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Membrane Surface Charges Attracted Protons are not Relevant to Proton Motive Force

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Only a half century ago, British scientist Peter Mitchell proposed the conceptual scheme known as "chemiosmotic theory" that identified the role of proton coupling in the formation of ATP in cells [1,2]. Mitchell's delocalized proton-coupling chemiosmotic theory was initially quite controversial. But it would win for him the Nobel Prize in Chemistry in 1978. However, questions about Mitchell's chemiosmotic hypothesis have never gone away and a number of credible studies indicated the full extent of Mitchell's idea didn't always hold up in experiments.

In Mitchell's view, the ATP synthase is coupled to the redox proton (H^+) pumps via bulk phase-to-bulk phase proton electrochemical potential gradients generated across a biological membrane such as the thylakoid membrane; while the membrane is regarded as an insulator between the two bulk phases that plays no role in the lateral transduction of the protons to the ATP synthase. That is, the Mitchellian view treats protons as free solutes like sugar molecules in water so that they would be distributed everywhere within the water body bulk phase.

Williams as early as in 1961 first questioned the validity of Mitchell's delocalized proton-coupling chemiosmotic hypothesis and subsequently noted in his 1975 FEBS LETTERS publication [3] as follows: "If charge is thrown into the medium, as in osmotic theories, then we face the problem of equilibration of the energy of a single cell on its outer side with the whole of the volume in which it is suspended, say the Pacific Ocean". This comment remains valid even as of today since Mitchell's delocalized proton-coupling chemiosmotic hypothesis indeed cannot explain a number of experimental observations. The most clear-cut observations that cannot be explained by the Mitchellian delocalized view are in alkalophilic bacteria [4,5] such as *Bacillus firmus*, for which the application of Mitchell's chemiosmotic theory in this case yields a pmf value so small that it has remained as an enigmatic problem for decades as to how these organisms can synthesize ATP [6].

In the first issue of the Bioenergetics journal in 2012, this author published a new proton-electrostatics hypothesis for localized proton coupling bioenergetics [7]. This hypothesis is based on the idea that a microscopic water body, such as the water within a thylakoid lumen, could be thought as a quasi proton conductor. It is known that protons can quickly transfer among water molecules by the "hops and turns" mechanism [8]. This understanding suggests that free excess protons in a small and/or microscopic water body may behave like electrons in a perfect conductor. By the same token, it is reasonable to expect that free excess protons in a small and/or microscopic water body will move to its surface. Adapting this view to the excess protons injected into the thylakoid lumen during photosynthesis, they will be electrostatically localized along the water-membrane interface. In addition, their positive charges will attract the negatively charged species, namely the hydroxyl anions (OH^-), to the membrane-water interface at the stromal side of the thylakoid membrane, as illustrated in Figure 1.

This hypothesis has now led to a new bioenergetics equation for the proton motive force (pmf) that may provide a unified framework for understanding the energetic of many biological systems:

$$pmf = \Delta\psi - 2.3RT/F\times\Delta pH^{L}_{eff} - 2.3RT/F\times\Delta pH \quad (1)$$

where ΔpH^{L}_{eff} in the second term is an effective change in pH due to the localized excess protons at the membrane-water interface causing a proton concentration gradient across the ATP synthase. The last term accounts for the concentration gradient across the ATP synthase due to the delocalized protons.

As discussed in Lee [7], the proton-electrostatics localization model may help to explain a wide range of experimental observations in bioenergetics conducted since 1960s in relation to the proton localization and delocalization phenomena. For instance, according to the proton-electrostatics localization model, the proton concentration density near the membrane-water interface, represented in Equation 1 by the term of $-2.3RT/F\times\Delta pH^{L}_{eff}$, could be significantly higher than the bulk phase-to-bulk phase pH difference, represented by $-2.3RT/F\times\Delta pH$. This could provide a natural explanation as to why the pmf in alkalophilic bacteria is large enough to synthesize ATP.

Since the publication of the proton-electrostatics localization hypothesis, this Bioenergetics journal published a well-balanced editorial by Pastore [9]. However, based on some comments that this author has received, there seems to be a significant misunderstanding as to the difference between the bioenergetics roles played by the electrostatically localized excess protons versus the protons that are attracted to membrane surface charges.

It is worthwhile to note that typical biological membranes contain negatively-charged surface groups, such as the negatively-charged phosphate groups of the membrane's phospholipid molecules, at its two surface sides. This type of membrane-fixed surface charges can attract protons and other cations, and form "electrical double layers" along membrane surfaces as expected by the Debye-Hückel and Gouy-Chapman theories [10]. Because of the electric attraction of protons by the membrane surface charges, the "local proton concentration" at the vicinity near the membrane surface charges could be somewhat higher than that in the bulk aqueous phase. However, this type of the "local proton concentration" resulted from the electrostatic attraction by membrane's fixed surface charges has absolutely nothing to do with the proton motive force (pmf) that drives the flow of protons across the membrane through the coupling factor CFoCF1 for ATP synthesis.

