**Predictive response biomarkers in rectal cancer neoadjuvant treatment**

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**1. ABSTRACT**

Locally advanced rectal cancer (RC) treatment is a challenge, because RC has a high rate of local recurrence. To date preoperative chemoradiotherapy (pCRT) is widely accepted as standard protocol of care for middle-low RC, but complete tumour response rate ranges from 4 to 44% and 5-year local recurrence rate is 6%. Better understanding of molecular biology and carcinogenesis pathways could be used both for pre-neoplastic lesions and locally recurrence diagnosis, and for tumour response prediction to therapy. Circulating molecules, gene expression and protein signature are promising sources to biomarker discovery. Several studies have evaluated potential predictors of response and recently, cell-free Nucleic Acid levels have been associated to tumour response to neoadjuvant therapies. Alternative method is the serum or plasma proteome and peptidome analysis. It may be ideally suited for its minimal invasiveness and it can be repeated at multiple time points throughout the treatment in contrast to tissue-based methods which still remain the most reliable and specific approach. Many studies have analyzed preoperative rectal tissue prognostic factor, but data are controversial or not confirmed.

**2. INTRODUCTION**

Surgery is the primary treatment for rectal cancer (RC). In locally advanced stages of the disease, surgery is usually supported by radiation or a combined therapy to reduce risk of local recurrence (1-5). Preoperative chemoradiotherapy (pCRT) is particularly attractive for the following reasons: 1) *a priori* not curatively resectable tumours can be downsized to achieve the tumour cell-free surgical margins (R0 resection); 2) preoperative treatment reduce tumour burden and increase the possibility for preservative surgery; and 3) skip postoperative clinical complications precluding subsequent adjuvant chemoradiotherapy. The chemotherapeutic drug commonly used in RC treatment is 5-fluorouracil (5-FU), which arrests DNA synthesis and causes interruption of the duplication of the cell. Current standard treatment includes the administration of ionizing radiation for 45-50.4 Gy in 25-28 fractions associated with 5-FU. After pCRT the complete pathological response is approximately 20%, whereas in 20 to 40% of patients the response is poor or absent (6, 7). This poses a considerable clinical dilemma because patients with *a priori* resistant tumour could spare radiations or DNA-damaging exposure treatments with
substantial adverse effects and so undergo to surgery without delays. In this frame, the identification of predictive markers of cancer response to pCRT is surely of significant clinical relevance. Several studies have been performed in this way, but findings are still unclear and controversial (8, 9): patient selection, sample size, study design, treatment modality and tumor response definitions are the major discrepancies and the only accepted marker is Carcinoembryonic Antigen (CEA) (10, 11).

Here, we summarized some approaches used for tumor response prediction through the study of genomics, gene expression (by microarray technology) and the description of the circulating peptidome (by mass spectrometry analysis) and cell-free nucleic acids. In our opinion, a systemic approach aiming at integrating different data (e.g. gene expression data with proteins/peptides biomarkers and molecular/histological determinants of cancer staging and progression) has the potential to provide high content information about patients' diagnosis and prognosis.

3. TISSUE-BASED BIOMARKERS ANALYSIS

Gene expression signatures found in different study has limited overlap of genes and results of testing published on different tumor cohorts is useless. Results are conflicting and still remain inconclusive both for technical and clinical differences. Collection of tumour biopsy before the treatment, usually carried out during colonoscopy or rectal exploration, rarely give enough tumour material. The lack of standardized clinical management rules, differences on the sample manipulation (collection, storage and processing) and differences in result evaluation make difficult a comparison between data. Furthermore, several recent publications have provided evidence of tumour microenvironment involvement in modulating tumour response to chemoradiotherapy. This is due to molecular factors expressed by neighbouring cells involved in tumour resistance (chemotactic molecules, growth factors, death factors) and regulating immune system cells recruitment. Moreover, irradiated cells can induce mutagenic response in neighbouring cells not directly traversed by particle radiation by gap junctions (12-15).

3.1 DNA alterations: polymorphisms

To date pharmacogenetics plays an important role in cancer chemotherapy and prognosis can be explained with genetic background or individual influence (16).

