Defining the Impact of Mutation Accumulation on Replicative Lifespan in Yeast Using Cancer-associated Mutator Phenotype

Mutations accumulate within somatic cells and have been proposed to contribute to aging. It is unclear what level of mutation burden may be required to consistently reduce cellular lifespan. Human cancers driven by a mutator phenotype represent an intriguing model to test this hypothesis, since they carry the highest mutation burdens of any human cell. However, it remains technically challenging to measure the replicative lifespan of individual mammalian cells. Here, we modeled the consequences of cancer-related mutator phenotypes on lifespan using yeast defective for mismatch repair (MMR) and/or leading strand (Polε) or lagging strand (Polδ) DNA polymerase proofreading. Only haploid mutator cells with significant lifetime mutation accumulation (MA) exhibited shorter lifespans. Diploid strains, derived by mating haploids of various genotypes, carried variable numbers of fixed mutations and a range of mutator phenotypes. Some diploid strains with fewer than two mutations per megabase displayed a 25% decrease in lifespan, suggesting that moderate numbers of random heterozygous mutations can increase mortality rate. As mutation rates and burdens climbed, lifespan steadily eroded. Strong diploid mutator phenotypes produced a form of genetic anticipation with regard to aging, where the longer a lineage persisted, the shorter-lived cells became. Using MA lines, we established a relationship between mutation burden and lifespan, as well as population doubling time. Our observations define a threshold of random mutation burden that consistently decrease cellular longevity in diploid yeast cells. Many human cancers carry comparable mutation burdens, suggesting that while cancers appear immortal, individual cancers cells may suffer diminished lifespan due to accrued mutation burden.