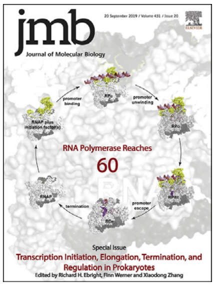
Review



Transcription Regulators in Archaea: Homologies and Differences with Bacterial Regulators

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Abstract

The fitness and survival of prokaryotic microorganisms depends on their ability to adequately respond to environmental changes, sudden stress conditions and metabolic shifts. An important mechanism underlying this response is the regulation of gene expression mediated by transcription factors that are responsive to small-molecule ligands or other intracellular signals. Despite constituting a distinct domain of life from bacteria and harboring a eukaryotic-like basal transcription apparatus, it is well established that archaea have similar transcription factors pointing to the existence of shared ancestral proteins and to the occurrence of inter-domain horizontal gene transfer events. However, while global structural features of bacterial and archaeal transcription factors are indeed similar, other characteristics imply that archaeal regulators have undergone independent evolution. Here, we discuss the characteristics of Lrp/AsnC, MarR, ArsR/SmtB and TrmB families of transcription factors, which are the dominant families that constitute the transcription factor repertoire in archaea. We exemplify the evolutionary expansion of these families in archaeal lineages by emphasizing homologies and differences with bacterial counterparts in terms of ligand or signal response, physiological functions and mechanistic principles of regulation. As such, we aim to define future research approaches that enable further characterization of the functions and mechanisms of archaeal transcription factors.

Introduction

A wide diversity of prokaryotic microbial species can be classified within the archaea, constituting a monophyletic group distinct from bacteria. The archaeal domain of life encompasses the most extreme extremophiles and poly-extremophiles living in specialized habitats such as hydrothermal vents or high-salt lakes, but also species with specialized metabolisms such as ammonia oxidizers thriving in ocean or soil ecosystems and methanogens in human or rumen gut microbiomes. Most of these habitats are characterized by fluctuating environmental conditions, requiring the archaeal microorganisms to precisely tune gene expression levels in response to these changes. Archaea perform gene regulation at different levels, including transcriptional regulation, for which gene-specific transcription regulators, also named transcription factors (TFs), play crucial roles for an adequate adaptation to environmental and nutritional changes in order to preserve the survival and fitness of the organism. Archaeal TFs structurally resemble typical bacterial TFs [1], with common DNA-binding folds and classification into similar families, pointing to a shared evolutionary ancestry and widespread occurrence of horizontal gene transfer events [1,2].

In contrast to the observed global similarities between their regulatory TFs, archaea and bacteria have fundamentally different basal transcription machineries, with which TFs interact during their mechanistic actions. The archaeal basal transcription machinery is a simplified version of the eukaryotic one with initiation of transcription being mediated by orthologs of the eukaryotic TATA-binding protein (TBP) and transcription factor IIB (TFIIB) [3]. These general TFs, TBP and transcription factor B (TFB), first form a complex assembled

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at the promotor region by binding of TBP to the TATA box, an AT-rich sequence approximately 25 base pairs (bps) upstream of the transcriptional start site, followed by TFB binding to the B recognition element (BRE), a purine-rich sequence just upstream of the TATA box. This complex then recruits the RNA polymerase (RNAP) to the promotor region by forming a closed preinitiation complex (PIC). The unique archaeal RNAP is related to the eukaryotic RNAP II and consists of 12–14 subunits [4–6]. In addition, also a homolog of the α-subunit of the eukaryotic basal transcription factor E (TFIIE) has been identified in archaea and, although not essential, plays a role in both the stabilization of the PIC and regulation of RNAP activity [7].

Early studies on archaeal TFs largely focused on unraveling the molecular mechanisms with which these bacterial-like proteins interact with the multiple components of a eukaryotic-like basal machinery, which represents an intriguing hybrid situation as compared to the well-understood regulatory mechanisms observed in eukaryotes and bacteria [8]. In this review, we aim to extend the comparison between archaeal and bacterial TFs beyond regulatory mechanisms by investigating the question if and to what extent archaeal TFs, despite sharing a common evolutionary origin with bacterial TFs, have undergone independent evolution. We discuss the classification of TFs in families, molecular mechanisms of the regulation of transcription initiation, the occurrence of one-component (OCS) *versus* two-component systems (TCS) and modes of signal transduction in archaea, with a focus on protein phosphorylation. By unraveling crucial homologies and differences between bacterial TFs, of which the function is well understood in several model species, and their less well-understood archaeal counterparts, we aim to define future research approaches that maximally aid in reaching similar levels of understanding of how TFs govern hierarchical transcriptional regulatory networks in archaea as in bacteria.

General Characteristics of Archaeal TFs

The majority of prokaryotic TFs are OCSs, of which some only consist of a single domain with a DNA-binding function and others have two domains: a DNA-binding domain (DBD) and a sensing domain, often called ligand-binding domain (LBD), that interacts directly with intracellular signals such as metabolites or redox signals. Compared to bacteria, archaeal species harbor a considerable higher number of single-domain TFs [9]. This is also reflected in the observation that archaeal TFs are on average smaller in size than bacterial ones (average size of 179 amino acids *versus* 236 amino acids, respectively). In addition, archaeal TFs tend to be significantly smaller as compared to the average protein size in its overall proteome, which is not the case in bacterial model systems such as *Escherichia coli* [9].

TFs interact with DNA when performing their regulatory function, typically by establishing sequence-specific interactions between the DBDs and base groups in the major grooves of the DNA. Structural diversity in DBDs is limited with the most prominent structural fold found in archaeal TFs being the helix–turn–helix (HTH) motif. This motif consists of three α-helices with the third, C-terminal α-helix, also termed recognition helix, establishing contacts with the major groove of the DNA [10]. Such interactions were demonstrated by structural analysis of an Lrp/AsnC-type TF from *Pyrococcus* sp. OT3 in complex with DNA [11]. Besides interactions mediated by the recognition helix, this protein–DNA complex is characterized by additional sequence-specific interactions between the second α-helix of the HTH motif and the major groove of the DNA. The dominance of HTH motifs among archaeal TFs is demonstrated by the observation that up to 84% of DBDs in OCSs harbor this fold [12,13]. A majority of these represent a winged HTH (wHTH) motif, a derivative of the HTH motif that contains a C-terminal β-hairpin, called the wing, in addition to the core three-helix bundle. This wing typically has a stabilizing role by interacting non-specifically with the minor groove in addition to sequence-specific interactions between the recognition helix and major groove. Exceptions are observed on this theme: for example, a wHTH-containing MarR-type TF in *Sulfolobus tokodaii* interacts in the major groove by its wing rather than by its recognition helix [14]. As an illustration for the widespread occurrence of wHTH folds, 73% of all TFs in the Euryarchaeon *Pyrococcus furiosus* are predicted to harbor a wHTH motif [15]. Also in bacteria, it is observed that most TFs harbor a HTH or wHTH motif [10]. For example, 36% of the TF repertoire in *E. coli* is predicted to harbor a wHTH motif [16]. The structural homology in DBDs between archaeal and bacterial TFs supports the notion of a shared ancestry of these proteins [1,10].

