課題番号（Project number） 26

Models for normal human aging by focusing on Werner syndrome and bioenergetics in cells and mice; Proteomic analysis of DNA polymerase β complex in mitochondria

［1］組織（Research group）
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研究費(Expenditure report of research funds)：
cost for the determination of human Polβ interacting proteins 392,000 YEN

［2］研究経過（Research setup）

The genome is under constant attack from exogenous genotoxic agents derived from the environment and from endogenous DNA damaging agents produced as by-products of oxidative phosphorylation. Cellular DNA repair is critical for genomic stability and the accumulation of DNA damage has been linked to many debilitating human disorders including accelerated aging, cancer and neurodegeneration.

The repair of mitochondrial DNA (mtDNA) is less understood and appears to be a simplified version of nuclear DNA (nDNA) repair with limited pathway overlap. Mitochondria lack nucleotide excision repair and the presence of double strand break repair is debated. Despite the mitochondria having attenuated DNA repair capabilities when compared to the nucleus, the accumulation of mtDNA damage is not without consequence. Ineffective mtDNA maintenance is the underlying cause of many human diseases including Alpers Syndrome and Chronic Progressive External Ophthalmoplegia (CPEO) caused by mutations in mitochondrial polymerase gamma (Polγ) or the TWINKLE helicase.

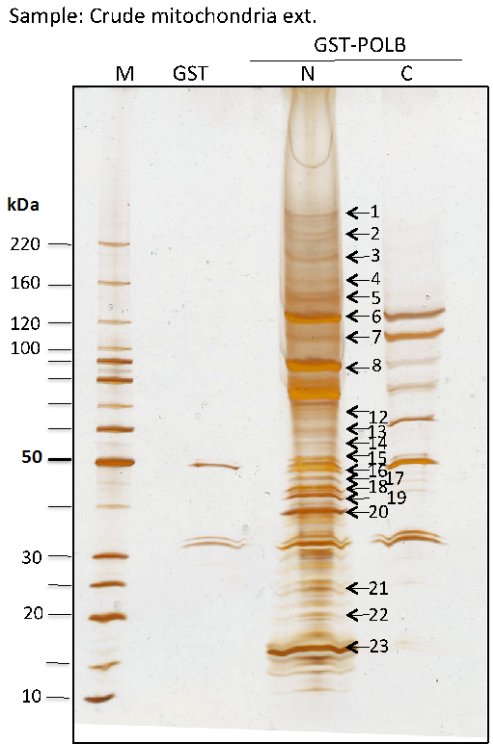
In the nucleus, the majority of 5'-dRP lase activity comes from the core BER enzyme Polß and the activity has been reported to be rate limiting step in SP-BER (Sobol et al., 2000). Considering that the 5'-dRP lyase activity of Polß was measured to be 17-fold higher than the same activity in Polγ (Pinz and Bogenhagen, 2000) we sought to re-investigate the potential role of Polß in the mitochondria.

We have discussed the experimental progress and manuscript preparation by using Skype.

［3］成果（Research outcomes）

（3－1）研究成果（Results）

Mitochondrial specific protein partners were identified using Polß fragment interaction studies. Identified proteins were involved in DNA maintenance, mitochondrial import and stress response. Of particular interest was the identification of DNA maintenance proteins TWINKLE, SSBP1 and TFAM, all of which are mitochondria specific and function in the nucleoid. Polß and TFAM interacted using the HMG1 domain in TFAM and the N-terminal of Polß. Further, a direct functional interaction was measured between Polß and TWINKLE, a mitochondrial helicase. Polß appears to have a role in mitochondrial DNA repair analogous to its role in nuclear repair.



（３－２）波及効果と発展性など（Future perspectives）

We are studying functional aspects of mitochondrial DNA repair in the presence and absence of DNA polymerase beta to characterize its role.

［4］成果資料（List of Papers）

A paper entitled with

“DNA polymerase beta participates in mitochondrial DNA repair

Sykora P, Kanno S, et al. Yasui A and Bohr VA

We submitted this paper and now in revision.