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Ancestral zinc-finger bearing protein MucR in alpha-proteobacteria: A novel xenogeneic silencer?

Jian Jiao [a,b], Chang-Fu Tian [a,b,*]

[a] State Key Laboratory of Agrobiotechnology, and College of Biological Sciences, China Agricultural University, Beijing, China
[b] MOA Key Laboratory of Soil Microbiology, and Rhizobium Research Center, China Agricultural University, Beijing, China

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ABSTRACT

The MucR/Ros family protein is conserved in alpha-proteobacteria and characterized by its zinc-finger motif that has been proposed as the ancestral domain from which the eukaryotic C2H2 zinc-finger structure evolved. In the past decades, accumulated evidences have revealed MucR as a pleiotropic transcriptional regulator that integrating multiple functions such as virulence, symbiosis, cell cycle and various physiological processes. Scattered reports indicate that MucR mainly acts as a repressor, through oligomerization and binding to multiple sites of AT-rich target promoters. The N-terminal region and zinc-finger bearing C-terminal region of MucR mediate oligomerization and DNA-binding, respectively. These features are convergent to those of xenogeneic silencers such as H-NS, MvaT, Lsr2 and Rok, which are mainly found in other lineages. Phylogenetic analysis of MucR homologs suggests an ancestral origin of MucR in alpha- and delta-proteobacteria. Multiple independent duplication and lateral gene transfer events contribute to the diversity and phyletic distribution of MucR. Finally, we posed questions which remain unexplored regarding the putative roles of MucR as a xenogeneic silencer and a general manager in balancing adaptation and regulatory integration in the pangenome context.

Contents

1. Introduction

Bacteria can benefit from gain of accessory genes via lateral gene transfer (LGT) to improve their fitness to new ecological niches [1,2]. However, the newly obtained members need to be

* Corresponding author.
E-mail address: cftian@cau.edu.cn (C.-F. Tian).

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concordantly integrated into the pre-existing regulatory network via cis- variations in their regulatory regions and recruiting local and global regulators. Gene silencing is an important function as it keeps newly acquired foreign DNA repressed, thereby avoiding possible deleterious effects in the host organism. In the past decades, a group of proteins denominated xenogeneic silencers (XSs) was shown to selectively bind to the horizontally acquired DNA, repressing the expression and contributing to the integration of the horizontally acquired genes into the host transcriptional network [3–6]. Hence, they have been proposed to play important roles in environmental adaptive regulations and bacterial genome evolution. Four families of XS proteins have been identified, including the H-NS and MvaT families present among several species of gamma- and beta-proteobacteria, the Lsr2 family found in Actinobacteria such as *Mycobacterium* spp. and Rok family found in *Bacillus* spp. [7–11]. Given that the LGT processes take place among all prokaryotes [1], it is possible that xenogeneic silencers are widely distributed.

The alpha-proteobacteria are a genetically diverse taxon and comprises genera with various metabolic features and/or lifestyles such as phototrophic bacteria (e.g., *Rhodobacter*), methylotrophic bacteria (e.g., *Methylobacterium*), symbiotic N_2-fixing rhizobia (e.g., *Rhizobium*, *Sinorhizobium*, *Mesorhizobium* and *Bradyrhizobium*), plant pathogen (e.g., *Agrobacterium*), mammalian pathogens (e.g., *Brucella* and *Bartonella*) as well as many others that are of environmental or other interest—including *Caulobacter* and the hugely abundant marine genus *Pelagibacter* [12]. Moreover, this class should include the protomitochondrion, an extinct member historically engulfed by the eukaryotic ancestor and gave rise to the mitochondria [13,14]. In this review article, we discussed the accumulated evidences for the zinc-finger bearing MucR/Ros family protein and proposed it as a candidate of XS in alpha-proteobacteria.

