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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

General guideline for Peer Review process:

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>



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<u>Compulsory</u> REVISION comments	1) Page 18, line 508 – “long standing hypoxia”. How long is it standing? It has to be noted that organism is able to compensate the hypoxic state immediately. 2) Page 18, lines 512-515 – How is it possible to detect the precancerous stage in the tissue to start the preventive therapy, in particular oxygen delivery to the cells? How can oxygen be delivered to the precancerous cells? How can selective oxygen delivery be received? What kind of organism response will be on the exogenous oxygen?	We appreciate so much the pertinent suggestion by the Reviewer and made the required changes. 1) It depends on the duration of action and intensity of stress agent. The “long standing hypoxia” is something relative. For example, a woman whose child died will suffer for 10 year or longer till she will be diagnosed of breast cancer, while a laboratory animal being injected with a powerful carcinogen will die from cancer in months. Important is not the quantity but the quality. We were interested in a biochemical and physiological mechanism to explain what happened with a cell before becoming malignant. Organisms may compensate hypoxia if the causal agent stops acting. If it is continuously acting, then it is difficult to balance the normal concentration of oxygen in various tissues as well as pH. 2) It is quite simple: avoiding powerfully stress agents. There is eustress related to adaptive reactions towards environment and distress caused by stress agents that overpassed the adaptive capacity of the organism. Qualitatively, a person with troubles has to become conscientious on the stress. Educations, relaxation, mild life conditions, deep understanding of life are thus all important. However, quantitative measures may be psychological evaluation, blood pressure, carbon dioxide in blood, glucose level, iron and copper concentrations in blood etc. Avoiding stress agents except those that enhance the body résistance (physical exercises, various emotions in school or job etc may be beneficial for the one'
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	3) Author discusses the precancerous state and solid tumors metabolism from the position of oxygenation and glycolysis (page 11). He writes: "In solid regions of tumors the most consistent finding is: a higher glucose utilization rate, a higher lactate production, and a higher pH than in the surrounding tissues.70". But, it is the example with malignant glioma only. It is well known that the most solid tumors are characterized by acidic extracellular pH that is lower than pH in surrounding tissues. It is a key feature of solid malignant tumors. This position of author is not correct and needs to be edited.	health. How can oxygen be delivered to the precancerous cells? Physical exercises, deep breathing, meditation, yoga etc. But the best measure is to release immediately the overstressed cells (an old wound, an excrescence under medical assistance - please note that we are biochemists and not doctors). 3) The reviewer is right (page 11). We corrected the mistake with " a lower pH". Moreover, the phrase "The acidic extracellular pH that is lower than pH in surrounding tissues is a key feature of solid malignant tumors." was added. A paper by Zeng et al (Hypoxia and hypoxia inducible factors in tumor metabolism Cancer Lett 2014) was cited, and which clarify the issue.
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Minor REVISION comments	1) Fig. 1 – Cancer I and Cancer II – it is not evidently and informative. The explanations on the page 5, line 124 and page 7, lines 182-193 are not clear. 2) Fig. 3 – it is not clear, it needs to be clarified. 3) References - 46. West, J. B. (2012) ... It neither is nor clears, to clarify. - 101. The year of publication is absent.	1) Fig. 1 was corrected to be more suggestive. 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". Done. We reformulate the phrases mentioned. Page 5, line 124: Alveolar ventilation is responsible for carbon dioxide elimination. A slight respiratory acidosis results primarily when alveolar ventilation is decreased or if carbon dioxide production is increased. However, the organism has several compensatory systems to minimize a decrease in pH. Page 7, line 182: Changed: The RpHI causes an oxygen crisis and the busiest cells divide faster and faster under anaerobic conditions. The preneoplastic cells thus appeared with become neoplastic and then form tumors; these ones and their fermentation products can kill the body, if they are not surgically or by other means removed. Page 7, line 184: " which created a local (in a target cell or tissue) RpHI " added. Page 7, line 187: " At this stage neoplastic cells and tumors may be found in the body. " was added. 2) Fig. 3 was much improved. More and clearer explanations were given in the legend. 3) - 46. West, J. B. (2008) ... Corrected. - 101. Corrected: 2011.