In the term of associations between cancer prognosis and genetic markers, DNA alterations are still regarded as great challenges in the field of tumour chemotherapy sensitivity. A widely used antineoplastic agent, oxaliplatin, acts as inhibitor of cell replication by DNA damage or macromolecular adducts formation. In colorectal cancer (CRC), the success of oxaliplatin chemotherapy is remarkable whether in advanced colorectal cancer (aCRC) or metastatic colorectal cancer (mCRC) (17, 18). However, drug resistance related to genetic variations is one of the main causes of treatment failure and the evaluation of pharmacogenetic markers may benefit cancer patients to individual prognosis (18-21).

In order to explore the influence of genetic variation by oxaliplatin-based chemotherapy XRCC1 (Arg399Gln) and GSTP1 (Ile105Val) polymorphisms have been widely studied on prognosis of colorectal cancer, but those conclusions were inconsistent each other (21-24). The XRCC1 Arg399Gln polymorphism has been considered to increase chemotherapeutical sensitivity, but reducing the function of DNA repair, it also leads to increase DNA damage and mutation induction (25). Indeed cells with a switch from arginine to glutamine, such as the Arg/Gln or Gln/Gln, show negative effect on the DNA repair activity. Theoretically, these cells would have larger amounts of DNA damage, and therapeutic effect of oxaliplatin-based chemotherapy should be turn better (26). Additionally, a proper tumour description (e.g. tumour classification and stages) may be another factor accounting for those inconsistent results, both for CRC and mCRC (20).

However, results showed tumour response rate is significantly lower in patients which carried Arg/Gln+Gln/Gln than Arg/Arg polymorphisms in XRCC1. For these patients, a stable or progressive disease was regarded as non-responsive event, which is opposite to the previous study (26) but is consistent with others (24, 27). Other genetic variations of XRCC1 may be also attributable to the prognosis, such as the linkage disequilibrium with other genes with similar mechanisms. The polymorphism combination with each other could result in significant different effect or contribute to strengthen the XRCC1 Arg399Gln polymorphism mechanism (25, 20). Platinum-based agents are commonly used in several solid tumours with successful (21). However, genetic variations influence the tolerance to drug-dependent DNA adducts, DNA repair protein complex function and drug metabolism that lead to negative effect on prognosis (18, 19, 25, 28).

3.2 Gene expression

Gene expression signatures by microarray technology may help to predict tumour response after pCRT. Recent studies have shown gene expression profiles of tumour cells discriminating responders and non-responders patients underwent neoadjuvant or adjuvant chemotherapy (29-32). However, several papers have been focused on the evaluation of gene expression profiles on RC biopsies after neoadjuvant therapy, but some authors using different treatment protocols: one using radiotherapy alone and two added Cetuximab to conventional pCRT, instead in other three works the study design shows small number of cases to draw firm conclusions (33-38). Each study provided classifiers with high predictive accuracy but a little overlap is observed between the gene lists. They predict similar outcomes when the same tissue type is carefully compared and only a handful of identical matches are evident. For example, in Agostini et al. (submitted), Rimkus et al. (37) and Kim et al. (38) are similar studies, about enrolling of patients, treatment protocol and technology to investigate.
response to pCRT in RC and no predictor gene is in common. Validation some common genes in previously published data highlights conflicting findings in studies on the same disease. Probably this occurs for various reasons such as: different technical methods of tissue preparation, different type of platform used or expression profiling technologies, different workplaces and different methods of data analysis (39).

Large-scale meta-analysis techniques remain the best way to identify gene sets associated with response to therapy and disease free survival by the integration of results of retrospective analysis and the de-novo analysis from raw data.

Recent advances in computational algorithms and computing power allows the analysis, management and use of large sets of genomic and proteomic information. Once statistically analyzed, results obtained might indicate treatment selection and predict patient outcome. In order to progress in this field, a deeper confidence in these classifiers must be established through repeated validations.

3.3 miRNA analysis

Mature miRNAs can interfere with protein expression in two ways: 1) in association with RISC (RNA-induced silencing complex) targets and cleaves mRNA, 2) or translational inhibition thought a imperfect complementarity sequence-dependent process, but the mechanism is still unknown (40). Excellent reviews describing the molecular biology of miRNAs have been published (41, 42). Here, we shall just summarize a few essential elements of miRNA involvement in tumour progression, treatment and outcome. Recently, the role of miRNA in drug resistance/sensitivity was realized.

