THE MECHANISM(S) MEDIATING DECREASED BER AT OLDER AGES AMONG TISSUES

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Inability to maintain genomic integrity results in an increased risk of carcinogenesis. Genomic integrity is challenged daily by numerous endogenous and exogenous factors, among which oxidative damage of DNA prevails, giving rise to oxidized bases and subsequently single strand breaks and double strand breaks. Among DNA repair pathways, base excision repair (BER) is one of the most important mechanisms to protect cells against mutagenic and carcinogenic environments. BER consists of two sub pathways, short-patch BER (a single nucleotide repair patch) and long-patch BER (a 6-8 nucleotide repair patch). It has been shown that tumor incidence increases with age. One of the factors contributing to increased tumorigenesis might be a decreased ability of cells to repair DNA damage with age. Previous work from our laboratory shows that short-patch BER of G:U mismatch decreases with age in mice and that this decrease correlates with increased mutant frequency in some tissues. A decreased abundance of AP endonuclease (Ape) was suggested as a primary cause of increased mutagenesis in spermatogenic cells, but did not correlate with decreased BER activity in brain. In order to assess the applicability to other lesions repaired by BER, we have assayed the activity in mouse spermatogenic cells, brain and liver obtained from different aged mice using two different lesions, G:U mismatch and 8-oxoG:C. To further understand the molecular mechanism mediating decreased BER activity with old age in different tissues we examined the BER pathway with above mentioned substrates as well as the AP endonuclease step substrates carrying a natural AP lesion or reduced AP site, respectively. We found the Ape activity limiting in nuclear extracts from mixed germ cells. Total BER activity decreased in liver and brain as well, but the BER activity on AP:G lesion was proportionally higher then in mixed germ cells. From the point of enzyme kinetics our data do not support the model, where the decrease in Ape activity is the sole reason for decrease of BER activity with age in mouse liver and brain. Other mechanisms, either working independently or in concert with decreased Ape activity have yet to be identified in these tissues.