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

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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.

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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
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 N₂-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 galactoclugan 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-uxc-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), 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 not be prevalent in all alpha-proteobacteria. DGTs, diacylglycerol-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.)
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 melitaiss [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

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

| Organism               | DEGs/Total | Up/down (mutant vs WT) | Condition for sampling | Ref. |
|------------------------|------------|------------------------|------------------------|------|
| MucR                   | Sinorhizobium fredii CCB145436 | 621/6850 (9.1%) | 597/6850 (8.7%) | 372/240 (1.5) | 417/180 (2.4) | TY broth at OD_{50} = 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) | 9M brothe, genistein-YM brothe, genistein* | [29] |
| Rhizobium leguminosarum bv. trifoli | 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 | 442/2951 (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_{50} = 2.0 | [7] |
| MvaT | Pseudomonas aeruginosa strain PA01 | 156/5572 (2.80%) | 104/52 (2.0) | LB broth at OD_{50} = 5.0 | [8] |
| Lsr2 | Mycobacterium smegmatis strain mc²155 | 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) | H-NS | H-NS | H-NS | H-NS | H-NS |
| Molecular Weight (kDa) | 35.8 | 4.2 | 12.0 | 21.8 | 21.8 |
| PDB ID | 2jsp (C-terminal)[52] | 1ni8/1lr1 (N-terminal)[76–78], 1hns (C-terminal)[75] | 2mxe (C-terminal)[8], 4ep (N-terminal)[76], 2kng (C-terminal)[10] | 2mxe (C-terminal)[8], 4ep (N-terminal)[76], 2kng (C-terminal)[10] | 2mxe (C-terminal)[8], 4ep (N-terminal)[76], 2kng (C-terminal)[10] |
| 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-hook [51] | DNA-binding, AT-hook [51] | DNA-binding, winged helix |
| DNA interaction | Major groove [53] | Minor groove | Minor groove | Minor groove | Minor groove |
| Nucleofilament | Unknown | AFM/TPM [82,83] | AFM/TPM [84] | AFM/TPM [84] | AFM/TPM [84] |
| DNA-bridging | Unknown | AFM/TPM [85–86] | AFM [81] | AFM [81] | AFM [81] |
| Heteromers | MucR2 [38] | MvaT, Pmr [93,94] | MvaT, Pmr | MvaT, Pmr | MvaT, Pmr |
| Paralogs | MucR2 [28,38] | MvaT, Pmr | LsrL [100] | LsrL [100] | LsrL [100] |
| Truncated derivatives | Unknown | Unknown | Unknown | Unknown | Unknown |
| Non-related partners | Unknown | Hha, YdgT, gp5.5, Ocr, Arn | Mip [107] | Mip [107] | Mip [107] |
| Complementation | Lsr2, MvaT [55,56] | Unknown | H-NS [35] | Unknown | Unknown |

Note: AFM, Atomic Force Microscopy; TPM, Tethered Particle Motion.
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 βββααα 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 Ni²⁺, Hg²⁺, Pb²⁺ than to Zn²⁺ and is not properly folded in the presence of 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 like domain, 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 mvtA 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.
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-
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, plasmids, or bacteriophages. Their known and potential roles in modulating expression of co-transferred genes and host genes 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, but the structure of intact MucR protein is challenging to be resolved due to its serious solubility problems. 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,
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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