STUDY OF THE ROLE OF LNCRNA H19 AND ITS INTRAGENIC MIRNAS IN HYPOXIA-INDUCED COLON CANCER PROGRESSION.

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The reduced O2 partial pressure, that occurs in growing tumor mass, prompts tumor cells to activate specific pathways driven by the transcription factor Hypoxia-inducible factor 1-alpha (HIF1a). HIF1a induces hypermetabolism to favor glycolysis, resistance to chemotherapy, neo-angiogenesis with an increase in local vasculature and finally, tumor metastasis. Our previous data demonstrated that under hypoxic stimulation, cancer cells up-regulate the expression of the long non-coding RNA H19 that, cooperating with its intragenic miRNAs (hsa miR-675-5p and hsa-miR-675-3p), mediates hypoxic responses.

Recently we found a positive correlation between miR-675-5p overexpression and metastatic phenotype in colon cancer; further we demonstrated that miR-675-5p supports the hypoxia-induced EMT (Epithelial to Mesenchymal Transition) regulating Snail transcription through a dual strategy: i) stabilizing the activity of the transcription factor HIF1a and ii) inhibiting Snail's repressor DDB2 (Damage-specific DNA Binding protein 2).

New unpublished data indicated that silencing of lncH19 and/or its intragenic miRNAs inhibits the hypoxia-induced nuclear translocation of Snail. Interestingly the same effects were observed for the nuclear translocation of beta-catenin letting us suppose a role of miR-675 as GSK3beta inhibitor.

Even if further studies are required to demonstrate the mechanism by which lncH19 and its miRNAs regulate the nuclear translocation of the investigated transcription factors, our data could explain the different evidence in the literature that associate the lncH19 and/or its miRNAs over-expression to both tumor growth and tumor progression.