2. Identification of MucR as a pleiotropic regulator in alpha-proteobacteria

Many members of alpha-proteobacteria establish chronic interactions with higher eukaryotes and have been intensively studied [15]. In 1985, a mutant of *Agrobacterium tumefaciens*, with a pleotropic phenotype including elevated expression of virulence genes and rough (nonmucoid) outer surface (ros) colonies, was designated as Ros [16]. Independently, a mutant allele of *Sinorhizobium meliloti* producing galactoglucan instead of succinoglycan was named *mucR* in 1989 [17], which was later identified as a homolog of Ros [18]. Then MucR/Ros/RosR/MI (thereafter MucR) have been intensively studied in *A. tumefaciens* [19–23], *S. meliloti* [18,24–27], *Sinorhizobium fredii* [28,29], *Rhizobium etli* [30,31], *Rhizobium leguminosarum* [32–35], *Mesorhizobium loti* [36,37], *Caulobacter crescentus* [38], *Brucella* spp. [39,40]. MucR is required for modulation of various symbiosis/virulence genes involved in interactions with plants or animals, and plays a pleiotropic role in cellular physiology under free-living conditions (Fig. 1). MucR represses its own transcription [24,39,41]. A non-comprehensive list of MucR regulon consists of genes involved in synthesis of various exopolysaccharides (*exo*, *uxs-uxe-aps*) and c-di-GMP signaling components (GGDEF and EAL containing proteins) [26,42,43]; machineries of motility & chemotaxis (VisNR, Rem, Fla, Fli, Mcp and Che) [25,27–29], and conjugation & secretion (Pilus, T4SS, T3SS and T1SS) [27,28]; and various transcriptional regulators and signalling components in general stress response (RpoE2, RpoE5 and CspA) [28,44,45], cell cycle (CtrA and SciP) [38], carbon and nitrogen metabolism (PTS^{Ntr}), uptake of potassium (Kdp), zinc (Znu), phosphorus (Pho, Pst and Phn), iron (Irr, RirA and Afu), molybdenum (Mod) and sulfur (Ssu) [28,29,46]. Collectively, the MucR regulon is multifaceted in life cycles of diverse alpha-proteobacteria.

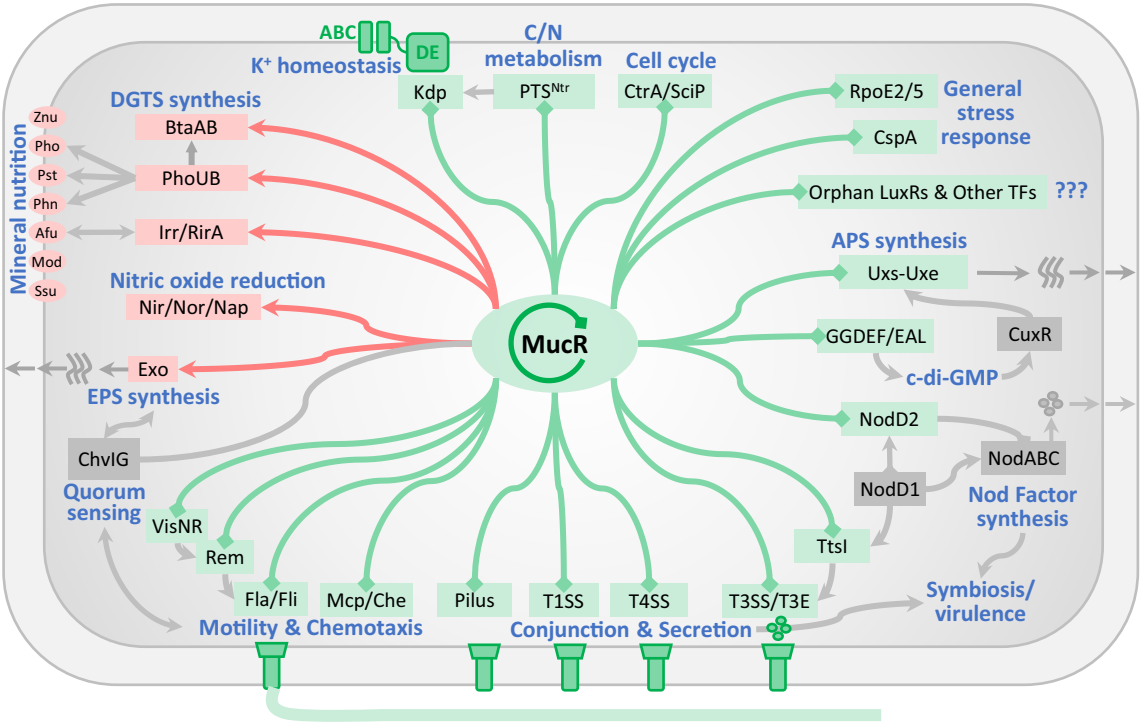

Fig. 1. Integrated view of regulatory pathways of MucR in alpha-proteobacteria. Red sharp arrows and green blunt arrows indicate the direct activations and inhibitions on the corresponding targets by MucR, respectively. Note that the pathways presented here are revealed in any of several "model" organisms and might be not prevalent in all alpha-proteobacteria. DGTS, diacylglyceryl-O-4′-N, N, N-trimethylhomoserine; EPS, exopolysaccharides; APS, arabinose-containing polysaccharide; T1SS/T3SS/T4SS, type I/III/IV secretion system; T3E, type III secretion system effectors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Comparison of regulons associated with MucR and representative xenogeneic silencers.

