Impact of mutant p53 on miRNA biogenesis in colon cancer. Dr. Aymone Gurtner

The global miRNA deregulation observed in human cancers is often the result of defects in the miRNA biogenesis pathway. Still, the mechanisms through which miRNAs are regulated in cancer and the connection between oncogenes and miRNA biogenesis remain poorly understood. Based on the above considerations, our main research interests are based in i) understanding the molecular mechanisms of miRNA deregulation in cancer, particularly in colon cancer; ii) discovering novel miRNA biomarkers in cancer.

The p53 oncosuppressor gene is mutated in more than 50% of human cancers, and often, these mutations produce a protein with new oncogenic properties, called "Gain Of Function" (GOF). The transcriptional factor NF-Y plays a key role in proliferation, and our group has previously described a physical interaction between mutant p53 (mutp53) and NF-Y, whose activity impacts on the proliferation of cancer cells (1). More recently, we have identified several miRNAs transcriptionally regulated by NF-Y in colorectal cancer cells (2).

Moreover, we have demonstrated that mutp53 is able to interfering with Drosha (3, 4) and Dicer activity (submitted), inhibiting miRNA biogenesis in colon adenocarcinoma. The relevance of the proposed mechanism resides on the oncosuppressor functions of miRNAs down-regulated by mutp53, such as induced cell death in colon cancer cells (3) and tumor growth inhibition in vivo (unpublished, in collaboration with Giulia Piaggio’s lab, Regina Elena National Cancer Institute, Rome). KEGG pathway and GO analyses of putative target genes of the mutp53-dependent miRNAs identifies several pathways and genes related to cancer among which EGF and FGF signaling, cell cycle, mitosis, cell death and stress response (in collaboration with Lorenzo Farina, Dipartimento di Ingegneria Informatica, Automatica e Gestionale, Sapienza). Interestingly, many of the genes belonging to these categories have oncogenic potential and are known as key regulators of altered molecular pathways in tumors. Therefore, our data support the idea that mutp53, inhibiting the expression of specific miRNAs, upregulates a subset of genes involved in tumor progression, including genes already targeted by molecular drugs. Therefore, in collaboration with Pathologic Anatomy Department at Regina Elena national cancer Institute IRE, we are now studying the mutp53 dependent miRNA/mRNA network on 270 human colon cancer patient's specimens. Moreover, in order to identify a molecular miRNA footprint useful as a biomarker in the prognosis of bladder cancer, in collaboration with Ouerhani’s lab we identified some miRNAs as potential biomarkers (5, 6).

References:


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