

Reconstruction of GABA and taurine metabolic regulons, controlled by MocR-subfamily transcription factors

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The GntR family is a large group of proteins widely distributed among diverse bacteria and regulating various biological processes [1]. Proteins from the GntR family share similar N-terminal HTH DNA-binding domains, but differ in the C-terminal effector-binding and oligomerization domains [1]. GntR family is divided into four main (FadR, HutC, MocR, and YtrA) and two minor (AraR and PlmA) subfamilies [1]. MocR-subfamily TFs are very different from the others, they have a large C-terminal domain, homologous to class I aminotransferases and, like these enzymes, use pyridoxal 5'-phosphate as a cofactor [2,3]. MocR subfamily is not very well studied; among few described TFs from this group there are GabR and TauR, activators of γ -aminobutyrate (GABA) and taurine metabolism, respectively [2,3,4]. Here we reconstruct GABA and taurine metabolic regulons, controlled by MocR-subfamily TFs. Data on composition of the characterized regulons, and respective binding sites are available in RegPrecise database (<http://regprecise.lbl.gov/RegPrecise/>).

GABA metabolism and MocR-subfamily regulators of GABA utilization

GABA is an important nitrogen and carbon source for many bacteria [2]. It can be produced from putrescine or glutamate, or imported into the cell via GABA permease GabP [2]. GABA is converted by various aminotransferases (GabT, OpaA, OpaB) into succinic semialdehyde, which is further oxidized to succinate by succinic semialdehyde dehydrogenase GabD [2,5,6]. We have identified several MocR-subfamily regulators of GABA metabolism: GabR in Firmicutes, GabR in Proteobacteria, GabR2 in Proteobacteria, OapR in Proteobacteria. Among Firmicutes, GabR is found only in Bacillaceae and Staphylococcaceae. GabR-regulons in Firmicutes apparently do not have any novel members and include only *gabT*, *gabD* and *gabP*.

One more MocR-subfamily regulator of GABA metabolism, GabR that is not orthologous to

GabR from Firmicutes, was identified in various Proteobacteria (Beta and Gamma).

Among Gammaproteobacteria, GabR is found in Enterobacteriales, Moraxellaceae and Psychromonadaceae. GabR-regulons in Moraxellaceae and Psychromonadaceae do not have any novel members besides *gabT*, *gabD*, *gabP*, and *gabR* itself, while in Enterobacteriales they also include *gbtABCD*, likely encoding GABA (or spermidine/putrescine) ABC-transport system.

Among Betaproteobacteria, GabR is found in Alcaligenaceae, Burkholderiaceae (*Burkholderia* spp. and *Ralstonia* spp.), Comamonadaceae and Rhodocyclaceae. In Alcaligenaceae, GabR controls expression of *gabT* (present in several paralogous copies), *gabD*, as well as genes, encoding ABC-type dipeptide transport system (*dppABCD*), aminoglycoside phosphotransferase (COG2334), and acetylornithine deacetylase (*argE*). ArgE deacetylates N-acetylornithine into L-ornithine, which can be further converted into putrescine. In Burkholderiaceae, GabR regulates *gabT*, *gabD*, *gbtABCD* (in *Burkholderia* spp. and *Ralstonia* spp.), and also *dppABCD* and *argE* (in *Ralstonia* spp.). Among Comamonadaceae, GabR regulates *gabT*, *gabD*, as well as *gbtABCD*, *gatP*, which encodes GABA transaminase, and *puuAD*, which are involved in the putrescine metabolism [6]. Since PuuR, that controls *puu*-genes in *E. coli* [6], is absent in Comamonadaceae, it is natural that GabR-regulation here was expanded from only GABA utilization onto the related putrescine metabolic pathway. Among Rhodocyclaceae, GabR-regulon includes *gabT*, *gabD* and *gbtABCD* in *Thauera* sp. MZ1T. Summing up, in Betaproteobacteria we observe an expansion of GabR-regulation onto adjacent metabolic pathways - N-acetylornithine and putrescine utilization; as well as two transport systems (GbtABCD and DppABCD) under GabR-regulation in several Beta- and Gammaproteobacteria.

GabR2, another MocR-subfamily regulator of GABA utilization, is present in some Beta- and Gammaproteobacteria. In Pseudomonadaceae GabR2 was shown to regulate only *gabP*. GabR2 is also present in Comamonadaceae, where it regulates *gabT*, *gabD* and *gbtABCD*, as well as agmatinase, encoded by *speB*, which converts agmatine to putrescine and thus is metabolically connected to the GABA utilization. Thus, in case of GabR2 in Betaproteobacteria we also observe an expansion of regulation onto adjacent metabolic pathway.