A minority of archaeal TFs harbor alternative structural folds in DBDs, such as the ribbon–helix–helix (RHH) motif or the typical eukaryotic-like motifs Zn-finger or leucine zipper [1]. The RHH motif differs from the HTH motif by having an N-terminal β-strand instead of an α-helix, which establishes extensive contacts with the DNA given its curved nature [1,10]. Despite being present in a minor fraction of archaeal TFs, RHH motifs are detected in a variety of phylogenetic archaeal lineages and are often present in toxin-antitoxin modules [1]. Moreover, the RHH motif is abundant among TFs encoded by archaea-specific viruses [17].

The LBD, the second domain in two-domain OCSs, is responsible for sensing environmental or metabolic changes, often by interacting with small-molecule ligands such as exogenous compounds taken up from the environment, for example, metal ions or aromatic compounds, or metabolites such as sugars and amino acids. Ligand binding allosterically induces conformational changes in the TF structure that typically affect the DNA-binding properties, either by causing a dissociation from the DNA or by stimulating DNA-binding affinity. In contrast to the DBD, the LBD of two-domain OCSs shows a large structural variability among TFs, both in bacteria and archaea [1]. This variability is demonstrated by the existence of unique archaeal sensing domains, such as the redox-sensing domain found in ArsR-type MsvR TFs in methanogenic archaea [18,19] (see below, "ArsR/SmtB family").

Genomic Occurrence of TF-Encoding Genes

The number of TF-encoding genes present in a given genome determines the regulatory potential of this organism. In prokaryotes, both in bacteria and archaea, this number displays a linear correlation with genome size [13]. In archaea, this ranges from as little as eight predicted TFs in *Nanoarchaeum equitans*, the archaeon with the smallest genome sequenced thus far, to 158 TFs in *Methanosarcina acetivorans* [9,20]. These predictions can be explained by the complexity of the organism's life style, with species living in specific niches, such as the symbiont *N. equitans*, harboring a smaller genome and in agreement less genes encoding TFs as compared to organisms living in complex habitats such as the metabolically versatile *M. acetivorans*. Notably, while the increment rate of enzyme-encoding genes is negative with increasing genome size leading to a loss of enzymatic diversity, it is positive for TF-encoding genes [21]. This increase is necessary to coordinate regulated expression of genes in the context of regulatory interaction networks, which become more complex in organism with larger genomes.

In archaea, less than 5% of the open reading frames in a genome code for TFs, a fraction that is significantly lower than the fraction observed in bacterial species with a similar total number of open reading frames (8%–10%) [9]. Upon comparing the two best-characterized archaeal phylogenetic lineages, it becomes apparent that Crenarchaeota tend to have fewer TFs than Euryarchaeota [22]. A lower fraction of TF-encoding genes might be explained by the higher number of characterized archaeal species living in very specific habitats, such as extremophiles. Niche specialization is especially the case for Crenarchaeota that harbor many (hyper-)thermophiles. Furthermore, there are indications that cross-interactions between paralogous TFs occur in archaea [23], thereby extending the regulatory capacity of species with a limited TF repertoire in a combinatorial manner. This has been demonstrated for TFs belonging to the Lrp/AsnC family in *Sulfolobus* spp. and *Halobacterium salinarum*. Within the same species, several Lrp/AsnC paralogs have extensive overlapping regulons, either caused by binding to neighboring binding sites and controlling the same genes [24–26], by binding to identical binding sites but having differing ligand specificities [25] or by forming hetero-oligomers enabling a combined response to multiple ligands and resulting in genomic co-association of different paralogs [11,27,28]. Similar strategies are less apparent for Lrp/AsnC-type TFs in bacteria, which are also well described. For example, the Lrp and AsnC TFs in *E. coli* have clearly distinct functions, suggesting that combinatorial interactions are more commonly occurring in archaea. Another possible explanation for compensating the underrepresentation of TF-encoding genes in archaeal genomes is the existence of extensive additional layers of regulation on post-transcriptional or post-translational levels, which are still largely unexplored.

Classification of TFs into Families

Prokaryotic TFs are classified in different TF families based on their structural similarity, rather than sequence similarity. Given the homology in DBDs, this classification is done based on the structural characteristics of the LBDs. Upon comparing the occurrence of different families in bacteria and archaea, it is apparent that not only the genomic abundance of TF-encoding families is lower in archaea, but also the diversity of TF families (Fig. 1) [29]. Archaea and bacteria share 18 TF families, for which it is suggested that the most abundant of these families are derived from common ancestral proteins [30]. In addition, up to 33 bacteria-specific TF families originated in bacteria that are not or rarely found in archaea, including the widespread LysR-type family (Fig. 1). In contrast, prominent archaeal TF families are little represented (e.g., Lrp/AsnC family) or even absent in bacteria (e.g., TrmB family) [9,29]. Overall, the most abundant families in archaea are Lrp/AsnC, MarR, ArsR and TrmB with on average 9.6, 8.3, 4.6 and 4.3 members per genome, respectively (Fig. 1) [29]. This is exemplified by the prediction that the most represented TF families in the Euryarchaeon *P. furiosus* are indeed the Lrp/AsnC, MarR and TrmB families [15]. In bacteria, these families are indeed underrepresented accounting for only 4.1%, 7% and 0.5% of the total number of bacterial TFs, respectively. On the other hand, the most common bacterial TF families, TetR and LysR (14.8% and 14.4%), represent a smaller proportion of all TFs in archaea

