ABSTRACT

THE INFLUENCE OF GENERAL AND INDUCIBLE HYPERMUTATION ON ADAPTATION DURING EXPERIMENTAL EVOLUTION

By

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Hypermutator (or mutator) strains of bacteria have been observed in a variety of clinical, environmental, and laboratory populations with up to 1000-fold increases in spontaneous mutation rates. Defects in DNA repair machinery responsible for general hypermutation most commonly include the inactivation of methyl-directed mismatch repair that result in constitutive increases in mutation rate. Alternatively, mutagenic DNA repair only transiently raises mutation rates through the activation of low-fidelity polymerases in response to DNA-damaging stress conditions. The widespread existence of both general and inducible mutator genotypes suggests that evolutionary strategies of bacteria include mechanisms for increasing mutability. This work investigates the influence of hypermutation on adaptation through experimental evolution with the contextually relevant model organisms Pseudomonas cichorii 302959 and P. aeruginosa PAO1. Following ~500 generations of growth, both model organisms exhibited comparable improvements in fitness, independent of mutator status, suggesting that hypermutation does not impede adaptation through mutation accumulation. Both general and inducible hypermutation facilitated genotypic diversification that was not observed in nonmutator lineages. The mechanistic differences underlying general and inducible hypermutation

were reflected in unique spectra of nucleotide substitutions but did not restrict access to parallel adaptive traits despite considerable variation in gene expression profiles. The diversity in colony

morphologies and gene expression traits observed in mutator lineages may represent a broad exploration of sequence space that is no doubt a favorable strategy for adaptation.