A cell-scale biomimetic model involving lipid vesicles: study of the Amyloid β induced failure of mitochondrial cristae dynamics

Nada Khalifat[1], Nicolas Puff [1,2], Mariam Dliaa[1], Miglena I. Angelova [1,2]

[1]Université Pierre et Marie Curie - Paris 6, [2]Matière et Systèmes Complexes (MSC) CNRS UMR 7057, Université Paris Diderot - Paris 7, Paris, France

INTRODUCTION

It is recognized now that neuronal mitochondria are among the important or even major early "victims" in the case of Alzheimer's disease. The observed abnormalities in the oxidative metabolism of mitochondria, reduced ATP production, and, mitochondrial damage were related, among others, to the excessive presence of Amyloid-β peptide (Aβ) in mitochondrial cristae. Interestingly, the mechanisms relating the accumulation of Aβ in the cristae with the large number of mitochondria with broken cristae was even not evoked, never mind that it is widely recognized now that mitochondria function and morphology are coupled. In our previous work (1), we developed a minimal model using giant unilamellar vesicles (GUVs) for mimicking mitochondrial inner membrane. Furthermore, we suggested a theoretical model (2) for elucidating the physical background of a particular membrane instability - membrane tubule formation, triggered by local pH modulation.

RESULTS

In this work, we studied the Aβ (1-42) effects on model cell-sized membranes, giant and large unilamellar vesicles (GUVs and LUVs) mimicking mitochondrial inner membrane. We showed that the Aβ interaction with lipid bilayers itself may take place without macroscopic (vesicle scale) membrane damage. Nevertheless, this "peaceful" (at first side!) association of the peptide with the lipid membrane, the Aβ thwarted the formation of cristae-like membrane structures upon a later local acidification. Using large unilamellar vesicles we showed as well that the Aβ induces membrane dehydration and rise of membrane viscosity.

CONCLUSIONS

The studies we carried out using our mito-mimetic model systems leads to the following hypothesis: the failure of mitochondrial inner membrane morphology might be due to very basic and purely physical mechanism - the deterioration of mechanical (visco-elastic) properties of the lipid membrane. As a result, the dynamic local strain created during cristae formation could provoke inner membrane rupture. That means, in the context of living mitochondria, that the Aβ might induce lipid bilayer incapacity to support the dynamics of shape changes underlying (and inherent to) mitochondrial inner membrane normal functioning.

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