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Abstract

Colorectal cancer – clinical and translational research

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Introduction: From having been "a simple one drug (ie 5-Fluorouracil) disease", drug treatment of colorectal cancer (CRC) is now more complex from the introduction during the last decade of new drugs, including two targeted antibodies. Although this has lead to improved efficacy, many patients still get futile treatment that will only give adverse effects and no benefit. This is problematic from an ethical perspective but also from a health-care budget point of view. Thus, there is need both for new drugs with better CRC activity and predictive tests to select optimal drugs for the individual patient.

Overall aims: To develop and validate predictive tests for individualized treatment of CRC and to identify new drugs with improved efficacy against CRC.

Key methods available: Clinically relevant in vitro models based on fresh tumour tissue obtained at primary surgery for colon cancer and cytoreductive surgery for peritoneal carinomatosis. Affymetrix gene-expression microarray analysis and bioinformatics, short-term 384-well tumour cell drug sensitivity test, the Fluorometric Microculture Cytotoxicity Assay (FMCA). Human CRC cell lines for drug screening and mechanistic evaluation.

Examples of results and ongoing research: Sensitivity to standard and experimental cancer drugs varies considerably between tumour cells isolated from individual patients, supporting the concept of treatment individualization. Using patient CRC tumour cells as screening target for commercial drug libraries, a drug with seemingly selective activity against CRC has been identified. The multi-target tyrosine kinase inhibitor sorafenib circumvents resistance to the EGFR inhibiting antibody cetuximab in patient samples of tumour cells. Similarly, the mTOR inhibitor rapamycin shows additive – synergistic effects with the standard drugs irinotecan and oxaliplatin. The prognostic and predictive accuracy of gene expression signatures derived from a panel of CRC cell lines and patient tumour tissue are investigated. The importance of patient derived cancer associated fibroblasts and reactive tumour stroma for drug and radiation sensitivity are investigated in the FMCA in cell lines and patient tumour cells as well as by gene expression analysis.

Conclusions: Drug sensitivity testing and gene-expression analysis of patient CRC tumour cells and tissue seemingly provides information predictive for drug sensitivity and identification of new drugs with promising activity against CRC.