ANSWERS TO THE REVIEWERS

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English language: The quality of the English was carefully checked by the second author of this manuscript, who is a native-english speaker (Pr. Dan A Dixon, Department of Molecular Biosciences, University of Kansas, Lawrence, Kansas, and University of Kansas Cancer Center, Kansas City, Kansas, USA).

We thank all the reviewers for their time and careful read of our manuscript. We considered all their suggestions to improve the quality of this review. We also thank the editor for valuable suggestions. All modifications have been highlighted in blue in the word document.

Reviewer #1:

This is an interesting paper that summarizes the knowledge on the oncogenic or tumor suppressive activities of several AUBPs on the colorectal cancer. Authors extensively describe the intracellular pathways involved in the effects of these proteins and their potential use as therapeutic targets. The importance of this study arises from the fact that levels of these AUBP could serve as biomarkers of the early-stages in colorectal cancer. Although this is a well carried out paper with correct English, I consider that some minor aspects should be corrected before it is published.

We thank this reviewer for the careful read and for the valuable suggestions.

In figure 1, HuR appears that positively regulates iNOS and TP53, however information about this topic does not appear in the text of the chapter corresponding to HuR.

The role of HuR on TP53 expression is explained in the paragraph 4.1.1.2 (highlighted in blue in the word document): "*Paradoxically, despite the numerous studies attributing a tumor promoting function to HuR, another study has reported that HuR can bind to the 3'UTR of p53 and enhance its translation in RKO cells under stress conditions (ultraviolet light irradiation)*"

For iNOS, indeed this information was missing in the HuR paragraph but was present in the KSRP paragraph. In a study of Linker *et al* (Nucleic Acid Research, 2005, PMID: 16126846), authors demonstrated that KSRP and HuR compete for the binding to iNOS 3'UTR. This study is now

mentioned in the HuR paragraph (*4.1.1.1 Prostaglandins biosynthesis and inflammation)*.

The same can be applied for TTP and IL1B.

We thank the reviewer for this remark. Indeed, this was a mistake in the figure and the interaction between TTP and IL1β has been removed.

In Figures 1 and 2, authors state the meaning of blue and dashed lines, but they do not indicate that the meaning of black lines is a negative regulation.

This information has been added in both figures.

In Figure 1, change "Il23" by "IL23" and "HIF1a" by "HIF1alpha" In Figure 1, I suppose that "CLDN1" is claudin 1. This abbreviation should be included in the text.

IL23 and HIF1a have been corrected. All abbreviations of Figure 1 and 2 are now explained in their corresponding legends.

In Figure 1, why miR-16, Lin28 and Let7 are in red color?

In this figure, we put all the miRNAs in red color in order to distinguish them from the other targets. This detail is now explained in the legend. Accordingly, the color of Lin28, which is a RNA-Binding Protein, has been changed in black.

The chapter "3. Role of AUBPs in CRC" should be renumbered "4. Role …".

We corrected this numbering mistake.

Some acronyms are repeated. Thus, "lysophosphatidic acid (LPA)" is repeated twice in the last paragraph of page 9.

The sentence

"For instance, HuR contributes to the regulation of lysophosphatidic acid (LPA) by controlling the regulation of autotaxin (ATX), a key enzyme involved in the biosynthesis of lysophospholipid mediators (i.e, lysophosphatidic acid), LPA"

has been replaced by

"*For instance, HuR contributes to the regulation of lysophosphatidic acid (LPA) by controlling the regulation of a key enzyme involved in its biosynthesis (autotaxin, ATX)"*.

In this new sentence, the repetition has been removed.

Similarly, "RNA-recognition motifs (RRM)" is repeated in the chapter "3.1. HUR (ELAVL1)" and in the chapter "3.3. TIA1".

The repetition in the chapter 4.3 has been removed as suggested by the reviewer.

Furthermore, "Autotaxin (ATX)" is repeated twice in the first paragraph of page 17.

We corrected this mistake. The second "Autotaxin (ATX)" has been simply replaced by its abbreviation.

In the chapter "3.3. TIA1", change "stress granules" by "SG".

This correction has been done.

This paper has a large amount of abbreviations and acronyms, most of them necessary. Thus it is better to remove some that are unnecessary such as "resveratrol (RSV)" in page 13, because it is used only once in the text.

"*RSV*" abbreviation has been removed.

"Nitric oxide (NO)" and "inducible nitric oxide synthase (iNOS)" should be abbreviated in the last paragraph of page 14.

Additional details about the role of HuR on iNOS/NO synthesis have been provided earlier in the manuscript (paragraph 4.1.1.1. "*Prostaglandins biosynthesis and inflammation"*). Accordingly, the acronyms were completely defined in this paragraph and only abbreviations have been used for the rest of the manuscript.