Organism	Gene number (ratio)		Condition for sampling	Ref.
	DEGs/Total	Up/down (mutant vs WT)		
MucR				
Sinorhizobium fredii CCBAU45436	621/6850 (9.1%) 597/6850 (8.7%)	372/249 (1.5) 417/180 (2.4)	TY broth at OD_{600} = 1.2 Bacteroid in soybean nodule	[28]
Sinorhizobium fredii HH103	393/6419 (6.1%) 904/6419 (14.1%)	227/116 (2.0) 615/289 (2.13)	YM broth_genistein-YM broth_genistein+	[29]
Rhizobium leguminosarum bv. *trifolii* Rt24.2	1106/7374 (15.0%)	699/407 (1.7)	79CA medium broth (24 h)	[33]
Brucella abortus 2308	91/3019 (3.0%)	76/15 (5.1)	Early stationary phase	[39]
Brucella melitensis 16M	442/2901 (15.2%)	310/132 (2.4)	TSB broth at log phase	[47]
H-NS				
Salmonella enterica sv. Typhimurium	587/4529 (13.0%)	409/178 (2.3)	LB broth at OD_{600} = 2.0	[7]
MvaT				
Pseudomonas aeruginosa strain PAO1	156/5572 (2.80%)	104/52 (2.0)	LB broth at OD_{540} = 5.0	[8]
Lsr2				
Mycobacterium smegmatis strain mc^2155	249/6480 (3.84%)	146/103 (1.4)	7H9 medium broth	[75]

Note: In different transcriptomic studies, differentially expressed genes (DEGs) are identified by RNA-seq [28,29,33,47] or microarrays [7,8,39,75] and defined by using different foldchange and p-value standards (see references for details).

Table 2
Characteristics of MucR and representative xenogeneic silencers.

	MucR/Ros	H-NS	MvaT	Lsr2	Rok
Source Organism	*Agrobacterium tumefaciens*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Mycobacterium tuberculosis*	*Bacillus subtilis*
Class (Gram stain)	α-proteobacteria (G-)	γ-proteobacteria (G-)	γ-proteobacteria (G-)	Actinobacteria (G +)	Bacilli (G +)
Molecular Weight (kDa)	15.5	15.5	14.2	12.0	21.8
PDB ID	2jsp (C-terminal)[52]	1ni8/1lr1 (N-terminal) [76–78], 1hns (C-terminal) [75]	2mxe (C-terminal) [8]	4e1p (N-terminal) [76], 2kng (C-terminal) [10]	5zuz (C-terminal) [9]
N-terminal domain	Oligomerization [38,48]	Oligomerization [80]	Oligomerization [81]	Oligomerization [79]	Oligomerization [9]
C-terminal domain	DNA-binding, zinc-finger [52,53]	DNA-binding, AT-hook [51]	DNA-binding, AT-pincer [8]	DNA-binding, AT-hook [51]	DNA-binding, winged helix [9]
DNA interaction target	Major groove [53]	Minor groove	Minor groove	Minor groove	Minor groove
Nucleofilament	Unknown	AFM/TPM [82,83]	AFM/TPM [84]	AFM [81]	Unknown
DNA-bridging	Unknown	AFM/TPM [85–86]	AFM [87]	AFM [81]	TPM [88]
Heteromers	MucR2 [38]	StpA, Hfp, H-NS2, Sfh [89–92]	MvaU, Pmr [93,94]	Unknown	Unknown
Paralogues	MucR2 [28,38]	StpA, Hfp, Sfh, $H\text{-}NS_{R27}$ [95–98]	MvaU [93], Pmr [99]	LsrL [100]	Unknown
Truncated derivatives	Unknown	H-NST [90]	Unknown	Unknown	sRok [101]
Non-related partners	Unknown	Hha, YdgT, gp5.5, Ocr, Arn [102–106]	Mip [107]	HU [108]	DnaA [109]
Complementation	Unknown	Lsr2, MvaT [55,56]	Unknown	H-NS [55]	Unknown

Note: AFM, Atomic Force Microscopy; TPM, Tethered Particle Motion.