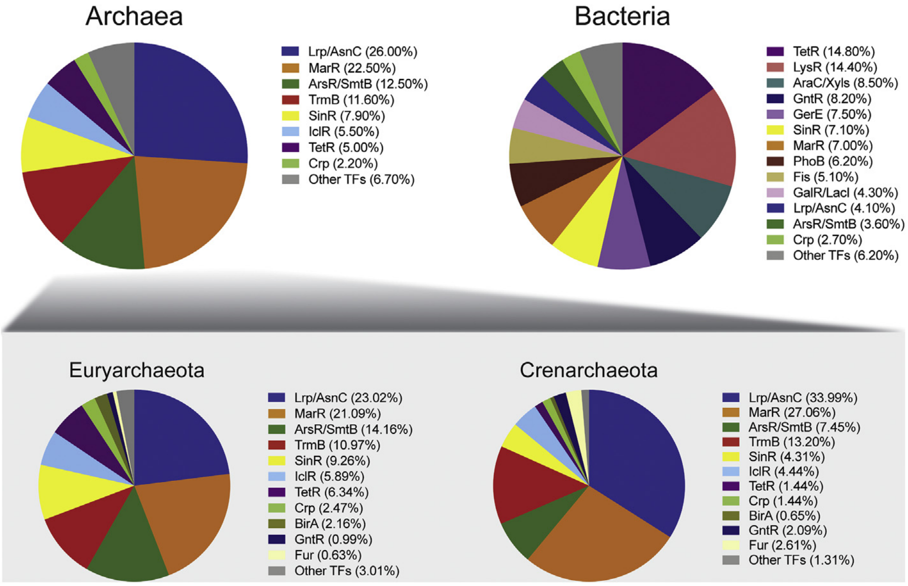

Fig. 1. TF families in archaea. Representation of the fraction of TFs families in archaeal and bacterial genomes, and for Eury- and Crenarchaeota separately [29].

(5% and 1%) (Fig. 1) [29]. It is clear that an evolutionary expansion occurred of distinct TF families after divergence of the two domain lineages, enabling archaeal species to build their own TF repertoire distinct from that of bacterial species.

Upon comparing Crenarchaeota and Euryarchaeota, the occurrence and abundance of different TF families is homogenously distributed (Fig. 1), which is a surprising observation as these clades are phylogenetically distant with representatives occupying widely differing habitats with a presumed minimal occurrence of horizontal gene transfer events. This suggests that differentiation of TFs in archaea has occurred early in evolution, short after divergence of the bacterial and archaeal domains. Nevertheless, expansion of individual families can be observed in distinct species as part of the evolutionary rewiring of transcriptional regulatory networks, in which paralogs of the same family arise through gene duplication events and evolve into functionally distinct TFs enabling the organism to occupy environmentally different niches [12,31]. Such an evolutionary expansion is nicely demonstrated for the Lrp/AsnC family in *H. salinarum*, for which eight different Lrp/AsnC paralogs were shown to have undergone neo- or sub-functionalization [25](see below, “Lrp/AsnC family”).

While most characterized archaeal TFs have a restricted regulon and a specific and dedicated regulation function, in some instances, members of the classical TF families have a more global regulatory function and/or a chromatin-structuring function. This has been demonstrated for proteins belonging to the Lrp/AsnC and TrmB families [25,32]. In addition, the archaea-specific Lrs14 family appears to consist solely of global regulators with the biofilm and motility AbfR1 regulator in *Sulfolobus acidocaldarius* as a key example [33]. As with bacterial counterparts, it is sometimes difficult to unambiguously classify a protein either as a TF or as a chromatin-associated protein.

Typically, archaeal TFs form homodimers or higher oligomers with N-terminal wHTH or HTH motifs as a common element albeit with a variable relative orientation depending on the family (Fig. 2). Furthermore, sizes and structural properties of the C-terminal LBDs are distinct for each of the families, some being all-helical domains and others also having β-strands that form β-sheets. Besides the sensing function, often through interaction with a small-molecule ligand, the LBD is also responsible for oligomerization of the protein (Fig. 2a).

Lrp/AsnC family

The Lrp/AsnC family is the most abundant and widespread TF family in archaea [9,29] (Fig. 1). They are represented in all characterized archaea with an average of five members per genome, including in *N. equitans* that is predicted to only possess eight TFs in total [25]. The Lrp/AsnC monomer consists of a wHTH-harboring DBD and a LBD that is also called Regulation of Amino acid Metabolism (RAM) domain [41,42] (Fig. 2a, Table 1). Amino acids are the typical ligands of the majority of characterized Lrp/AsnC-type TFs. While some regulators harbor a broad amino acid specificity range, others only interact with a single amino acid [41]. In contrast to bacterial Lrp/AsnC-type regulators for which only α-amino acids have been identified as ligand molecules, there are strong

