Wykład CVII JCET, 25.05.2018

Redox mechanisms of vascular remodeling: role of protein disulfide isomerases

Prof. Francisco R. M. Laurindo

Universidade de São Paulo

Instituto do Coração

Faculdade de Medicina

São Paulo, SP - Brasil

Vascular remodeling is a crucial mechanism of vascular caliber regulation in physiological and pathological conditions. Evidence mounts that redox processes regulate vessel remodeling and we have proposed a redox/biomechanical paradigm. Recently, we showed that expansive vessel remodeling is supported by the extracellular pool of Protein Disulfide Isomerase A1 (PDIA1). PDIs are thiol oxidoreductase chaperones from thioredoxin superfamily. As redox folding catalysts from the endoplasmic reticulum (ER), their roles in ER-related redox homeostasis and signaling are well-studied. PDIA1 exerts thiol oxidation/reduction and isomerization, plus chaperone effects. Substantial evidence indicates that PDIs regulate thiol-disulfide switches in other cell locations such as cell surface and possibly cytosol. Subcellular PDI translocation routes remain unclear and seem Golgi-independent. The mechanisms of PDIA1 effects in vascular remodeling may include effects on vascular smooth muscle cell (VSMC) differentiation via redox mechanisms. Our work has shown that PDIA1 is required for agonist-triggered Nox NADPH oxidase activation and VSMC migration. Moreover, PDIA1 appears to exert important effects on the noise minimization of the polarized cytoskeletal organization in response to a variety of mechanostimuli in VSMC. Extracellular PDIs also crucially regulate pathways involved in thiol redox signaling of thrombosis /platelet activation, e.g., integrins, via a reductase effect, although we detected an oxidase effect during short-

term mechanostimuli in endothelial cells. Furthermore, PDIA1 exerts an important regulation of RhoGTPases involved in cytoskeletal regulation and a physical association between PDIA1 and the RhoGTPase regulator RhoGDIalpha was reported by us recently. Moreover, the PDI family genes display a remarkable microsyntenic arrangement with RhoGDI genes, conserved through >800 million-years of evolution. Results from a novel transgenic model of PDIA1 overexpression further support the effects of PDIA1 on expansive remodeling. PDIA1 is redox-sensitive, although probably not a mass-effect redox sensor due to kinetic constraints. Rather, the "all-in-one" organization of its peculiar redox/chaperone properties likely provide PDIs with precision and versatility in redox signaling, making them promising therapeutic targets.

Short biography

Prof. Francisco R. M. Laurindo

Francisco R. M. Laurindo graduated in Medicine by the University of São Paulo School of Medicine, São Paulo, Brazil , in 1978 and completed his residence training in Internal Medicine and Cardiology at the Heart Institute(Incor), University of São Paulo School of Medicine. After a period (1982-84) as associate physician at the same institution, he underwent research training in Physiology and Pharmacology at the Uniformed Services University of the Health Sciences, in Bethesda, Maryland (under Dr. Robert Goldstein, 1984-87). Back to the Heart Institute, University of São Paulo School of Medicine, he started an investigative research track focused on mechanisms of redox signaling processes in the vascular system. He obtained his PhD in 1992, supervised by Dr. Protásio da Luz. Thereafter, he conducted several research projects through independent financial support from research agencies. In 2001, he started, together with Dr. Protásio da Luz, the Vascular Biology Laboratory at the Heart Institute (Incor), University of São Paulo School of Medicine and became its Director in 2008, until presently. His major research interests have focused on understanding mechanisms and regulatory processes underlying the production of oxidant species in vascular cells and tissues and their physiological implications for vessel remodeling in disease. The most important contributions of his group have been the original description of shear stress-dependent generation of superoxide radical from the endothelium, the multi-level characterization of redox response to vascular injury and, particularly, the original discovery that the endoplasmic reticulum chaperone protein disulfide isomerase interacts functionally and physically with oxidant-generating NADPH oxidase complexes. This finding had relevant implications regarding the role of endoplasmic reticulum

(patho)physiology on NADPH oxidase function and how redox processes regulate cell migration and vascular remodeling. More recently, Dr. Laurindo's group showed an important role for extracellular PDI in arterial remodeling after injury. Dr. Laurindo has authored or co-authored over 150 publications in peer-reviewed journals, cited >3500 times (h-index=35 (ISI)). He supervised 18 PhD students and 17 post-doctoral fellows, in addition to several undergraduate trainees. From 2008-14, he was the vice-coordinator of the National Institute for Science and Technology of Redox Processes in Biomedicine (CNPq/Fapesp) and since 2013 (until present) the Vice-coordinator and principal investigator of Cepid-Fapesp Redoxoma. He is a member of the Brazilian Academy of Sciences since 2012 and a member of its Board of Directors since 2016, a member of Fapesp Study Committee in Health Sciences from 2008-2016 and Fapesp Advisor Committee in Life Sciences since 2016, a member of Capes Federal Agency Committee (Medicine) from 1998-2017. He served as Council Member of the Society for Free Radical Biology and Medicine from 2010-2014 and belongs to the Editorial Board of Free Radical Biology and Medicine since 2008 and of Clinical Science since 2012. He has been an ad-hoc consultant for >35 publications and research agencies from Brazil and abroad. He was elected as vice-chair (2014) and chair (2016) of the Gordon Research Conference on Nox Family NADPH Oxidases.