The regulon of MucR/Ros/RosR ranges from 3% to 15% of gene pool in tested *S. fredii* [28,29], *R. leguminosarum* [33], and *Brucella abortus* [39] and *Brucella melitensis* [47] in a condition- and strain-dependent manner (Table 1), suggesting an adaptive and coordinative regulatory role of MucR in bacterial adaptation. Notably, 58%~84% of differentially expressed genes are up-regulated in the *mucR* mutant compared to the wild type strains (Table 1). These numbers are comparable to the known XSs such as H-NS in *Salmonella enterica* sv. Typhimurium, Lsr2 in *Mycobacterium smegmatis*, and MvaT in *Pseudomonas aeruginosa* (Table 1). Limited gel shift assay and a ChIP-seq study reveal that MucR binds AT-rich DNA substrates of fairly degenerate consensus motif [25,32,36,38,43]. As many as 227 direct target sites can be bound by MucR in *C. crescentus* [38]. These features support a working model that MucR can be a global repressor for genes associated with AT-rich promoters, i.e. a silencer for AT-rich foreign genes. Unfortunately, a combined transcriptomic and ChIP-seq analysis is not available for MucR yet.

3. MucR has convergent features of xenogeneic silencers

Despite intensive studies of MucR in symbiotic and pathogenic bacteria, it was just recently proposed as a potential H-NS-like protein [41] regarding that it is a heat-stable protein being able to form high-order oligomer and binds more than one target site in test promoters [32,36,41,48]. The known characteristic features of H-NS and other XSs have been summarized previously [49] and are further explored in Table 2 for comparison with MucR/Ros family protein. MucR/Ros is similar to these XSs in terms of size (15.5 kDa), and the ability of forming heteromers [38] and oligomerization, targeting AT-rich sequences and mainly acting as a repressor (Table 2). Nucleofilament and bridging models have been proposed for the nucleoprotein complex of XSs [3]. In the nucleofilament structure, the protein forms oligomeric filaments along the DNA complex of H-NS, while the bridging model involves bridging of distant regions of the nucleoprotein complex to form loops in the DNA [3]. The formation and rupture of these two

