Transcriptional Regulation of the Carbohydrate Metabolism in the *Bifidobacterium* Genus

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Background: Bifidobacteria, commensals of mammalian gut, are of increasing interest due to their positive effect on human health. The influence of non-digestible carbohydrates (known as prebiotics) on growth of Bifidobacteria and associated metabolic pathways are broadly studied. Although, transcriptional regulation of the carbohydrate metabolism in Bifidobacteria is still poorly understood.

Results: We used combined approach based on comparative genomics and analysis of transcriptomic and proteomic data for reconstruction of regulatory networks in 11 *Bifidobacterium* spp. Analysis of regulatory gene regions revealed candidate DNA-binding motifs for 48 orthologous transcription factors (TFs) from the LacI, ROK, DeoR, AraC, GntR and TetR families. The analyzed TFs are mostly local and control specific catabolic pathways for host- and diet-derived glycans and monosaccharides; their regulons contain up to 15 genes per genome including catabolic enzymes, uptake transporters and TFs. The reconstructed regulons and controlled pathways show mosaic distribution across the *Bifidobacterium* genus. The predicted capabilities to grow using an individual carbohydrate as the sole carbon source are in good consistency with the previously experimentally determined phenotypes. We predicted two novel TFs for the central carbohydrate metabolism, named AraQ and Crp, that are present in all the sequenced Bifidobacteria. The inferred AraQ regulon includes enzymes from the glycolysis, pentose-phosphate pathway and arabinose catabolism. A novel Crp-family TF presumably regulates genes involved in fermentation and other pathways. For the first time, we predicted novel group of TFs from the TetR family that presumably control carbohydrate metabolism (beta-glucoside and beta-galactoside utilization). We also observed an interesting case of extension of the ribose

utilization regulon RbsR that also controls the nucleoside utilization.

Conclusions: We performed genomic reconstruction of transcriptional regulation for sugar utilization pathways in the Bifidobacterium genus and report reconstructed regulons for 50 TFs. The reconstructed regulatory networks can provide new insights on metabolic capabilities of Bifidobacteria and their interactions with host and other microbial community members.