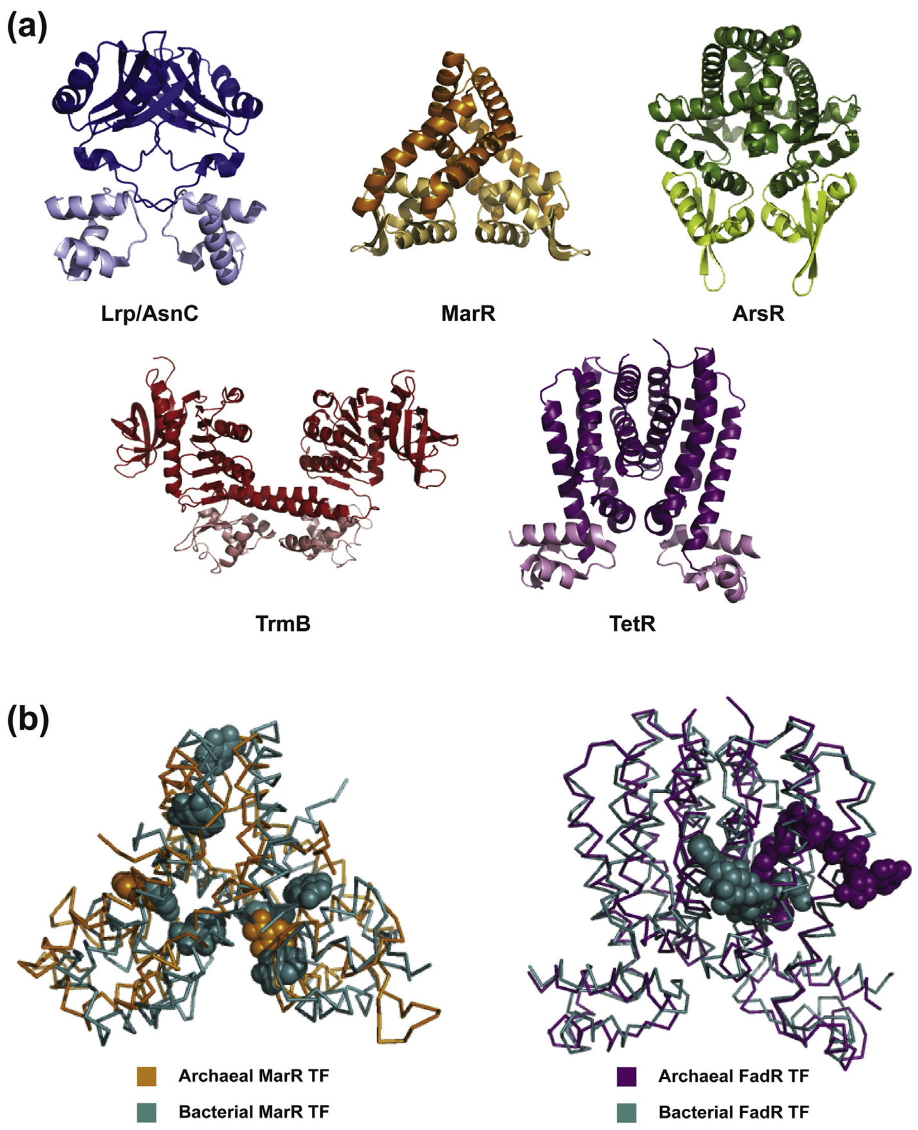

Fig. 2. Structural properties of prokaryotic TFs. (a) Ribbon structures of representatives of the four most abundant archaeal TF families and the most abundant bacterial one. Lrp/AsnC: Grp from *S. tokodaii* (PDB: 2E7W) [34]; MarR: MTH313 from *Methanobacterium thermoautothrophicum* (PDB: 3BPV) [35]; ArsR: PH1932 from *Pyrococcus horikoshii* OT3 (PDB: 1ULY) [36]. TrmB: TrmB from *P. furiosus* (PDB: 3QPH) [37]. TetR: FadR from *S. acidocaldarius* (PDB: 6EL2) [38]. (b) Ligand binding in bacterial and archaeal counterparts. Left panel: superposition of the MarR structure of *M. thermoautothrophicum* in complex with two salicylate molecules (PDB: 3BPX) and the MarR structure of *S. epidermis* in complex with eight salicylate molecules (PDB: 3KP6) [35,39]. Right panel: superposition of the TetR-like FadR structure of *S. acidocaldarius* in complex with a single lauroyl-CoA molecule (PDB: 5MWR) and the FadR structure of *B. subtilis* in complex with a single lauroyl-CoA molecule (PDB: 3WHB) [38,40]. Ligands are displayed in space-filling symbols.

indications that in archaea some Lrp/AsnC-like proteins interact with other small molecules as ligands [41]. For example, BarR from *S. acidocaldarius* interacts with the β-amino acid β-alanine [48]; Ss-LrpB from *Sulfolobus solfataricus*, LrpA from *P. furiosus* and Ptr2 from *Methanocaldococcus jannaschii* do not bind any of the 20 α-amino acids [49–51]. This is corroborated by the observation that a stand-alone RAM domain protein in *Pyrococcus* spp. interacts with 2-oxoacids instead of with amino acids [52].

Although bacterial and archaeal Lrp/AsnC-like TFs have similar structures and employ comparable molecular mechanisms for DNA binding, ligand binding and regulation, the archaeal subfamily is more abundant and involved in the regulation of more diverse metabolic and physiological conditions. Indeed, while the function of bacterial Lrp/AsnC-type regulators is restricted to the regulation of amino acid metabolism and transport, in some cases linked to central metabolism in a feast-or-famine

Table 1. Summary of general structural characteristics of major archaeal TF families

TF family	Structure of ligand-binding dimerization domain	Overall protein structure	Ligand-binding characteristics
Lrp/AsnC	αβ-Sandwich RAM domain consisting of four β-strands "sandwiched" between two α-helices [42]	Dimer formed by interaction between different β-strands arising from the RAM domains [11]	Ligand-binding pocket formed by β-sheets and loop formation in the RAM domains [11]
MarR	Predominantly helical domain [35]	Pyramidal shape dimer with pseudo-2-fold symmetry [35]	Porous structure with several distributed cavities for ligand binding [39]
ArsR/SmtB	Domain composed of four α-helices and one 3_{10}-helix (ArsR) [36] or two α-helices (SmtB) [43].	Hat-shaped helix bundle upon dimerization [36]	Acidic cavity accommodating ligand binding (ArsR) [39] or ligand interaction with the C-terminal α-helix [43,44]
TrmB	Extensive, structurally complex C-terminal domain composed of two subdomains: an eight-stranded β-sheet flanked by multiple large α-helices and an irregular flattened seven-stranded β-barrel [37,45]	Large W-shaped structure with long α-helices that link N- and C-terminal domains, each arising from a monomeric subunit, forming a coiled-coil domain mediating dimerization [45,46]	Ligand-binding pocket formed by a cleft in the connection between the different C-terminal subdomains [37,45]
TetR	All-helical domain [47]	Typical Ω-shaped structure [47]	Ligand-binding pocket formed in between C-terminal α-helices [47]

All TF families are characterized by a (winged) HTH DNA-terminal domain. The structural properties described in this table are relevant for all family members, and notable differences between bacterial and archaeal members are mentioned in the text.

mode, archaeal Lrp/AsnC-family regulators are also involved in the direct regulation of central and energy metabolism, and even of cellular maintenance processes such as translation and DNA repair [24,25,41,51,53]. The evolutionary success of Lrp/AsnC-type regulators in archaea, with a functional expansion beyond amino acid metabolism, is exemplified by *H. salinarum*: in this Euryarchaeon, eight Lrp/AsnC paralogs are shown to have regulatory roles in response to a variety of physiological conditions such as oxidative stress, growth phase and even circadian rhythm phase [25].

MarR family

In addition to Lrp/AsnC, the MarR family is another widespread and prominent prokaryotic TF family, with the occurrence of on average eight genes encoding putative MarR-like TFs per genome in archaea and bacteria [29]. Given the lower total occurrence of TF-encoding genes in archaeal genomes, MarR-like TFs are predicted to make up an abundant 22.5% of all archaeal TFs, which is significantly higher than in bacteria (7%) [29] (Fig. 1). Despite their abundance, only a handful of archaeal MarR-type TFs are described thus far. The best characterized ones are BdlR and BdlR2 in *S. solfataricus*, which are involved in the detoxification of aromatic compounds [54,55]. Structural studies revealed that archaeal MarR-like TFs behave as homodimers with a pyramidal shape [14,35,54,56,57] (Fig. 2a, Table 1). Again, structural similarities unify this family across bacteria and archaea [54,58]. Furthermore, in both domains of life, characterized MarR members were shown to be involved in conferring resistance to antibiotics, phenolic compounds and organic solvents [54,58–60].

