Reviewer's report

Title: Epigenetic inactivation of the NORE1A gene correlates with malignant progression of colorectal tumors

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Reviewer: Koichi Suzuki

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Major compulsory revisions
1) NORE1 isoforms: NORE1 encodes two major transcripts (NORE1A and NORE1B), which are derived from alternate splicing and different promoter usage. Macheiner et al. reported that NORE1B was epigenetically silenced in human hepatocellular carcinoma. On the other hands, Hessen et al. reported that NORE1A was inactivated in several human cancers. In this manuscript, the authors demonstrated both NORE1A and NORE1B expression were commonly decreased in colorectal cancer cell lines. The authors should consider which transcript is responsible for malignant progression of colorectal tumors. Otherwise, it is hardly to state that only NORE1A gene correlates with malignant progression of colorectal tumors. In addition, the authors should elucidate whether epigenetic inactivation inhibited the NORE1B expression as well.

2) In abstract, the authors describe as follows; Our data indicate that epigenetic inactivation of NORE1A due to promoter hypermethylation is a frequent event in colorectal tumorigenesis and might be implicated in the malignant progression of colorectal tumors. However, the author did not show any direct evidence such that inactivation of NORE1A was associated with colorectal tumorigenesis. Is NORE1A implicated with the initiation of colorectal tumors or progression? I am interested whether epigenetic inactivation of the NORE1A gene is associated with poor prognosis in each stage as well.

3) The authors demonstrated that NORE1A promoter was completely or partially methylated in 6 of 10 (60%) colorectal cell lines while Hessen L. et al. reported NORE1A promoter was methylated in 1 of 6 colorectal cell lines. What do the authors explain this discrepancy?

Minor essential revisions
4) Fig 3B does not show all of the low expressors and SNU-C4 (Page 10 Line 6). Fig 3C is collect.

5) A grammatical mistake was found as follows; NORE1A expression correlates with tightly with loss of p21 (Page 4 Line 7).

Level of interest: An article of limited interest

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests