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Journal Name:	International Journal of Biochemistry Research & Review
Manuscript Number:	2013_IJBcRR_8617
Title of the Manuscript:	Mini-review: Respiratory and pH imbalance at the early precancerous stage
Type of the Article	Mini-review

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This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment <i>(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i>
<u>Compulsory</u> REVISION comments	The authors should to systematize the use of the acronym RpHI, sometimes they use the acronym other times they write respiratory and pH imbalance. Abstract The first sentence is difficult to understand, please rephrase this sentence. <u>Keywords</u> What is the reason to use the term precancerous stage instead of preneoplastic? In my opinion the authors should to use cancer development as a keyword <u>Introduction</u> The authors should to explain better the cancer etiology. Cancer etiology is not only based in environmental factors. Line 59, page 2; the authors 20-22, cited Warburg. Please make the proper citation. Line 76, page 3; What means first malign cell?	We appreciate so much the pertinent suggestions of the Reviewer. The Reviewer is right, and we made the required changes: acronym RpHI is all around the manuscript, whereas "respiratory and pH imbalance (RpHI)" is for the abstract. The first sentence was replaced with "Cancer prevention is a global priority, yet the proximate causes of most cancers are still little understood." Keywords: "Preneoplastic stage" was introduced both in the Abstract and Keywords. Keywords contain now cancer development, as suggested. <u>Introduction</u> Corrected: A definition of cancer was given: Cancer is a multifactorial disease with contributions from environmental, genetic, and lifestyle factors. Correct citation was introduced: Warburg, O. On the origin of cancer cells. Science. 1956;123:309-14. Line 76, page 3: Changed with preneoplastic



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	According to the knowledge of cancer development, after the exposition to a carcinogen (chemical, physical, viruses, parasites, etc...) first appear preneoplastic cells and latter these cells develop to neoplastic cells. However, according to the manuscript authors RpHI induce cell divisions producing benign and malignant tumors (lines 66 to 69). Can the authors explain better this idea? Page 6, figure 1. In opinion the legend of the figure is not adequate. The figure intended to explain the relation between the degree/level of RpHI and local stress with cancer development. In cancer development, independently of the cancer etiology, appear first preneoplastic cells. Why put the authors in the figure benign tumors? The figure 1 is also difficult to understand. What means Cancer, Cancer I and Cancer II? Line 166, page 6. The authors said: "A stronger action of the stress agents could kill the body at this stage", please clarify this idea. Page 7, It is difficult to understand what is Cancer I and	cells. The Reviewer was right. Thank you. We changed "faster producing first benign or malignant tumors." with "faster producing first preneoplastic cells, and, then, malignant tumors." Fig 1 was improved. Indeed, we removed "benign tumors" and introduced "preneoplastic cells". "A stronger action of the stress agents could kill the body at this stage" was followed by an explanation: "It is the case of microorganism- or virus-induced diseases, which, if untreated, have a bad prognostic." In the same paragraph "Long standing infectious pathologies may thus result in a RpHI, which create the conditions for either the transformation of normal cells into preneoplastic cells followed by preneoplastic to neoplastic pathway or for the multiplication of malignant cells. It is well-known that only the bodies with a significant amount of morbidity may become cancerous" was added to explain more correctly the stress action. Fig. 1 was corrected to be more suggestive.
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	Cancer II. Page 8, topic <u>Chemical carcinogenicity...of carcinogen</u> Line 242 The authors generalize that all body cells have the same capacity to biotransform/metabolize chemical carcinogens. This is not correct. Please perform the adequate corrections. The authors should to explain in particular the chemical carcinogens biotransformation and its influence in RpHI.	Cancer I and Cancer II were replaced with more informative notions. Cancer I changed into: "imbalanced body, suitable environment for malign transformation". Cancer II becomes "isolate neoplastic cells". The following explanation was given: "Metabolic processes of carcinogens occur in cells in organisms [Manahan, 2003]. The most important degradation pathways are oxidation reactions, particularly those classified as microsomal monooxygenation reactions. Monooxidations occur with oxygen as the oxidizing agent, generating a long standing hypoxia if carcinogen degradation is a multi-step process, this one is not too toxic to kill the cell, and its degradation products are also difficult to be eliminated. Besides, at page 8, in "<u>Chemical carcinogenicity...of carcinogen</u>", we wrote: "The degradation pathway of carcinogens is based on oxidation reactions, particularly those classified as microsomal monooxygenation reactions. These reactions occur with oxygen as the oxidizing agent, generating a long standing hypoxia if carcinogen degradation is a multi-step process". Indeed, the Reviewer correctly observed that we generalized the capacity of metabolizing carcinogens by the cells. Therefore, we corrected the text. Done. Please, see what we introduced "Metabolic processes of carcinogens occur in cells in
