Point-by-point responses to the reviewers' comments of manuscript NO.18921:

We appreciate the positive response from the reviewers and thank you very much for all the helpful suggestions and criticisms. As described below in detail, we made our manuscript succinct, carefully revised it and added one table in light of corresponding comment. Our specific responses to different points raised by the reviewers are listed below:

Reviewer#1:
Comment:
The paper is heavily written and requires major improvement. First of all, not all miRNAs linked to CRC are described and the statement after each class (subclass) of miRs lacks any recommendations. I strongly suggest to place all mentioned miRNAs in a Table and define not only the references and some obvious facts (increased or decreased levels) but also give them a score of reliability - what can (should) be use as a prognostic marker. It is otherwise hard, especially for the clinicians, to figure out what they can rely on. Carefully proofread the manuscript. There are very many typos, misspellings and bad written sentences which makes this paper very hard to read. In particular (although not all) I found the following errors to correct: Page 1 "and more datA suggest"; "ploYps" should be polyps; "X-ray test could bring about harmful radiation and isn't sensitive..." - rephrase and avoid any constructions to comply with scientific style; page 3 - "taken together, current methodologies .." - what about oncomarkers currently used for CRC diagnoses? page 3, 1st para "More, some...." can not write like this also - rephrase the last sentence Page 3, 1 sentence, 2d para - give the appropriate reference; space between CRC.Mir-21 decypher abbreviation for RECK Page 4 again, "ploYps will progress..." should be polyps; "to become to invasive" - > become too invasive; again! "ploYps, and is" should be polyps; CRC.MiR-21- spacing; the acronym FFPE stands for Formalin-Fixed, Paraffin-Embedded; qRT-PCR abbreviation already mentioned earlier; what is PDCD4?; in the next sentence pdcd4 is not capitalized - what is right? Page 5 the end of the first para should be rewritten the one before the last sentence, para 2 should be "has been made" para 3 "what's more,.." can not use constructions like that; Page 6 again... polypS; Page 7 qRT-PCR was already abbreviated oin page 4; "serum miR-29a" - please explain; Page 8 "with stage II disease,..." - rephrase; last sentence, 1st para DFS was already abbreviated on page 5; loci.MiR-29b - spacing ; Page 9 NOTCH1 and Notch - what is correct? Page 12 - what is HV? ccRCC - is it a right abbreviation? Page 14 BIC gene - please explain; page 15 CEA - decipher; Page 18 "miRNAs are both introduced, since..." re-write the sentence.

Comment 1. I strongly suggest to place all mentioned miRNAs in a Table and define not only the references and some obvious facts (increased or decreased levels) but also give them a score of reliability - what can (should) be use as a prognostic marker.

It is otherwise hard, especially for the clinicians, to figure out what they can rely on.

Answer 1. We appreciated these valuable comments. As suggested, we put all of miRNAs we addressed in a table (See **Table** below) to make our manuscript more succinct to readers. In the revised version, we inserted the following Table into page 29.

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Table. Overview of functions of microRNAs in colorectal cancer

