hsa-miR-196a2 and Dicer: new possible players in the pharmacogenetics of rectal cancer?

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BACKGROUND: Non-coding RNAs are important players in cell biology and they are also involved in different kind of malignancies. microRNAs (miRNA), a class of 20-24nt non coding-RNAs, control gene expression. They are subject to a complex maturation regulated by different proteins. There are increasing evidences that polymorphisms (SNPs) affecting miRNAs activity can have a biological effect and could represent useful predictive biomarkers of therapy outcome in cancer.
The pathological response to neo-adjuvant treatment in locally advanced rectal cancer patients is strictly related to long-term survival. Identification of predictive biomarkers of this treatment could have a relevant clinical impact.

AIM: In this study we aimed to identify genetic polymorphisms related to miRNAs activity that could be used as predictive biomarkers for the tumor response to neo-adjuvant chemoradiotherapic treatment in locally advanced rectal cancer patients.

METHODS: To select candidate polymorphisms possibly affecting miRNAs activity and maturation, we adopted a research strategy based on the use of different algorithms freely available on-line (TargetScanHuman, Microcosm, miRanda, Pictar, PolymiRTS, microSNiper) and literature analysis. We optimized the obtained list in order to select 144 tagging SNPs analyzable by BeadXpress (Illumina) technology. Among the selected SNPs, 80 were localized in genes codifying for proteins involved in the miRNA maturation, 27 in genes codifying for miRNAs directed to POLR2A, Drosha, DGCR8, Dicer, and 37 in their genomic target regions.
This panel was applied to a group of 255 locally advanced rectal cancer patients homogeneously treated with fluoropyrimidines-based chemo-radiotherapy in presence or absence of oxaliplatin in neo-adjuvant setting. Clinical end-point of pathological tumor response was the tumor regression grade (TRG), considering TRG=1 as complete response and TRG=2-5 as lack of response.

RESULTS: The BeadXpress SNPs panel was applied to the genomic DNA form PBMC of 255 samples of rectal cancer patients. 127 assays out of this panel were successful.
A preliminary analysis of the data highlighted that TRG was significantly predicted by rs11614913 polymorphism, in the gene encoding for hsa-miR-196a2 according to an additive model. The SNP increases the chance to get a complete pathological response (TRG=1) to neo-adjuvant treatment. In particular, every variant allele confers an increase probability of tumor response (OR=2.14, CI=1.18-3.86, P-value=0.0117). This polymorphism is located in hsa-miR-196a2, a miRNA predicted to be involved in the translational control of Dicer, a key factor in miRNA maturation process.

CONCLUSION: In this study we preliminarily pointed out rs11614913 polymorphism as a possible predictive marker of complete pathological response (TRG=1) in locally advanced rectal cancer, treated with fluoropyrimidines-based neoadjuvant chemoradiotherapy. If confirmed in further studies, this biomarker could be useful for better treatment personalization.