Gene expression and DNA damage responses in human aging and premature aging syndromes

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ABSTRACT

The studies underlying this PhD dissertation were carried out at the Laboratory of Molecular Gerontology, National Institute on Aging, USA and at the Institute of Human Genetics, University of Aarhus.

Understanding the mechanisms and genetic programmes involved in human aging remains an unsolved problem. A major theory of aging, and the mechanisms underlying age-associated disease such as cancer, holds that these processes occur as a result of accumulated DNA damage. The aim of the project was to use DNA microarrays to characterize age-associated gene expression changes of 7000 human genes with and without cellular stress, in cell lines from normal aged donors and from patients suffering from the progeroid diseases Werner syndrome (WS) and Cockayne syndrome (CS).

Differential expression in CS cell lines included more than one hundred genes and particularly several transcription factors and DNA processing proteins suggesting that CSB protein plays an upstream role in the transcriptional regulation following oxidative damage. We propose that the mechanisms underlying the repair deficiency and premature aging phenotype of CS include the observed dysregulation of transcription, protein turnover, cell cycle regulation and altered signal transduction in CS-B cells after oxidative DNA damage. Of 6912 genes analyzed 6.3% (435 genes) displayed >1.5-fold difference in expression when cells from WS patients or old people were compared with cells from young controls. This result demonstrated that the transcription defect in WS is not global, but specific to certain genes. Exposure to 4-nitroquinoline-1-oxide (4NQO), gamma-irradiation or UV-irradiation elicited damage specific gene expression changes of up to ten fold; 85 genes had similar changes in expression of 3-40 fold after all three kinds of stress.

Our results suggest that aberrant DNA damage-induced gene regulation may contribute to the aging process and the premature aging in WS. We have established that there is a connection between altered gene expression, particularly of DNA metabolism related genes, and the age-associated decline in DNA repair capacity seen with aging, something which has not previously been clear. In time, this research is expected to lead to important therapeutic advances and could eventually alleviate disabilities and diseases of old age, e.g. cancer, as well as improve quality of life and productivity in the elderly population.