A systems biology approach to identifying the native function of Hg methylation proteins in *Desulfovibrio desulfuricans* ND132

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To date, little is understood about the physiological function of MeHg production by anaerobic microorganisms. It is postulated that the native function of Hg methylation proteins (HgcAB) is not Hg methylation, but the methylation of an unknown metabolite. Hg methylation has been linked to C1 carbon metabolism for acetyl-CoA and methionine biosynthesis, sometimes as part of the Wood-Ljundahl pathway, yet a specific biochemical pathway remains elusive. Here we take a systems biology approach to exploring the physiological function of Hg methylation using *Desulfovibrio desulfuricans* ND132 as a model organism. For this study, we compared growth and metabolite profiles of various *D. desulfuricans* ND132 gene deletion strains related to carbon and Hg cycling to wild-type. Mutant strains (e.g. Δ*hgcAB,* Δ*metH,* Δ*cobT,* Δ*hgcA:*T101A) that exhibited differences in Hg methylation capability compared to wild-type (e.g. 0–246%) were grown in defined media under both fermentative and sulfate-reducing conditions. Organic acid, anion, and metabolite concentrations were monitored throughout the growth of the cells to determine if changes in central metabolism coordinated to changes in MeHg generation between wild-type and mutant strains. While significant differences in substrate consumption or acetate production were not observed between the strains, differences in metabolite profiles were observed. These results along with proteomic and transcriptomic analyses further elucidate the metabolic role for Hg methylation proteins in *D. desulfuricans* ND132. Understanding the mechanism by which methylation occurs will help to determine the physiological role of this gene pair, including how microbes acquired the ability to produce the neurotoxin, MeHg.