miRNA deregulation as novel clinical biomarkers in GIST

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Gastrointestinal stromal tumors (GIST) are worldwide considered as a paradigm of molecular biology in solid tumors. Indeed, after the discovery of specific alterations in the KIT and PDGFRA genes, they have emerged from anonymity to become a model for targeted therapy (Nannini et al, 2016). GIST are rare disease of the gastrointestinal tract, 75-85% characterized by KIT and PDGFRA gain-of-function-mutation. A small proportion of GIST (10-15%) represents a groups with distinct molecular hallmarks, including defects in SDH complex, and mutations of NF1, BRAF or KRAS genes (Angelini et al, 2013; Nannini et al, 2014). Next to these we distinguish quadruple wild-type (WT) GIST, a genomic subgroup lacking KIT/PDGFRA/RAS/RAF pathways mutations, with an intact succinate dehydrogenase (SDH) complex (5% of all GIST) (Pantaleo et al, 2015). The existence of different subgroups of GIST should translate into different treatment opportunities. Actually, in GIST patients the available therapies - first to third line – have all been developed as target therapies for KIT/PDGFRA mutant GIST, so that all the other subgroups can be considered as a kind of therapeutic orphans. Besides oncogenic changes at the genomic level, epigenetic changes, as miRNA deregulation, may act as core disease phenotype, driving disease course. In recent years epigenetics, MicroRNAs (miRNA) in particular, have an emerging and relevant role in different steps of GIST biology such as tumorigenesis, disease progression, prognosis and drug resistance. miRNA are a class of short noncoding RNAs, that play a relevant role in multiple biological processes, such as differentiation, proliferation and apoptosis (Croce, 2009). In view of these considerations, we integrated multiple expression profiles of miRNA and mRNA to construct an original miRNA–mRNA regulatory network in KIT/PDGFRA WT-SDH deficient GIST patients (Pantaleo et al, 2016). In this studies we found the miR-139-5p, 455-5p and let-7b signatures may represent a potential onco-miR mark in KIT/PDGFRA WT-SDH deficient GIST driving the carcinogenesis and developmental of KIT/PDGFRA WT-SDH deficient GIST. In particular, the miR-139-5p, 455-5p and let-7b signature, may represent an important therapeutic target in KIT/PDGFRA WT-SDH deficient GIST, usually characterized by IGF1R overexpression. In a further study we aim of this work is to improve the diagnostic process of quadruple WT GIST through a wide comprehensive molecular characterization of this subset of patients, essential for the identification of the driver molecular abnormalities as potential markers and targets of new treatments (Pantaleo et al, 2017). In particular, to fully define the signature of quadruple WT GIST we analyzed the miRNA expression profile against KIT/PDGFRA mutant and KIT/PDGFRA WT-SDH deficient GIST. A total of 66 differentially expressed miRNA were identified as specific of quadruple WT GIST. The integration of gene expression levels with the targets of differentially expressed miRNA allowed the identification of a network of interactions where we identified 17 miRNA as putative regulators of the 12 genes of neuroendocrine lineage and Neuroactive ligand-receptor interaction pathway. Up to now none of the discussed miRNA profiles have been translated into clinical practice and many efforts are still needed in order to better define the exact role of epigenetics in GIST development progression and treatment.

Angelini et al. (2013). Pharmacogenomics. 14, 941-56.

Croce (2009). Nat. Rev. Genet. 10, 704–14.

Nannini et al. (2013). BMC Cancer. 14, 685.

Nannini et al. (2016). Epigenomics. 7, 1033-49.

Pantaleo et al. (2015). Cancer Med. 4, 101-3.

Pantaleo et al. (2016). Epigenomics. 8,1347-66.

Pantaleo et al. (2017). Mol Cancer Res. Epub ahead of print.