MIR-221 AND -222-BASED THERAPEUTIC APPROACH IN MELANOMA AND GIST (GASTROINTESTINAL STROMAL TUMOR): *IN VITRO* AND *IN VIVO* PRECLINICAL STUDIES

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MicroRNAs (miRs) are small (~ 22 nucleotides) non coding RNAs involved in gene expression, as negative regulators of specific mRNA targets. Growing evidences indicated miR functional roles in all the main biological processes, including cancer where they can act as oncogenes as well as tumor suppressor genes. Several studies reported the involvement of miR-221 and -222 in the induction and/or progression of different neoplasias.

We have analyzed miR-221/-222 functional role in a panel of differently staged melanoma cell lines and primary bioptic samples, showing their capabilities to regulate two distinct, but functionally convergent pathways of melanocyte transformation through the cell cycle inhibitor p27Kip and c-kit receptor. We also demonstrated the lack of the tumor suppressor gene PLZF as a direct cause of miR-221/-222 upregulation in melanoma cells. *In vitro* and, more important, *in vivo* studies confirmed that suppression of miR-221/-222 strongly reduced melanoma growth and dissemination.

C-kit receptor represents also the main oncogene involved in gastrointestinal stromal tumors, being constitutively expressed as a consequence of activating mutations. Patients are therapeutically treated with Glivec but, after an initial satisfactory response, they often develop drug resistence possibly because of newly induced mutations. Expression studies demonstrated miR-221/-222 downregulation in a panel of primary surgical samples. Accordingly, *in vitro* restored expression of these two microRNAs decrease tumor cell growth and induced programmed cell death through c-kit downregulation and the activation of the caspase pathway. A therapeutic approach based on miR-221/-222 may then prove beneficial also in this pathological context.

Considering microRNAs as possible innovative therapeutic tools, it is important to point out their functional complexity, remembering that single miRs are able to regulate several target genes and each gene can be controlled by several miRNAs. In principle modulation of a single miR may influence an entire gene network. The functional role of miR-221 and -222 in melanoma and GIST is a good example of this versatility. Since these two miRs display opposite patterns of expression, being upregulated in melanoma and downregulated in GIST, a hypothetical miR-221/-222-based treatment should require their silencing or restored expression, respectively.

Finally we would like to point out our parallel study on the muscle specific miRs, miR-1 and -133, in cardiac hypertrophy. Besides being important *per se* considering that adult heart diseases are still the primary cause of mortality in the industrialized world, these results might also pave the way for future studies on tumors as muscle-related sarcomas. Preliminary reported results showed that miR-1 and -133 are significantly modulated in specific subgroups of sarcoma, as leiomyosarcoma and rabdomyosarcoma.

Publications of the project

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