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Regulation of miR-483 locus in hepatocarcinoma cancer cells

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Hsa-mir-483 is located within the INS-IGF2 gene encompassed in 11p15.5. This region is implicated in several tumors. We have previously shown oncogenic features of miR-483-3p; it targets the pro-apoptotic gene BBC3/PUMA (P53 up-regulated modulator of apoptosis gene) and miR-483-3p enforced expression could protect cells from apoptosis.

During the course of our study we found that the chemotherapeutic drug 5-fluoruracyl (5-FU) induces increased expression of miR-483-3p in HepG2 and Hep3B cells. 5-FU treatment does not affect the expression of miR-483 expression in all the HCC cell lines that we tested, suggesting a possible heterogeneity in cellular apoptosis resistance depending on the miR-483-3p induced expression. Although the IGF2 and miR-483 expressions are strictly correlated, we have demonstrated that the oncoprotein β-catenin cooperates with the USF1 to transcribe the miR-483 by a separate mechanism. In addition we found that also CMYC is involved in the regulation of miR-483 expression. In Hepatocarcinoma (HCC) IGF2/483 locus is often over-expressed by Loss of Imprinting (LOI) at the IGF2/H19 imprinted control region (ICR) and HepG2 and Hep3B HCC cell lines shown the entire IGF2/483 locus up-regulated. As a matter of fact we found that the treatment with the de-methylating agent 5-azacytidine, induces an important down-regulation of IGF2 and miR-483-3p genes.

Since the transcriptional factor USF1 is described be activated by cellular glucose uptake and that miR-483 lies in the Insulin growth factor 2 gene, we tested a glucose involvement in the miR-483 regulation. We found that glucose deprivation suppresses miR-483 expression in HepG2 cells. This result suggests that at least one of the mentioned transcriptional factors (β-catenin, USF1, CMYC) could be regulated by glucose thereby influencing the miR-483 expression.

In this scenario understanding the mechanism involved in the 5-FU/miR-483 and glucose/miR-483 regulation could be an important step to improve the effectiveness of drug induced apoptosis on HCC cancer cells.

Biography

Dr. Angelo Veronese has completed his Ph.D under the supervision of Prof. Carlo Maria Croce at the University of Ferrara. He spent 2 years as Visiting Scholar at The Ohio State University. At present he is working at "Fondazione Universita' G.d'Annunzio" as Principal Investigator carrying out his research granted by European and Italian grant programs. From 1996 he has always worked in the field of molecular and cellular biology of cancer although he started his own research at the beginning of his PhD program in 2008. He is coauthor or author of 37 papers published in reputed journals.

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