MicroRNA profiling in KIT and SDH mutated Gastrointestinal stromal tumor (GIST)

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Background. Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. The molecular mechanism of GIST formation is among the best characterized of all human tumors. Activating mutations of the c-Kit-kinase (KIT), a member of the receptor tyrosine kinase III family, are present in 80% of GISTs (Antonescu, 2011; Corless, 2011). Gain-of-function mutations of platelet-derived growth factor receptor A (PDGFRA), a member of the same kinase family, are present in 35% of GISTs that lack KIT mutations. In a small subset of patients, the disease does not harbor any mutations on these receptors and is defined as wild type (WT) (Nannini, 2013). The gene expression profiling and SNP analysis are strongly different between WT and mutated cases. Up to now, really few data are available on microRNA in GIST. We studied the microRNA profiles in GIST correlated with kinase genotype.
Material and methods: First, we analyzed the miRNA profile of 13 GIST tumor samples, of which nine carry either KIT or PDGFRA mutation, and 4 samples are from patients with a WT disease. Total RNA was labeled, hybridized to Agilent microRNA microarrays; differential microRNA were selected by a two-fold change cutoff and Benjamini and Hochberg-corrected unpaired t test results and discussion.
Second, we validated deregulated miRNAs in 27 GIST samples.
Results: The microRNA profile is different in WT and mutated GIST samples, with 56 microRNA differentially expressed at the 0.05 cutoff p-value. Mutated GIST show enrichment in microRNA targeting tumor suppressor genes, as TP53 and PTEN, but also tyrosine kinase receptors, in particular IGF1R. Indeed WT GISTs show a marked overexpression of IGF1R, not supported by gene amplification, that could be explained by the downregulation of specific microRNA, targeting these genes.
We started process the validations with 10 upregulated miRNAs and 3 of those, miR-148a, miR-193b, miR-330, were confirmed. Evaluations of target genes showed an involvement of Cyclin D1 signaling cascade. Transfection with specific miRNAs inhibitors are ongoing.
Conclusions: Mutated GIST have a different microRNA profile compared with WT patients. This difference needs to be more investigated in order to understand the biological role on the pathogenesis, clinical behavior and treatment responsiveness.