Establishment and characterization of models of chemotherapy resistance in colorectal cancer: Towards a predictive signature of chemoresistance

Current standard treatments for metastatic colorectal cancer (CRC) are based on combination regimens with one of the two chemotherapeutic drugs, irinotecan or oxaliplatin. However, drug resistance frequently limits the clinical efficacy of these therapies. In order to gain new insights into mechanisms associated with chemoresistance, and departing from three distinct CRC cell models, we generated a panel of human colorectal cancer cell lines with acquired resistance to either oxaliplatin or irinotecan. We characterized the resistant cell line variants with regards to their drug resistance profile and transcriptome, and matched our results with datasets generated from relevant clinical material to derive putative resistance biomarkers. We found that the chemoresistant cell line variants had distinctive irinotecan- or oxaliplatin-specific resistance profiles, with non-reciprocal cross-resistance. Furthermore, we could identify several new, as well as some previously described, drug resistance-associated genes for each resistant cell line variant. Each chemoresistant cell line variant acquired a unique set of changes that may represent distinct functional subtypes of chemotherapy resistance. In addition, and given the potential implications for selection of subsequent treatment, we also performed an exploratory analysis, in relevant patient cohorts, of the predictive value of each of the specific genes identified in our cellular models.

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