Review of: "The role of pH in cancer biology and its impact on cellular repair, tumor markers, tumor stages, isoenzymes, and therapeutics"

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Potential competing interests: No potential competing interests to declare.

Referee report concerning the manuscript:

The role of pH in cancer biology and its impact on cellular repair, tumor markers, tumor stages, isoenzymes, and therapeutics,

by Maher Akl and Amr Ahmed

The authors reviewed and discussed the role of pH in cancer biology. The addressed the impact of acidic environment present in cancerous cells on the function enzymes, receptors, transporters, and DNA. Acidic microenvironment could be detected for the purpose of diagnosis and applied for novel strategies of chemotherapy.

The manuscript is clearly written. I can recommend the manuscript for publication after a minor revision. The authors should add some discussion and references concerning pH dependent processes relevant for neuroscience.

1) I would add some discussion regarding demanding pKa measurements and calculations. See some work of Arieh Warshel and Al Mildvan. See for example:

Biochemistry. 2001 Feb 20;40(7):1984-95.

Biochemistry 1996, 35, 814-823

J. Phys. Chem. B 1997, 101, 4458-4472

J. Phys. Chem. B, 118 (2014) 4326-4332

Quote, comment!

2) I would clearly state that altered pH values may change protonation states of biological macromolecules giving rise in the worst case to unfolding and complete loss of function.

Free energy cost to (de)protonate an ionizable group with certain pKa value to the solution with certain pH value reads

deltaG (in kcal/mol)= 1.38*(pH-pKa)

For application to pH dependent reactions in enzyme and in water see:

J. Phys. Chem. B, 124 (2020) 8259–8265.

Front. Mol. NeuroSci. 11 (2018) article 467, doi: 10.3389/fnmol.2018.00467

The latter study might explain dopamine autoxidation giving rise to Mb Parkinson.

Quote, comment!

3) Protonated drugs are less prone to enter lipophilic compartments e.g. membranes. What happens with the neuron's cytoplasm pH in the vicinity of acidic cancerous cells? I would expect that local anesthetics are less effective if neuron cytoplasm pH value drops. I something known about that? Local anesthetics under the conditions of local acidosis work poorly. See for example

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Quote, comment !

4) Do you expect that receptors still work properly under such acidic conditions. Especially problematic might be GPCR.

Comment !

--End of comments--