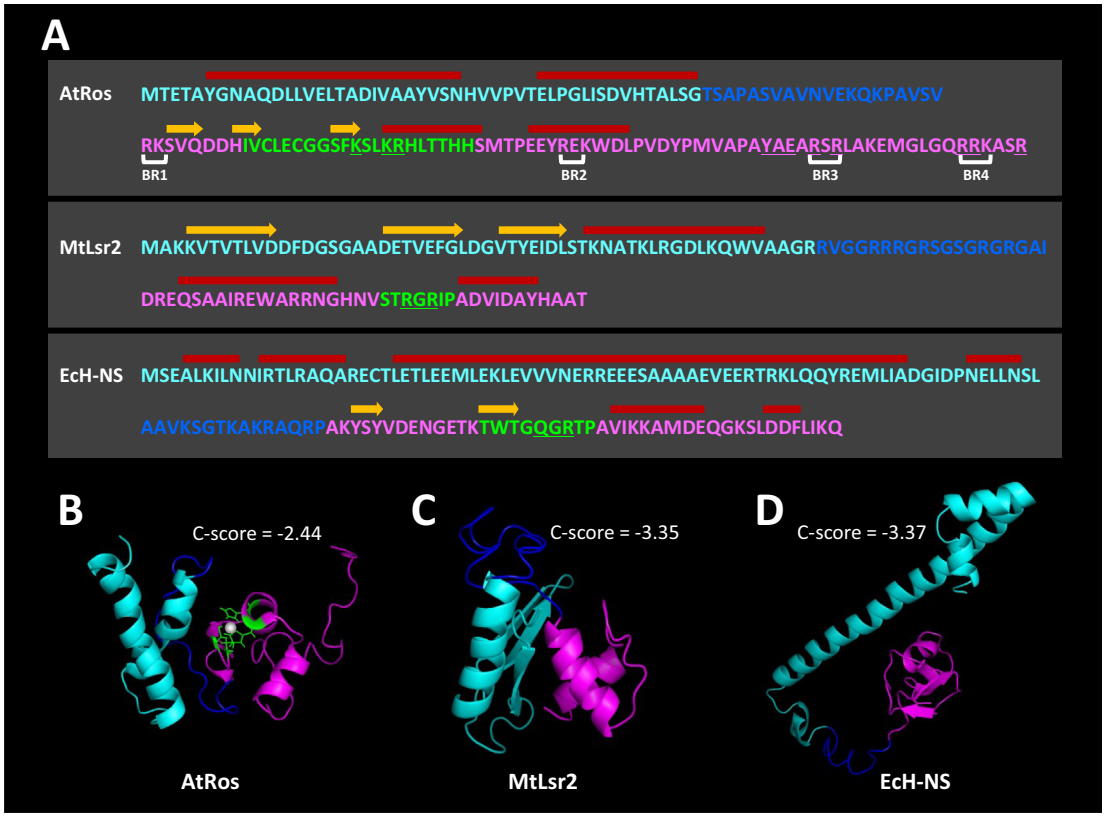

Fig. 2. Structural analysis of MucR/Ros, Lsr2 and H-NS. (A) Protein sequences of Ros from *Agrobacterium tumefaciens* (WP_003512037.1), Lsr2 from *Mycobacterium tuberculosis* (NP_218114.1) and H-NS from *Escherichia coli* (NP_415753.1). Each protein comprises 3 parts: the N-terminal oligomerization domain (cyan), the flexible linker (blue) and the C-terminal DNA binding domain (magenta). The secondary structure elements are designated by red lines (α-helix) and orange arrows (β-sheet). Specially, four basic regions (BR1-4) and the C2H2 zinc-finger containing hydrophobic core (green) required for DNA binding are indicated and underlined residues are those involved in DNA interaction identified in a Ros87-DNA docking model [53]. The conserved region harboring AT-hook-like motif (underlined residues) of Lsr2 and H-NS is in green. (B-D) 3D structural models of MucR, Lsr2 and H-NS build by I-TASSER server with default parameters. The zinc ion and coordinating side chains are shown in B. The confidence scores of the three structural models are indicated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

nucleoprotein structures may respond differently to fluctuating intracellular conditions including temperature and ionic strength [50], and also involve interacting paralogs and partner proteins [3]. However, it remains largely unexplored whether MucR interacts with DNA in a similar manner to known XSs.

Available evidence suggests that unrelated H-NS and Lsr2 utilize a similar AT-hook-like motif (Q/RGR) inserting into the minor groove of AT-rich sequences (Table 2 and Fig. 2A) [51], while MvaT showing an overall fold similar to H-NS uses a AT-pincer motif (R-GN) intercalating into the minor groove and a network of Lys side chains interacting with DNA sugar-phosphate backbone (Table 2) [8]. Rok adopts a totally different winged helix fold to recognize the minor groove through non-consecutive residues N-T-R, with assistance by four Lys residues interacting with DNA backbone [9]. MucR/Ros is characterized by its C-terminal zinc-finger domain, exemplified by the structure of AtRos87 (PDB: 2jsp), which is arranged in a ββββαα topology (Fig. 2A) [52]. Four basic regions within the C-terminal region of AtRos are necessary for DNA-binding activity (Fig. 2A) [23]. Similar to eukaryotic zinc finger proteins [20], the helix within zinc finger region of AtRos87 is inserted into the major groove of DNA (Table 2 and Fig. 2A) [53]. The AtRos87-DNA interaction at least involves two Lys and one Arg residues within the zinc finger containing hydrophobic core, and is mainly stabilized by several residues around basic regions of the C-terminal tail of the zinc finger (Fig. 2A) [53]. There is a natural variation in zinc-finger of MucR homologs and the zinc ion can be dispensable in certain variants [37] but essential in others [25,37,39]. The C-terminal region has lower affinity to Ni^{2+}, Hg^{2+}, Pb^{2+} than to Zn^{2+} and is not properly folded in the presence of these toxic metals [54]. MucR can form dimer, trimer and oligomer [32], and its N-terminal region is responsible for oligomerization and necessary for its wild-type regulatory function [48]. This conserved organization of a N-terminal oligomerization domain, a putative liker region, and a C-terminal DNA-binding domain in known MucR homologs is convergent to known XSs (Fig. 2B–D and Table 2) [38,48,52,53], despite contrasting variation in protein sequences and secondary structures (Fig. 2A). Indeed, various defects of the *h-ns* mutant of *E. coli* can be rescued by *mvaT* or *lsr2*, and the phenotype of the *lsr2* mutant of *Mycobacterium smegmatis* can be complemented by *h-ns* (Table 2) [55,56].

4. The phyletic distribution of MucR family proteins

According to Pfam database and online BlastP analysis, the MucR family proteins are mainly presented in bacterial species belonging to alpha- and delta-proteobacteria, with a few exceptions being coded by actinobacteria (10), bacteriophages (5), archaea (4) and eukaryotes (5) (Figs. 3 and 4A). The MucR homologs in actinobacteria and archaea (group C in Fig. 3) are divergent (Fig. 4A) and truncated (Fig. 4B) compared to those of group A and B. Sequence alignment analysis indicates that these truncated MucR homologs are characterized with substitutions in the key residues (Lys/Arg) of the zinc finger region and its C-terminal basic regions BR2, BR3 and BR4 involved in binding DNA, and the absence of a N-terminal oligomerization domain (Fig. 4B). These group C MucR homologs are also characterized by their overrepresented additional domains (Fig. 3), which are rare in group A and B.