In 2006, Nakajima et al. observed the expression level of miR-200c was significantly over-expressed in their colorectal tumour samples compared to the normal corresponding ones (43). Let-7g, which is known to target more than 200 mRNAs (including genes such as: RAS, cyclin D, c-myc and E2F transcriptional factors family), was over-expressed in tumour samples and was significantly associated with chemosensitivity to S-1-based therapy. Also, the expression of miR-181b (which is probably target miRNAs encoding genes such as cytochrome c, ECIP-1, MAPKPPKK1, TEM6, E2F5, GATA6, PP2B and eIF5A) was strongly associated with patients’ response to S-1 drug, but it is not significant for patient survival.

Rossi and colleagues demonstrated 5-FU can significantly change the expression levels of miRNAs in human colon carcinoma cell lines (HT-29 and HCT-116) (44). Quantitative Real-Time PCR revealed that 5-FU up-regulates 19 miRNAs, like miR-133a, whose targets are pro-apoptotic proteins (Bax and K-Ras), miR-147 and miR-27b, and down-regulates 3 miRNAs like miR-200b and miR-210, which were associated to tumour cell proliferation inhibition and increase target cell apoptosis. A potential target gene of miR-200b is the Tyrosine-protein phosphatase non-receptor type 12 (PTPN12), which can bind dephosphorylated and inactivated products of oncogenes such as c-Abl, Src or Ras.

In another work, Svoboda et al. evaluated miRNAs expression in tumour biopsies from patients with RC before and two weeks after starting preoperative capecitabine chemoradiotherapy (45). They observed post-therapy increase levels of miR-125b and miR-137: miR-125b up-regulation seems down-regulate the insulin-like growth factor 1 receptor (IGFR-1), as well as the vascular endothelial growth factor (VEGF) and its receptor (VEGFR), thus suppress tumour growth and angiogenesis through insulin/insulin-like growth factor pathway, while miR-137 up-regulation could be important to maintain tumour state.

4. BLOOD-BASED BIOMARKERS ANALYSIS

The dynamic nature of circulatory system and its constituents reflect physiological or several pathological states and the easiness of sampling procedures are a logical choice like source for biomarker discovery. DNA, mRNA and miRNA (cfNA, cell-free Nucleic Acid) are released in the blood of cancer patients. Changes in the levels of circulating nucleic acids have been associated with tumour burden and malignant progression. In the past decade, a wealth of information on the possible use of circulating nucleic acids for screening, prognosis and monitoring the anticancer therapies efficacy has emerged. cfDNA, cfmRNA and cfmiRNA might be excellent blood cancer biomarkers, as they may be more informative, specific and accurate than usual protein biomarkers.

4.1 cfDNA

Physiological events leading to cfNA increase during cancer development and progression are still not well understood. However, analysis of circulating DNA allows the detection of tumour-related genetic and epigenetic alterations during development and progression of cancer. The presence of nucleic acids into bloodstream is thought to be related to the apoptosis and necrosis of cancer cells in the tumour microenvironment. Necrotic and apoptotic cells are usually phagocytosed by macrophages or other scavenger cells and digested DNA is released into tissutal environment (46). It has been estimated for a tumour that weighs 100g, which corresponds to 3 × 10^10 tumour cells, up to 3.3% of tumour DNA may enter in the blood every day (47). On average, the DNA size range between small fragments of 70 to 200bp and large fragments of approximately 21 kb (48). Secretion has also been suggested as a potential source of cfDNA (49, 50). Finally, tumour cells circulating in the bloodstream and micro-metastatic deposits present at distant sites, such as the bone marrow and liver, can also contribute to the release of cfNA (51, 52).

Although the major end-point of some studies was focussed on the role of cancer-related circulating cfDNA in early diagnosis, a most interesting challenge is the evaluation of its role in tumour response to pCRT in RC. Agostini et al. were confirmed significantly lower levels of circulating cfDNA in patients having relevant
of patients with different malignancies, including colorectal cancer (65, 66). Because high levels of cfmiRNA have also been found in benign conditions, such as the placenta-derived cfmiRNA in maternal circulation and other non-malignant conditions, its specificity should be considered with caution (67, 68). Conversely, hTERT expression is inappropriately activated in the most tumors and, because absent in non-neoplastic somatic tissues, its detections into bloodstream may be considered as a specific neoplastic marker.

