miRNA-related SNPs as new predictive biomarkers of response to neo-adjuvant treatment in rectal cancer patients? An explorative analysis

E. Dreussi[1,2], J. Polesel[3], A. De Paoli[4], M. Agostini[5], S. Pucciarelli[6], F. De Marchi[7], L. Giodini[1], C. Zanusso[1], S. Gagno[1], R. Roncato[1], G.Toffoli[1], E.Cecchin[1]

[1]Experimental and Clinical Pharmacology Unit, CRO-National Cancer Institute, Aviano, Italy
[2]Doctoral School in Chemical and Pharmaceutical Sciences and Technologies, University of Trieste, Italy
[3]Division of Epidemiology and Biostatistics, CRO-National Cancer Institute, Aviano, Italy
[4]Radiation Oncology Unit, CRO-National Cancer Institute, Aviano, Italy
[5]Dept. of Surgical, Oncological and Gastroenterological Sciences, Padova, Italy, Italy
[6]Surgical Clinical Unit, Padua University, Padova, Italy
[7]Division of Surgical Oncology, CRO-National Cancer Institute, Aviano, Italy

Background

The pathological tumor response, defined as tumor regression grade (TRG), in locally advanced rectal cancer (LARC) patients (pts) treated with neoadjuvant chemoradiotherapy (CRT), is the most reliable marker of prognosis up to date. Nonetheless, complete response is achieved only in 20-30% of cases, so tailoring pts treatment is a compelling need. Specifically, for non-responders, other therapeutic strategies should be planned, without delaying surgery and sparing patients from useless and potentially toxic CRT.

The complexity of tumour response requires more comprehensive approaches, less focused on a single biological pathway. microRNAs (miRNAs), brief non-coding RNAs (ncRNAs) involved in gene expression regulation, represent a very interesting and still not deeply explored field.

This study aims to define potential biomarkers among miRNAs-related genetic variants (SNPs) that could be used as predictive factors of pathological tumor response of neoadjuvant CRT in LARC pts.

Patients and methods

280 LARC pts treated with a neoadjuvant fluoropyrimidines (FL)-based CRT were enrolled: 202 underwent a 50.4Gy RT and 72 a 55Gy RT. A panel of 114 miRNA related-SNPs was used to genotype pts germline DNA samples by BeadXpress (Illumina). We compared genotype frequencies between complete responders (TRG1) and non responders (TRG2-5). SNPs with a concordant effect according to the Wald X^2-test in the 2 subgroups were analyzed in the pooled population and validated by bootstrap analysis (1000 resampling).

Results

3 SNPs located in *SMAD3* (rs17228212 OR=2.00, 95% CI=1.21-3.29, p=0.0049; rs744910 OR=0.45, 95% CI=0.24-0.85, p=0.0153; rs745103 OR=0.49, 95% CI=0.25-0.95, p=0.0471), one in *DROSHA* (rs10719 OR=1.83, 95% CI=1.08-3.10, p=0.0274), and one in *TRBP* (rs6088619 OR=0.40, 95% CI=0.20-0.80, p=0.0125) were defined as predictive biomarkers of response to neoadjuvant treatment.

Conclusions

Our major finding was the identification of 3 independent SNPs (rs17228212, rs744910, and rs745103) in *SMAD3*, along with a SNP (rs10719) in *DROSHA*, predictive of complete pathological response in LARC patients. SMAD3 and DROSHA cooperate in miRNA maturation in response to inflammatory cytokines like TGFβ. Moreover, DROSHA is also involved in DNA repair. A further predictive biomarker is located in TRBP, which forms a complex with Dicer and can also interact with other factors, like the MAPK ERK, that regulates cell cycle, apoptosis, and DNA damage response.

Finally, based on our findings, we could hypothesize that SMAD3, DROSHA, and TRBP, through their involvement in miRNA maturation and in other pathways as inflammation and DNA repair, that are crucial in RT response, could affect the CRT response in LARC patients.

These data, if confirmed, could help clinicians in cancer treatment tailoring.