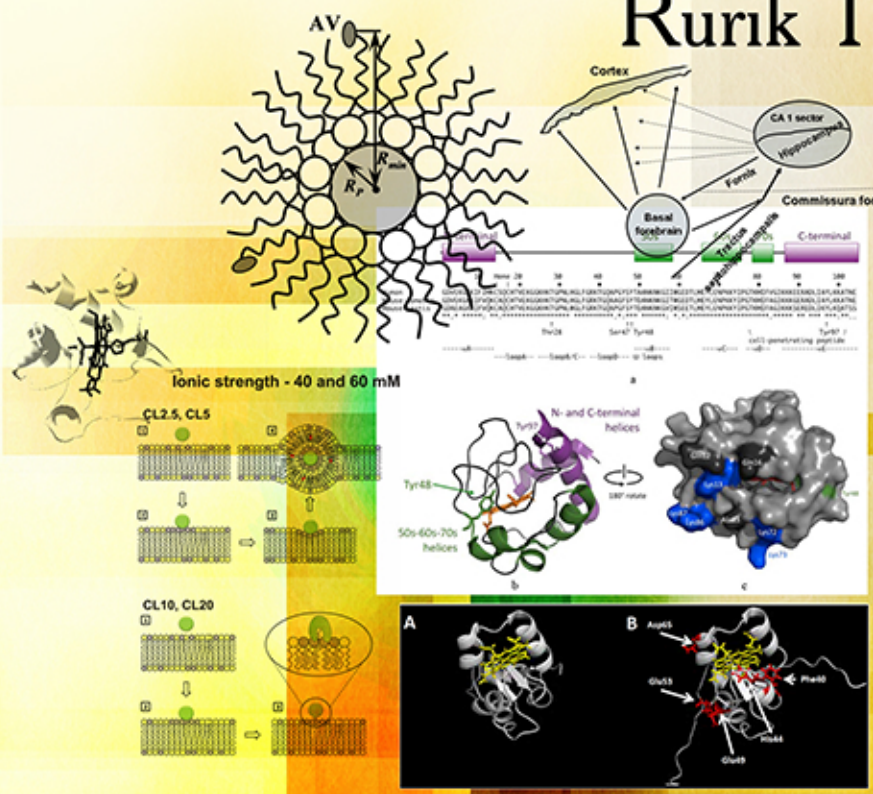
Cytochromes b and c

Biochemical Properties, Biological Functions and Electrochemical Analysis

Rurik Thom
Editor



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RURIK THOM
EDITOR

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Chapter 6

STRUCTURAL ASPECTS OF CYTOCHROME *C*-CARDIOLIPIN INTERACTIONS: FÖRSTER RESONANCE ENERGY TRANSFER STUDY

Valeriya M. Trusova[1,*], Julian G. Molotkovsky[2], Paavo K. J. Kinnunen[3] and Galyna P. Gorbenko[1]

[1]Department of Nuclear and Medical Physics,
V. N. Karazin Kharkov National University, Kharkov, Ukraine
[2]Shemyakin–Ovchinnikov Institute of Bioorganic Chemistry,
Russian Academy of Sciences, Moscow, Russia
[3]Department of Biomedical Engineering and Computational Science,
School of Science and Technology, Aalto University,
Espoo, Finland

ABSTRACT

Cytochrome *c* (cyt *c*) is a mitochondrial membrane hemoprotein of high physiological importance. Fisrt, cyt *c* is one of the key elements of respiration chain transferring electrons from cyt *c* reductase (*bc*1 complex) to cyt *c* oxidase. Second, release of cyt c from the intermembrane space of mitochondria into the cytosol triggers the apoptotic pathway. The idea that specific interactions between cyt *c* and

* Address for correspondence: Valeriya M.Trusova, 19-32 Geroyev Truda St., Kharkov 61144, Ukraine. E-mail: valtrusova@yahoo.com.

cardiolipin (CL), the main lipid component of mitochondrial membrane, are crucial to the protein biological activities, constantly receives further corroboration from both theoretical and experimental studies. Despite considerable progress achieved in the field of cyt *c* – CL biophysics, the detailed structural description of protein-lipid complexation is still lacking. In the present study we applied Förster resonance energy transfer (RET) technique to give comprehensive characterization of cyt *c* binding to the model lipid membranes composed of the mixtures of zwitterionic lipid phosphatidylcholine (PC) with anionic lipids phosphatidylglycerol (PG), phosphatidylserine (PS) or cardiolipin (CL) in different molar ratios. The donor-acceptor pairs were represented by either anthrylvinyl-labeled PC (AV-PC) or anthrylvinyl-labeled CL (AV-CL) incorporated in trace amounts in lipid vesicles, and heme moiety of cyt *c*. Association of the protein with the lipid bilayers led to the decrease in donor fluorescence reflecting energy transfer from AV fluorophore to heme. The most effective RET was found for CL-containing membranes. This observation has been interpreted in terms of higher affinity of cyt *c* to CL as compared to other anionic lipids. In order to get understanding of protein specificity to CL, RET was measured as a function of CL content and ionic strength. Monte Carlo analysis of multiple datasets revealed a complex interplay between several processes, namely i) lipid demixing; ii) CL transition into extended conformation; iii) formation of hexagonal phase. The switch between these states was found to be controlled by CL content and salt concentration. These characteristics of cyt *c* – CL interaction are of great interest not only in the context of regulating cyt *c* electron transfer and apoptotic propensities, but also from the viewpoint of the protein biogenesis.

1. INTRODUCTION

Cytochrome *c* (cyt *c*) is a small mitochondrial membrane metalloprotein, which delicately holds the balance between cell functioning (respiration) and cell death (apoptosis) [1-3]. Fulfilling its canonical function in the electron-transport chain, this protein employs its prosthetic group as a redox intermediate to shuttle electrons from cyt *c* reductase (complex III) to cyt *c* oxidase (complex IV) [4]. Electron transfer occurs via the redox cycling between the ferric and ferrous state of His18/Met80 – coordinated heme. The reaction of cyt *c* reduction by cyt *c* reductase proceeds at the outer side of cytosolic surface of the inner membrane. Then ferrocytochrome *c* is donates four electrons to cyt *c* oxidase which, in turn, catalyzes the reduction of molecular oxygen to two water molecules. Hydrophobic and charged amino