Abstract # 1231

Prognostic and predictive drug-induced gene signatures for colorectal cancer patients personalized based on p53 status and treatment with FOLFOX, 5-FU, oxaliplatin, or irinotecan

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Abstract

Metastatic colorectal cancer (CRC) is a deadly disease with a 13% survival rate. CRC is often treated with chemotherapeutic agents 5-fluorouracil, irinotecan, and oxaliplatin, but predictive biomarkers are limited. We hypothesized that tumor expression of genes related to extent of drug exposure, stratified by p53 status, is associated with clinical outcomes on these regimens. To this end, we evaluated the prognostic and predictive significance of genes within p53-independent, p53-dependent, pan-drug, and drug-specific gene signatures established in CRC cells treated with 5-FU, irinotecan, or oxaliplatin. CRC patient samples were analyzed by DNA/RNA next-generation sequencing at Caris Life Sciences, and real-world survival outcomes were inferred from insurance claims data and Kaplan-Meier estimates. Samples with benign or no *TP53* mutations detected (wt) (n=2983) or *TP53* loss-of-function (LOF) mutations (n=6229) were stratified (high/low) by median expression of signature genes for comparison. Overall prognostic and predictive values in response to 5-FU, irinotecan, or oxaliplatin, regardless of line of therapy or concurrent therapies, or first-line FOLFOX were evaluated to estimate the contribution of each drug. From signatures established in CRC cell lines, a prognostic effect was observed for genes in p53 wt (n=19) and LOF (n=22) subgroups, with a similar survival effect observed for several genes (n=16). Both prognostic and non-prognostic gene expression had a significant effect on survival outcomes following specific drug treatments. Predictive genes included BTG2, a p53-dependent gene upregulated by 5-FU, irinotecan, and oxaliplatin in CRC cells that predicted better outcomes when expressed at high levels in p53 wt patients. Several genes in drug-specific signatures were predictive in a drug-specific manner including RABGAP1L and RAD51B (irinotecan), and SAT1 (oxaliplatin), suggesting their particular relevance for patients receiving these drugs. For some genes such as RABGAP1L and RAD51B, drug treatment downregulated gene expression but high expression predicted better survival in patients, suggesting benefit of combination therapy to limit such effects. From a real-world cohort of p53 wt and LOF CRC tumors, we demonstrate the prognostic and predictive potential of candidate gene expression in response to commonly used chemotherapeutics. Accompanying data on drug regulation of predictive genes provides valuable information in evaluating clinical impact of pan-drug or drug-specific mechanisms. Future directions include associations with clinically relevant features (microsatellite instability, tumor sidedness, and age), establishment of multi-gene signatures to improve clinical utility, and evaluation of other regimens including FOLFIRI and FOLFOXIRI.

Results

Signature	# of genes	Genes with prognostic or predictive power in CRC
Pan-drug	18	
p53-dependent	17	*BTG2, SESN1*
p53-independent	1	
5-FU-specific	82	
p53-dependent	13	*HIST1H2BG, HIST2H4A, RASSF6, ZNF658*
p53-independent	69	*CCNE1, DTL, HIST1H1C, HIST1H2BF, HIST2H3A, KIRREL1*
Oxaliplatin-specific	63	
p53-dependent	22	*C3orf14, HOXB8, SUSD2, TDGF1, TGM2*
p53-independent	41	*EGR1, FOS, SAT1*
Irinotecan-specific	175	
p53-dependent	55	*DRAM1, OR51B2, RAD51B, SUPT3H, TLR3*
p53-independent	120	*CCNB1, MPZL2, MYB, RABGAP1L, STAT4*

Table 1. Treatment of CRC cells with chemotherapy reveals prognostic and predictive gene signatures. CRC cells treated with 5-FU, oxaliplatin, or irinotecan and differentially expressed genes were determined using Clariom D microarrays. Prognostic or predictive power of each signature was evaluating using Caris Life Sciences CODEai database.

