THE WISTAR INSTITUTE

Previous Projects and Past Accomplishments by the Nishikura lab

Identification of ADAR Genes and Characterization of A-to-I RNA Editing Mechanisms

The Nishikura laboratory identified and cloned the first ADAR gene family member, ADAR1. This led to the cloning of human and rodent ADAR2 and ADAR3 genes and eventually to the identification of other vertebrate and invertebrate ADAR family genes. The Nishikura group conducted extensive biochemical studies on the molecular mechanism of ADAR action, carried out mutagenic analysis of ADAR1 and identified critical amino acid residues involved in the formation of the catalytic center, and demonstrated the requirement of homodimerization of ADAR1 and ADAR2 for their enzymatic activity. More recently, the Nishikura laboratory participated in global screening of A-to-I RNA editing sites in human, primate, and mouse transcriptomes as a multi-group joint effort. The study revealed many millions of editing sites, mostly in non-coding regions that contain the repetitive elements *Alu* and *LINE*.

Requirement of ADAR1 for Embryo Development

The Nishikura laboratory created and characterized ADAR1 null mutant mice and demonstrated that inactivation of ADAR1 results in defective erythropoiesis, massive apoptosis, and death of ADAR1 null embryos, revealing the requirement for ADAR1 in embryonic development. ADAR1 hyper-edits *Alu* dsRNAs and thereby suppresses aberrant activation of interferon signaling pathways and consequent apoptosis.

Biological Significance of microRNA Editing

The Nishikura laboratory investigated A-to-I RNA editing of microRNAs (miRNAs). We have shown that miRNA primary transcripts are subject to A-to-I RNA editing and demonstrated that miRNA editing results in inhibition of miRNA processing at Drosha or Dicer cleavage steps or in suppression of RISC loading, or leads to expression of edited mature miRNAs that silence genes different from those targeted by the unedited miRNAs. Our findings revealed a previously unknown role for A-to-I RNA editing in the control of miRNA biogenesis as well as in the miRNA-mediated gene silencing mechanism.

Interaction Between RNAi and RNA Editing Mechanisms

The Nishikura laboratory unraveled the interaction between the RNA editing mechanism and the RNAi machinery. ADAR1 forms a complex via direct protein-protein interaction with Dicer, an RNase III gene family member involved in the RNAi mechanism. ADAR1 in the Dicer complex promotes pre-miRNA cleavage by Dicer and facilitates loading of miRNA onto RNA-induced silencing complexes, giving rise to an unsuspected stimulative function of ADAR1 on miRNA processing and RNAi mechanisms.