

【Grant-in-Aid for Scientific Research(S)】

Integrated Science and Innovative Science (New multidisciplinary fields)



Title of Project : Molecular pathology and regulatory mechanisms involved in the breakdown of nucleotide pool homeostasis under environmental stress

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Research Area : New multidisciplinary fields

Keyword : damage, nucleotide pool, DNA, RNA

【Purpose and Background of the Research】

For living organisms, maintaining the integrity of their genomic DNA harboring the genetic information and transmitting them precisely from parents to offspring or from cell to cell are essential biological functions in order to maintain the species and individuals, respectively. DNA is always in danger of modification by reactive molecules generated by environmental factors such as radiation or by cellular metabolisms such as respiration. We have demonstrated that DNA lesions cause mutations or cell death if not repaired, and the former may initiate carcinogenesis while the latter may result in various degenerative diseases. We have unveiled that genomic damage is caused not only by direct lesions generated in DNA, but also by modification of its precursor mononucleotides. Given that more than ten-billion molecules of mononucleotides are required for an entire replication of human genome, the quality control of nucleotide pool – “a source of mononucleotides” – is undoubtedly important for maintaining the integrity of genomic DNA. Moreover, mononucleotides are essential for various cellular functions such as energy transfer and signal transduction. The aim of this project is to identify and investigate the molecules essential for the maintenance of the nucleotide pool homeostasis.

【Research Methods】

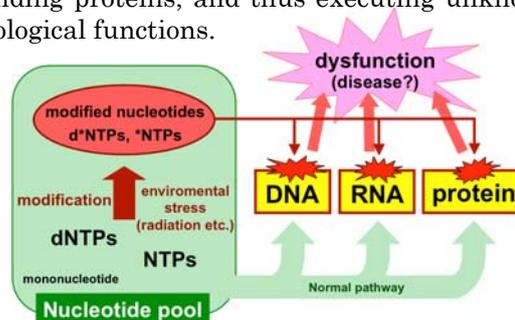
We explore biological phenomena caused by the breakdown of nucleotide pool homeostasis:

- (1) We identify modified nucleotides generated by radiation or chemicals using LC-MS/MS. We then establish methods to quantify the modified nucleotides in cells and tissues. Using these methods, we evaluate effects of the modified nucleotides generated in cells as well as in tissues under various environmental stresses.
- (2) Using affinity chromatography with modified nucleotide-immobilized resins, we purify and identify proteins whose functions are affected by various modified nucleotides, or which degrade modified nucleotides. We then clone and characterize genes for these proteins.

- (3) We examine biological effects of modified nucleotides on cultured cells and mouse. Using strategies based on disruption/knockdown or over-expression of genes identified in (2), we clarify roles of these genes *in vivo*.
- (4) Using mouse models for Alzheimer's disease and cancer, we explore the mechanisms how modified nucleotides modulate the pathologies.

【Expected Research Achievements and Scientific Significance】

Mononucleotides are important not only as precursors of DNA, but also as precursors of RNA and regulatory ligands for various proteins. Elucidation of mechanisms for quality control of nucleotide pool may lead to the development of new research fields. For example, it is likely that the modified nucleotides derived from ATP/GTP interact with many kinds of well-known ATP/GTP binding proteins, and thus executing unknown biological functions.



【Publications Relevant to the Project】

- Oka S, Tsuchimoto D, Sakumi K, Nakabeppu Y *et al*. Two distinct pathways of cell death triggered by oxidative damage to nuclear and mitochondrial DNAs. *EMBO J*, 27: 421-432 (2008)
- Behmanesh M, Sakumi K, Abolhassani N, Oka S, Tsuchimoto D, Nakabeppu Y *et al*. ITPase-deficient mice show growth retardation and die before weaning. *Cell Death Differ*, 16: 1315-1322 (2009)

【Term of Project】 FY2010-2014

【Budget Allocation】 167, 000 Thousand Yen

【Homepage Address and Other Contact Information】

<http://www.bioreg.kyushu-u.ac.jp/nfg/>