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Quick guide

MarR family transcription factors

Anne Grove

What are MarR proteins? Members of the Multiple Antibiotic Resistance Regulator (MarR) family of transcriptional regulators are named for *Escherichia coli* MarR. In *E. coli*, MarR regulates an operon that encodes a drug efflux pump, and mutations in proteins that participate in this system lead to a multiple antibiotic resistance phenotype, hence the name. MarR proteins are members of the winged helix-turn-helix family of transcription factors.

Where are they? MarR proteins are encoded by bacteria and archaea, and their abundance typically correlates with a free-living lifestyle and large genome size. In general, obligate parasitic species feature reduced genome sizes and encode fewer transcription factors while organisms with complex lifestyles (such as species with both free-living and parasitic or symbiotic stages) encode numerous transcriptional regulators, including MarR homologs. Consistent with this trend, MarR homologs serve physiological roles as sensors of changing environments.

How do they regulate gene expression? While some MarR homologs activate transcription, most repress gene activity. A genomic locus consisting of divergently oriented genes encoding the MarR homolog and the gene(s) under its control is common (Figure 1). This layout allows the transcription factor to bind site-specifically to the intergenic regions between divergently transcribed genes to repress transcription of both. On binding of a small molecule ligand or in response to oxidation of specific cysteines, DNA binding is attenuated, resulting in activated gene expression. This general mechanism also results in the expression of MarR proteins being autoregulatory; as the cellular concentration of the MarR protein increases, negative autoregulation shuts off further transcription of the *marR* gene and prevents excessive protein accumulation. The advantage of this mechanism is that the MarR protein concentration fluctuates within a narrow range that allows a more sensitive response to ligands.

In addition to adjacent genes, distant genes may also be regulated by a given homolog.

Many MarR homologs bind cognate sites that overlap the -10 and -35 promoter elements. However,

