ID: 00955
Type: Poster
Topic: Tumor treatment

EME1 as a predictive biomarker for radiosensitivity in locally advanced rectal cancer patients undergoing preoperative radiochemotherapy

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To date, none of the identified signatures or molecular markers related to response to pre-operative chemoradiation (CRT) in locally advanced rectal cancer (LARC) has been successfully validated as a diagnostic or prognostic tool applicable to routine clinical practice. To gain insight into the molecular signatures associated with response to treatment after CRT, RNAs from 27 patients with LARC without metastasis were obtained and subsequently cDNA and cRNA were synthesised for hybridization on Human WG CodeLink bioarrays. Tumor tissue biopsies were obtained before CRT.

We identified 257 genes with an adjusted $p< 0.05$, which clearly differentiate these responder and non responder patients after CRT. A detailed analysis identified genes encoding proteins associated with several canonical pathways, such as Pyrimidine and Purine Metabolism, and Colorectal Cancer Metastasis Signaling. They also included a broad range of genes involved in DNA repair, as C12orf15, EME1, GMNN, LIG3, POLA1, RAD18, RIF1, RRM1, SMC1L1 and USP7.

Here, Eme1 expression was investigated as a predictor of neoadjuvant radiotherapy treatment response in LARC. Two colorectal cancer cell lines were chosen specifically because they showed medium (SW480) and high (SW837) resistance to radiotherapy and because SW837 expressed lower mRNA and protein levels of EME1 than SW480. The clonogenic assay with ionizing radiation showed inverse correlation between survival clonogenic at 6Gy and Eme1 expression levels. In a new set of patients, we observed that EME1 was down-expressed in LARC patients compared with healthy tissues ($p< 0.05$), confirming the tumour suppressor role of this DNA repair gene in rectal cancer. However, changes in EME1 expression, between patients who responded versus those who did not respond to CRT, did not show statistically significant differences.

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ID: 00961
Type: Poster
Topic: Tumor treatment

Impact of miR-1301-3p and miR-205-5p on Wnt and AR signalling pathways in castration resistant prostate cancer.

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Introduction: Prostate cancer (PCa) is the second leading cause of cancer mortality in western countries. Prostate tumours initially respond well to androgen-deprivation therapy (ADT). Unfortunately, the majority of tumours evolve, after androgen deprivation, from a hormone-sensitive to a castration-resistant prostate cancer (CRPC). For that reason new agents, targeting the androgen receptor (AR) signalling pathway (abiraterone, enzalutamide among others), have been approved in the last decade. Unfortunately, the emergence of resistance to these treatments is common and CPRC remains highly lethal. Therefore, new approaches and better knowledge of the molecular mechanisms leading to CRPC is still needed. Mechanisms related to CRPC transition include increased expression of AR and activating mutations in this receptor. As in other tumours, there are other signalling pathways that could interfere with AR activation such as Wnt signalling pathway, which has been suggested to play an important role in CRPC. On the other hand, emerging evidences indicate that certain miRNAs are involved in the appearance of treatment resistances in several diseases.

Objective: The aim of this project was to study miRNA and mRNA expression profiles to identify deregulated miRNAs and genes involved in the Wnt signalling pathway in CRPC.

Methodology: A set of 20 PCa tumour samples, 10 radical prostatectomy (RP) specimens from hormone-naïve patients vs 10 transurethral resection of prostate (TURP) samples from castration resistant patients, were analysed. Total RNA was obtained to study miRNA and mRNA expression using Affymetrix GeneChip miRNA 4.0 and GeneChip Clariom S human arrays, respectively. To identify deregulated miRNAs and their corresponding predicted target mRNA related to AR and Wnt signalling pathways, both miRNA and mRNA expression profiles were integrated by correlation analysis using the TAC software (appliedbiosystems). The miRWalk software tool was used to identify predicted target mRNAs for the differentially expressed miRNAs. This software allows simultaneous searches of several data bases, the potential targets that were identified by at least three of these data bases were selected. Differentially expressed mRNAs (CRPC vs HNPC) which were miRNAs predicted targets were selected for further analyses. Among these miRNAs, those that potentially regulate mRNAs involved in Wnt and AR signalling pathways were selected.

Results: When hormone-naïve samples vs castration-resistant samples were compared, 28 miRNAs and 1023 mRNAs were found differentially expressed. Further identification of potential target pathways by enrichment analysis showed involvement of AR and Wnt signalling pathways with 17 and 14 genes significantly deregulated respectively. After assuming an inverse correlation between miRNA and mRNA expression, a strong correlation between expression levels of miR-1301-3p with *SFRP1* / *SFRP2* and a correlation between miR-205-5p with *WNT-5A* / *AR* expression levels were found.

Conclusions: miR-1301-3p and miR-205-5p could have an important role in CRPC by regulating *SFRP1* / *SFRP2* and *WNT-5A* / *AR* mRNA genes respectively. However these results deserve further validation in independent patient's series, as they could represent novel biomarkers.

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