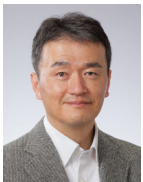


Understanding the core metabolism of Archaea

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Project Information	Project Number : 25H00432	Project Period (FY) : 2025-2029	
	Keywords : Archaea, metabolism, enzyme, genome		

Purpose and Background of the Research

●Outline of the Research

Life on our planet can be classified into three domains; Eukarya, Bacteria and Archaea. Extensive studies on the metabolism of model organisms such as the mammalian, plant and yeast cells of eukaryotes and *Escherichia coli* and *Bacillus subtilis* of bacteria have been reported, and a wealth of information has accumulated. Representative pathways including the Embden-Meyerhof or Entner–Doudoroff pathways in glycolysis, the pentose phosphate pathway and the tricarboxylic acid pathway have been proposed and can be found in our textbooks. Some of these pathways have been considered to be ubiquitous among all forms of life. Interestingly however, the dramatic increase in genome sequences has suggested that many microorganisms, including archaea, do not harbor some of these classical pathways. Here we will examine metabolism in archaea, using genome information as a guide to identify pathways where classical enzymes do not seem to be present (Figures 1, 2).

The hyperthermophilic archaeon
Thermococcus kodakarensis

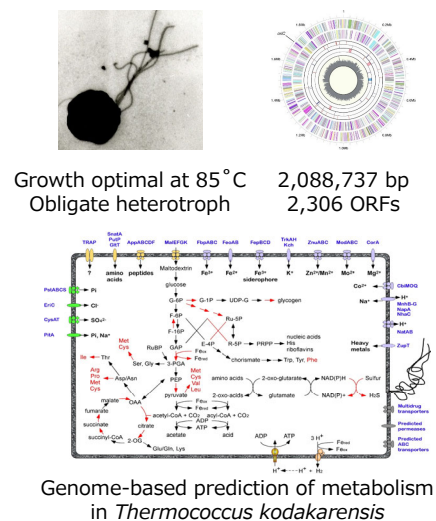


Figure 1. Genome annotation and metabolism prediction

By identifying enzymes and pathways in archaea that replace the “missing” classical pathways, we also hope to contribute in elucidating the function of the many hypothetical proteins that are present on microbial genomes.

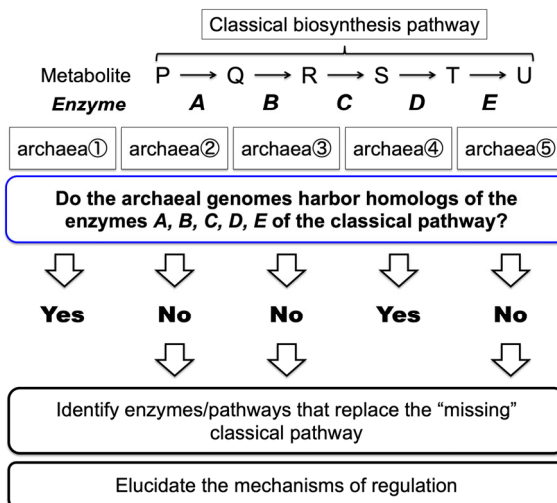


Figure 2. Research strategy based on the presence or absence of classical metabolic pathways

●Background: Genome sequences and the increase in hypothetical proteins

With the dramatic increases in sequencing capacity, we now have access to a large number of genome sequences. Among the genes on a given genome, the functions of approximately half of the genes can be predicted based on the sequence and are annotatable, whereas the functions of the other half are unknown (Figure 3).

The strategies applied here aim to identify gene function without relying on sequence similarity. The results should thus contribute in elucidating the functions of the many hypothetical protein genes on the microbial genomes.

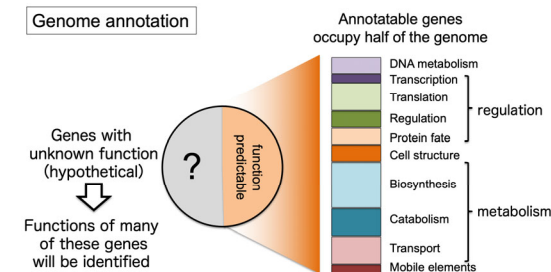


Figure 3. Genome annotation and hypothetical proteins

Expected Research Achievements

●Major targets

The organisms: The main organism of focus will be the hyperthermophilic archaeon *Thermococcus kodakarensis*. We will also evaluate the genome information and predicted metabolism of other archaea, including the halophilic archaeon *Halobacterium salinarum*, the aerobic hyperthermophilic archaeon *Pyrobaculum calidifontis*, the methanogenic archaeon *Methanothermobacter thermautotrophicum*, and the acidophilic archaeon *Sulfolobus acidocaldarius*. We will also examine metagenome sequences for organisms that have not been isolated and/or sufficient biomass cannot be obtained by cultivation.

The pathways: We will examine both energy-conserving catabolic pathways and anabolic pathways necessary for biosynthesis. For the former, we will focus on heterotrophic modes of growth and examine catabolic pathways using sugars, amino acids and lipids as substrates. Concerning anabolism, pathways involved in the biosynthesis of amino acids, cofactors, lipids, nucleotides and sugars will be studied.

Regulation: Metabolism is strictly regulated to avoid unnecessary loss of energy and substrates. We also plan to examine the mechanisms involved in regulation of metabolism in *Thermococcus kodakarensis*.

Elucidating enzymes, pathways, and regulation of the core metabolism in archaea

New enzymes
New biomolecules
New structure-function relationships
Update of the metabolic map
Distribution of enzymes & pathways in nature
Evolution of metabolic pathways

Gain a better understanding and wider perspective on microbial metabolism and its diversity

Figure 4. Expected achievements