) in both activities (Previously published in: Vallejos-Baccelliere G et al. (2022) FEBSJ. 289(23):7519-7536). This enzyme is a member of the ADP-dependent sugar kinase family, which includes bifunctional ADP-GK/PFK, specific ADP-GK, and specific ADP-PFK enzymes. In this work, we perform a comprehensive evolutionary study using ancestral protein reconstruction to trace the trajectory of the appearance and disappearance of this regulatory trait. We found that AMP regulation is an ancestral trait conserved only in bifunctional ADP-PFK/GK lineages, which exclusively includes enzymes belonging to methanogenic organisms. Although activation by AMP is a conserved trait, the underlying kinetic mechanism of activation presents important divergences through evolution. Mechanisms ranging from an increase in either sugar or MgADP affinity to an increase in catalysis or a combination of them, are randomly distributed across the evolutionary trajectory of AMP activation. Moreover, important differences are found between the activation mechanisms of both activities in a single enzyme. Based on these results, we propose the mechanistic drift concept, which can be extrapolated to a wide range of phenomena in macromolecular evolution and has interesting theoretical and philosophical consequences to be explored.

Funding: FONDECYT 1231263

* The authors marked with an asterisk equally contributed to the work.