Mapping the KRAS Proteoform Landscape in Colorectal Cancer

Lauren M. Adams[1], Caroline J. DeHart[2], Byron S. Drown[1], Lissa C. Anderson[3], William Bocik[2], *et al.*

1. Northwestern University; 2. NCI-Frederick National Laboratory 3. National High Magnetic Field Laboratory

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The so-called "KRAS gene" is a gene that makes a protein (called "KRAS") that is involved in the regulation of cell division as a result of its ability to relay external signals to the cell nucleus. *Mutations in the KRAS gene are found in nearly 30% of all human tumors*. Post-translational modification (PTM) of KRAS is known to influence cell signaling. However, the relationship between KRAS PTMs and cancer-causing mutations remains unclear because high sequence identity (>90%) within KRAS' family of proteins greatly confounds traditional biochemical techniques.

MagLab users employed the MagLab's 21 tesla Ion Cyclotron Resonance mass spectrometer to measure intact KRAS protein molecules. This capability enabled the production of the first clarified map of the KRAS proteoform landscape in colon cancer tumors. A novel class of truncated KRAS proteoforms was identified that lack the C-terminal residue (C185*) and associated PTMs. The functional relevance of these proteoforms was further examined with live cell imaging. *Truncated KRAS exhibited striking differences in localization (see **Figure**), such that normal KRAS is localized in the cell membrane and truncated KRAS is distributed throughout the cell. Striking differences between truncated KRAS and normal KRAS were also found in the activation of the MAPK pathway*, a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell.

These findings indicate that cellular signaling pathways are far more complex and operate by mechanisms different than previously thought, information that will prove critically important for future development of anti-KRAS therapeutics that target membrane association in the battle against cancer.

Facilities and instrumentation used: 21 T Fourier-Transform Ion Cyclotron Resonance (21 T FT-ICR)

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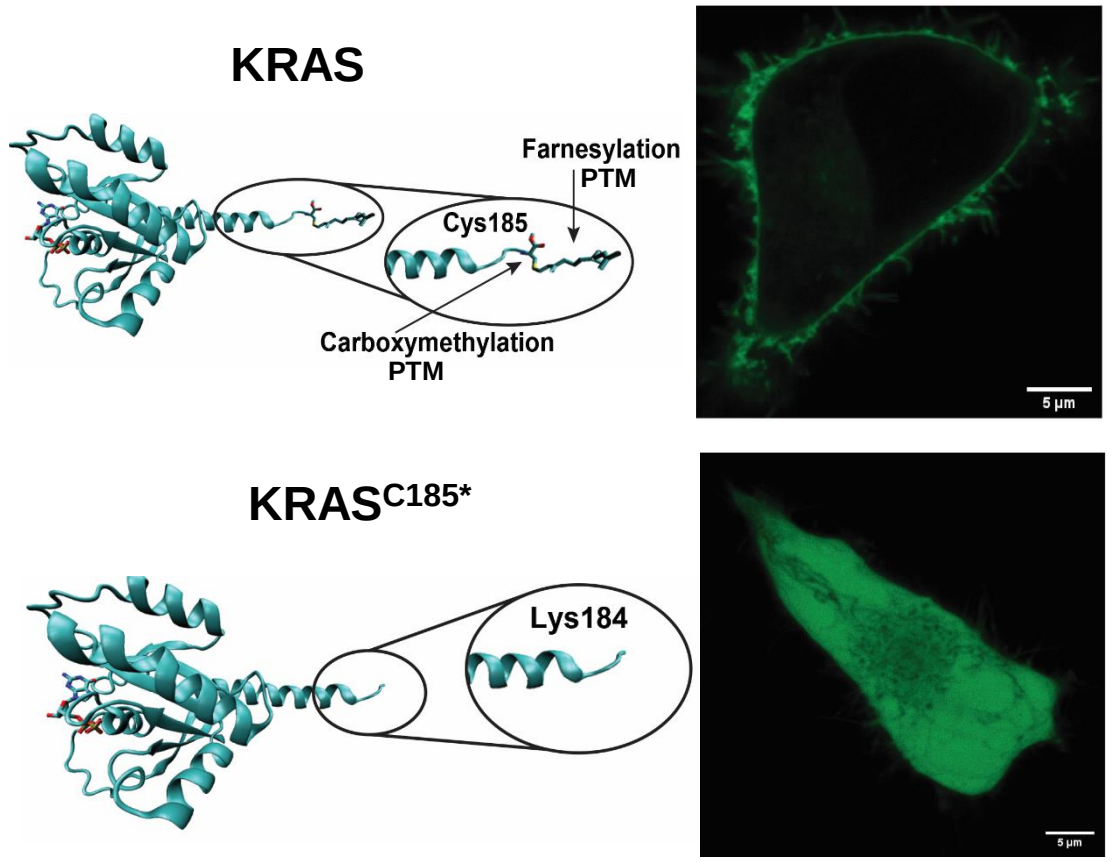

Figure: (Left) X-ray crystal structure of normal (KRAS4B) and truncated (KRAS4B^{C185*}) KRAS proteins. (Right) Images of two living cells that expressed fluorescent KRAS4B proteoforms. Normal KRAS (top) is localized tightly to the plasma membrane whereas truncated KRAS (bottom) is diffuse throughout the cell. (Image Credit: PDB 5TAR)