Background

• Activating mutations in the extended RAS (KRAS, NRAS, and BRAF) genes confer resistance to anti-EGFR Ab (e.g., Cetuximab) therapy of colorectal cancer (CRC) patients

• Left sided RASWT tumors are incorporated in NCCN guideline as predictor of anti-EGFR Ab therapy

• However, only 40% - 45% RASWT patients have been found to respond to the therapy

• Identification of novel biomarkers is required for better stratification of the metastatic CRC patients for anti-EGFR Ab therapy

Objective

• Identification of transcriptomic determinants for predicting and understanding the primary resistance mechanisms to anti-Cetuximab) therapy of colorectal cancer (CRC) patients1

• Identification of novel biomarkers is required for better stratification of the metastatic CRC patients for anti-EGFR Ab therapy

• However, only 40% - 45%

• Left sided CRC patients

• Activating mutations in the extended RAS (KRAS, NRAS, and BRAF) genes confer resistance to anti-EGFR Ab (e.g., Cetuximab) therapy of colorectal cancer (CRC) patients1

Materials and Methods

• Gene expression datasets of two retrospective clinical cohorts and two pre-clinical cohorts were downloaded from Gene Expressions Omnibus

• Gene expression datasets of two retrospective clinical cohorts and two pre-clinical cohorts were downloaded from Gene Expressions Omnibus

• Transcriptomic datasets used in this study

• CMS may be used as biomarker for classifying RASWT & MSS CRC patients for anti-EGFR antibody therapy

• Both left and right-sided RASWT/MMSS/CMS2 tumors may be benefitted from cetuximab therapy

• RAS-MAPK independent signaling pathways may regulate primary resistance to anti-EGFR antibodies

Results

• Percentages of clinically benefited CMS2 RASWT patients (92% and 68%), PDX models (84%), and sensitive CRC cell lines (60%) were highest in both clinical and preclinical cohorts

• Median PFS (7.47 months and 3.06 months) of CMS2 RASWT patients in two clinical cohorts were higher than the other CMS subclasses

• Response to anti-EGFR antibody therapy was higher for left-sided (DCR: ~83% (58/70) vs 62.5% (58/93)) compared to right-sided CRC tumors

• However, after controlling for CMS, DCR for right and left sided CMS2/RASWT tumors were similar

• MTORC1, E2F, and MYC pathway gene-sets were found significantly enriched (FDR < 0.3) in the cetuximab refractory CMS2 RASWT samples of both clinical and preclinical cohorts

• Single sample GSEA revealed that MTORC1, E2F, and MYC pathways were heterogeneously active (NES > 1) in the cetuximab refractory RASWT samples

• HT55 and SNUC1 cell lines were resistant to cetuximab (IC50 > 10µg/ml)

• Single agent inhibitors of E2F (AZD7762 and MK-8776), mTOR (Everolimus), and MYC (JQ1) pathways could not inhibit HT55 and SNUC1 cell growth (IC50 > 10µM)

Conclusions

• CMS may be used as biomarker for classifying RASWT & MSS CRC patients for anti-EGFR antibody therapy

• Both left and right-sided RASWT/MMSS/CMS2 tumors may be benefitted from cetuximab therapy

• RAS-MAPK independent signaling pathways may regulate primary resistance to anti-EGFR antibodies

References


Funding

This work was supported by the National Cancer Institute (2017CA121000 and CA232446 to J.P.S., J.P.S., and A.C. Chmiel in Cancer Research); the Cancer Prevention & Research Institute of Texas (RP180013 to J.P.S., J.P.S., and A.C. Chmiel in Cancer Research); and the Col. Daniel Connolly Memorial Fund. This study was also supported by the Colorectal Cancer Moonshot Program and SPORRE program (RPC20110701) of The UT MD Anderson Cancer Center.

Acknowledgement

We acknowledge the support of the High-Performance Computing for research facility at The University of Texas MD Anderson Cancer Center for providing computational resources that contributed to the research results reported in this work.