The large functional and structural similarities between archaeal and bacterial MarR-type TFs suggest the presence of ancestral MarR TFs in the last universal common ancestor (LUCA). This statement is reinforced by comparing ligand binding in archaea and bacteria. BldR and Bldr2 from *S. solfataricus* interact with the aromatic compounds salicylate and benzaldehyde [54,55]. Most of the residues involved in salicylate binding in the archaeal BdlR are conserved in the bacterial homologs in *E. coli* and *Staphylococcus epidermis* [39,54]. A superposition of the MarR-ligand structure from *Methanobacterium thermoautotrophicum* with a bacterial one highlights a conserved binding pocket [14,58] (Fig. 2b). Furthermore, the bacterial MarR is known to have a porous structure with several cavities for additional potential ligand binding events [39].

ArsR/SmtB family

The ArsR/SmtB family of TFs is another abundant family in archaea, representing 12.5% of the TF repertoire, but despite its abundance, very little research has been performed on archaeal ArsR regulators [29] [9]. Only a single crystal structure of an archaeal ArsR-like TF with unknown function has been reported so far [36]. Upon dimerization, this TF forms a "hat-shaped" structure creating an acidic cavity that might accommodate ligand binding (Fig. 2a, Table 1). Comparing this archaeal ArsR-like crystal structure with its closest bacterial neighbor, *Synechococcus* spp. SmtB, reveals a clear difference in the C-terminal domain as it is much smaller in the bacterial variant [43,44].

Bacterial ArsR/SmtB TFs are metalloregulatory transcriptional repressors of operons linked to stress-inducing concentrations of heavy metal ions [44]. Several of the limited sets of characterized archaeal ArsR-family regulators are also involved in metalloregulatory processes [61–63]. In contrast to bacterial ArsR-like TFs, for which all characterized ArsR-like TFs are shown to interact with metal ions, archaea have also evolved ArsR-like TFs with different physiological roles and signal responses. This is exemplified by the ArsR-like regulator of *Methanothermobacter thermautothrophicus*, MsvR, which regulates the expression of an operon involved in oxidative stress response [18]. Oxidized and reduced forms of the regulator, mediated by the oxidation and reduction of cysteine residues in the C-terminal domain, influence its protein–DNA interactions, indicating that MsvR plays a role in detecting the cellular redox state and regulating the expression of genes involved in oxidative stress response and respiratory pathways [18,19]. Likewise, SurR from *Thermococcales* is a redox-responsive ArsR-like TF [64,65].

Similar to the Lrp/AsnC and MarR families, the archaeal ArsR/SmtB family is in terms of physiological function partly similar to its bacterial counterpart family but became more prominent and successful in archaea, leading to an extended repertoire of functions. In addition, archaeal ArsR-like TFs display significant structural differences compared to the bacterial ones. This raises the question whether ArsR TFs have arisen from a common ancestor as is postulated for the Lrp/AsnC and MarR families, or whether they originated through functional convergent evolution with respect to bacterial regulators. Further insights in ligand-binding mechanisms and signaling response need to be obtained through the study of more archaeal members of the ArsR/SmtB family to clarify this issue.

TrmB family

The TrmB family was initially considered as a archaea-specific TF family as it was first discovered in the archaeon *Thermococcus litoralis* [66] and occurs abundantly in both Eury- and Crenarchaeota, although it is also present in Thaum-, Kor- and Nanoarchaeota [29] (Fig. 1). Only later on, it was found that TrmB-like regulators are also represented in some but not all gram-negative and gram-positive bacteria, although with a very low abundance (on average 0.6 members per species) [9,32,46]. TrmB-like TFs have, besides an N-terminal wHTH motif, an extensive and structurally complex C-terminal domain consisting of two subdomains [37,45] (Fig. 2a, Table 1).

Archaeal TrmB-like TFs play important roles in the transcriptional regulation of diverse metabolisms, often sugar metabolism through interaction with sugar metabolites such as maltose and sucrose [46,67]. The latter has been shown for TrmB homologs in euryarchaeal Thermococcales and *H. salinarum*, but also in the crenarchaeon *S. acidocaldarius* [46,67–73]. Besides the regulation of sugar metabolism, euryarchaeal TrmB-like regulators have also been described as global regulators of different methanogenic pathways or as chromatin-organizing proteins [66,67,73].

The widespread occurrence of TrmB-like TFs in archaea, in contrast to the less prominent occurrence in bacteria, suggests that this OCS family originated from an archaeal ancestor early in the evolutionary history of the archaeal domain of life and dispersed to bacterial species through horizontal gene transfer events. Although initially postulated that TrmB-like proteins originated from an euryarchaeal ancestor and were acquired by Crenarchaeota through horizontal gene transfer as well [32], this view is challenged by recent bioinformatic predictions that point out an almost ubiquitous and abundant presence of TrmB-like TFs in Crenarchaeota as well (with on average 3.8 members per genome *versus* 4.5 in euryarchaeal genomes) [29] (Fig. 1).

TetR family

A last TF family that is placed in the spotlight in this review is the TetR family. While this family is a prime example of a widespread and abundant family in bacterial species, particularly in species exposed to frequent environmental fluctuations [29,47], it is less common in archaea, representing 5% of the total population of TFs (Fig. 1). Bacterial TetR TFs are generally repressors involved in diverse metabolisms such as multidrug resistance, antibiotic biosynthesis, osmotic stress and catabolic pathways [47]. They are characterized by a typical Ω-shaped structure constituting of an N-terminal wHTH motif and a C-terminal LBD that interacts with different small molecule ligands depending on the physiological function of the TF (Fig. 2a, Table 1).

Thus far, only a single archaeal TetR-like TF has been described, which is the acyl-CoA-responsive FadR from *S. acidocaldarius* involved in the regulation of fatty acid and lipid metabolism [38]. Despite low sequence similarities with bacterial TetR-like TFs, especially in the C-terminal domain, the structure of *S. acidocaldarius* FadR is very similar to acyl-CoA-responsive FadR TFs of the bacteria *Thermus thermophilus* and *Bacillus* spp. [38,40,74,75]. Nevertheless, a closer look into the position of the ligand-binding pocket in the protein structures demonstrates that the acyl-CoA ligand interacts in a different manner with the archaeal and bacterial proteins (Fig. 2b). These findings suggest that the archaeal TetR-like TF has most likely arisen through functional convergent evolution rather than by sharing a common ancestor or through a recent horizontal gene transfer event [38].