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Optional/General comments	The material presented in the manuscript is interesting and actual. The idea that respiratory and pH imbalance impact on tumor development was presented. The exploited literature data partly confirm author's idea. At the same time some there are basic questions that need to be clarified. 1) What does it mean "an early precancerous stage"? How can it be identified? It is very important because how will we know the time to start the preventive therapy? 2) Page 1 (abstract), lines 12-14 and page 18, lines 509-511 – It is very simple explanation of cancerogenesis. It needs to be presented more correctly.	We appreciate so much the appreciations the the Reviewer on the manuscript. Indeed, it is necessary to give more answers to questions raised. 1) We changed to "preneoplastic stage" as suggested by another Reviewer. It begins as a result of a stressor, which distresses the body. This one adapts toward normally intense stressors, which strength it. If the powerful stress agent will act day, weeks or months, then the body is becoming imbalanced and preneoplastic cells may appear. Preventive therapy is already applied, without saying it is against cancer. Long ago, I myself had for months a wound on a leg that the doctor burnt it. Yet, biopsy was negative. Divorced women, they with troubles go to psychologist. Hence, the RpHI may state the idea: "Go for investigation and treatment when feel that something is wrong with you not to become cancerous". 2) "Carcinogenesis is a process by which normal cells are transformed into cancer cells." was added in Abstract. Moreover, at page 18, lines 509-511 a more suitable explanation of cancerogenesis was given. The phrase "Mutations of certain genes have been identified as risk factors for development of certain cases of cancer." was there added. To be presented more correctly, the definition was doubled by some new references appeared in 2014 and
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	3) Page 1 (abstract), line 15 and – How can the overstressed cells be detected in whole organism? How will organism response to these cells? 4) page 1 (abstract), line 17 – What does it mean “most cancer disease”?	2013. 3) The overstressed cells can easily be detected in whole organism, since there are the results of experimental tumors. Benzpyren produces inflammation, benign and malign tumors. If a hormone acts continuously then some cells will begin to multiply in excess. However, finding out of overstressed cells is not important. Important is to decrease the intensity and period of local stress. RpHI hypothesis shows how normal cell becomes preneoplastic and then neoplastic. A hypothesis or a theory cannot by itself heal. But it can explain our observations. Moreover, a suffering person from stress (no job, troubles with the job, troubles in family etc) may become ill and, in time, a simple cold could provoke a lung cancer. What about the smokers and the decrease of lung cancer incidence on abort smoking? The healing art should change "how to detect and remove a tumor" into "how to avoid becoming cancerous". RpHI is a natural response of an organism against stress agents; the hypothesis explains what happens when the adaptive capacity of this organism is overruled. How will organism response to these cells? The whole organism reacts against the overstressed cells, and the inflammation is a sign. Therefore, it is better to help the body to remove the stress agent or the conditions that stress the body as a whole or locally. 4) The words “most cancer diseases” were replaced by “cancer incidence” in order to avoid any confusion. In fact, RpHI seems to be involved
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	5) Author proposes to use the oxygen delivery as one of preventive means. How will oxygen reach “overstressed cells” only? And what kind of response of organism will be on the exogenous oxygen? Is there selectivity of such effect and what level? Please clarify ethical issue, if any	in all forms of neoplasm . 5) The oxygen delivery could be one of preventive means only to improve the organism reaction against stress. Suppose a carcinogen acting on a tissue. Microsomal oxidation using molecular oxygen is in charge with its degradation and removing. More oxygen is needed supplied by blood. If the whole body is hypoxic (high blood glucose, lack of physical exercises, stress, fear etc), then the process of degradation takes longer. Moreover, a better oxygenation of the body will calm the individual. Oxygen will reach not only the “overstressed cells” but all the cells. The exogenous oxygen penetrates all the tissues but the partial pressure is different from a place to another. However, deep respiration of clear air seems to improve both the O₂ partial pressure around the body and general state of the organism (relaxation, calm, focusing, trust etc). No ethical issue to be clarified.
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