Title:	Molecular insights into effector binding by gntr/fadr family sugar acid transcriptional regulators
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Abstract:	Bacteria use a variety of carbohydrates as a source of carbon and energy. Sugar acids, the oxidized derivatives of sugars, represent an important class of carbohydrates whose metabolism is highly implicated in bacterial colonization and virulence. Sugar acids are widely prevalent in nature; they are an essential component of plant cell wall and animal tissues, and are produced as a metabolic intermediate of simple sugars by several microbes. In bacteria, the metabolism of sugar acids is often regulated by specific transcriptional regulators (TRs) that bind the operator DNA and activate or repress metabolic genes. The DNA binding ability of the sugar acid TRs is modulated by binding to cognate effectors, which are either the sugar acid itself or its metabolic intermediate. Several sugar acid TRs belong to the FadR subfamily within the GntR family of regulators. Although the DNA binding features and the effectors have been identified for a few FadR subfamily sugar acid TRs, the molecular details of effector-binding are completely unknown. Using Escherichia coli DgoR as a model, we presented the first comprehensive details into effector-binding among sugar acid TRs of GntR/FadR family. DgoR is a transcriptional repressor of D-galactonate metabolism and employs D-galactonate, the substrate of the metabolic pathway, as its specific effector. Through a combination of genetics, biochemical, and bioinformatics approaches, we identified the effector-binding cavity in DgoR. We employed a random mutagenesis-based genetic screen that exploited the accumulation of a toxic phosphorylated intermediate in the ΔdgoA strain, defective in D-galactonate metabolism, as a positive selection, to isolate several dgoR superrepressor alleles insensitive to D-galactonate. Blind molecular docking identified a potential effector-binding cavity in the C-terminal domain of DgoR and indicated that the amino acid residues corresponding to the eight dgoR superrepressor alleles constitute a part of the effector-binding pocket. The in-depth in vivo and in vitro analysis showed that the superrepressor alleles compromised the inducibility of DgoR without affecting its secondary structure, oligomeric status, and DNA binding ability. Further, taking Bacillus subtilis GntR, a repressor of D-gluconate metabolism, as a representative, we demonstrated that the effector binding pocket is similar among FadR subfamily sugar acid TRs. Finally, a comparison of sugar acid TRs with other FadR subfamily members suggested conserved features of effector-regulator recognition in FadR members that bind structurally similar effectors. Several studies have shown that genetic variations in carbohydrate sensing regulators affect their responsiveness to cognate effectors and ultimately influence the interaction of bacteria with their host. Thus, our study besides providing the basis for a detailed molecular understanding of sugar acid-responsive regulation in the FadR subfamily sets the ground to examine the influence of naturally occurring genetic variations in FadR subfamily regulators on their sensitivity to sugar acids and eventually their impact on bacterial colonization and virulence.
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