Molecular Regulatory Mechanisms

At the core of a TF's function is its capability to interact with the transcription machinery in order to negatively or positively influence the transcription process. Despite divergent evolution of TFs in archaeal lineages, as explained above, and the profound distinct nature of the archaeal basal transcription machinery with respect to the bacterial one, the global regulatory principles of archaeal TFs are similar to those observed for bacterial TFs [76,77] (Fig. 3). Typically, specific TF–DNA interactions are established close to the promoter, enabling the TF to affect the formation of the PIC through direct interference or interaction and to influence the transcription initiation process [8]. The regulatory

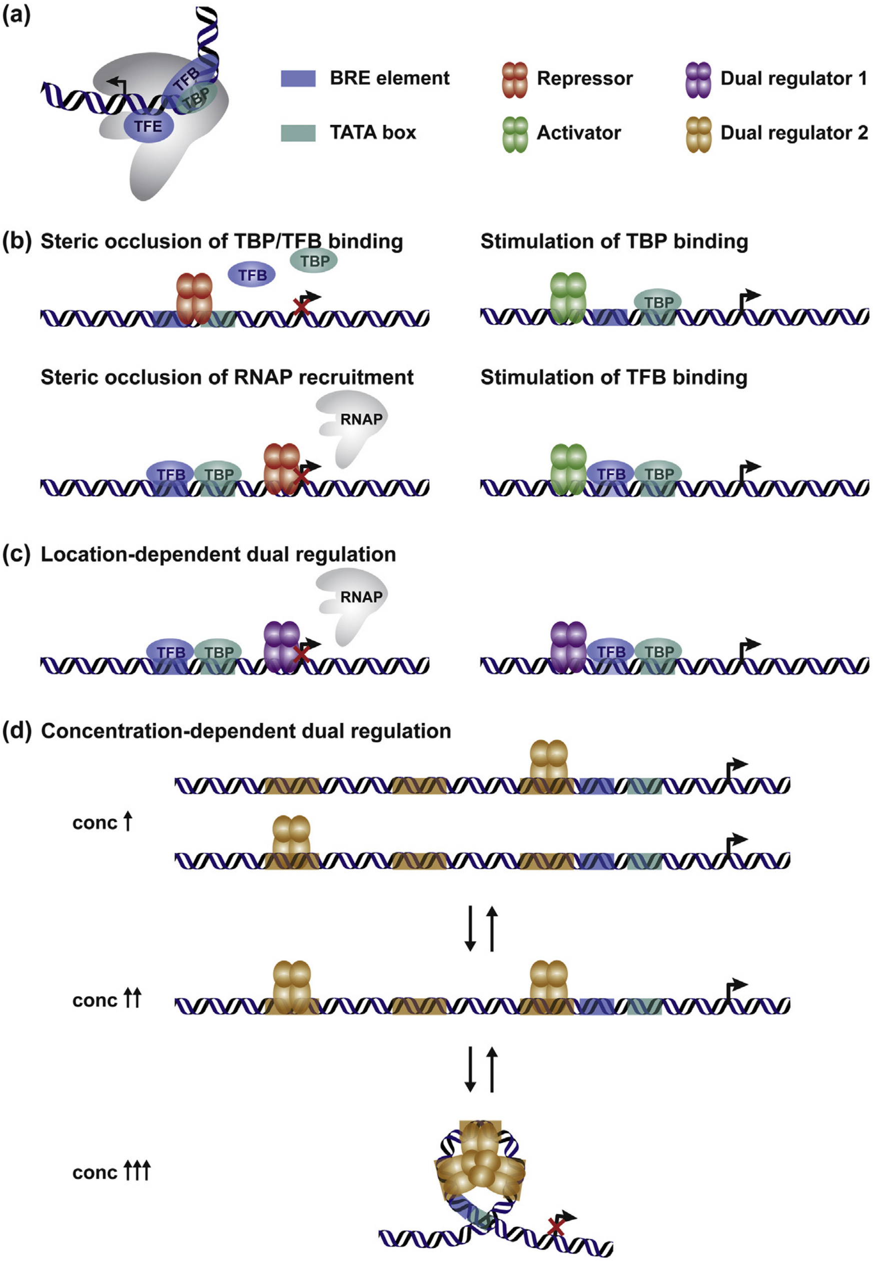

Fig. 3. Direct transcriptional regulatory mechanisms of archaeal TFs. Schematic representation of the most commonly observed molecular mechanisms of regulation with (a) general assembly of the pre-initiation complex, (b) overview of direct repression or activation mechanisms through interaction with PIC components, (c) representation of location-dependent dual regulation and (d) representation of concentration-dependent dual regulation as observed for the Lrp/AsnC-like Ss-LrpB in *S. solfataricus* [8].

role of a TF is partly dictated by its binding location: activators generally bind upstream of the TATA box and BRE promoter elements while repressors tend to bind downstream or overlapping the promoter elements [8].

Two types of repression mechanisms are observed (Fig. 3b): when the TF interacts with a binding site overlapping the TATA box and/or BRE element, the binding of TBP and/or TFB is sterically prevented, thereby interfering with the initial steps of PIC formation. A promoter occlusion mechanism, which is also typically observed for bacterial repressors, is exemplified by TrmB in *P. furiosus* [78]. On the other hand, upon binding downstream of the TATA box region at the level of the transcriptional start site, simultaneous binding occurs of the TF and the basal factors TBP and TFB, but the recruitment of RNAP is blocked. Such a repression mechanism has been observed for MDR1 from *Archaeoglobus fulgidus*, LrpA and Phr from *P. furiosus* [79–81]. It is postulated that the latter mechanism enables a faster responsiveness of derepression [79]. Activators typically stimulate recruitment of TBP and/or TFB to the promoter by binding directly upstream of the BRE and TATA box elements and by stabilizing the nascent PIC through the established protein–protein interactions [8] (Fig. 3b). For example, the Lrp/AsnC-type Ptr2 from *M. jannaschii* is a specific TBP-interacting TF [82]. Activators often act on weak promoters in which the TATA box or BRE elements display deviations from their respective consensus sequences. This is nicely demonstrated for the *P. furiosus* TFB-RF1 factor, which regulates genes preceded by promoters with weak BRE elements through the establishment of specific protein–protein interactions with TFB [83]. In other cases, the TF is able to interact with both TBP and TFB, as demonstrated for the gas vesicle regulator GvpE in *H. salinarum* [84].

