Phenotypic analysis of primary colorectal cancer to inform the management of metastatic disease

Paul Sutton
CR(UK) Clinical Research Training Fellow
Disclosures

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• Recent personal awards from ESSO, BASO, and RCS (England)
• Member of NICE standing committee for updates to guideline CG131 (Colorectal Cancer)
Priorities in Colorectal Cancer Research: Recommendations From the Gastrointestinal Scientific Leadership Council of the Coalition of Cancer Cooperative Groups


• Demographics and screening
• Prevention
• Detection and diagnosis
• Adjuvant treatment for rectal cancer
• Adjuvant treatment for colon cancer
• Advanced colorectal cancer and novel therapies
Biopsy of resectable colorectal liver metastases causes tumour dissemination and adversely affects survival after liver resection

O. M. Jones, M. Rees, T. G. John, S. Bygrave and G. Plant

Department of Hepatobiliary Surgery, North Hampshire Hospital, Aldermaston Road, Basingstoke RG24 9NA, UK
Correspondence to: Mr M. Rees (e-mail: myrddinrees@btconnect.com)

• Retrospective review of prospectively collected data
• 90 of 598 patients received pre-operative needle biopsy
• Radiological evidence of tumour deposit in cutaneous tract in 19%
• No difference in 30 day mortality
• 4 year survival 32.5% vs 46.7% (p=0.008)
PRIMARY LESION
Genomic Proteomic

METASTATIC LESION
Therapeutic management

Predictive markers of therapeutic response
Proteomic profiling of primary and metastatic tumour - iTRAQ

Extract samples

Label proteins with iTRAQ reagents

Mass spectrometry

Normal liver

Liver metastasis

Normal colonic mucosa

Primary tumour

Proteomic profiling of primary and metastatic tumour - iTRAQ

Extract samples

Label proteins with iTRAQ reagents

Mass spectrometry

MS/MS spectrum

identification

quantification

Normal liver

Liver metastasis

Normal colonic mucosa

Primary tumour
Histopathological Response

FIBROSIS

NECROSIS

TUMOUR

Pathologic Response to Preoperative Chemotherapy: A New Outcome End Point After Resection of Hepatic Colorectal Metastases

Proteomics

- 5768 proteins identified
- 1814 present in all samples
- Analysis
SHORT COMMUNICATION

Cells deficient in the base excision repair protein, DNA polymerase beta, are hypersensitive to oxaliplatin chemotherapy

J Yang¹, J Parsons¹, NH Nicolay¹, S Caporali², CF Harrington³, R Singh⁴, D Finch¹, S D’Atri², PB Farmer⁴, PG Johnston³, WG McKenna¹, G Dianov¹ and RA Sharma¹

¹Cancer Research UK–Medical Research Council Gray Institute for Radiation Oncology & Biology, University of Oxford, Oxford, UK; ²Laboratory of Molecular Oncology, Istituto Dermanopatico dell’Immacolata-IRCCS, Rome, Italy; ³Trace Element Laboratory, Centre for Clinical Science and Measurement, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey, UK; ⁴Cancer Biomarkers and Prevention Group, Biocentre, University of Leicester, Leicester, UK and ⁵School of Medicine, Dentistry and Biomedical Sciences, Institute of Health Sciences, Queen’s University Belfast, Belfast, UK
Proteomic analysis of primary tumour and colonic mucosa
Proteomic analysis of primary tumour and colonic mucosa

Heatmap

Cytoskeletal remodelling

METACORE pathway analysis
Principal Component Analysis
Differentially Expressed Proteins

- No proteins significantly different between primary and metastatic tumours
- 25 proteins significantly differentially expressed between primary and normal colon
- 53 proteins significantly differentially expressed between liver metastases and normal colon
Predictors of Response

Responder vs Non-responder

Metastatic (27) 22 5 165 Primary (170)
## Predictors of Response

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>HLA class II histocompatibility antigen, DRB1-4 beta chain</td>
<td>Binds peptides derived from antigens that access the endocytic route of antigen presenting cells (APC) and presents them on the cell surface for recognition by the CD4 T-cells.</td>
</tr>
<tr>
<td>NAD(P)H dehydrogenase [quinone] 1</td>
<td>The enzyme apparently serves as a quinone reductase in connection with conjugation reactions of hydroquinons involved in detoxification pathways as well as in biosynthetic processes such as the vitamin K-dependent gamma-carboxylation of glutamate residues in prothrombin synthesis.</td>
</tr>
<tr>
<td>Sterol 26-hydroxylase, mitochondrial</td>
<td>Catalyzes the first step in the oxidation of the side chain of sterol intermediates; the 27-hydroxylation of 5-beta-cholestane-3-alpha,7-alpha,12-alpha-triol. Has also a vitamin D3-25-hydroxylase activity.</td>
</tr>
<tr>
<td>Lambda-crystallin homolog</td>
<td>The uronate cycle functions as an alternative glucose metabolic pathway, accounting for about 5% of daily glucose catabolism. This protein catalyzes the dehydrogenation of L-gulonate into dehydro-L-gulonate in the uronate cycle. The enzyme requires NAD(H) as a coenzyme, and is inhibited by inorganic phosphate.</td>
</tr>
<tr>
<td>Brefeldin A-inhibited guanine nucleotide-exchange protein 1</td>
<td>Promotes guanine-nucleotide exchange on ARF1 and ARF3. Promotes the activation of ARF1/ARF3 through replacement of GDP with GTP. Involved in vesicular trafficking. Required for the maintenance of Golgi structure; the function may be independent of its GEF activity. Required for the maturaion of integrin beta-1 in the Golgi. Involved in the establishment and persistence of cell polarity during directed cell movement.</td>
</tr>
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</table>
A potential therapeutic target?

MTS assay SW480 cells 72hr incubation

- NQO1 knockdown
- DMSO control

Percentage viability (%)

Log concentration irinotecan (μM)
Summary

• We are dependent upon biological information from the primary colorectal tumour to inform management of metastatic disease
• This information is highly predictive of the metastatic phenotype
• Putative pathways which may be implicated in carcinoma progression have been identified
• NQO1 is a potential response biomarker and therapeutic target
Supervisors
Dan Palmer
Chris Goldring
Hassan Malik
Dale Vimalalchandran

The Rest of the Team
Roz Jenkins
Jane Hamlett
Jithesh Puthen
Neil Kitteringham
Inter-Tumoural Variation

1 2 3 4 5 6 7 8 9 10

CES 1

Actin

Inter-Metastatic Variation

1 2 3

CES 1