On the other hand, in Pucciarelli et al. study, cfmiRNA and hTERT variation have been correlated to response to pCRT (69). Plasma levels significantly decrease in patients with response to therapy, while remaining unchanged -or even increased- in non-responder patients. Since cfmiRNA is released by different mechanisms (cell necrosis of large and advanced tumors, cell apoptosis or spontaneous and active release) their higher levels in non-responder patients could suggest a more active necrosis or a major tumor extension than responder patients (65, 70). Because of hTERT was found to be absent in plasma of healthy subjects, it was intriguing that hTERT was present in patients with a pathologic complete response. Circulating microscopic disease or low hTERT clearance from plasma are both possible explanations (66, 69). This can be further clarified by assessing hTERT levels at different time points after the completion of pCRT (i.e., several months after surgery).

Despite this study has limitations related to its retrospective nature, the relatively small number of patients and the non-uniform regimen of treatment, results prompted seem to be a good background to verify the predictive value of both cfRNA and hTERT in rectal cancer.

### 4.3 cfmiRNA
Recent findings demonstrate that blood contains stably expressed tumour-specific miRNAs (71). Serum or plasma miRNAs are easily accessible and are stable even under severe condition changes, such as pH and temperature variations. This represent an ideal starting point for biomarker assessment, and a lot of studies have been

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**Table 1. Circulating cfmiRNA expression related to response to chemotherapy**

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Cancer type</th>
<th>Body fluid source</th>
<th>Patients (n)</th>
<th>Received therapy</th>
<th>Therapy-related significant associated end points</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-21</td>
<td>Prostate (hormone refractory)</td>
<td>Serum</td>
<td>10</td>
<td>Docetaxel and prednisone</td>
<td>Biochemical response (PSA)</td>
<td>(72)</td>
</tr>
<tr>
<td>miR-21</td>
<td>Metastatic NSCLC</td>
<td>Plasma</td>
<td>35</td>
<td>Cisplatin- or carboplatin-based chemotherapy</td>
<td>Radiologic tumour response</td>
<td>(73)</td>
</tr>
<tr>
<td>miR-210</td>
<td>Breast</td>
<td>Plasma</td>
<td>29</td>
<td>Neoadjuvant paclitaxel followed by FEC plus trastuzumab</td>
<td>Pathological tumour response</td>
<td>(74)</td>
</tr>
<tr>
<td>miR-375</td>
<td>Breast</td>
<td>Serum</td>
<td>34</td>
<td>Neoadjuvant doxorubicin and cyclophosphamide followed by carboplatin and nab-paclitaxel plus trastuzumab</td>
<td>Pathological tumour response</td>
<td>(75)</td>
</tr>
<tr>
<td>miR-184</td>
<td>Breast</td>
<td>Serum</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-1299</td>
<td>Breast</td>
<td>Serum</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-196a</td>
<td>Breast</td>
<td>Serum</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-381</td>
<td>Breast</td>
<td>Serum</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-1246</td>
<td>Breast</td>
<td>Serum</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-125b</td>
<td>Breast</td>
<td>Serum</td>
<td>56</td>
<td>Adjuvant FEC or Docetaxel endocrine treatment according to hormonal receptor status</td>
<td>Radiologic tumour response</td>
<td>(76)</td>
</tr>
</tbody>
</table>

Abbreviations: FEC, 5-fluorouracil, epirubicin and cyclophosphamide; NSCLC, Non-small cell lung carcinoma; PSA, Prostate-specific antigen.
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focused on their potential role as diagnostic/prognostic biomarkers for cancer detection and monitoring (Table 1).

In the last years, a few studies have pointed out an encouraging correlation between circulating miRNA expression levels and response to a specific anticancer treatment. A first study has been performed on a small set of hormone-refractory prostate cancer patients and specific serum levels of miR-21 were measured in all docetaxel-treated patients (72). Circulating miR-21 was over-expressed in patients resistant to chemotherapy and resulted predictive of the response to docetaxel-treatment and to indicate the transformation to hormone refractory disease.

In a similar way, authors highlighted a predictive role of circulating miR-21 expression level in patients affected by NSCLC and treated with platinum derivative-based chemotherapy (73). More recent publications have discussed the predictive role of circulating miRNAs in breast cancer. The study by Jung and colleagues considered the baseline expression of 4 candidate miRNAs (miR-210, miR-21, miR-29a and miR-126) in breast cancer plasma samples and only miR-210 appeared to be significantly over-expressed in patients resistant to the trastuzumab-based treatment (74).

In the study by Wu et al. small ncRNAs (not coding RNA) miRNA extracted from patients’ serum were analyzed by next-generation deep sequencing to detect differential expression levels between different classes of breast cancer patients (75). The relationship between tumour response to neoadjuvant trastuzumab-based treatment and miRNA levels was investigated in 23 patients. A seven miRNA signature was associated with pathological complete response (76). Findings were further tested on primary cancer cells isolated from pre-treatment biopsies and they confirmed miR-125b over-expression in primary breast cancer cells with poor tumour response.

