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miR-146 and miR-155, two key modulators of the immune response and of the oncogenic transformation

Micro-RNA (miRNAs or miRs) are small noncoding RNAs that negatively regulate protein coding gene transcripts and exert an important role in the control of gene expression. miRs are deregulated in many tumors and play an active role in tumor development and maintenance; furthermore, some miRs are important regulators of immune responses in different types of cancers. miR-146 (miR-146a and 146-b) and miR-155 are among the most studies miRs for their numerous roles in the control of the immune innate responses and for their deregulation and oncogenic role in some tumors.

The studies carried out in the last 20 years have supported the view that miR-146 and miR-155 play an opposite role in the control of the immune response, acting at the level of various cell types involved in innate and adaptive immune responses. Both the miRs are transcriptionally regulated by NF-kB and are induced in macrophages by Toll-like receptor (TLR) activation: miR-146 acts to dampen in multiple context, at the level of various cells of the immune system, by repressing NF-kB and AP1 signalling and reduces the acute inflammatory response and increases endotoxin tolerance. miR-146a deficient mice have a condition of chronic inflammation and develop myeloproliferative disorders and cancers. miR-155 expression is essential for the development of the T-, B- and myeloid-cell lineages and for their physiological functions. miR-155 expression is deregulated in B-cell malignancies and leukemia. Enforced expression of miR-155 in bone marrow cells causes myeloproliferation and leukemia. Studies carried out during T-cell antitumor responses, T-follicular helper cell development and acute inflammatory response suggest that miR-155 exerts an epistatic, antagonistic effect on miR-146. Thus, miR-155 promotes, while miR-146 inhibits interferon-g (IFNγ) responses by T cells and reduces solid tumor growth *in vivo*.

The expression of these miRs may be deregulated in tumor cells or in the tumor microenvironment, and through this mechanism, may favor tumor development.

miR-146a deregulation plays a potential role in the development of some tumors. The predominant evidence is that miR-146a acts as a tumor suppressor and its deficiency favors tumor development. Mice deficient in miR-146a develop various hematolymphoid cancers in their older age due to constitutive NF-kB signaling. Similarly, ablation of miR-146b in mice induces the development of hematopoietic malignancies. Deletion of a genetic region including the miR-146a locus has been found in myelodysplastic syndrome associated with chromosome 5q deficiency; miR-146a and miR-145 deficiency is responsible for many abnormalities observed in this syndrome and particularly of abnormal and dysmorphic megakaryopoiesis, with platelet defects.

Recent studies suggest a potentially important role of deregulated miR-155 expression in various tumors. Thus, in various solid tumors there is growing evidence that miR-155 expression in tumor microenvironment favors immune anti-tumor response and correlates with an immune-enriched subtype in melanoma and many solid tumors. In contrast, in lymphoma and leukemia, miR-155 expression is associated with poor prognosis. In patients with various hematological malignancies, miR-155 overexpression was associated with reduced overall survival and progression-free survival. In acute myeloid leukemia patients, elevated miR-155

expression was associated with the presence of FLT3/ITD mutation, WT1 mutation and less CEBPA mutation.

miR-155 overexpression was involved in the clinical progression of mycosis fungoides, the most common form of cutaneous T-cell lymphoma. It was recently developed Cobomarsen (MRG-106), a locked nucleic acid-modified oligonucleotide inhibitor of miR-155. *In vitro*, this agent de-repressed multiple targets of the miR-155 gene, decreased expression of several genes involved in cell proliferation, reduced cell survival and activated an apoptotic signaling. On the basis of these results, a phase I clinical study with MRG-106 in cutaneous T-cell lymphomas (CTCL) was started: the preliminary results of this study were encouraging showing that the drug is well tolerated, has clinical activity and impacts the quality of life of CTCLC patients. These encouraging results support the continued investigation of MRG-106 and the enrollment of patients with other hematologic malignancies in which miR-155 expression is elevated.

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