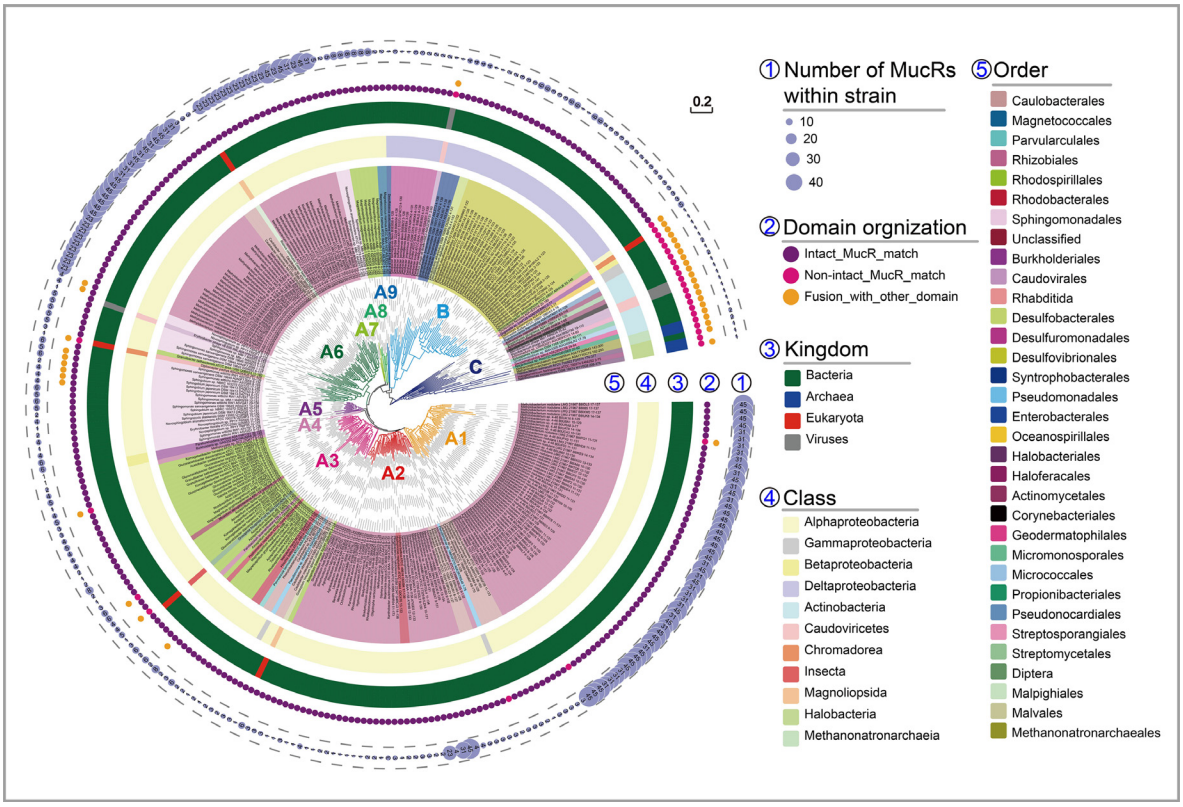

Fig. 3. Distribution and phylogeny of the MucR family proteins. The neighbor-joining phylogenetic tree of MucR was constructed based on the multiple alignment of truncated protein sequences retrieved from Pfam. Three major phylogenetic groups of MucR are indicated: group A mainly contains MucR encoded by alpha-proteobacteria and can be divided into 9 subgroups (A1-9), while group B and C contains those encoded by delta-proteobacteria and other prokaryotic strains (mainly Actinobacteria and archaea), respectively. MucR encoded by eukaryotes and viruses are unregularly distributed across the whole phylogenetic tree.

By contrast, MucR homologs with the conserved residues in N-terminal oligomerization domain, and in zinc finger and basic regions essential for DNA binding can be found in bacteriophages (Eph|A0A1P8VVG0) and eukaryotes (Rco|B9TQJ9, Ghi|A0A1U8N818, and Dpa|A0A2A2K4U5) (Fig. 4B). These non-prokaryote homologs are sporadically distributed in the MucR phylogeny (Fig. 3), while MucR homologs from prokaryotes are generally clustered in a way consistent with the phylogeny of the taxa at the class level. This indicates a possible ancestral origin of MucR and subsequent multiple independent LGT and gene loss events in the evolutionary process. In contrast to alpha- and delta-proteobacteria, MucR is rarely found in gamma- and beta-proteobacteria (Fig. 3). This may be partially explained by that these two classes emerged later than the divergence of alpha- and delta-proteobacteria [57] and have evolved alternative XSs such as H-NS and MvaT [7,8]. The absence of MucR and other known XSs in alpha-proteobacteria of AT-rich genomes (AT% above 70%), such as those belonging to Pelagibacterales, Rickettsiales and Holosporales [12,58,59] seems to be reasonable, given the intrinsic high-affinity of these XSs to AT-rich sequences [3,36] likely leading to lethal silencing effects on essential genes.