Although a huge literature is present, more accurate and extensive studies are needed to appreciate the real value of circulating miRNA expression as a predictive tool in personalized cancer treatment. In particular, some clarifications are necessary: although short ncRNA have been detected in the extracellular culture medium of mammalian cells in vitro, the release mechanism from tumour cells is still unclear. Extracellular miRNAs seem to be transported by lipoprotein complexes originating from endocytosis of endosomal cellular membranes called micro-vesicles or exosomes, also containing miRNAs and proteins (77). This mechanism of extracellular transport would justify the stability of miRNA in circulating body fluids. However, some authors have recently demonstrated the most of circulating miRNAs are outside exosomes and their stability could be owing to complex formation with Ago proteins (78).

Therefore, the source of cfmiRNAs and the extraction methods could bias the results of studies and thus limit the searching field and ignoring the vast majority of the circulating miRNAs or focusing on non-tumour miRNAs. These controversial data highlight the necessity of more studies to establish standardized and robust methods for detecting circulating tumour cfmiRNA.

5. CIRCULATING PROTEINS/PEPTIDES

Circulating proteins reflect the complexity of molecular processes involved in cancer, and their identification and characterization in the field of proteomic studies (79). To date, proteome profiling for identification of therapy-related changes, which could be used for monitoring progression, efficacy and toxicity of the treatment in rectal cancer, has been scarcely investigated.

In a study, Smith et al. performed a SELDI-based serum profiling in patients with RC undergoing pCRT at several time points during the therapy: before and after each serial radiation treatment (80). This study revealed specific features of proteomic profiles, discriminating patients with good and poor histological response to the therapy. In particular, a pattern of 14 differentially abundant proteins has been found to predict the ultimate pathologic response with 87.5% sensitivity and 80% specificity. If these results suggest that early proteins changes after cytotoxic therapy are clearly detectable, proteins identity was not clarified and needed further investigation. In a similar way, Helgason et al. found 2 proteins having changed serum level correlated with therapy response in CRC patients treated with oxaliplatin and capecitabine (81).

Proteins have been tentatively identified as a probable fragment of hemoglobin alpha-chain fragment (MW 2kDa) and the acute phase Apo A-I protein (MW 28kDa). If these proteins were found useful for therapy monitoring, data obtained were not conclusive regarding their predictive value and required further test.

Beside proteome, peptidome has been recently recognized as a novel source of biomarkers, which could improve diagnosis, prognosis and monitoring of various diseases including cancer (82). Peptidome is the sub-proteome fraction, including intact peptides or active peptides released form precursors under specific physiological conditions (e.g. immune response), or peptides originating from protein degradation pathways. Tumour microenvironment, through its aberrant processes of cell growth, cellular invasion, alteration of immune system function and angiogenesis generate a unique cascade of events that lead to specific protein fragmentation products (83). Moreover tumour-related peptides can be originating both from apoptosis and necrosis events of cancer cells in the tumour microenvironment, and from released proteases into the bloodstream. In literature, comparative analyses of circulating peptidome profiles in healthy subject and patients with different kinds of cancer have been performed, allowing the identification of peptide signatures that could be peculiar of pathology or tumour site (79, 84, 85).
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Even if these studies are promising, a positive application in the detection of peptidome changes in pCRT treated rectal cancer patients is still lacking.

6. CONCLUSION

Predictive factors of tumour response in patients receiving neoadjuvant treatments are clinically relevant. Currently, although many molecular markers are studied as potential candidate predictors, none have been introduced in clinical practice. Many results were obtained by gene expression signatures to predict tumour response after pCRT. Different research approaches to identify sub-phenotypes of rectal cancer are the best opportunity to head the clinical research to individualized therapy. Despite all advances obtained, few studies have attempted to demonstrate the value in integrating genomic and proteomic information with the traditional biomarkers for providing a detailed assessment of clinical risk and improving prediction of response to therapy. The presented studies could significantly improve knowledge and application of gene expression, peptidome profiling and characterization and quantification of circulating cfNA, to a clinical predictive classifier of therapeutic response in rectal cancer. Novel interpretation ways we could go through integrating the various findings and leading to identify important molecular factors in the prediction of response to treatment.

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