THE PREMATURE AGEING SYNDROME PROTEIN COCKAYNE SYNDROME B MODULATES THE REPAIR OF OXIDATIVE DNA LESIONS

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Genomic instability is one of the most common features of aging. Old cells and organisms display several markers of genetic instability, such as aneuploidy, telomere shortening, chromosomal aberrations and accumulation of base lesions. The elevated genomic instability in old individuals suggests a role for DNA repair in aging; however the precise molecular pathways involved remain elusive. DNA base modifications, such as those generated by oxidative stress, are repaired by the base excision repair (BER) pathway. BER is initiated by substrate-specific DNA glycosylases that cleave the N-glycosyl bond, thus releasing the damaged base. Recent evidence suggests that BER efficiency can be modulated by protein interactions. Cockayne syndrome is a segmental premature aging disease, caused by mutations in one of two genes, CSA and CSB. The CSB protein is involved in transcription, but it has been recently implicated in BER. We found that CSB interacts physically and functionally with the DNA glycosylase NEIL1, which initiates the repair of ring-opened oxidized purines (formamidopyrimidines). NEIL1 catalyses two distinct enzymatic steps: the release of the modified base and the cleavage of the resulting abasic site. Recombinant CSB significantly stimulated both catalytic activities, in a concentration-dependent manner. Co-immunoprecipitation from cellular extracts confirmed the physical interaction in vivo, while co-localization in cells exposed to DNA damaging agents further suggested that the two proteins cooperate in response to DNA lesions. Moreover, we found a significant accumulation of formamidopyrimidines (FapyA and FapyG) in tissues from mice lacking CSB, indicating that the CSB protein is required for proper repair of such lesions. These results provide a mechanistic association between efficient BER and a premature aging phenotype.
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