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	The authors should read and cite a chemical carcinogenesis paper. Page 10, line 278, "...from an early dysplastic lesion to full-blown metastatic malignancy seems to be associated with increases in genomic instability." In my opinion, this idea is not entirely correct. I will write: from preneoplastic lesions to cancer seems to be associated gradually increases in genomic instability. The authors said in the same page, line 283-284 that the interference of hypermethylation and hypomethylation in cancer cells is unclear, based in a reference from 1994. I recommend reading the following paper and make the appropriate corrections: Characterizing DNA methylation alterations from The Cancer Genome Atlas. Weisenberger DJ. J Clin Invest. 2014 Jan 2;124(1):17-23. doi: 10.1172/JCI69740. Epub 2014 Jan 2.	organisms [Manahan, 2003]." P450-associated degradation of 3-methylcholanthrene was depicted in Kaminsky LS, Fasco MJ. Small intestinal cytochromes P450. Crit Rev Toxicol. 1992. Besides, some other papers were referred to such as: Loeb LA, Harris CC. Advances in chemical carcinogenesis: a historical review and prospective. Cancer Res. 2008; 68:6863-72, or Conney et al. Cancer Res. 1956. New sentences such as "In the two-stage skin carcinogenesis, the initiation phase is carried out by the application of a sub-carcinogenic dose of a carcinogen [Abel et al. Nat Protoc. 2009]. Done. The Reviewer's suggestion was correct. The phrase "The significance of these alterations in the genesis of cancer is, however, unclear" was deleted. The literature from 2014 and 2013 on this topic was introduced and discussed. Consequently, we read and cited papers by Weisenberger, Jones and other authors.
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	Page 11 remove the acronym ER, line 299. The phrase: "The molecular details of this connection are still being elaborated". Lines 328-329 in page 12. Contradicts the phrase 436-437 in page 15: Tissue hypoxia is a well-known stimulus to angiogenesis" Please clarify this idea. Page 16, lines 468 and 469. Enumerate cancers that are beneficially affected by physical activity and cancer that are associated with overweight and obesity. Page 16 lines 473 and 475, please clarify the interference of anxiety and depression in cancer survive.	Done. In fact, tissue hypoxia is a well-known stimulus to angiogenesis [Knighton et al. 1981]. Moreover, "molecular insights into these processes are rapidly being generated [Carmeliet, 2003]." The phrase: "The molecular details of this connection are still being elaborated" was deleted. We added: "Although the lung is a well oxygenated environment, hypoxia has been demonstrated in the center of an invasive lung tumor [Serfin, 2011]. The molecular markers of hypoxia like HIF-1α and CA9 suggest that carbon dioxide removal rather than oxygen supply is expected from the physical exercises." On the other hand, overweight and obesity are associated with a RpHI within the whole body and a long standing hypoxia that may result in cancers like those in the following organs: colon, breast, endometrium, oesophagus, and kidney [Bianchini et al. 2002]. Cancer and depression commonly co-occur, while chronic and severe depression may be associated with elevated cancer risk [Spiegel & Giese-Davis, 2003]. Some evidence shows that providing psychosocial support to reduce depression, anxiety, and pain may increase survival time with cancer. "Depression and emotional disorders may reduce treatment success in cancer [Gripp et al. 2007]. A bidirectional relationship between cancer and depression was thus found" was added.
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	Concluding remarks, last sentence, lines 519 and 520; according to the author's oxygen tension, hypoxia and carbon dioxide are parameters that may influence cancer development. Is this influence positive or negative? <u>References</u> In references number 11, 18, 32, 33, 34, 35, 36, 37, 57; 74 and 98 lack pages. In reference 74, please put 335(6064):29. doi: 10.1126/science.335.6064.29. In reference 100, please remove the DOI number and put the volume number and pages	Positive. The phrase was reformulated: " our theoretical approach suggests that hypoxia, and carbon dioxide loading are key parameters that positively influence cancer development in some tissues." Done. Done Done
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<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments	In this manuscript the authors review the interference of respiratory and pH imbalance in cancer development. Despite being an interested and novel theme, to be accepted for publication the authors should to clarify several aspects. I identify a lack of strength. - The manuscript title is not appropriate to this mini-review. In my opinion: "The influence of respiratory and pH imbalance in cancer development" is more suitable. - I recommend the manuscript revision by an English native. - The references should be actualized; some bibliographic references are old and not appropriated to a mini-review.	We appreciated so much the effort and understanding our research. Indeed, the reviewer is right: some references are old and some others unsuitable. We made the necessary changes. - The manuscript title was changed with "The influence of respiratory and pH imbalance in cancer development". We thankfully accept the suggested title: "The influence of respiratory and pH imbalance in cancer development". - The manuscript was checked by a teacher of English. - Indeed, the reviewer is right; we introduced more references. First we put the original work by Warburg. Then, we introduced a lot of actual references in 2013 and 2014 on the topic discussed in the manuscript. - Ref 20 and 21 were the same; Ref 21 (Cairns et al. 2011) was replaced with another one on the same topic: Seyfried, 2012.