

Sub: Resubmission with Edits: **MicroRNAs potential utility in Colon Cancer: Early Detection, Prognosis, and Chemosensitivity**

Dear Editor,

Please find enclosed an original article for your consideration for Review Article.

I have included changes as recommended by the reviewers.

Changes:

1. Tables edited to have titles: "Table 1 Summary of miRNA and Early Detection", "Table 2 Summary of miRNA and Prognosis", and "Table 3 Summary of miRNA and Chemosensitivity"
2. Page 9, First paragraph: The acronym TNM was expanded to explain each letter. "...extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M) or TNM stage, ..."
3. Addition of brief statement in the introduction of the TNM staging system for CRC. "The Tumor Node Metastases (TNM) staging system of the American Joint Committee on Cancer/Union for International Cancer Control is the preferred staging system for CRC."
4. Page 10, Line 12: corrected patients instead of "patents".
5. Page 11, the sentence "The gene known as Dicer, which is an RNA III endonuclease involved in the processing of miRNA, has also demonstrated poor prognosis in patients with elevated expression" was reworded to "The RNA III endonuclease known as Dicer is involved in the processing of miRNA and its expression is associated with poor prognosis."
6. Page 12, First paragraph: The word "ushers" was exchanged for "allows for"
7. Page 12, Second paragraph: the sentence "Up-regulation of miR-153 and was associated..." was started with "For example..." for completion. Also, addition of the word "Additionally" to bridge the following sentence.
8. Page 14, First paragraph: stated that miR-122 is downregulated in 5-Fu-resistant CRC cells. "...and consequently, miR-122 is downregulated in 5-FU-resistant CRC cells."
9. Addition of "Results" title for body of document on Page 4
10. Tables 1 and 2 were extensively revised with additional information on each miRNA if additional information was available. For example, in Table 1 miR-135b revised to, "Diagnosis of CRC, involved in feedback loop associated with APC and PTEN/P13K which leads to up regulation, Expression reduced when CRC resected", miR-106a revised to, "Diagnosis of CRC, Improves sensitivity of FOBT, Suppresses TGFBR2", miR-431, miR-15b, miR-139-3p, miR-532-3p, miR-331, miR-195, miR-17, miR-142-3p, miR-15b, miR-532, miR-652 all revised to, "Diagnosis of CRC, Dysregulation leading to increased levels", miR193a-3p with "Diagnosis of CRC, Significantly up regulated in CRC, Unknown mechanism", miR-23a with "Diagnosis of CRC, Up regulated in CRC, Down regulates MTSS1 gene", miR-338-5p, miR-18a, miR-20a, miR-21, miR-29a, miR-92a, miR-106b, miR-133a, miR-143, miR-145 all revised with, "Diagnosis of CRC, Increased expression level in CRC", miR-1288 revised with, "Stable endogenous control for miRNA in CRC". miR-200c revised to, "Increased expression a predictor of lymph node metastasis", miR-378 revised to "Functions as a tumor suppressor, Low level correlates with increased tumor size", miR-126 revised to "Increased expression level protective as positively correlates with progression free survival", miR-224 revised

to “Up regulation promotes proliferation, invasion and relapse of CRC”, miR-429 revised to “Up regulation prevents anti-apoptotic function by targeting SOX2”, miR-182, miR-32 revised to “Up regulation promotes lymph node metastasis and poor overall survival”, miR-214 revised to “Down regulation causes increased FGFR1 leading to metastatic disease”, miR-182 revised to “Up regulation correlated with adverse clinical characteristics and poor prognosis”, miR-92a revised to “Overexpression leads to tumor metastasis and poor overall prognosis”, miR-124 revised to “Down regulation correlates to lower grade of differentiation and worse overall survival”, miR-30b revised to “Decreased expression correlates to poor prognosis via effect on KRAS, PIK3CD and BCL2”, miR-625 revised to “Decreased expression associated with tumor metastasis and poor prognosis”, miR-155 and miR-210 revised to “Elevated expression associated with recurrent disease, distant metastasis and poor prognosis”, miR-215 revised to “Decreased expression associated with higher likelihood of CRC relapse after radical resection”, miR-130b revised to “Elevated expression promotes tumor development and poor overall prognosis”, miR-148a revised to “Decreased expression associated with lower disease free intervals”, miR-16 revised to “Down regulation leads to poor prognosis”, miR-21 revised to “Upregulated in CRC, associated with tumor size, distant metastasis, poor survival and independent biomarker”. No revisions were made to Table 3 as there was no additional descriptive information to be added to each miRNA.

Thank you

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