HYPERTHERMOPHILIC ARCHAEA AS A SOURCE FOR NOVEL ENZYME DISCOVERY

Haruyuki Atomi, Kyoto University
atomi@sbchem.kyoto-u.ac.jp
Takaaki Sato, Kyoto University
Tamotsu Kanai, Kyoto University

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The Archaea are a group of microorganisms that are phylogenetically distinct to the Bacteria and Eucarya. Their size and shape resemble bacteria, but display stark differences in the structure of their membrane lipids and machinery that are responsible for DNA replication and transcription. In addition, Archaea seem to utilize metabolic pathways that differ to previously recognized, classical pathways in bacteria and eukaryotes. Based on the genome sequences of the Archaea, there are many cases in which a particular metabolic pathway seems to be absent or incomplete. The search for these “missing” pathways or enzymes has been an exciting field of research in the Archaea, and has led to the discovery of structurally novel enzymes or enzymes with novel activity. Until now, we have been focused on the metabolism of the hyperthermophilic archaeon *Thermococcus kodakarensis*. The organism is an obligate anaerobe and heterotroph, utilizing a wide range of organic compounds including peptides/amino acids, starch and maltooligosaccharides, and organic acids such as pyruvate. By searching for missing genes, we have identified a structurally novel fructose-1,6-bisphosphatase [1], a key enzyme in gluconeogenesis, and enzymes with novel activity, such as pantoate kinase and phosphopantothenate synthetase, both involved in coenzyme A biosynthesis in *T. kodakarensis* [2].

A number of genes predicted to encode kinases are present on the *T. kodakarensis* genome. Although more than half display similarity to characterized enzymes high enough to predict their substrates, there are still nearly 20 genes whose substrates are unknown. One of them turned out to be a *myo*-inositol 3-kinase [3]. Another was found to display an ADP-dependent ribose-1-phosphate kinase activity, which participates in a pentose bisphosphate pathway, a previously unidentified route to direct the ribose moieties of nucleosides to central carbon metabolism [4]. Another kinase was identified through studies on serine and cysteine metabolism in *T. kodakarensis*. The protein was initially annotated as a chromosome-partitioning protein ParB, but displayed ADP-dependent serine kinase activity. The enzyme was necessary for the conversion of Ser to Cys *in vivo*, and is most likely involved in Ser assimilation in this archaeon [5]. The structure of the enzyme explains the specificity of the enzyme towards Ser and ADP, and raises the possibility that structurally related proteins may also be present not only in archaea but also in bacteria [6]. These studies indicate the potential of archaea as a source for novel enzyme discovery demonstrate various means to identify gene function through genome sequence information.

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