活性酸素によるゲノム障害から神経変性疾患の発症や発がんの分子メカニズムを理解する

■研究概要
我々は、生体がその代謝や信号伝達、生体防御反応、環境応答など様々な過程で発揮する活性酸素による増殖性細胞障害として「活性酸素と発癌」に、さらに非増殖性細胞障害として「酸化ストレスと神経変性」に注目して「活性酸素によるゲノム障害とその防護機序」の解明を進めている。

フェニルアラニン（Phe）の過剰摂取は物理的、化学的ストレスにより酸化ストレスを引き起こし、MTHF（腺チミシンDNA酸化物）のDNA内への塩基換えを引き起こす。MTHFはDNA内への塩基換えを引き起こす。

■Research Projects
Our aim is to understand mechanisms protecting our genomes from damage caused by reactive oxygen species. We are investigating mutagens in proliferative cells and carcinogens, and also cell death in p53-negative cells and neurodegeneration.
8-Oxoguanine (8-oxoG) causes mutagenesis and carcinogenesis in mammals, which are prevented by MTHFR (8-oxoG-DTPase), OGG1 (8-oxoG DNA glycosylase) and MUTYH (adenine DNA glycosylase). MTHFR and OGG1 prevent cell death by suppressing 8-oxoG accumulation in DNA, while MUTYH triggers cell death by excising adenine opposite 8-oxoG in DNA. MUTYH induces neuronal dysfunction and microglial activation in nerve tissues under oxidative stress, thus enhancing neurodegeneration.

ITPA hydrolyzes deoxyinosine triphosphate accumulated in nucleotide pools. ITPA deficiency causes premature death with growth retardation, heart failure and epileptic seizure. ITPA deficiency causes deoxyinosine accumulation in genome, thus inducing growth arrest dependent on MTHFR/PMS2 and p53.

Inborn errors and inborn signalings are impaired in Alzheimer disease (AD) brain, and thus impaired glucose metabolism and mitochondrial dysfunction increase oxidative damage and enhance neurodegeneration. Human TFA expression in AD mouse brain effectively suppresses the mitochondrial dysfunction, thereby suppressing AD pathogenesis. Gene expression profiling in AD cortex demonstrates a link between amyloidosis and neuroinflammation.

Fosl is an immediate early gene induced by brain stress, promotes hippocampal neurogenesis, thus avoiding epilepsy or hippocampal atrophy. Fosl regulates C5OR1 expression in microglia thus controlling neuro-immunomodulation. Fosl regulates galectin-1 expression in neural stem cells and astrocyte and its deficiency results in impaired neurogenesis. Galectin-1 is involved in axonal swelling of motor neurons in amyotrophic lateral sclerosis.

■Major Recent Publications