In the first paragraph of page 18, authors stated, "These discrepancies might be explained by the physiological context in which the studies were conducted". Why the differences in the physiological contexts between both studies are not given?

Additional information have been provided to better explained these discrepancies. The following paragraph has been added: "*These discrepancies might be explained by the fact that oncogenic functions of RBM3 were mostly demonstrated in vitro in colon cancer cells out of their physiological context. Moreover, the localization of the protein might be associated with different functions as demonstrated for HuR or TTP. However, the molecular mechanisms involved in RBM3 activity localization are currently unknown in CRC*."

Reviewer #2:

Congratulations for relevant works of the authors. I carefully read their paper with a strong interest. The authors summarized the past findings on Adenylate-Uridylate-rich elements binding proteins in a review form. That review is useful.

We thank the reviewer for his/her careful read and we appreciate this positive feedback.

Minor Essential Revisions #1. The authors may disregard my suggestion. In my opinion, if authors show their own research results for Adenylate-Uridylate-rich elements binding proteins (research perspective, strategy, results to date), I believe that the review will be better.

We thank the reviewer for this comment. However, our current work is more focused on the role of these proteins in another context (Liver). For this reason, these data are beyond the scope of this review.

Reviewer #3:

Thank you for the opportunity to review this paper. This is a well-written and comprehensive manuscript on adenylate-uridylate-rich elements binding proteins, spanning from their involvement into colorectal cancer initiation and progression to translational exploitation as attractive therapeutic targets. Only minor comments for possibly improving the quality of the paper:

1) Please double-check the number of subheading for appropriateness in ordering.

We thank the reviewer for this pertinent comment. These errors have been corrected.

2) I would suggest adding some additional evidence regarding interactions between AUBPs other than TTP and HuR and noncoding-RNAs, since also the latters are master regulators of gene expression at post-trascriptional level with a proved role in colorectal cancer development.

Indeed, the crosstalk's between AUBPs and lncRNA/miRNAs is an interesting topic. Unfortunately, there are very few reports mentioning such interactions in the context of colorectal cancer. Nevertheless, we found an additional study showing the role of miR-19a in the regulation of TIA1 in colorectal cancer tissue and cell lines. This study is discussed in the paragraph 4.3.2 "*Regulation of TIA1 in CRC*" and the corresponding miRNA has been added in Figure 1 and in Figure 2 (pathway "epigenetic" inhibiting TIA1).

3) I would suggest placing miR-21 and miR-155 into Figure 1.

The goal of the Figure 1 is to summarize the know targets of AUBPs in the context of colorectal cancer. Since the HuR/miR-21 interaction has been shown in another cancer (Breast cancer cell line MCF7 cells), we would like to keep this information only in the text. However, miR-155 is a positive regulator of HuR in CRC. Therefore, it is pertinent to add this miRNA in this figure. This change has been done.

Reviewer #4:

In this manuscript, Noémie Legrand and co-workers clearly summarized and discussed the recent advances in the role of Adenylate-Uridylate-rich elements binding proteins in the development of colorectal cancer.

Minor concerns: The serial number of subheadings in the manuscript should be carefully revised: "3.Role of AUBPs in CRC" (Page 7) should be replaced by "4.Role of AUBPs in CRC", and the following serial number ("3.1", "3.1.1", "3.1.1.1") should be also revised accordingly. "3.1.1.1. Cell Death" (Page 10) and "3.1.1.1. Cancer cell migration /invasion" (Page 10)

We thank the reviewer for this pertinent comment. These errors have been corrected.

Additional changes:

- In the paragraph 4.1.2, "Regulation of HuR expression/activity in CRC", for a better clarity, we replaced the following sentence:

"In agreement with the role of HuR in the regulation of cell cycle-related genes, OCC1-dependent HuR downregulation leads to an arrest of cancer cells phase of cell cycle arrest in G0/G1 as well as a decrease of direct HuR target genes (i.e, eIF4E, NEK2, MAD2L1, HNRNPA1, HNRNPK). "

by:

"In agreement with the role of HuR in the regulation of cell cycle-related genes, OCC1-dependent HuR downregulation leads to an arrest of cancer cells in G0/G1 phase of cell cycle, as well as a

decrease of direct HuR target genes (i.e, eIF4E, NEK2, MAD2L1, HNRNPA1, HNRNPK).“

- As requested by the editor, we provided the postal code in the first page; the audio tip and we completed the legends of figure 1 and 2 with the abbreviations.

- In the first page, in the section related to the funding, the following sentence:

“The work of Dr. Cyril Sobolewski is currently supported by the “Ligue Genevoise Contre le Cancer” (Grant no. 1711)”

has been replaced by:

“The work of Dr. Cyril Sobolewski is currently supported by a grant of the Geneva Cancer League (Grant no. 1711).”

In order to meet the requirement of this funding source.