

The role of non-coding RNAs in pathogenesis of gastrointestinal stromal tumors

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Revised

The changes are made according the peer-review report:

1) *In the methodology section of the present review, the authors did not discuss the literature search strategy and the selection process for the identification of studies relevant for the review. What are the key words they have used for literature survey? Due to this lacunae, the authors have missed some of the important papers on the topic*

We created a new chapter dedicated for the Methodology we followed to collect the papers. The text also goes with a graph which explains the paper selection process.

2) *The description of the GIST in the introduction would have been more relevant followed by the clinical studies carried out and the treatment options etc. The molecular pathways and the mutational studies carried out to understand the molecular targets have been worked out in detail by many authors, therefore, it appears to be more repetitive since the authors have not been able to build up a hypothesis to follow and support subsequently with the literature available which would make the study more interesting for the readers*

From the Introduction chapter, in the description of GISTs, we deleted much of the information concerning the molecular pathways and oncogenic mutations in GISTs. Instead we added the current treatment guidelines based on clinical trials.

3) *The authors have missed out the study by Badalamenti G et al (2019) in the Journal of Oncology where data suggest a potential role for both H19 and MALAT1 lncRNAs as prognostic biomarker for the clinical selection of the best candidate to first-line treatment with imatinib.*

We included the study by Badalamenti et al, at the end of the paragraph: Potential diagnostic and prognostic biomarkers and once again we discussed this study at the end of the paragraph: Gene regulating non-coding RNAs and their role in GIST carcinogenesis. We also added this paper correspondingly in table number 2.

4) *An excellent review has been published by Juozas Kupcinskas (2018) on 'Small Molecules in Rare Tumors: Emerging Role of MicroRNAs in GIST' in IJMS where the role of non coding RNA has been extensively discussed. The authors failed to quote this reference in their review*

We mentioned these two reviews in paragraph: Non-coding RNAs in GISTs.

5) *The tables presented in the review reflect the references which are not new and most of them are quoted in the previous reviews on the subject*

We added five latest studies (Gyvite et al. 2019, Hu et al. 2018, Badalamenti et al. 2019, Paterczyk et al. 2020 and Yan et al 2019) in tables 2 and 3.

6) *In this paper, Ioannis et al. summarized the recent findings on the role of non-coding RNAs in GISTs. The paper is well-written and easy to read. My main concern is that the references cited in this minireview contains too many papers that have been published over 5 years. Indeed, there are some newly published articles in recent years but I cannot find them in this paper*

We added 3 recent papers (Hu et al. 2018, Badalamenti et al. 2019, Paterczyk et al. 2020) in the “Potential diagnostic and prognostic biomarkers” paragraph. One paper (Yan et al) in “The role of non-coding RNAs in Imatinib resistance. Six papers (Lu et al, Long et al, Badalamenti et al, Long et al, Xue et al and Chen et al.) in “Gene regulating non-coding RNAs and their role in GIST carcinogenesis” paragraph.

In summary we added thirteen papers to the revised version and we deleted six.

Added:

- Chaudhry U, DeMatteo R, Management of Resectable GIST. *Hematol Oncol Clin North Am.* 2009 Feb; 23(1): 79–viii. [PMID: 19248972 DOI: 10.1016/j.hoc.2009.01.001]
- Shah K, Chan K, Ko Y, A systematic review and network meta-analysis of post-imatinib therapy in advanced gastrointestinal stromal tumor. *Curr. Oncol.* 2017 [PMID: 29270063 DOI: 10.3747/co.24.3463]
- Miettinen M, Sobin, L, Lasota J, Gastrointestinal stromal tumors of the stomach: A clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am. J. Surg. Pathol.* 2005, 29, 52–68 [PMID: 15613856 DOI: 10.1097/01.pas.0000146010.92933.de]
- Nannini M, Ravegnini G, Angelini S, miRNA profiling in gastrointestinal stromal tumors: implication as diagnostic and prognostic tumor markers. *Epigenomics* 2015;7(6):1033-49. [PMID: 26447534 DOI: 10.2217/epi.15.52]
- Kupcinskas et al, Small molecules in rare tumors: Emerging role of microRNAs in GIST. *International Journal of Molecular Sciences* 2018 Jan 30;19(2):397. [PMCID: PMC5855619 DOI: 10.3390/ijms19020397].