5. Duplication and lateral transfer events of MucR family proteins

Multiple copies of MucR are frequently observed in alpha- and delta-proteobacteria, and MucR homologs in alpha-proteobacteria can be roughly divided into nine subgroups in the phylogenetic tree (Fig. 3). It is obvious that multiple independent duplication events occurred during the evolutionary process of alpha-proteobacteria, particularly in *Methylobacterium* which harbors as many as 31 ~ 45 MucR homologs belonging to subgroups A1, A2, and A6. At least a subset of these duplication events can predate the divergence of taxa at the levels of orders, families, genera or species (Fig. 3). Duplication events are usually associated with neofunctionalization [60]. This view holds true for MucR paralogs. For example, ChIP-seq analysis of two MucR copies in *Caulobacter* revealed distinct binding sites of individual MucR copies in addition to a considerable number of shared targets [38]. Of course, not all MucR paralogs within a genome are essentially functional, as demonstrated in *Sinorhizobium fredii* CCBAU45436 which harbors a chromosomal MucR involved in multiple cellular processes and symbiosis with soybean plants, and a second copy carrying a frameshift mutation with no observable function [28]. Moreover, MucR carrying additional domains are found in subgroups A3, A5 and A6 (Fig. 3), implying potential neofunctionalization events which remain unexplored.

Independent MucR duplication events are coupled with potential LGT events mediated at least by bacterial phages (Fig. 3) and transferable plasmids such as the symbiosis plasmid of *Sinorhizobium* [28]. Notably, the symbiosis plasmid of rhizobia is characterized by its AT-rich feature [61–63], leading to an intriguing hypothesis that MucR and its targets can be co-transferred. The AT-rich symbiosis genes of rhizobia are specifically transcribed under symbiotic conditions rather than free-living conditions without legume hosts [61,64]. Consequently, co-transfer of MucR and AT-rich target genes can be one of the important mechanisms balancing adaptation and regulatory integration. This hypothesis is in line with the view that AT-rich foreign genes providing adaptive benefits to recipients under ever-changing circumstances should however be tightly controlled to avoid unnecessary metabolic bur-

