**Identifying resistant mechanisms to direct KRAS-inhibitors**

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Mutations in the KRAS oncogenic driver gene are frequently found in malignancies such as pancreatic, colorectal, and lung cancers. The replacement of the amino acid glycine at position 12 (e.g., G12C, G12D, G12V) is a frequent mutation that traps the protein in an active state and promotes uncontrolled cell proliferation. KRAS was regarded as "undruggable" for many years due to insufficient drug-binding pockets on the protein's surface. Recent breakthroughs, however, have resulted in the development of covalent inhibitors capable of selectively targeting the KRAS G12C mutation, like Sotorasib (AMG510) and Adagrasib (MRTX849) which are approved by the FDA due to their encouraging effects in clinical trials. The identification of selective inhibitors of other oncogenic KRAS alleles, such as the noncovalent KRAS-G12D inhibitor, MRTX1133, and a pan-KRAS-inhibitor drug, BI3706674 is also a promising next step in the treatment of KRAS-dependent malignancies. While these inhibitors have shown initial success, with some receiving FDA approval, their use frequently leads to resistance, the mechanisms of which largely remain unknown. To fill this essential research gap, we are employing our pre-clinical syngeneic mouse models and KRAS mutant allele-specific cell lines to investigate the underlying molecular processes of acquired resistance to direct KRAS allele-specific inhibitors. Using these murine syngeneic cell lines and human NSCLC cell lines, we have generated a panel of cell lines with acquired resistance to these direct KRAS inhibitors. To elucidate the molecular underpinnings of acquired resistance to direct KRAS inhibitors, we performed proteomic profiling of the sensitive and resistant cells by RPPA analysis. Among the several proteins whose expressions were altered in the KRAS-inhibitor-resistant cells, we identified the YAP/TEAD1 pathway that was commonly upregulated in the cells resistant to MRTX849 (G12Ci) or MRTX1133 (G12Di). We also observed significant re-sensitization of the resistant cells to the specific KRAS inhibitors upon co-treatment with a TEAD inhibitor, *in vitro.* Tumors from syngeneic mice that were implanted with KRAS inhibitor-resistant cells or their sensitive versions and treated with the specific KRAS inhibitors for 3-4 weeks, also exhibited increased nuclear YAP1 localization in the resistant tumors. We are currently performing in vitro and In vivo studies to understand the therapeutic efficacy of a TEAD inhibitor (VT107) in combination with KRASi (MRTX849 or MRTX1133) to either reverse or prevent resistance to the direct KRAS inhibitors. Successful completion of this research will help address the urgent need to understand ways to overcome resistance to KRAS inhibitors and increase their clinical efficacy.