- Paterczyk H, Paziewska A, Kulecka M, Signatures of circulating microRNA in four sarcoma subtypes *J Cancer*. 2020 Jan 1;11(4):874-882. [PMID: 31949491 DOI: 10.7150/jca.34723]
- Hu J, Wang Q, Jiang L, Effect of long non-coding rna AOC4P on gastrointestinal stromal tumor cells. *Onco Targets Ther*. 2018 Sep 26;11:6259-6269 [PMID: 30288061 DOI: 10.2147/OTT.S174524]
- Badalamenti G, Barraco N, Incorvaia L, Are Long Noncoding RNAs New Potential Biomarkers in Gastrointestinal Stromal Tumors (GISTs)? The Role of H19 and MALAT1. *J Oncol* 2019 Nov [PMID: 31827510 DOI: 10.1155/2019/5458717]
- Yan, Jingyi, Chen et al. Downregulation of lncRNA CCDC26 contributes to imatinib resistance in human gastrointestinal stromal tumors through IGF-1R upregulation. *Braz J Med Biol Res*. 2019;52(6):e8399. [PMID: 31166382 DOI: 10.1590/1414-431x20198399]
- Lu, Jie H, Yan et al. MicroRNA-152 inhibits tumor cell growth while inducing apoptosis via the transcriptional repression of cathepsin L in gastrointestinal stromal tumor [PMID: 29278883 DOI: 10.3233/CBM-170809]
- Long Z, Wu J, Hong et al MiR-374b Promotes Proliferation and Inhibits Apoptosis of Human GIST Cells by Inhibiting PTEN Through Activation of the PI3K/Akt Pathway. *Mol Cells*. 2018 Jun;41(6):532-544 [PMID: 29902839 PMCID: DOI: 10.14348/molcells.2018.2211]
- Xue F, Liu Z, Xu J, Neferine Inhibits Growth and Migration of Gastrointestinal Stromal Tumor Cell Line GIST-T1 by Up-Regulation of miR-449a [PMID: 30551450 DOI: 10.1016/j.biopha.2018.11.029]
- Chen Y, Qin C, Cui X et al MiR-4510 acts as a tumor suppressor in gastrointestinal stromal tumor by targeting APOC2. *J Cell Physiol*. 2020 Jul;235(7-8):5711-5721. [PMID: 31975384 DOI: 10.1002/jcp.29506]

Deleted:

- Heinrich MC, Rubin BP, Longley BJ, Fletcher JA. Biology and genetic aspects of gastrointestinal stromal tumors: KIT activation and cytogenetic alterations. *Hum Pathol* 2002 May; 33: 484-95. [PMID: 12094373 DOI: 10.1053/hupa.2002.124124]
- Zhi Xu, Xinying Huo, Chuanning Tang et al. Frequent KIT Mutations in Human Gastrointestinal Stromal Tumors. *Sci Rep*. 2014 Aug 1;4:5907. [PMID: 25080996 DOI: 10.1038/srep05907]
- Stenman G, Eriksson A, Claesson-Welsh L. Human PDGFA receptor gene maps to the same region on chromosome 4 as the KIT oncogene. *Genes Chromosomes Cancer* 1989 Nov; 1: 155-8. [PMID: 2562117 DOI: 10.1002/gcc.2870010208]

- Went PT, Dirnhofer S, Bundi M, Mirlacher M, Schraml P, Mangi- alaio S, et al. Prevalence of KIT expression in human tumors. *J Clin Oncol* 2004 Nov; 22: 4514-22. [PMID: 15542802 DOI: 10.1200/JCO.2004.10.125]
- Duensing A, Medeiros F, McConarty B, Joseph NE, Panigrahy D, Singer S, et al. Mechanisms of oncogenic KIT signal transduction in primary gastrointestinal stromal tumors (GISTs). *Oncogene* 2004 May; 23: 3999-4006. [PMID: 15007386 DOI: 10.1038/sj.onc.1207525]
- Kyu Kim, Won Yang et al. MicroRNA Involvement in Gastrointestinal Stromal Tumor Tumorigenesis. *Current Pharmaceutical Design* 2013;19(7):1227-35. [PMID: 23092343 DOI: 10.2174/138161213804805748]