Another MocR-subfamily regulator of GABA utilization, OapR, is found in some Alpha- (Rhizobiales, Rhodospirillales) and Betaproteobacteria (Alcaligenaceae, Burkholderiaceae). Among Rhizobiales, OapR regulates *oapT*, encoding another GABA aminotransferase, homologous to GabT. In Rhodospirillales group, OapR controls expression of *oapT* and its own gene, *oapR*. OapR-regulon in Alcaligenaceae and Burkholderiaceae includes *oapT* and *oapD*, which encodes succinic semialdehyde dehydrogenase, homologous to GabD.

Taurine metabolism and MocR-subfamily regulators of taurine utilization

Taurine can be used as a source of carbon, energy, nitrogen or sulfur for growth by various bacteria [3,4]. Taurine is imported into the cell either by ABC-transporter TauABC or by TRAP transporter TauMLK [3,4]. There are two taurine utilization pathways active under different metabolic situations [4]. The first one includes taurine transamination via Tpa or TauXY (TDH) into sulfoacetaldehyde [3,7] and its further desulfonation by Xsc, yielding acetyl phosphate and sulfite ion [3,4,7]. Acetyl phosphate is further converted by Pta into acetyl-CoA [3,4]. Sulfite ion is either exported by sulfite exporter TauE or is oxidized into sulfate, which is exported by sulfate transporter TauZ [7]. Other degradative pathway includes desulfonation of taurine to aminoacetaldehyde via TauD [4].

Among Alphaproteobacteria, TauR is identified in Rhizobiales and Rhodobacterales. TauR-regulon in Rhizobiales includes *tauABC*, *tauXY*, *tauZ*, *xsc* and *pta*. TauR-regulon structure varies among Rhodobacterales. TauR in this taxonomic group regulates: *tauE*, *tauMLK*, *tauR*, *tauX*, *tauY*, *tauZ*, *tpa* and *tpa2*, *xsc*, *pta*, *ackA*. We also predict novel members of TauR-regulons in Rhodobacterales, which include: genes, encoding alkylhydroperoxidase AhpD family protein (COG2128), aminotransferase (COG161, homologous to Tpa), and FAD dependent oxidoreductase (COG665, homologous to TauD), and also *bisC*, *dmsC* and *hybA*. The latter three genes encode oxidoreductase subunits, thus their presence in TauR-regulons might be natural, since it is known that cytochrome *c* functions as the potential electron acceptor for TDH [7].

Among Betaproteobacteria, TauR is present in Burkholderiaceae (*Burkholderia* spp. and *Ralstonia* spp.) and Comamonadaceae. In Burkholderiaceae, TauR regulates *tauABC*, *tauXY*, as well as *tauE*, *xsc*, *pta* and *gabP* (in *Burkholderia* spp.), and *tauD*, *tauMLK* (in *Ralstonia*

spp.). We also predict *bisC*, *dmsC* and *hybA*, and genes, encoding GCN5-related N-acetyltransferase (COG456, RimI) and phosphonoacetaldehyde dehydrogenase (PhnY, PF00171), to be members of the TauR-regulon in Burkholderiaceae.

In Comamonadaceae, TauR regulates *tauABC*, *tauXY*, *gabP*, as well as novel members of the regulon: *dppABCDF* (encoding oligopeptide ABC transporter), and genes, encoding amidohydrolase (COG1574) and P47K protein (COG0523).

Among Gammaproteobacteria, TauR is identified in Enterobacteriales, Oceanospirillales and Psychromonadales. In Enterobacteriales TauR regulates amino acid ABC transporter. TauR-regulon in Oceanospirillales also comprises genes, encoding this ABC transporter, *tpa*, and *tauABC*. In Psychromonadales TauR regulates *tauABC* and *tpa*.

TauR is also identified in Nocardiaceae, where it controls *tpa*, *pta*, *tauE*, *tauR*, *ald*, *thiG*, encoding thiazole biosynthesis protein, and two copies of *gabP*. TauR also regulates *pdxS* in *Rhodococcus* sp. RHA1.

Here we also describe TauR2, another MocR-subfamily regulator present in some Alphaproteobacteria (Rhizobiales and Rhodobacterales). In Rhizobiales, TauR2-regulon includes *tauR2*, *tauE*, gene, encoding aldehyde dehydrogenase (COG1012), and also (similar to TauR in Comamonadaceae) *dppABCDF* (encoding oligopeptide ABC transporter), and genes, encoding amidohydrolase (COG1574) and P47K protein (COG0523). TauR2 in Rhodobacterales regulates genes, encoding aldehyde dehydrogenase (COG1012), epoxide hydrolase domain protein (COG596, MhpC), and TRAP transporter of unknown specificity.

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