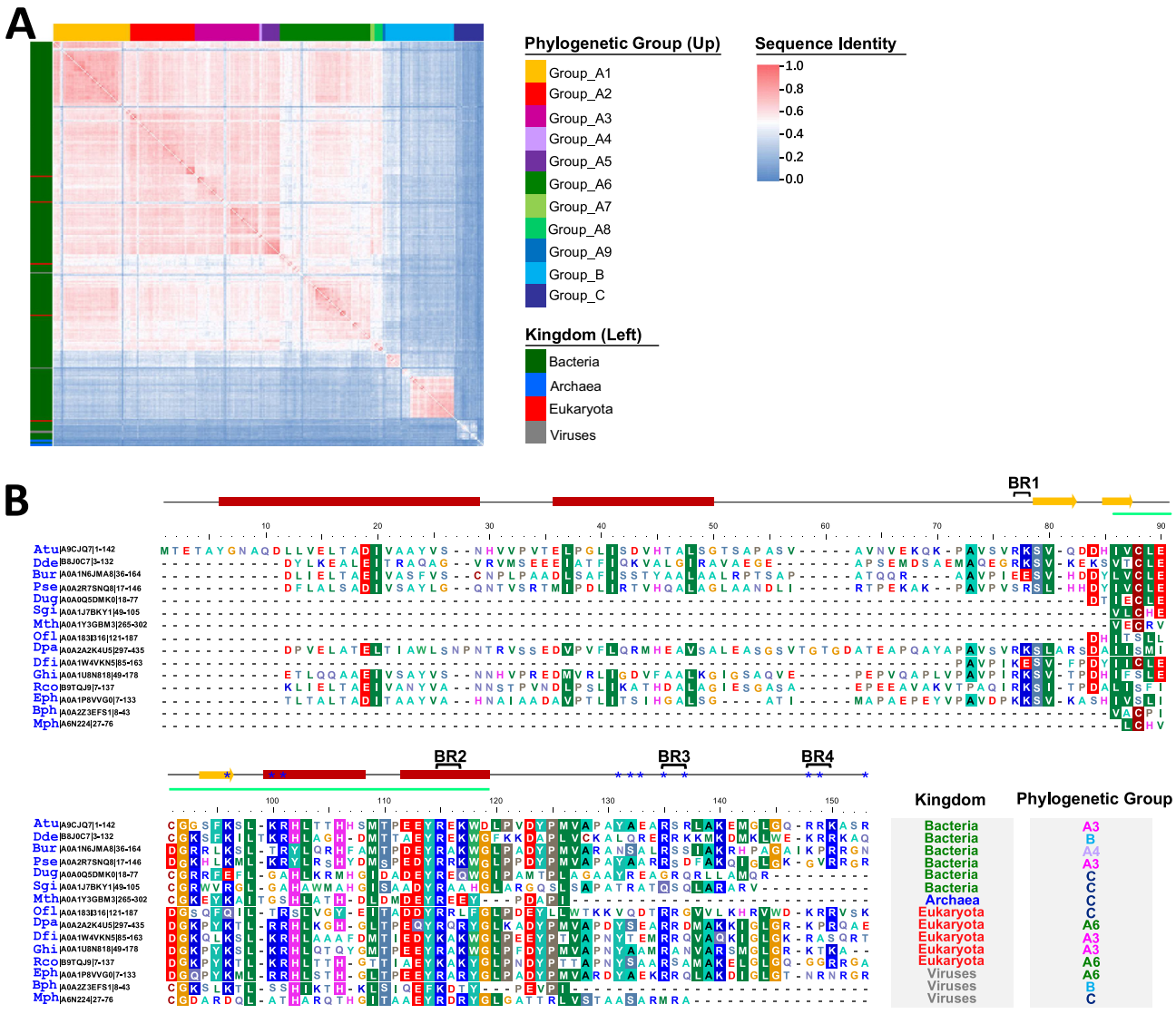

Fig. 4. Pairwise identity and alignment of the MucR family proteins. (A) Pairwise identity matrix of MucR family proteins with organism types (left) and phylogenetic groups (top) indicated. (B) Alignment of representative MucR family proteins. The secondary structure elements (α-helix, red lines; β-sheet, orange arrows), the C2H2 zinc-finger containing hydrophobic core (green line), and four basic regions (BR1-4) are indicated corresponding to the most upper sequence of AtRos. Blue asterisks indicate the residues that involved in DNA interaction identified in a Ros87-DNA docking model [53]. Atu, *Agrobacterium tumefaciens* C58; Pse, *Pseudomonas* sp. HMWF010; Ghi, *Gossypium hirsutum*; Dfi, *Drosophila ficusphila*; Bur, *Burkholderia* sp. GAS332; Eph, *Erythrobacter* phage vB_EliS_R6L; Rco, *Ricinus communis*; Dpa, *Diploscapter pachys*; Dug, *Duganella* sp. Leaf126; Dde, *Desulfovibrio desulfuricans* ATCC 27774; Ofl, *Onchocerca flexuosa*; Sgi, *Streptomyces gilvigriseus*; Mph, *Microbacterium* phage Min1; Mth, *Methanonatronarchaeum thermophilum*; Bph, *Bacillus* phage vB_BceM-HSE3. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

den and toxicity [3,65–67]. When we look at the complete genome of *Methylobacterium* sp. 4-46, 15 out of 31 MucR copies are located within AT-rich genomic islands. Certain homologs of H-NS, MvaT, Rok and Lsr2 were also identified in horizontally transferable genomic islands [68], plasmids [69,70], or bacteriophages [71,72]. Their known and potential roles in modulating expression of co-transferred genes and host genes [66] highlight that XSs are important players in managing the evolution of pangenome, which is essential for prokaryotes to explore the unlimited niches on the earth.

6. Summary and outlook

Accumulated evidences suggest that the MucR family protein conserved in alpha-proteobacteria can be a novel member of XSs which are functionally convergent and individually exhibit distinct phyletic distribution patterns. However, several questions remain unexplored for MucR. The zinc-finger of MucR family protein is proposed as an ancestral version of eukaryotic zinc-finger structure [20,73], but the structure of intact MucR protein is challenging to be resolved due to its serious solubility problems [74]. We know nothing about the MucR nucleoprotein complex, the dynamic structure of which is essential for understanding the adaptive regulatory mechanisms of MucR responding to environmental changes. How many and when partners interact with MucR? Why the copy of MucR can range from one to dozens in different organisms? Despite their major role in repressing AT-rich targets, functional genes subject to positive regulation by MucR and other XSs have been reported. Given the ever-changing content of prokaryote pangenome, does this imply a general role of XSs in balancing adaptation and regulatory integration?

CRediT authorship contribution statement

Jian Jiao: Formal analysis, Visualization, Investigation, Writing - original draft. **Chang-Fu Tian:** Conceptualization, Supervision,

Funding acquisition, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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