Molecular Therapy
Letter to the Editor

Potential Therapeutic Impact of miR-145 Deregulation in Colorectal Cancer

We have read with interest the recently published work by Zhu et al.,[1] which suggested that the SNAI-1/miR-145 pathway could represent a novel therapeutic target to reverse radiotherapy (RT) resistance in colorectal cancer (CRC). Zinc finger protein SNAI1 (sometimes referred to as Snail) is a family of transcription factors that promote the repression of the adhesion molecule E-cadherin to regulate epithelial to mesenchymal transition (EMT) during embryonic development. Interestingly, the authors showed that ectopic expression of SNAI-1 led to increased Nanog levels together with a decrease in both miR-145 expression and RT sensitivity. Inversely, enforced miR-145 expression resulted in reduced expression of cancer stem cell (CSC)-related transcription factors and spheroid formation but increased RT sensitivity. The authors demonstrated that SNAI-1 negatively regulates miR-145 by binding its promoter. Finally, differential expression of SNAI-1, miR-145, and CSC-related transcription factors were confirmed by comparing CSCs and non-CSCs from rectal patient-derived xenografts.

Based on their observations, the authors proposed the SNAI-1/miR-145 axis as a new therapeutic target to overcome RT resistance in CRC. This issue is of particular importance in the subgroup of locally advanced rectal cancer (LARC) patients because they are homogeneously treated with 5-fluorouracil (5-FU)-based chemoradiotherapy (CRT). In fact, miR-145 has been described to predict response to CRT in LARC, further supporting its relevance as a therapeutic target.[2] However, it remains to be determined if there exists a potential miR-145-independent role for SNAI-1 in modulating RT sensitivity of CRC cells, a function previously described in other tumor types.[3] This could be addressed by modulating its expression in CRC cells following stable silencing of miR-145. Another important consideration is that miR-145 has also been reported to be regulated by mechanisms distinct from SNAI-1, and their potential contribution to the miR-145-dependent RT sensitization should be investigated. The oncoprotein KRAS leads to miR-145 downregulation through the transcriptional repressor RREB1, which is upregulated in CRC tumors and inversely correlates with miR-145 expression.[4] Considering that KRAS-activating mutations have been reported in around 50% of CRC cases, this mechanism to regulate miR-145 could be of high importance. In addition, several long non-coding RNAs (lncRNAs), such as ROR, SNHG1, SOX21-AS1, and CCAT2, have been found to be overexpressed in CRC tumors and act as a sponge of miR-145, negatively regulating its function.[5–8] It would also be interesting to determine the specific molecular mechanism by which miR-145 modulates sensitivity of CRC cells to RT. OCT4 would be one of multiple potential candidates because it is a direct miR-145 target that mediates miR-145 radiosensitization of cervical cancer cells.[9] The fact that the transcription factor OCT4 is a pluripotency marker would also reinforce the role of miR-145 in regulating stemness in CRC cells.[10]

To clarify the significance of miR-145 in LARC, another relevant issue is to evaluate whether miR-145 affects CRC chemosensitivity. Interestingly, miR-145 has been reported to strongly enhance sensitivity of CRC cells to the chemotherapeutic agents 5-FU, oxaliplatin, and irinotecan.[11] Moreover, miR-145 reverses 5-FU resistance of CRC cells by directly targeting the DNA damage-related gene RAD18.[12] In addition to SNAI-1, it has been reported that SNAI-2 also negatively regulates miR-145, thereby enhancing the sensitivity of CRC cells to 5-FU.[13] Altogether, these data further support miR-145 as a novel target for LARC and also suggest its potential impact in metastatic CRC patients that receive FOLFOX or FOLFIRI as chemotherapy blackbones.

Finally, it has been reported that miR-145 induces changes in EMT markers, including negative regulation of *SNAI-1* at the transcriptional level.[14] Therefore, it would be very interesting to clarify the potential existence of a reciprocal regulatory loop between SNAI-1 and miR-145 to fully understand the molecular mechanism underlying the SNAI-1/miR-145 interplay and its usefulness as a therapeutic target in CRC.

CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

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