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[P03-313] Transcriptional regulatory networks of the human gut symbiont *Bacteroides thetaiotaomicron* are uncovered using machine-learning

○Jiwon Lee[1,3], Kangsan Kim[1,2], Chaewon Lee[3], Donghui Choe[4], Sun Chang Kim[2], Sung Sun Yim[1,2,3], Ki Jun Jeong[3,5], Bernhard Palsson[4], Suhyung Cho[2], Byung-Kwan Cho[1,2,3] (1. Department of Biological Sciences, Korea Advanced Institute of Science and Technology (Korea), 2. KI for the BioCentury, Korea Advanced Institute of Science and Technology (Korea), 3. Graduate School of Engineering Biology, Korea Advanced Institute of Science and Technology (Korea), 4. Department of Bioengineering, University of California San Diego (Korea), 5. Department of Chemical and Biomolecular Engineering, Korea Advanced Institute of Science and Technology (Korea))

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Bacteroides thetaiotaomicron VPI-5482 is a prominent human gut symbiont of increasing importance to human health and therapeutic applications. Despite its significance, the transcription regulatory network (TRN) governing its survival and resilience in vivo remains poorly understood. Here, we present BtModulome, a comprehensive transcriptional regulatory framework derived from independent component analysis (ICA) of 461 RNA-Seq datasets spanning diverse niche-specific conditions and genetic backgrounds. This analysis revealed the BtModulome consisting of 110 independently modulated gene sets (iModulons), explaining 72.9% of the variance in the RNA-Seq data set. We validated strong associations with 39 known regulators and identified 311 novel regulator-regulon relationships, accounting for 22.4% expansion of the known TRN of *B. thetaiotaomicron*. In addition, we functionally characterized 11 ECF-σs, including SigW-1, which orchestrates arylsulfatase expression critical for host colonization, and SigH-1, which mediates (p)ppGpp-dependent stringent response. Integration of iModulon activities with multi-omics datasets provided mechanistic insights into stress responses and carbon utilization both in vitro and in vivo. This comprehensive TRN framework establishes a foundation for understanding adaptive mechanisms in gut commensals and demonstrates the utility of module-centric analysis for biological discovery in non-model organisms.This work was supported by the Korea Bio Grand Challenge (RS-2018-NR029581 to B-KC), the Bio and Medical Technology Development Program (RS-2021-NR056597, and RS-2021-NR056566 to B-KC) through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT, and the Basic Science Research Program through NRF funded by the Ministry of Education (RS-2023-00246928 to SC). This work was also funded by the KAIST Jang Young Sil Fellow Program.This work was supported by Korea Environmental Industry & Technology Institute (KEITI) through Technology Development Program for CO_2 Mitigation and Conversion to Value-Added Products Using Indigenous Organism, funded by Korea Ministry of Climate, Energy and Environment (MCEE) (RS-2026-25505528).