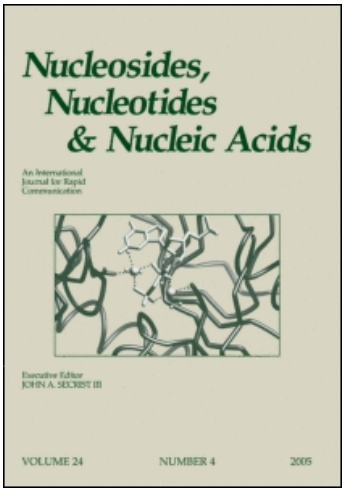

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THYMIDINE KINASES IN ARCHAEA

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□ *Twenty-six fully sequenced archaeal genomes were searched for genes coding for putative deoxyribonucleoside kinases (dNKs). We identified only 5 human-like thymidine kinase 1 genes (TK1s) and none for non-TK1 kinases. Four TK1s were identified in the Euryarchaea and one was found in the Crenarchaea, while none was found in Nanoarchaeum. The identified TK1s have high identity to Gram-positive bacteria TK1s. The TK1s from archaea, Gram-positive bacteria and eukaryotes share the same common ancestor, while the TK1s from Gram-negative bacteria belong to a less-related subgroup. It seems that a functional deoxyribonucleoside salvage pathway is not crucial for the archaeal cell.*

Keywords Thymidine kinase; Deoxyribonucleosides kinase; Salvage pathway; Archaea; Evolution

INTRODUCTION

Based on comparison of the nucleotide sequence of rRNA of prokaryotes, the group can be divided into archaea and bacteria, and together with eukaryotes they comprise the three major divisions of the living world.[1] Archaea are a chimera of bacterial and eukaryotic features; and at the molecular level, their core metabolic functions resemble those of bacteria, while their information processing (replication, transcription and translation) are distinctly eukaryotic.[2]

So far 26 archaea, belonging to 3 subgroups: 20 from Euryarchaea, 5 from Crenarchaea, and 1 from Nanoarchaea are sequenced. Only one strain, *Nanoarchaeum equitans,* a parasitic archae that lives in coculture

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with the archaea *Ignicoccus,* tentatively is assigned to the separate group of Nanoarchaea.[3]

Deoxyribonucleoside kinases (dNKs) have been well studied in some bacterial and eukaryotic organisms. The diversity is large, while bacteria contain from none to 3 dNKs and their TK1s can be divided in 2 groups,[4] insects have only 1 multisubstrate dNK and mammals have 4 dNKs.[5] To simplify the nomenclature, any homologues to human TK1 are called TK1, while other dNKs are called non-TK1. We have performed a BLAST search with the well-characterized dNKs, like *Drosophila melanogaster* dNK, human TK1, human deoxycytidine kinase, human deoxyguanosine kinase (dGK), *Bacillus subtilis* TK1, *B. subtilis* deoxyadenosine kinase, *B. subtilis* dGK, and *Escherichia coli* TK1 on 26 archaeal genomes to investigate, if there are any homologues present in this group of organisms.

MATERIALS AND METHODS

Twenty-six sequenced archaeal genomes were searched for putative dNKs with BLAST at NCBI (http://www.ncbi.nlm.nih.gov/sutils/genom_table.cgi).[6] The genomes and their accession numbers are given in Table 1. Amino acid sequences of the identified dNKs were aligned with ClustalX,[7] phylogenetic analysis was performed with TreeCon,[8] and graphical visualization was done in BioEdit.

RESULTS AND DISCUSSION

Only 5 organisms contained a human-like TK1-gene and none had any homology to non-TK1 (Table 1). Four of these TK1s were found within the Euryarchaeota *(Halobacterium* species NRC1, *Thermococcus kodakarensis* KOD1, *Ferroplasma acidamanus* Fer1, and *Thermoplasma acidophilum* DSM 1728), while one TK1 was found in the Crenarchaeota *(Pyrobaculum aerophilum* IM2).

