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Multiscale genomic, transcriptomic and proteomic analysis of colorectal cancer cell lines to identify novel biomarkers

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Introduction: Resistance to colorectal cancer (CRC) therapies is a significant cause of treatment failure. We used an in vitro model to identify novel therapeutic targets, explain mechanisms of carcinogenesis and resistance to therapy, and ultimately aid patient stratification for therapy.

Methods: A panel of 15 CRC cell lines was profiled by comparative genomic hybridisation, gene expression profiling, reverse phase protein array analysis, and chemosensitivity assays with respect to 5fluorouracil, oxaliplatin, and BEZ235. As proof of concept, fluorescence in situ hybridization and automated quantitative protein analysis were employed to investigate a candidate biomarker in a CRC patient cohort (n=118).

Results: Integration of frequently amplified regions with gene expression data resulted in 47 significantly correlated genes, suggesting that at least 7% of the genes found in the frequently gained regions might be regulated, at least in part, by copy number changes. 20/47 of these genes were associated with treatment responses; for example, PDCD6 was differentially expressed with respect to all three treatments. The FISH scores of TRIB1 (a frequently amplified gene and candidate biomarker) and MYC (r^2=0.783, p=0.0001) were highly correlated, consistent with coamplification.

Conclusion: This multiscale analytical approach generated candidate predictive biomarkers for responses to important CRC therapies. This approach is valuable for understanding the mode of action of different treatments and guiding personalised therapy. We also show, for the first time, that TRIB1 is coamplified with MYC in a proportion of CRCs and may be an attractive target for intervention in this group of patients.

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