Molecular genetics on human disorders with a defect in cellular response to DNA damage which inhibits a transcription

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【Outline of survey】

DNA carrying genetic information is continuously challenged by various exogenous and endogenous DNA-damaging agents. The DNA damage leads to cell death and mutation, which may cause aging and cancer. However, a wide variety of DNA lesions are eliminated by various DNA repair mechanisms in the cells. Nucleotide excision repair (NER) is a versatile DNA repair system that removes a wide range of DNA lesions including UV-induced lesions. There are several NER-deficient disorders, such as xeroderma pigmentosum (XP), Cockayne syndrome (CS) and UV-sensitive syndrome (UVsS). On the other hand, DNA damage that blocks ongoing transcription on the transcribed strand of active genes causes apoptosis that leads to aging. These lesions on the transcribed strand are specifically repaired by transcription-coupled DNA repair (TCR), which is selectively deficient in CS and UVsS. However, the exact mechanism of TCR in mammals remains to be clarified. In this project, molecular mechanism of TCR and molecular basis for XP, CS and UVsS will be analyzed.

【Expected results】

TCR functions of CSA, CSB, XPG, TFIIH and XAB2 responsible for XP and CS will be analyzed. In addition, cloning and analysis of the responsible genes for UVsS and its related diseases will be intended. In addition, in vitro TCR reactions will be constituted. These researches will provide clues for understanding a new cellular function regarding a cross-talk between transcription and DNA repair. In addition, molecular analysis of pathogenesis of XP, CS and UVsS will provide a new strategy for preventing an abnormal neurological and physiological development and aging.

【References by the principal researcher】

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【Term of project】 FY 2005 - 2009 | **【Budget allocation】** 87,300,000 yen

【Homepage address】 http://www.fbs.osaka-u.ac.jp/labo/03a.html