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miR-148A INHIBITS COLON CANCER STEM CELL PROPERTIES BY TARGETING PREGNANE X-RECEPTOR SIGNALING

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Therapeutic failure seen in patients with colorectal cancer (CRC) frequently involves post-treatment tumor recurrence, due to the enhanced resistance of cancer stem cells (CSCs). Recently, we reported that the nuclear receptor Pregnane X-Receptor (PXR, NR1I2) behaves as a key driver of CSC-mediated tumor recurrence where it drives the expression of a large network of genes involved in self-renewal and chemoresistance (Planque C et al. Oncotarget, 2016). In order to determine the molecular mechanisms that define PXR enrichment in CSCs, we investigated the role of miR-148a on PXR expression and CSC phenotype. The miR-148a has been reported to post-transcriptionally regulate PXR in human liver (Takagi S et al. J Biol Chem, 2008) and has been proposed as a predictive biomarker in patients with advanced CRC (Takahashi M et al. PLoS One 2012).The present study demonstrated that miR-148a is down-regulated in CSC-enriched colonospheres and ALDHbright cells or after cytotoxic treatments. We also observed a negative correlation between miR-148a-3P and PXR and PXR target genes expression in these conditions. Moreover, transient transfection of miR-148a-3P mimics in CRC cell lines and in patient-derived CRC cells decreased PXR and PXR target genes expression (ALDH1A1, ABCG2, FGF19) and PXR-induced promotion of the CSC phenotype (proportion of ALDHbright cells, sphere forming potential and self-renewal following serial spheroid passaging). Finally, we observed that miR-148a-3P overexpression impairs chemotherapy-induced enrichment of ALDHbright cells after Firi treatment. In conclusion, we propose that the deficiency of miRNA-148a-3P is associated with the preferential expression of PXR in colon CSCs. In addition, our findings highlight miR-148a as a promising therapeutic agent that may reduce cancer relapse by selectively sensitizing CSC to chemotherapy via PXR signaling inhibition.

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