

Name of journal: World Journal of Gastroenterology

Manuscript NO.: 19051

Column: Topic Highlights

Title: Epigenetic Regulation of Insulin-like Growth Factor Axis in Hepatocellular Carcinoma

Authors: Hend Mohamed El Tayebi and Ahmed Ihab Abdelaziz

Dear Editor,

Please find enclosed the resubmitted revised manuscript for the mini-review titled;

Epigenetic Regulation of Insulin-like Growth Factor Axis in Hepatocellular Carcinoma; Manuscript NO.: 19051.

We have read thoroughly all the reviewer comments with the constructive criticism which I do respect for the perfection of the manuscript.

We have taken all comments into consideration and we answered the questions and revised the text accordingly (all changes are highlighted in bold).

I am herewith attaching the revised manuscript and the point to point replies to the reviewers.

I always do appreciate very much your support.

With my best regards,

Sincerely,

Ahmed Ihab

Reply to reviewers:

1. Please add figures and tables in this paper!

According to your recommendation, a table and a figure has been added to the mini-review and cited in the text. The table and figure titles are: “Table 1: microRNAs regulating the key players of the IGF axis in HCC” and “Figure 1: Regulation of IGF signaling pathway by microRNAs in HCC”, respectively.

The figure as well as figure legend has been inserted at the end (pages 15 and 16) of the manuscript before the References section. The table is submitted as a separate word file.

2. You'd better offer us one paper with word format next (such as, .doc or .docx), which is easy to be edited and helpful to publish earlier. Thank you very much!

Based on your request, the revised manuscript will be submitted as a word file.

3. **Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B). For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in ‘The Revision Policies of BPG for Article’.**

According to your request, the manuscript has been revised thoroughly and edited by an English native speaker in the English center, German University in Cairo (GUC). The English department is acknowledged in the acknowledgment section in the revised manuscript.

4. **Running title: (Less than 6 words)**

A running title has been added as follows: El Tayebi HM *et al microRNAs and Insulin-like growth factor pathway*

5. **Please rearrange all the authors’ affiliations with Department, University or Institute, City, Postcode, Country, etc. (without any symbol or figure like * or ¹, postcode must be there) Such as: full name, address**

According to your request, the author affiliations have been rearranged as follows:
El Tayebi H.M

The Molecular Pathology Research Group, Department of Pharmacology and Toxicology, Faculty of Pharmacy and Biotechnology, German University in Cairo, Cairo,11835, Egypt

Abdelaziz A.I.

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6. **Please provide the author contributions. Authors must indicate their specific contributions to the published work. This information will be published as a footnote to the paper. See the format in the attachment file-revision policies. The format of this section should be like this: Author contributions: XXX (family name should be put first in full, followed by middle names and first name in abbreviation with first letter in capital) designed research; XXX performed research; XXX contributed new reagents or analytic tools; XXX analyzed data; XXX wrote the paper. An author may list more than one contribution, and more than one author may have contributed to the same aspect.**

The author contribution has been added in the front page of the manuscript as follows:

Author contribution: El Tayebi H M contributed in literature reviewing, manuscript writing and editing, Abdelaziz A I contributed in designation, revision and correction of the manuscript

**7. Supported by
Conflict-of-interest statement:**

According to your WJG guidelines, a “ Conflict of interest statement” has been added.

8. Core tip: Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

A paragraph of less than 100 words has been added to the manuscript and highlighted in Bold in the place suggested for Core tip according to WJG guidelines.

Audio core tip:

In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information.

An Audio core tip has been recorded as .mp3 file and uploaded in the online submission page.

2. Please provide all authors abbreviation names and manuscript title here. World J Gastroenterol 2015; In press

This part has been added to the text and highlighted in Bold.

3. Some files [Conflict-of-Interest Statement (COI), Copyright (need signature of all authors) and language Certificate (.pdf)] and Audio core tip (.mp3)

All these required documents and files are either attached in the manuscript or submitted with the manuscript in the online submission.

9. Please distinguish the title level, level I used all capital letters and bold, level II used Italic effect and bold, level III was just bold.

All titles in the manuscript has been distinguished accordingly

10. Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI. PMID(<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) DOI (<http://www.crossref.org/SimpleTextQuery/>) (Please begin with DOI: 10.)**

All references are edited with the addition of the PubMed citation numbers and DOI citation as well as the required reference style.

11. Google Scholar :

The screenshot shows a Google Scholar search results page. The browser's address bar displays the URL: <https://scholar.google.com.eg/scholar?hl=en&q=Epigenetic+Regulation+of+Insulin-like+Growth+Factor+Axis+in+Hep>. The search bar contains the text "Epigenetic Regulation of Insulin-like Growth Factor Axis in Hepatocellular Carc". The page indicates "About 5,150 results (0.06 sec)".

On the left sidebar, there are filters for "Articles", "Case law", and "My library". Under "Any time", there are options for "Since 2015", "Since 2014", "Since 2011", and "Custom range...". Under "Sort by", there are options for "relevance" and "date". There are checkboxes for "include patents" and "include citations". At the bottom of the sidebar is a "Create alert" button.