A multiple alignment was performed with the identified archaeal TK1s together with other bacterial, human, and plant kinases belonging to the TK1 group. It revealed that *B. subtilis* TK1 has a high identity to all 5 archaeal TK1s. Surprisingly, the identity of *T. kodakarensis* TK1 to *B. subtilis* TK1 is 51% and the similarity even 69%. Aligned sequences are given in Figure 1. Apparently, several motifs are highly conserved, like the P-loop GKS-motif, the VIGIDE-motif, and the 2 cysteine residues in the lasso loop. Therefore, the overall structure might be the same as for human and *Ureaplasma urealyticum* TK1.[9]

From the multiple alignment a phylogenetic tree was built (Figure 2). The phylogenetic analysis reveals that the archaeal TK1s group together with the human TK1 and in particular the TK1s from Gram-positive

TABLE 1 The Searched Archaeal Genomes and Their Accession Numbers. + Indicates the Presence of a Gene Coding for a Human-Like TK1 Enzyme in the Genome. TK1s are Found in Euryrarchaeota and Crenarchaeota. No Other dNKs, Belonging to the non-TK1 Group, can be Found in the Analyzed Genomes

	Accession number	TK1
Euryarchaeota		
Archaeglobus fulgidus DSM 4304	NC_000917	
Ferroplasma acidarmanus Fer1	NZ_AABC00000000	+
Haloarcula marismortui ATCC43049	NC_006396. NC_006397	
Halobacterium species NRC-1	NC_002607	+
Haloferax volcanii DS2	NC_006809	
Methanocaldococcus jannaschii DSM 2661	NC_000909	
Methanococcoides burtonii DSM 6242	NZ_AADH00000000	
Methanococcus maripaludis S2	NC_005791	
Methanopyrus kandleri AVI9	NC_003551	
Methanosarcina acetivorans C2A	NC_003552	
Methanosarcina barkeri str. fusaro	NC_007355	
Methanosarcina mazei Gol	NC_003901	
Methanothermobacter thermoautotrophicus str. Delta-H	NC_000916	
Picrophilus torridus DSM 9790	NC_005877	
Pyrococcus abyssi GE5	NC_000868	
Pyrococcus furiosus DSM 3638	NC_003413	
Pyrococcus horikoshii OT3	NC_000961	
Thermococcus kodakarensis KOD1	NC_006624	+
Thermoplasma acidophilum DSM 1728	NC_002578	+
Thermoplasma volcanium GSS1	NC_002689	
Crenarchaeota		
Aeropyrum pernix K1	NC_000854	
Pyrobaculum aerophilum str. IM2	NC_003364	+
Sulfolobus acidocaldarius DSM 639	NC_007181	
Sulfolobus solfataricus P2	NC_002754	
Sulfolobus tokodaii str. 7	NC_003106	
Nanoarcaeota		
Nanoarchaeum equitans Kin4-M	NC_005213	

bacteria. The TK1s from Gram-negative bacteria and some Gram-positive bacteria make a group of their own.[4] The phylogenetic tree of TK1 is in contrast to the tree based on 16s rRNA where 3 distinct groups: archaea, prokaryotes, and eukaryotes are observed. However, a similar close relationship between archaea and Gram-positive bacteria has also been shown for several other protein sequences: Hsp70, glutamine synthetase I, asparginyl tRNA synthetase and diaminopimelate epimerase, GroEL, and acetolactate synthase.[10]

How can we explain the phylogenetic relationship and low abundance of dNKs in archaea? Are the 5 TK1s of ancient or recent origin? Two scenarios are possible: Either the Gram-positive and archaeal TK1s have the same origin from the common progenitor TK1, or Gram-positive TK1s have been "recently" horizontally transferred to archaea. A few archaea have a TK1,

