Pathoadaptation of a Human Pathogen Through Non-Coding Intergenic Mutations - DTU Orbit (08/11/2019)

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Most knowledge gained from evolutionary studies of bacteria in natural and experimental settings center around contribution of intragenic mutations on bacterial evolution. While cases of adaptive intergenic mutations have sometimes been reported or explored, none of these studies consider intergenic mutations in broader context as key players in evolutionary adaptation of bacteria.

The focus of this thesis has been to provide novel insights on contributions of non-coding intergenic mutations in natural evolution of bacteria. The model system used for these investigations is adaptation of opportunistic pathogen Pseudomonas aeruginosa in long-term chronic airway infections of Cystic fibrosis (CF) patients. Using sequenced genomes of P. aeruginosa isolated from this setting, 88 intergenic regions under positive selection for adaptive mutations within and across isolates of different P. aeruginosa lineages were identified. Mutations within core promoter are more frequently found than other elements in these intergenic regions and intergenic mutations made a larger numerical contribution to selection of adaptive genes than intragenic. Several genes present within these regions had established roles in CF adaptation of P. aeruginosa and their expressions are altered by the mutation. It was established that mutations upstream ampR increased tolerance of P. aeruginosa to some β-lactam antibiotics.

Mutations in promoter of phuR, encoding receptor of pseudomonas heme uptake system, conferred growth advantage in the presence of hemoglobin demonstrating that P. aeruginosa has adapted towards utilization of iron from hemoglobin. Further investigation of phuR promoter mutation revealed pleiotropic effects on expression of many other genes. The pleiotropic effect by this mutation was contingent on epistatic effects of other mutations in CF adapted genotype of P. aeruginosa. It was also established that this mutation leads increased inhibition of S. aureus and decreased fitness of P. aeruginosa during anoxic growth.

The findings presented in this thesis provide a new dimension for bacterial evolution through intergenic mutations. The knowledge gained here can be applied to future treatment of patients suffering from chronic bacterial infection. Moreover, direct evolution or genetic manipulation of intergenic region offer ample opportunities for better outcomes in biotechnological applications of bacteria.

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