General Summary of Division of Molecular Pathology

Our main research interest is to clarify how cells recognize DNA damage and transduce signals to cell cycle control, DNA repair and apoptotic machineries. To achieve this goal, we are currently using a gene knockout approach in chicken DT40 cell lines.

A) Direct ATM activation by toxic metabolites

ATM (ataxia-telangiectasia mutated) is activated by a variety of noxious agent, including oxidative stress, and ATM deficiency results in an anomalous cellular response to oxidative stress. However, the mechanisms for ATM activation by oxidative stress remain to be established. We provide evidence that ATM is activated through the direct modification of its SH groups, independent of DNA damage, and this activation leads, downstream, to apoptosis.

B) c-ABL tyrosine kinase stabilizes RAD51 chromatin association

It is unclear how ABL tyrosine kinase mechanistically regulates Rad51 functions during homologous recombination repair (HRR). We show that phosphorylation on Tyr-315 by c-ABL is required for chromatin association of oligomerization-defective RAD51 mutants, but is insufficient to restore oligomerization, suggesting a new model for the regulation of early steps of HRR.

C) NBS1 is directly involved in ATR activation

Many recent studies have provided evidence for a role for Nbs1 as a damage sensor and activator acting upstream of ATM in cellular response to DSB. We provides evidence that Nbs1 but not the Mre11/Rad50/Nbs1 complex, plays unique role in ATR-mediated Chk1 phosphorylation and FANCD2 ubiquitination, induced by various DNA replication-stalling agents, such as cisplatin, pierisin, UV and hydroxyurea.

D) Cell cycle and chromatin control by nuclear small G protein Ran

The Ran GTPase system regulates the direction and timing of several cellular events, such as nuclear-cytosolic transport, centrosome formation, and nuclear envelope assembly in telophase. Most nuclear Ran localizes to chromatin, by both RCC1-dependent and independent mechanisms. Our results suggest that active Ran GTPase opens the heterochromatin structure at the telomere in yeast.

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