Investigation of Methylation at Site K117 in KRAS Protein

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RAS proteins are founding members of the RAS superfamily of GTPases and have been extensively studied as they play key roles in cell growth, differentiation, and survival. They function as molecular switches that cycle between an active GTP-bound state and an inactive GDP-bound state. Mutations in RAS cause disruptions in this cycle and have been identified in various types of human cancer and RASopathies. In addition to mutations, lysine post-translational modifications (PTMs), such as methylation, acetylation, and ubiquitination, can modulate RAS cycling and activity. We have recently identified novel lysine methylation sites in RAS, in collaboration with the Sasaki lab. One of the methylation sites, lysine 117, is strictly conserved in the RAS superfamily. Mutations at this residue have been linked to human disease and cancer. Thus, we hypothesize that methylation at lysine 117 may disrupt KRAS nucleotide cycling. To study the effects of methylation at lysine 117, novel alkylation strategies utilizing "methyl-lysine analogues" and enrichment strategies utilizing "methyl binding domains" are being developed to generate site specific KRAS methylation. To verify the successful methylation of K117, SDS-PAGE gel electrophoresis and mass spectrometric characterization are being implemented.