Interplay Between Capsule Expression and Uracil Metabolism in Streptococcus pneumoniae D39

Pyrimidine nucleotides play an important role in the biosynthesis of activated nucleotide sugars (NDP-sugars). NDP-sugars are the precursors of structural polysaccharides in bacteria, including capsule, which is a major virulence factor of the human pathogen S. pneumoniae. In this work, we identified a spontaneous non-reversible mutant of strain D39 that displayed a non-producing capsule phenotype. Whole-genome sequencing analysis of this mutant revealed several non-synonymous single base modifications, including in genes of the de novo synthesis of pyrimidines and in the -10 box of capsule operon promoter (Pops). By directed mutagenesis we showed that the point mutation in Pcps was solely responsible for the drastic decrease in capsule expression. We also demonstrated that D39 subjected to uracil deprivation shows increased biomass and decreased Pcps activity and capsule amounts. Importantly, Pcps expression is further decreased by mutating the first gene of the de novo synthesis of pyrimidines, carA. In contrast, the absence of uracil from the culture medium showed no effect on the spontaneous mutant strain. Co-cultivation of the wild-type and the mutant strain indicated a competitive advantage of the spontaneous mutant (non-producing capsule) in medium devoid of uracil. We propose a model in that uracil may act as a signal for the production of different capsule amounts in S. pneumoniae.

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