



# MicroRNA shuttling impacts on cholangiocarcinoma pathogenesis

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Comment on: Mansini AP, Lorenzo Pisarello MJ, Thelen KM, *et al.* MicroRNA (miR)-433 and miR-22 dysregulations induce histone-deacetylase-6 overexpression and ciliary loss in cholangiocarcinoma. *Hepatology* 2018. [Epub ahead of print].

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Cholangiocarcinoma (CCA) is a heterogeneous and very aggressive disease of the bile ducts. CCA is often diagnosed in advanced stages due to the absence of evident clinical manifestation. Since patients affected by CCA are constantly increasing and the conventional chemotherapeutic approaches are not improving long-term survival, novel and more effective strategies are urgently needed. Specific parasites, local inflammation and the exposure to toxic agents are frequently associated to the development of the malignancy in the biliary tree (1). However, their pathogenic role is still object of active investigation.

Interestingly, CCA cells are characterized by loss of primary cilia, a feature that distinguishes normal cholangiocytes. This deficiency is dependent on HDAC6 overexpression. HDAC6 is the only HDAC member localized in the cytoplasm and involved in the deacetylation of  $\alpha$ -tubulin, thus modulating the microtubule stability of ciliary axoneme (2). The critical role of HDAC6 in CCA was previously reported by Gradilone's group (3). However, the mechanism by which HDAC6 was deregulated in this tumor type remained unknown.

Our genome encodes more non-coding RNAs (ncRNAs) than genes, and microRNAs (miRNAs) play a pivotal role in the control of gene function at the post-transcriptional level (4). MiRNAs are the most important class of short (20–23-nucleotide), evolutionarily conserved ncRNAs. MiRNAs are mainly transcribed by RNA polymerase II as long primary transcripts characterized by hairpin structures (pri-miRNAs) and processed into the nucleus by Drosha RNase III into 70- to 100-nt long pre-miRNAs. These precursor molecules are exported by an

Exportin 5-mediated mechanism to the cytoplasm, where an additional step mediated by Dicer RNase III generates a dsRNA of approximately 22 nt. The mature single stranded miRNA product is then incorporated together with Argonaute proteins into the RNA-induced silencing complex, a ribonucleoprotein complex that mediates post-transcriptional gene silencing. MiRNA dysregulation is frequently observed in cancer and many miRNAs can act as both oncogenes and oncosuppressors (5–6). Since one miRNA can recognize till hundreds of different genes, the gain or the loss of a miRNA can impact on cellular homeostasis, sometimes promoting tumorigenesis. On the other hand, the identification of critical miRNA-targeted genes can be extremely useful to pick out novel pathways for therapeutic intervention. Since miRNAs are rarely found mutated in cancer, a common mechanism of miRNA dysregulation is associated to methylation of their promoter or regulatory regions.

Interestingly, Mansini *et al.* (7) have hypothesized the involvement of miRNA dysfunction to explain HDAC6 overexpression in CCA. Using different bioinformatic tools, the authors have identified two miRNAs, miR-433 and miR-22, as potential HDAC6 regulators. Accordingly, both candidates were down-modulated in either CCA cell lines or clinical specimens, while their ectopic expression profoundly impacted on CCA cell proliferation, colony formation, migration and ciliogenesis. Molecularly, the ability of miR-433 to directly modulate HDAC6 level was demonstrated, while how miR-22 influences CCA behavior still remains unknown. This aspect is particularly relevant, since miR-22 can act both as a proto-oncogenic and as an oncosuppressive miRNA. In breast cancer, miR-22 regulates

cancer stem cell function and metastasis (8), whereas in rhabdomyosarcoma as well as in other tumor types, miR-22 interferes with tumor growth and dissemination (9-11). MiR-22 function seems more controversial in the hematopoietic compartment (12). While, originally, miR-22 was described as oncogenic for its ability to promote hematopoietic stem cell (HSC) self-renewal and transformation (13), two recent papers support a tumor-suppressive role of miR-22 in acute myeloid leukemia (AML) (14-15). In particular, instead of triggering HSC transformation, miR-22 was shown to modulate monocytic differentiation and was therefore proposed as a novel potential therapeutic option for AML patients (15). Likely, these apparent contradictory results depend on the complexity of miR-22 function as well as on the cell types and the context in which the experiments were performed. In any case, a detailed investigation of miR-22 function in CCA could be extremely useful to better characterize the biological significance of this double-faced miRNA in tumorigenesis.

The most exciting finding reported by Mansini *et al.* is the accumulation of the immature miR-433 and miR-22 precursors in the nucleus of CCA cells. Given that Exportin-5 (XPO5) is actively involved in pre-miRNA nuclear export, the authors focused their attention on this protein. Interestingly, XPO5 was strongly downmodulated in CCA cells and its ectopic expression re-established normal miR-22 and miR-433 maturation, exerting also a therapeutic effect on CCA cells proliferation, focus forming ability and migration. Importantly, blocking miR-22 and miR-433 in this setting partially interfered with the effects observed with XPO5 overexpression. Finally, the down-modulation of XPO5 in normal cholangiocytes resulted in the increase of cell proliferation, shorter cilia formation and accumulation of miR-22 and miR-433 precursors.

Overall, this paper clearly indicates that a global miRNA down-modulation in CCA may exert a pivotal role in the dysregulation of normal cholangiocytes, contributing to their transformation. In the next future, it will be of interest to investigate in an *in vivo* setting whether the modulation of XPO5 function and/or expression could be beneficial for the treatment of CCA, or if the selection of specific miRNA candidates (miR-433 and/or miR-22) could be more effective. In conclusion, a lot of work is still necessary to deconstruct the complexity of CCA but, although tiny, miRNAs have already showed their might.

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