Although TFs, or even entire TF families, are typically classified as being either repressors or activators, a dual regulatory function is often observed for a single TF, thereby overruling such a classification. Dual regulatory functions have been observed for archaeal TFs belonging to the MarR, Lrp/AsnC and TrmB families [8]. In most cases, a TF acts as a repressor on specific promoters and as an activator on others, depending on the location of the binding site relative to the promoter elements (Fig. 3c). For example, SurR and TrmBL1 from *P. furiosus* exert different regulatory effects depending on the binding site location [69,85]. On the other hand, the regulatory role of a TF could also be determined by its concentration level (Fig. 3d), as shown for the Lrp/AsnC-like Ss-LrpB from *S. solfataricus* [8]. While at low TF concentrations, binding at one or two binding sites causes transcriptional activation, occupation of all three binding sites induces a DNA-wrapping event, thereby repressing transcription [8].

Phosphorylation of TFs as a Signal Transduction Mechanism

Besides OCS, prokaryotes also harbor TCSs that are composed of a membrane-bound sensor kinase (SK) and a response regulator (RR) enabling the microorganism to sense extracellular signals [86]. Upon sensing a specific signal, the sensor domain in a SK transmits the signal to the intracellular histidine kinase domain through auto-phosphorylation, followed by a transduction of the signal to the cytoplasmic RR by transferring the phosphoryl group to a specific aspartate residue in its receiver domain. In response, the RR regulates transcription or metabolism to elicit a relevant cellular response [87]. Transcriptionally, acting RRs are similar to OCS TFs and typically contain a HTH motif in their output domain.

In bacteria, TCSs are widespread and abundant among all phyla with the exception of certain pathogens and endosymbionts with reduced genomes. In contrast to bacteria, TCSs are only present in about 50% of archaeal genomes [86]. While their occurrence is reported for the Eury- and Thaumarchaeota, they are completely absent in Cren-, Kor- and Nanoarchaeota [86,88,89]. Studied examples of archaeal TCSs include the temperature-responsive LtrK/LtrR from the psychrophilic archaeon *Methanococcoides burtonii* [90] and the FilI/FilR1/FilR2 TCS from *Methanosaeta harundinacea* involved in acetoclastic methanogenesis [91]. The observation that TCSs are more prevalent in bacteria led to the suggestion that archaea obtained TCSs by horizontal gene transfer from bacteria [88]. This hypothesis is supported by the higher abundance of these systems in mesophilic archaea, particularly methanogens and halophiles, that co-exist with diverse bacterial populations [88]. A phylogenomic analysis of archaeal TCS-encoding genes demonstrated that the number of SK-encoding genes exceeds that of RR-encoding genes, in contrast to the situation in bacteria in which the SK/RR ratio typically approaches one [89]. This suggests that archaeal TCSs do not function as strict pairs as in bacteria. Furthermore, only 6% of the archaeal RR output domains are predicted to harbor HTH DNA-binding motifs, indicating that TCS signaling occurs more often through protein–protein interactions rather than through transcriptional regulation [89]. As such, it can be concluded that TCSs rarely contribute to the transcriptional regulatory potential in archaea.

In contrast to the limited occurrence of transcriptionally acting TCSs, protein phosphorylation is a widespread phenomenon in archaea [92]. Phosphoproteomic studies have been performed for the archaeal model organisms *H. salinarum*, *S. acidocaldarius* and *S. solfataricus* [93–95], which revealed high numbers of phosphoproteins and -peptides with respect to bacteria such as *E. coli* and

Bacillus subtilis [96,97] (Fig. 4a). Protein phosphorylation is especially abundant in the Crenarchaeota *S. acidocaldarius* and *S. solfataricus* [94,95] and it has been postulated that this might have arisen throughout evolution to compensate for the absence of TCSs [95]. These phosphoproteomic studies furthermore revealed the widespread occurrence of direct phosphorylation of OCS TFs on serine, threonine and tyrosine residues (Fig. 4a) [92,94,95].

Phosphorylation of OCS TFs can affect their function by different mechanisms depending on the site of the phosphorylation and the conformational change that it induces [99]. For example, phosphorylation occurring in the HTH motif can directly affect protein–DNA interactions by conferring a negative charge on the recognition helix of thus inhibiting the establishment of electrostatic interactions with the DNA backbone. Other phosphorylation events occur in the LBD, affecting oligomerization of the protein, ligand interactions or inducing a conformational change that alters the relative position of the DBDs, thereby indirectly affecting DNA binding [99]. In *S. acidocaldarius* and *S. solfataricus*, respectively, 72% and 41% were phosphorylated in the HTH motif indicating a direct effect on their DNA-binding function (Fig. 4a) [94,95].