The main content area displays three search results:

- Result 1:** "Growth hormone, the insulin-like growth factor axis, insulin and cancer risk" by PE Clayton, I Banerjee, PG Murray... - Nature Reviews ..., 2011 - nature.com. The abstract mentions "... resulting in acromegaly) could predispose patients to other tumors and/or epigenetic mechanisms that ... 2, BRAF, serine threonine protein kinase B-raf, ERK, extracellular signal-regulated kinase, HIF ... & LeRoith, D. Circulating insulin-like growth factor-I levels regulate colon cancer ...". It is cited by 133. Links for "Related articles", "All 6 versions", "Cite", and "Save" are provided.
- Result 2:** "Unraveling insulin-like growth factor binding protein-3 actions in human disease" by S Jogie-Brahim, D Feldman, Y Oh - Endocrine reviews, 2009 - press.endocrine.org. The abstract mentions "... of heteromeric Smad complexes to the nucleus where they can potentially regulate the transcription of ... to the nuclear receptor superfamily, consisting of a large number of ligand-regulated transcription factors ... Insulin is another important hormone in IGFBP-3 up-regulation (108). ...". It is cited by 170. Links for "Related articles", "All 6 versions", "Cite", and "Save" are provided.
- Result 3:** "Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer" by MS Sandhu, DB Dunger... - ... of the National Cancer ..., 2002 - jnci.oxfordjournals.org. The abstract mentions "... Experimental data suggest that IGF-I itself may also regulate hepatic IGFBP-3 production (44 ... These signaling pathways may also be differentially regulated by the relative availability of immediate ... The IGF-I signal transduction pathway involved in the regulation of apoptosis and ...". It is cited by 385. Links for "Related articles", "All 5 versions", "Cite", and "Save" are provided.

Below the third result, there is a link to a full view of an article: "[HTML] Maternal high fat diet during pregnancy and lactation alters hepatic expression of insulin like growth factor-2 and key microRNAs in the adult offspring" by J Zhang, F Zhang, X Didelot, KD Bruce... - BMC ..., 2009 - biomedcentral.com. The abstract mentions "... deficiency causes global and Igf2 gene DNA hypermethylation through up-regulation of Dnmt1 ... Let-7a-3 hypomethylation facilitates epigenetic reactivation of the gene and elevates ... Interestingly, several important proteins involved in epigenetics are predicted targets for those ...". It is cited by 106. Links for "Related articles", "All 21 versions", "Cite", "Save", and "More" are provided.

The bottom of the screenshot shows a Windows taskbar with the "start" button and several open applications: "Inbox - Microsoft ...", "Epigenetic Regula...", "IGF-mR Review", "Guidelines and Re...", and "البحث العلمي في ...". The system clock shows "12:28 PM".

12. Plagiarism Checker:

The screenshot displays the Plagiarism Checker website interface. The browser's address bar shows the URL: www.plagtracker.com/report_new/82c58ff761be2926234633309d27c104/#. The page header includes the PlagTracker logo, social media links (Facebook Like 5.5k, Follow @plagtracker), and navigation links (PLAGTRACKER'S API, GET PREMIUM ACCOUNT, LOGIN). The main content area reports: "Your paper contains **0%** of non-unique content that appears in **0 Sources**". Below this, a sample text is provided for analysis. The text discusses the Insulin-like Growth Factor (IGF) signaling pathway in hepatocellular carcinoma (HCC). It mentions that IGF network dysregulation is a clear essential evidence in many cancers and developmental abnormalities. It also notes that a minority of patients are eligible for curative treatments such as tumor resection or liver transplant. The text further states that recent researches are focusing on targeting IGF axis members in an attempt to find therapeutic means for many health problems. In this review, the authors are shedding the lights on the regulation of the IGF axis member mainly by microRNAs in HCC where microRNAs are trying desperately to halt the aberrantly expressed IGF network by the fact that single microRNA can have multiple downstream targets in one or more signaling pathways. This is an approach in an attempt to find an efficient radical cure for HCC. Keywords: Hepatocellular carcinoma, Insulin-like Growth Factors, Insulin-like growth factor receptors, epigenetics, microRNAs. Introduction: Insulin-like growth factor (IGF) axis is a highly conserved signaling pathway throughout evolution and has a crucial role in cellular and tissue regeneration through its proliferative and anti-apoptotic activities and its dysregulation is evidenced in many diseases [1]. IGF network possess important key players; IGF-I and IGF-II ligands that bind to their

On the right side, there is a section titled "Sources found:" with a link to "Click on the highlighted sentence to see sources" and a link to "View all sources". A vertical button labeled "Support & Feedback" is also visible.

The bottom of the screenshot shows the Windows taskbar with the Start button, several open applications (Inbox - Mic..., www.plagtra..., 2 Windows..., Guidelines an..., البحوث العلم..., Revised 3 se...), and the system clock showing 12:37 PM.