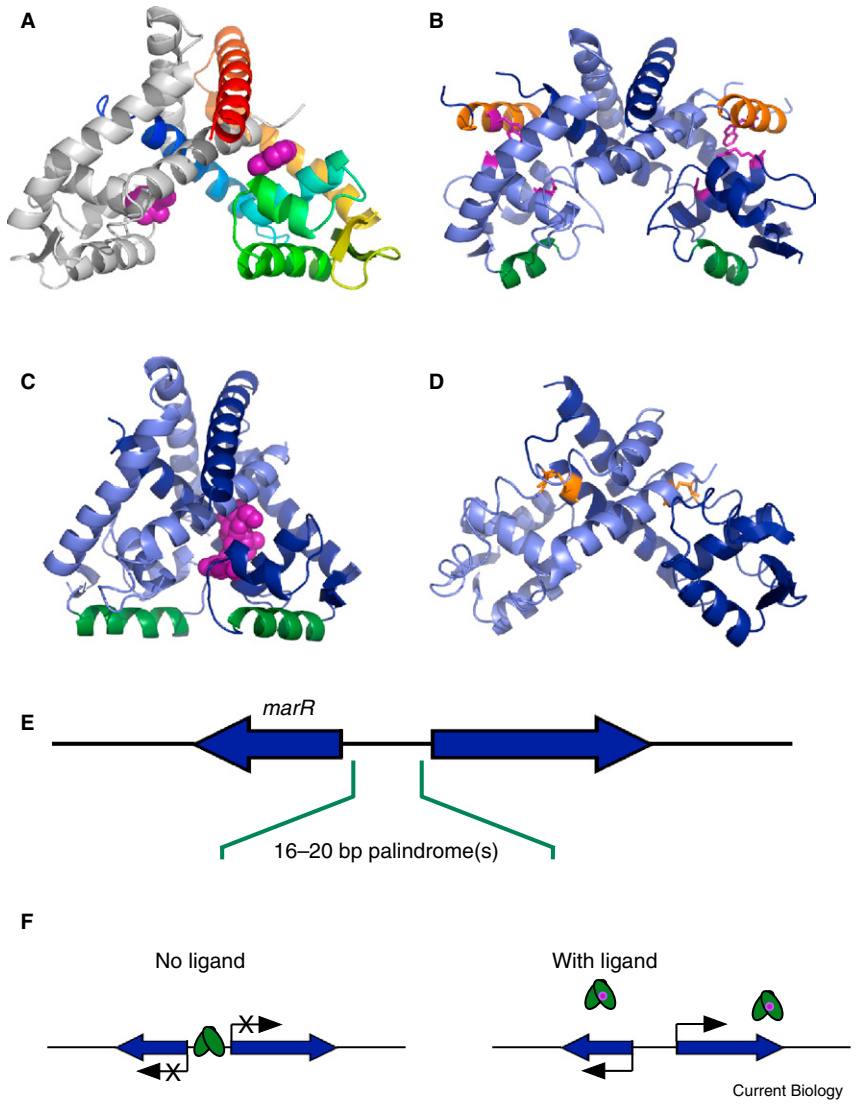

Figure 1. Representative MarR homologs and their mode of gene regulation.
(A) Structure of MTH313 (3BPX), a MarR homolog of unknown function from *Methanobacterium thermoautotrophicum*, in complex with the ligand salicylate (shown in magenta). One monomer is shown in gray, the other is colored from amino to carboxyl terminus (blue to red). Note the asymmetrical ligand binding; only ligand binding at the primary site (at the right) is associated with protein conformational changes and is therefore considered physiologically relevant. (B) Structure of *Deinococcus radiodurans* HucR (2FBK). Each monomer is shown in light and dark blue. HucR includes an amino-terminal extension conserved among a subset of MarR homologs (shown in orange) that is not seen in other reported MarR protein structures. DNA recognition helices are colored green and residues required for binding of the ligand urate are shown in magenta. (C) Structure of *Staphylococcus epidermidis* TcaR (3KP5) in complex with kanamycin (shown in magenta). Note that the symmetry-related site is unoccupied. Each monomer is shown in light and dark blue, with the DNA recognition helices in green. (D) Structure of oxidized OhrR from *Xanthomonas campestris* (2PFB). Each monomer is shown in light and dark blue with oxidized cysteines in orange. (E) Typical organization of genomic locus comprising gene encoding MarR homolog. Genes are depicted as blue arrows. The intergenic region between divergently encoded genes contains cognate DNA site(s). (F) In the absence of ligand, the MarR homolog (green symbol) binds the intergenic region, repressing expression of both genes. In the presence of ligand, DNA binding is attenuated and genes are expressed.

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mechanisms of transcriptional repression beyond competition for RNA polymerase binding have also been proposed, including hindering transcriptional elongation and competing with other transcriptional regulators.

What signals do they respond to and what genes do they regulate? Generally, MarR homologs regulate activity of genes involved in stress responses, virulence, or degradation or export of harmful chemicals such as phenolic compounds, antibiotics, and common household detergents. *E. coli* MarR (the namesake of the protein family) regulates resistance to organic solvents, disinfectants, detergents, oxidative stress, and antibiotics. In general, homologs that regulate drug efflux pumps may bind antibiotics or other substrates for the associated efflux system. MarR homologs may also regulate metabolic enzymes, in which case the cognate ligand may be the substrate for the enzyme in question or a closely related compound; in this capacity, MarR proteins may control genes involved in degradation of environmental toxins. Ligands are commonly small phenolic compounds, although metal ions and small peptides have also been shown to bind specific MarR homologs. As noted above, in addition to response to small molecule ligands, some MarR homologs respond to oxidative stress by oxidation of specific cysteine residues.

You mentioned virulence genes. How do MarR proteins contribute to pathogenicity? MarR homologs are exceptionally well suited as regulators of virulence genes in pathogenic bacteria because they can respond to the environmental changes that are associated with occupancy of the new ecological niche. For example, many human pathogens (e.g., *Salmonella* and *Staphylococcus*) utilize MarR homologs such as SlyA and SarZ as central regulators of virulence gene expression, with the transcription factor responding to either small molecule ligands or redox conditions. In plant pathogens such as *Erwinia*, the MarR homolog named PecS plays a key role in virulence gene expression, including expression of enzymes responsible for the maceration of plant tissue that characterizes disease progression. Other MarR homologs may contribute to virulence by specifically controlling expression of antibiotic efflux pumps, as already noted.

What do MarR proteins look like and how do they bind DNA? MarR homologs are winged helix-turn-helix (wHTH) DNA-binding proteins that exist as dimers and bind palindromic sequences within cognate promoters (Figure 1). The proteins generally have a triangular shape with pseudo-two-fold symmetry. The amino- and carboxy-terminal helices interdigitate to create a dimerization interface that dictates the distance between the DNA recognition helices, thus controlling DNA-binding affinity. The DNA-binding domains usually make few direct contacts with each other. The recognition helix of the wHTH domain binds the DNA major groove while the wing contacts the adjacent minor groove. MarR proteins associate with 16–20 bp inverted repeats, and cognate sites may comprise a single palindrome or multiple adjacent inverted repeats. The spacing between DNA half-sites places two consecutive major grooves ~34 angstroms apart on one face of the DNA helix; thus, the spacing between the two DNA binding domains, determined by the dimer interface, is critical for binding to cognate DNA.

How does ligand binding attenuate DNA binding? Ligand binding or cysteine oxidation results in a protein conformation that is incompatible with DNA binding. Homologs that bind small molecule ligands include proteins that regulate metabolic pathways and proteins that regulate efflux pumps, as they typically share substrate preferences with the enzymes or efflux pumps they regulate. Other ligands, such as organic hydroperoxides, may interact transiently with a MarR homolog to cause cysteine oxidation; this covalent modification also results in attenuated DNA binding due to conformational changes. MarR proteins that are regulated by cysteine oxidation (e.g., SarZ and OhrR) often function in oxidative stress responses and in the regulation of virulence. Notably, both structural studies and biochemical mapping have identified a common effector site in a cleft nestled between the dimer interface and the DNA-binding lobe. Occupancy of this site by a small molecule ligand or a covalent modification of cysteine residues may therefore either directly displace the DNA-binding lobe or modulate the dimer interface, in either event inducing a protein conformation that is unfavorable for DNA binding. While MarR proteins are dimers and theoretically feature two equivalent ligand-binding pockets, occupancy of one primary ligand-binding site may induce an asymmetry that precludes occupancy of the symmetry-related site, an observation that also suggests that filling one ligand-binding site is sufficient to attenuate DNA binding (Figure 1). Some structures reveal alternative ligand-binding sites, the physiological relevance of which remains uncertain.

What are the future challenges? MarR homologs are abundant and they regulate pathways that are critical to bacterial physiology. Undoubtedly, the full spectrum of MarR protein involvement in gene regulation has yet to be revealed, in large part because the ligands to which they respond are often unknown. A molecular understanding of mechanisms by which ligands effect regulation of gene activity is critical; notably, recent advances in identifying ligand-binding pockets may furnish a much needed tool towards identifying the ligands for MarR homologs for which the effector remains unknown.

Where can I find out more?

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