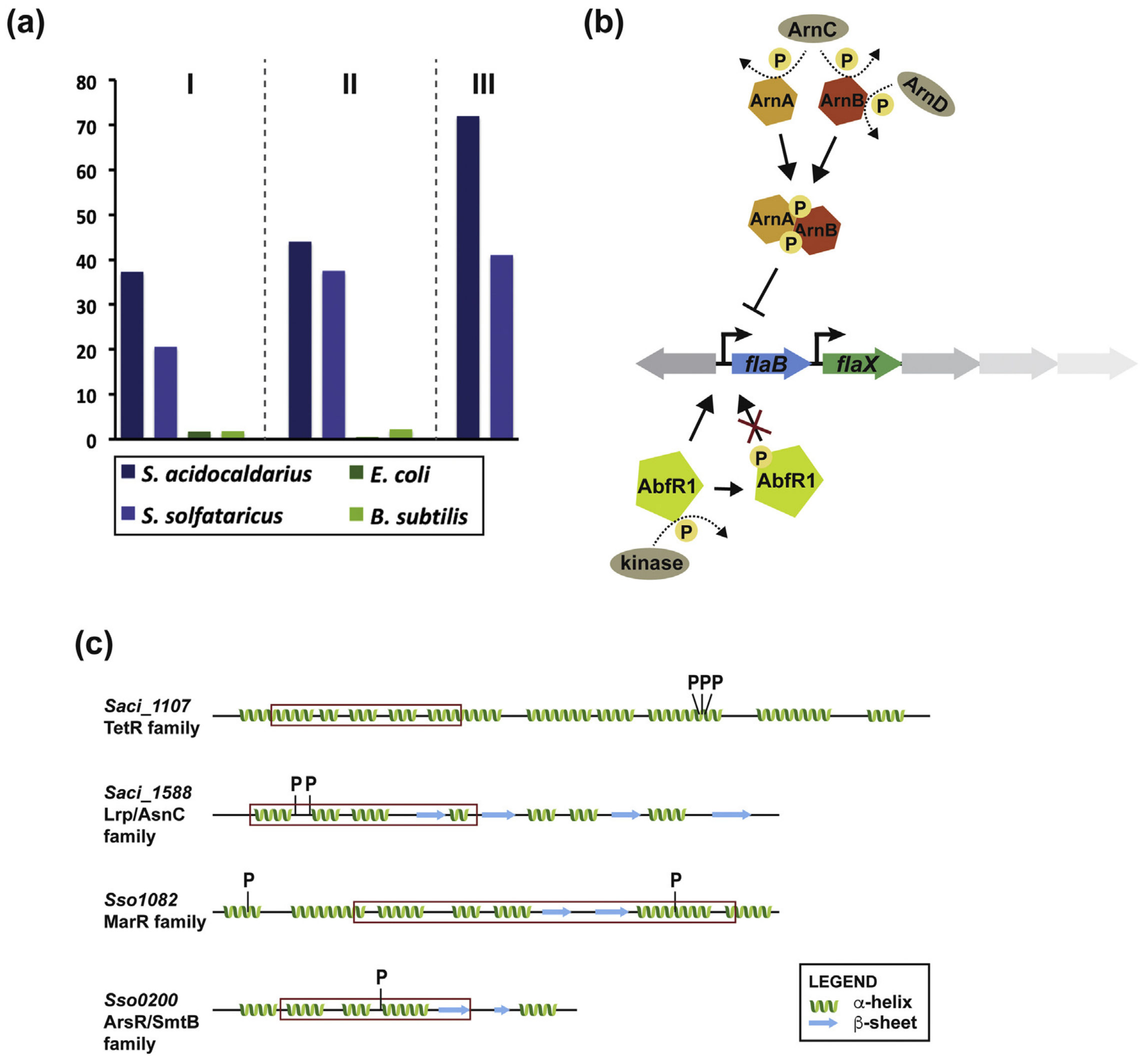

Fig. 4. Phosphorylation of OCS TFs in archaea. (a) A comparison between the phosphoproteomes of the archaea *S. acidocaldarius* [95] and *S. solfataricus* [94] and the bacteria *E. coli* [97] and *B. subtilis* [96]. Subpanel I: percentages of total phosphorylated proteins. Subpanel II: percentages of total phosphorylated TFs. Subpanel III: percentages of TFs phosphorylated in the HTH DNA-binding motif. (b) Schematic representation of a section of the archaellum network in *S. acidocaldarius* as an example for phosphorylation-orchestrated transcription regulation. This scheme is based on Ref. [98]. (c) Schematic representation of secondary structures of selected TFs from *S. acidocaldarius* and *S. solfataricus* with indication of the locations of phosphorylation sites observed in phosphoproteomic studies [94,95]. HTH DNA-binding motifs are indicated by red rectangles.

Only a limited number of studies have been performed on direct phosphorylation of OCS TFs as a signal transduction mechanism in archaea, with the best-known example being the phosphorylation-controlled transcriptional regulatory network of archaellum synthesis in *S. acidocaldarius* (Fig. 4b) [33,98,100–103]. Multiple activators and repressors regulate transcription of archaellum-encoding genes, each being controlled through reversible phosphorylation involving different kinases. For example, in nutritionally favorable conditions, the repressors ArnA and ArnB are phosphorylated and interact to repress the expression from the *flaB* promoter [95]. When nutrients are scarce, the AbfR1 TF activates the expression of the operon [33]. This regulatory action is directly controlled by phosphorylation of AbfR1. Indeed, when phosphorylated on a serine and a tyrosine residue in the wing of its wHTH motif, the DNA-binding ability of AbfR1 is abolished leading to a diminished cellular motility, and additionally to a stimulation of biofilm formation [102].

A survey of the phosphoproteomic data sets [94,95] indicates that the above-described example of direct phosphorylation of TFs in the context of the archaellum regulatory network likely represents only a subnetwork and that phosphorylation-mediated signal transduction is a widespread phenomenon in Crenarchaeota that contributes to expanding the regulatory capacity of the transcriptional regulatory networks in these organisms. Indeed, representatives of each of the dominant TF families have been found to be phosphorylated in *S. acidocaldarius* and/or *S. solfataricus*, often on multiple positions (Fig. 4c) [94,95], although the exact functions and mechanisms are unclear. The postulated importance of phosphorylation for TF functioning is supported by the observation that the expression of several TF-encoding genes is highly regulated upon the deletion of a phosphatase in *S. acidocaldarius* [95].

Conclusions and Perspectives

In conclusion, archaea harbor less diverse OCS TFs as compared to bacteria. The Lrp/AsnC, MarR, ArsR/SmtB and TrmB families of TFs are the most represented families in archaeal genomes and it can be postulated that gene duplication events underlie evolutionary expansion resulting in sub- or neofunctionalization of different paralogs. Although these families are also present in bacterial species, mechanistic details of functional properties such as ligand binding are not always conserved minimizing the cases that share an ancestral bacterial/archaeal TF or that emerged *via* recent horizontal gene transfer events. Furthermore, this underscores the need for future research efforts, as the extensive knowledge of bacterial TFs cannot easily be projected on archaeal counterparts. Thus far, only about 60 TFs have been characterized in total in archaea [23] in contrast to many more in bacteria. Ideally, systems-level approaches such as chromatin immunoprecipitation in combination with high-throughput sequencing (ChIP-seq), RNA-sequencing (RNA-seq) of TF knockout strains or "systematic evolution of ligands by exponential enrichment" (SELEX) are combined with reductionistic genetic and biochemical approaches in an effort to systematically characterize the TF repertoire of a variety of archaeal species.

Archaea are predicted to harbor fewer TFs and only a limited number of TCSs with respect to bacteria. This limited repertoire raises the question as to how these microorganisms perform an efficient regulation of transcription comparable to the gene regulatory capacity in bacteria. Initial indications exist that archaeal TFs employ more complicated regulatory principles, such as combinatorial interactions among different TFs or the existence of extensive additional layers of regulatory systems that are interlinked with the TF network. Post-translational modifications such as protein phosphorylation are a prime example and might play a more important role than previously anticipated.

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Abbreviations used:
TF, transcription factor; TBP, TATA-binding protein; BRE, B recognition element; RNAP, RNA polymerase; PIC, preinitiation complex; one-component system, OCS; two-component system, TCS; DBD, DNA-binding domain; LBD, ligand-binding domain; HTH, helix–turn–helix; RHH, ribbon–helix–helix; RAM, Regulation of Amino acid Metabolism; SK, sensor kinase; RR, response regulator.

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