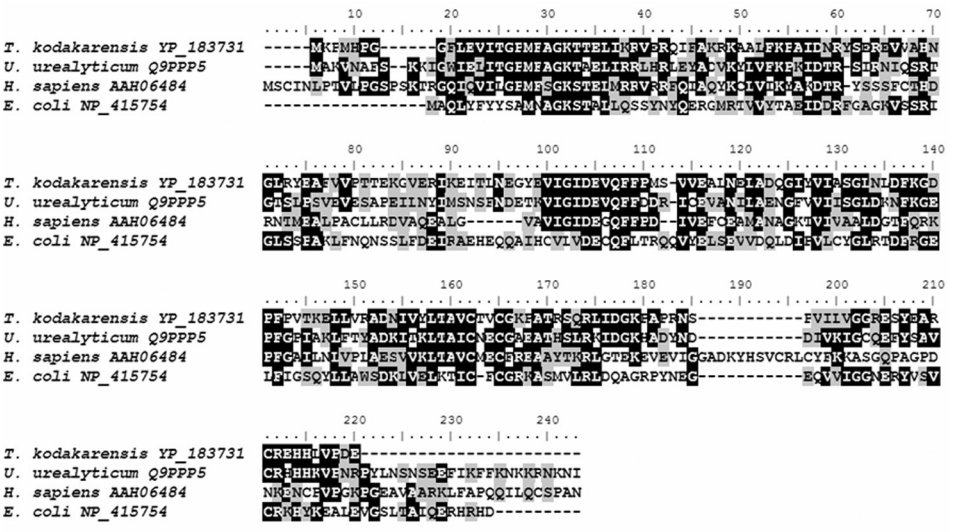

FIGURE 1 Multiple amino acid alignment of TK1s from *T. kodakarensis, U. urealyticum, H.sapiens*, and *E. coli*. TK1s from typical Gram-positive bacteria are high identical with the archaeal TK1s. The identical residues present in at least 2 kinases are shadowed in black, while similarities are shadowed in gray. The accession number of the TK1s follows the name of the organism.

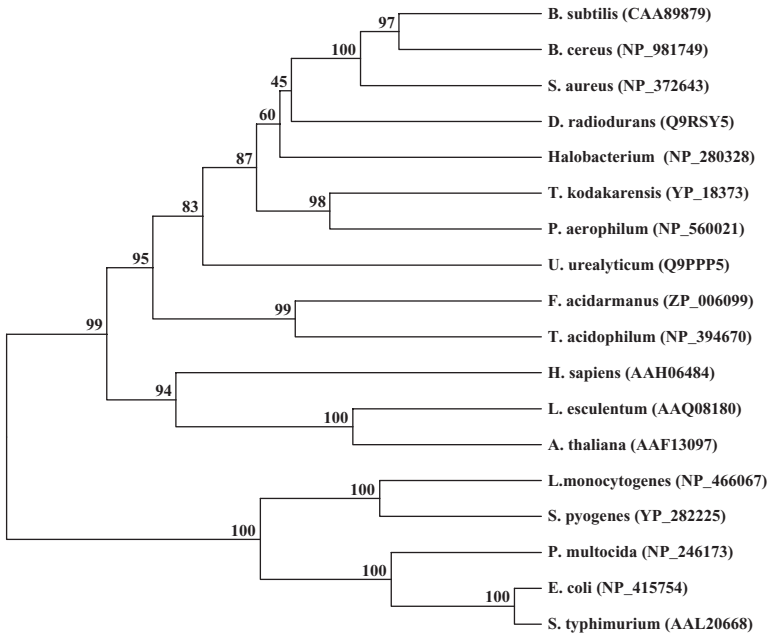

FIGURE 2 Phylogenetic tree of archaea, bacteria, and eukaryote TK1s. TK1s from Gram-positive bacteria and archaea group together, TK1s from Gram-negative and some Gram-positive bacteria make a group of their own.

however the TK1s are present in both, Crenarchaeota and Euryarchaeota. If acquisition of the TK1s happened via horizontal gene transfer, several independent lateral gene transfer events could have happened from Gram-positive bacteria to the 2 archeal subgroups, or a TK1 could be transferred to the progenitor of Crenarchaeota and Euryarchaeota. Another possible mechanism could be gene loss of the originally abundant TK1 from a variety of lineages. Similarly, some bacteria, as *Helicobacter pylori* and *Pseudomonas aeruginosa,* have independently lost their dNKs.[4] Our findings indicate that the dNKs are not crucial for the archaeal cell, which apparently relies on the de novo synthesis of nucleic acid precursors or has a novel class of dNK activities.

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