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The identification of putative biomarkers of radioresistance in rectal cancer tissue using antibody microarray

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Purpose/Objective: Despite significant research input aiming to improve therapy regimens, rectal cancer remains as one of the cancers with significant morbidity rates. Radiotherapy has been shown to lower 10-year local recurrence by approximately 50%. A substantial number of rectal tumours fail to respond to radiotherapy which not only presents a barrier for effective cancer treatment bu also means that those patients with therapy resistant tumours endure the harmful side effects of radiotherapy for no therapeutic gain. Therefore, it is important to identify biomarkers capable of predicting a tumour's response to radiotherapy prior to treatment which can improve therapy outcomes. The aim of this study is to identify putative protein biomarkers of radiotherapy resistance using rectal cancer tissue biopsy samples by employing comparative proteomic tools. Ultimate aim is to translate these biomarkers into an assay panel for routine cancer screening aiding the personalisation of cancer treatment.

Materials and Methods: Following ethical approval (Sheffield REC ref 10/H1308/37), two pairs of pre-treatment rectal cancer biopsy samples (radioresistant versus radiosensitive) were investigated using antibody microarray to identify differentially expressed proteins (DEPs) involved in mediating radiotherapy resistance. Data obtained from the experiments were subjected to data mining using Ingenuity Pathway Analysis (IPA) which mapped these DEPs onto their most relevant canonical signalling pathways.

Results: The antibody microarray analysis of the clinical samples revealed 25 DEPs and 46 DEPs from the first and the second experiment, respectively. The IPA analysis of these combined generated 253 canonical pathways. Amongst these, the most interesting pathways included p53 signalling (12 DEPs mapped), death receptor signalling (7 DEPs mapped), apoptosis signalling (5 DEPs mapped) and EGF signalling (4 DEPs mapped). Radiotherapy is known to initiate cellular apoptosis via the intrinsic (mitochondrial) apoptotic pathway. However, the identification of some regulatory proteins involved in the extrinsic pathway (death receptor) apoptotic pathway (**Figure 1**) has revealed a potential link between radiotherapy and this pathway.

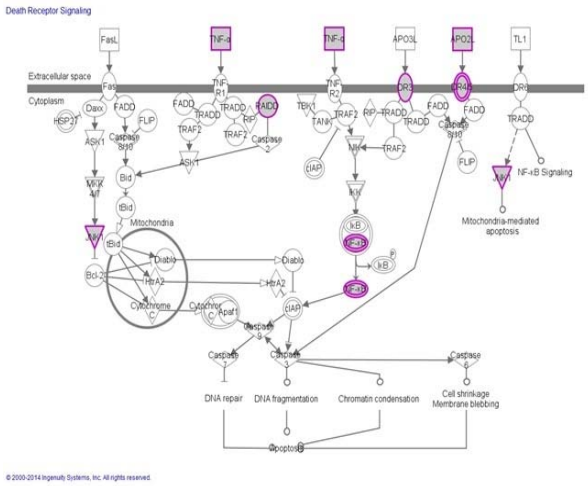

Figure 1: Death Receptor Signalling

A total of 7 DEPs were mapped onto the Death Receptor Signalling pathway, namely CRADD, TNFRSF25, MAPK8, TNFSF10, NFKB1, TNFRSF10A and TNF.

Conclusions: Antibody microarray analysis of rectal cancer biopsy samples has enabled the identification of a number of DEPs which may be involved in mediating response to radiotherapy. However, further confirmation with western blotting and validation with immunohistochemistry are required before such biomarkers can be introduced into routine clinical management of cancer patients.

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Validation of a rectal cancer outcome prediction model in routine Chinese patients

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Purpose/Objective: The risk of local recurrence, metastases and overall survival of locally advanced rectal cancer after preoperative chemoradiation and curative surgery can be estimated by prediction models and visualized using nomograms, which have been trained and validated in European clinical trial populations. This study aims to validate these prediction models in a routine clinical Chinese cohort.

Materials and Methods: From 2006 to 2012, clinical data of 277 consecutive locally advanced rectal adenocarcinoma patients treated with preoperative chemoradiation and curative surgery from a single Chinese Cancer Center, were retrospectively collected and used for external validation. Concordance index (C-index) and calibration curves were used to assess the performance of the previously developed