miRNA	Disease progression	Biomarker	Treatment
miR-21	1. Overexpression correlated with CRC cell proliferation, invasion, lymph node metastases, and advanced clinical stage [22,24] 2. MiR-21 increased from precancerous ploYps to early cancer, and keeps increasing from the early stage to advanced stage [20] 3. High expression in tumor is associated with poor survival in the stage II/III Japanese [11,21], USA, Hong Kong cohorts [25] , stage II German cohorts [21], Czech [26] and Danish [27, 28] cohorts of CRC patients.	1. Upregulation in tissues as an independent prognostic factor for Duke stage [29] and TNM stage [21]. 2. High expression in serum [33] and stool [34-35] indicates poor prognosis.	Less miR-21 enable better effectiveness of adjuvant therapy[21]
miR-29	1. MiR-29a in precancerous lesion is significantly elevated [38] and high expression correlated with metastasis, especially liver metastasis [39,42] . 2. Contrarily, another reports [43,44] prove high level of miR-29a has a better survival at 12th month. 3. High miR-29b expression associated with higher 5-year DFS (disease-free survival) and OS (overall survival) [46,48]	1. Increasing plasma miR-29a as an noninvasive biomarker for early detection of CRC and metastasis in routine clinical practice [38]. 2.Opposite view indicates high miR-29a is associated with a longer DFS [44]. 3. High miR-29b related with longer 5-year DFS and OS(stage III CRC) [48].	
miR-34a	1. MiR-34a is downregulated in the CRCs, leading to aberrant cell proliferation and CRC development [57] 2. MiR-34a inhibits recurrence of CRC through inhibiting cell growth, migration and invasion, inducing cell apoptosis and cell cycle arrest in a p53-dependent manner [59] 3. Increasing miR-34b/c are observed in more advanced tumors and are associated with poor cancer-specific mortality [60] .	Low expression as a recurrence biomarker for stage II and stage III CRC patients [59]	Introduction of miR-34a into resistant CRC cells significantly induce an attenuation of 5-FU-resistance [58]
miR-124a	1. Among various cancers, CRC showed the highest frequency of methylation of miR-124a [65, 66], and aberrant methylation of miR-124a results in chronic inflammation [69] 2. Ulcerative colitis (UC) patients with both pancolitis and long-standing ulcerative colitis have 7.4-fold higher methylation levels than those without these risk factors [71]	The more methylation level of miR-124a, the more risks for carcinogenesis of UC and precancerous lesions [71]	
miR-130b	1. Higher levels were found in advanced tumor stages (III-IV), MiR-130b-PPARγ axis promotes CRCS toward more invasive[77]. 2. Conversely, our previous study indicates miR-130b inhibits CRC cells migration[75]	The expression level of miR-130b increased in advanced tumor stages (III-IV [77]).	
miR-139-3p	The levels of miR-139-3p in CRC tissues are significantly lower than those in adjacent noncancerous tissues [82,83	Low level of miR-139-3p is significantly associated with poor overall survival, especially in patients with TNM stages I and II [82].	
miR-155	1. MiR-155 facilitates cell migration and invasion. High expression correlated with an advanced TNM stage, lymph node and distant metastasis [85]. 2. Increasing expression correlated with recurrence and metastasis of the tumor postoperatively [87] .	MiR-155 has independent prognostic values for OS and DFS of CRC patients [86], OS and DFS with high miR-155 shows significantly worse survival rates than those with low miR-155 [11],	
miR-224	1. Increased expression associate with an aggressive phenotype, poor prognosis, tumor growth [89], and metastasis of CRC[90]. 2. On the contrary, another study reports miR-224 negatively regulating CRC cells migration [95].	High expression predicts the short-time relapse and shorter metastasis-free survival [90-93].	Enhanced miR-224 result in an increased resistance to chemoradiotherapy in CRC cell lines [94]
miR-378	1. MiR-378 is up-regulated in CRC samples [96, 97] and promotes cell survival, invasion, and angiogenesis [98, 99]. 2. Expression increased significantly in plasma of CRC patient, in addition, miR-378 decreased in patients who have no relapse within 4-6 months after surgery [25, 103-105].	Upregulation of plasma levels of miR-378 can discriminate CRC patients from normal individuals [103].	

Comment 2. Page 1 "and more datA suggest"; "ploYps" should be polyps; Page 6 again... polypS;

Answer 2. Thanks for the revision. We revised the manuscript carefully and inserted "and more data suggest" into line 52, page 2 and " again... polyps" into line 162, page 6.

Comment 3. "X-ray test could bring about harmful radiation and isn't sensitive..." - rephrase and avoid any constructions to comply with scientific style;
Answer 3. We revised the sentence and inserted the following sentence into the 59 line, page 2: "CT has low sensitivity for the diagnosis of early colon cancer and could bring radiation exposure".