We can confirm this point by the following analysis with thermodynamic principles. Because the membrane surface charges are

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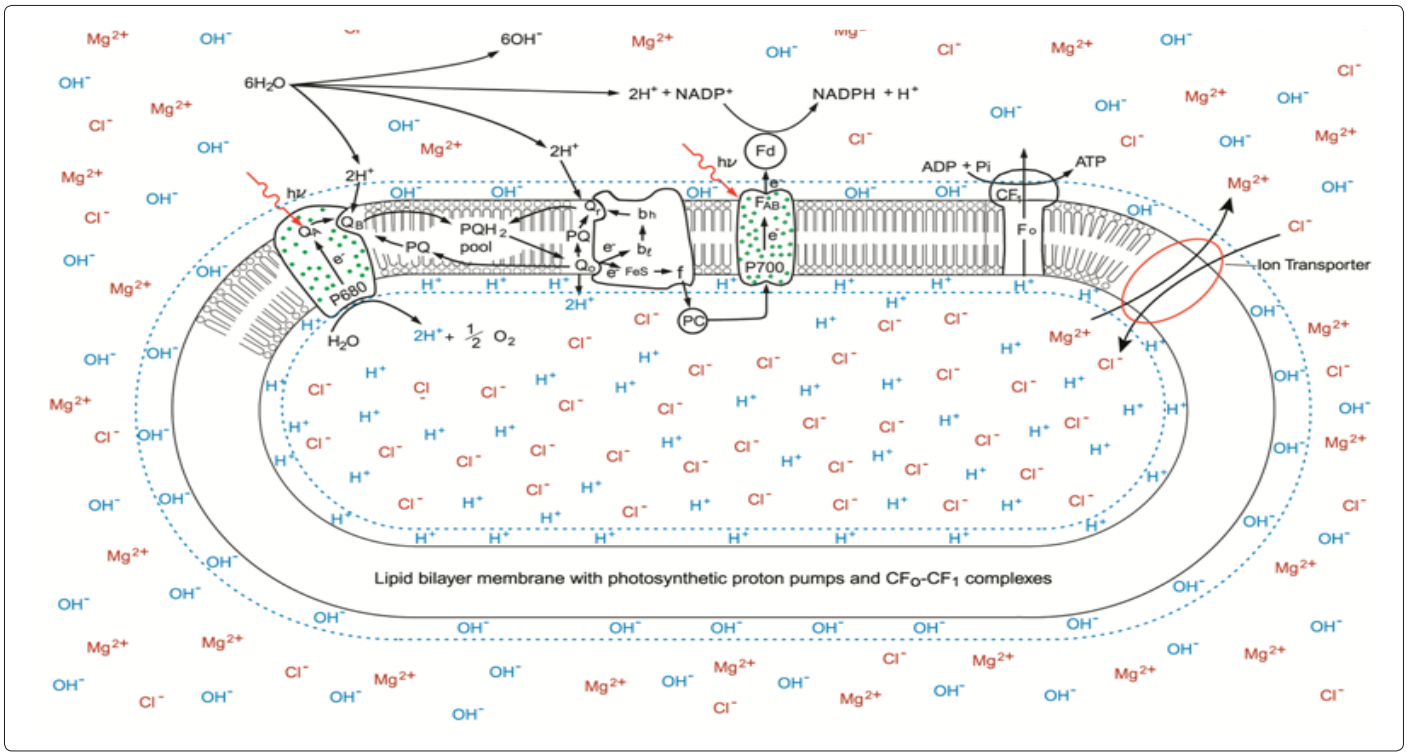

Figure 1: Proton-electrostatics localization schematic explaining the effect of ion migration across thylakoid membrane: the localized excess protons could be delocalized when the trans-membrane potential difference is near zero so that the bulk pH difference may become a dominant driving force for ATP synthesis [7].

fixed, their attracted protons as part of the "electrical double layers" along membrane surfaces is there at all the time even when the proton motive force (pmf) is zero such as in a fully relaxed resting state before and after photosynthetic (or respiratory) energyzation. If the "local proton concentration" resulted from the electric attraction by membrane's fixed surface charges as expected by the Debye-Hückel and Gouy-Chapman theories could somehow contribute to the proton motive force that drives the flow of protons across the membrane through the coupling factor CFoCF1 for ATP synthesis, then it would result in a system that could produce useful energy such as ATP without the need to use light (photosynthetic) and/or chemical (respiratory) energyzation. That kind of system would constitute a perpetual motion machine doing work without requiring external energy, which is clearly false since it would violate the fundamental laws of thermodynamics. It is well known that ATP synthesis through photophosphorylation and/or oxidative phosphorylation requires the input (use) of light and/or chemical energy. Therefore, it is thermodynamically impossible for the membrane's fixed surface charges-attracted local protons which are part the "electrical double layers" along membrane surfaces to sustainably drive any flow of protons across the membrane through the coupling factor CFoCF1 for ATP synthesis.

According to the proton-electrostatics localization model as shown in Figure 1, excess protons are generated by use of external energy such as by use of light energy in a photosynthetic electron transport-coupled proton translation process; and the excess protons may be electrostatically localized on top of the membrane-fixed-surface-charge-attracted "local proton concentration". It is these excess protons that contribute to the proton motive force (pmf) which drives the flow of protons across the membrane through the coupling factor CFoCF1 for ATP synthesis. Because the membrane surface charges are fixed, their attracted protons (and/or cations), including the associated electrical double layers, do not contribute to the proton motive force (pmf) that drives protons through the ATP synthase. Therefore, these surface-charges-attracted protons and/or cations including their associated electrical double layers are not shown in Figure 1, which focuses on illustrating the fundamental concept of protons-electrostatics localization model that is relevant to the pmf.

As a conclusion, membrane surface-fixed-charges-attracted protons are not relevant to the proton motive force that drives ATP synthesis. Therefore, one must not confuse those membrane-fixed-charge-attached protons with the "excess protons" that are electrostatically localized at the water-membrane interface. It is these "excess protons" generated by the photosynthetic or respiratory electron transport systems that are relevant to the proton motive force. More conversations and discussions are needed to clarify this misunderstanding and move the field of bioenergetics forward.

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