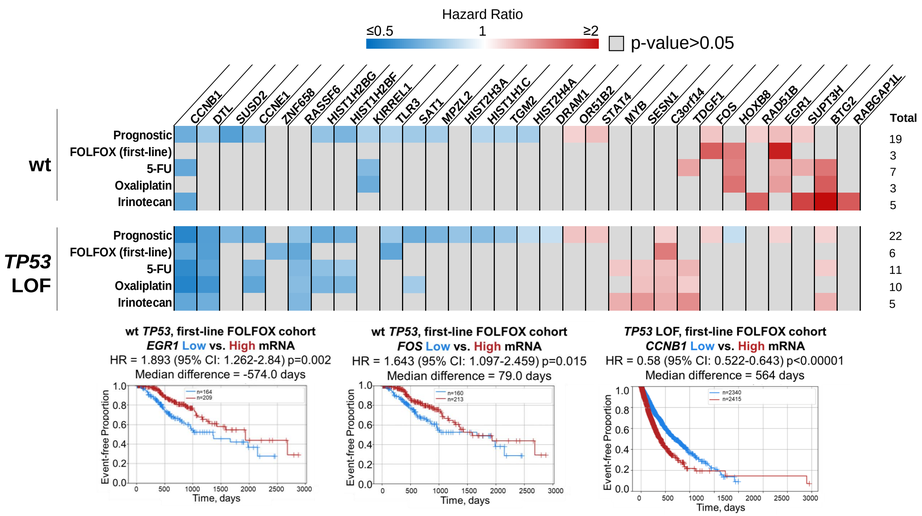

Figure 1. Low versus high expression of drug-induced signature genes impact on CRC patient outcomes. Genes with the strongest independent predictive value (highest/lowest HR) include EGR1 and FOS in the wild-type p53 cohort and CCNB1 in the p53 LOF cohort.

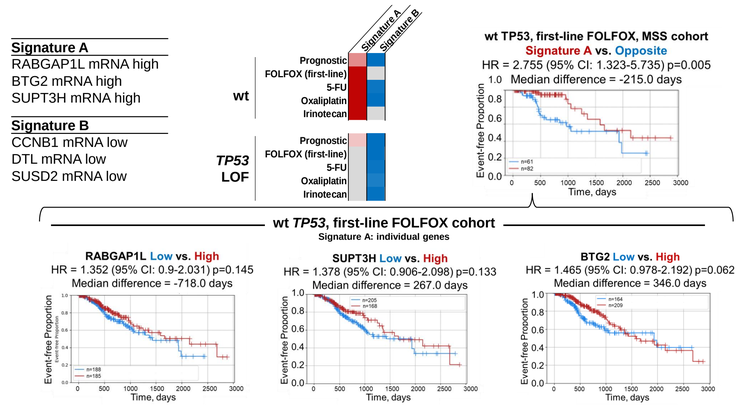

Figure 2. Gene expression signatures have enhanced predictive power compared to individual genes. High expression of each gene in Signature A has no independent predictive power, but when combined predict response to FOLFOX in patients with wild-type p53 tumors. A similar effect was observed for Signature B.

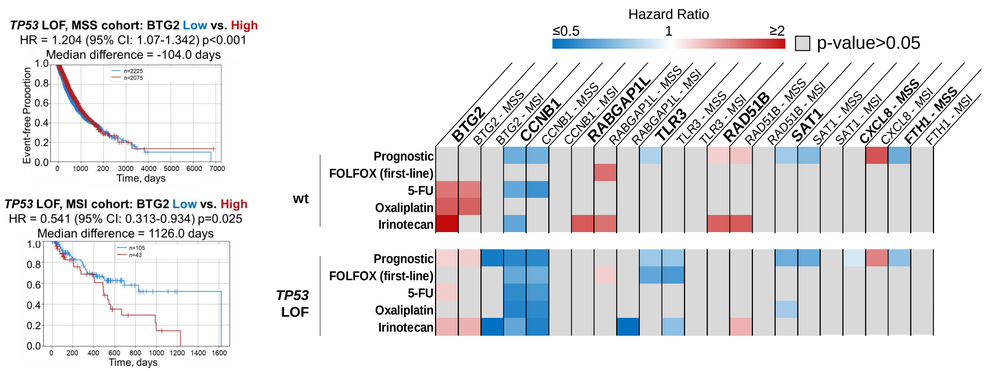

Figure 3. MSS/MSI status of CRC tumors may impact the effect of chemotherapy-induced genes on patient outcomes. High expression of BTG2 predicts better prognosis in patients with MSS p53 LOF tumors, but low expression predicts better prognosis in patients with MSI p53 LOF tumors. CXCL8 is only prognostic for patients with MSI tumors. Effects of other transcripts such as CCNB1, RABGAP1L, TLR3, RAD51B, and SAT1 on patient outcomes were consistent across MSS/MSI patient cohorts.

Conclusions

Tumor expression of genes related to extent of drug exposure can predict outcomes after chemotherapy treatment.

- High EGR1 and FOS mRNA independently predict response to FOLFOX in patients with wild-type p53 tumors.
- Low CCNB1 mRNA correlates with good prognosis of CRC patients with tumors harboring *TP53* LOF mutations.
- Gene signatures may demonstrate enhanced predictive ability as compared to individual transcript effects.
- MSI status impacts the predictive of BTG2.

Future Directions

- Further evaluation across age, tumor sidedness, age, and additional treatment regimens.
- Evaluate predicted immune cell infiltrate across patient cohorts and correlate with clinical outcomes.