Comment 4. page3 - "taken together, current methodologies.." - what about oncomarkers currently used for CRC diagnoses?
Answer 4. We should have made our expression more concisely. Actually, we mentioned the current methodologies in line 58, page 2: "In recent years, there has been significant advance in CRC early diagnosis. Up to now, the common methods for CRC early diagnosis are CT (computed tomography), colonoscopy and fecal occult blood test (FOBT)". Regarding current methodologies, we revised our manuscript and added the following sentence into line 66, page 3: "Taken together, current methodologies for early detection are neither sensitive nor specific".

Comment 5. page 3, 1st para "More", some....can not write like this also - rephrase the last sentence
Answer 5. As suggested, we changed the "more" to "What's more" in line 69, page 3. In addition, we rewrote the last sentence as follows: "Here, we review the literatures to summarize the association of some significant miRNAs with early-stage diagnosis, prognosis and recurrence of CRC, and among them, some might give a hint to guide treatment decisions".

Comment 6. Page 3, 1 sentence, 2d para - give the appropriate reference. space between CRC.Mir-21. loci.MiR-29b - spacing; "to become to invasive" - > become too invasive;
Answer 6. We added the corresponding reference [21, 25, 33] to line 79, page 3. We corrected the sentence and inserted "to become too invasive" into line 96, page 4.

Comment 7. Decypher abbreviation for RECK Page 4 again
Answer 7. We thank this comment. To make the sentence more clearly, we added the full name of RECK "reversion-inducing cysteine rich protein with Kazal motifs" into line 88, page 3.

Comment 8. the acronym FFPE stands for Formalin-Fixed, Paraffin-Embedded;
Answer 8. We followed this suggestion to add the full name "Formalin-Fixed, Paraffin-Embedded" into line 105, page 4.

Comment 9. qRT-PCR abbreviation already mentioned earlier; Page 7 qRT-PCR was already abbreviated in page 4; last sentence, 1st para DFS was already abbreviated on page 5
Answer 9. To make the manuscript more concise, we deleted the following abbreviations "qRT-PCR" and "DFS" in our revised manuscript.

Comment 10. what is PDCD4?; in the next sentence pdcd4 is not capitalized - what is right? Page 9 NOTCH1 and Notch - what is correct?
Answer 10. We thank this comment very much. To keep the same expression in our manuscript, we revised corresponding words to "Pdcd4" and "NOTCH1" on Page 4，line 112 and Page 9, line 266, respectively.

Comment 11. Page 5 the end of the first para should be rewritten
Answer 11. We rewrote the last sentence of the first paragraph in Page 5 and inserted the following sentence "Taken together, these findings suggested that miR-21 serves as a potential prognostic biomarker for CRC." in our revised manuscript.

Comment 12. the one before the last sentence para 2 should be "has been made" para 3 "what's more,.." can not use constructions like that;
Answer 12. We made the corresponding revisions and added the following sentences "has been made" and "More importantly" into Page 5, line145 and line 149.

Comment 13. "serum miR-29a" - please explain;
Answer 13. To make the sentence more concisely, we added the following words "the expression of miR-29a in the serum" into line 206, Page 7.

Comment 14. Page 8 "with stage II disease,..." - rephrase; Page 12 - what is HV? ccRCC - is it a right abbreviation?
Answer 14. We thank this comment very much. We corrected the sentence and inserted "with stage II CRC" into line 224, page 8. In addition, we reviewed corresponding papers and we found the abbreviation "HV" and "ccRCC" are right.

Comment 15. Page 14 BIC gene - please explain; page 15 CEA - decipher;
Answer 15. As suggested, we added the following words "BIC gene (B-cell integration cluster gene)" into line 406, Page 14 ， and "CEA (serum carcinoembryonic antigen)" into line 424, Page 15.

Comment 16. Page 18 "miRNAs are both introduced, since..." re-write the sentence.
Answer 16. We thank the reviewer for the carefully revision for our manuscript. We rewrote the sentence without changing the original meaning and added the following one into Page 18, line 523 as follows: "contradictory findings regarding some miRNAs are introduced, since we consider that…".