

Overall research theme:

The molecular basis of myocardial tolerance to ischemia/reperfusion: the role of Unfolded Protein Response and its contribution to ischemic preconditioning.

Latest update:

July 5, 2002

Senior staff member(s):

Position(s):

Degrees:

E-mail addresses:

Marek Treiman	Associate Professor	MD, Dr. Med. Sci.	M.Treiman@mfi.ku.dk
---------------	---------------------	-------------------	--

Department/institution/address/telephone/fax:

Department of Medical Physiology, University of Copenhagen
The Panum Institute 12.5, Blegdamsvej 3, DK-2200 Copenhagen
Tel.: 3532 7510 Fax: 3532 7418

Characteristics of the research group:

Our laboratory focuses on the molecular and cellular approaches to elucidation of the basis of ischemic tolerance. An in vitro model of myocyte ischemia is used based on a cell line derived from embryonic rat heart. For the time being, the analytical scope of the lab includes cell survival assays, immunological detection and quantitation of protein expression, calcium fluxes, enzyme assays, and protein phosphorylation assays.

Running projects: Titles and abstracts:

Molecular basis for ischemic stress tolerance in heart muscle

About 50% of all deaths due to cardiovascular disease are due to ischemic heart disease. There is extensive evidence to indicate that previous ischemic episodes induce a state of increased myocardial tolerance to subsequent ischemia/reperfusion stress (ischemic preconditioning). A so-called late variant of ischemic preconditioning becomes evident about 12-24 hours after the conditioning insult and entails a degree of protection lasting a few days. This time profile reflects activation of a number of genes. Some of these have been identified, e.g. heat-shock proteins, antioxidation enzymes, cyclooxygenase or nitric oxide synthetase. However, one entire area of cellular stress responses involving the endoplasmic reticulum-resident proteins remains largely unexplored with regard to ischemic tolerance.

Several types of cellular stress upregulate the sarco/endoplasmic reticulum (S/ER)-resident chaperones and helper proteins, whose function is essential for proper maturation, folding and movement of proteins through the S/ER-Golgi system en route to their destinations in plasma membrane (channels, connexins, transporters, receptors, etc.). This coordinated upregulation of the S/ER protein genes in response to stress is referred to as Unfolded Protein Response (UPR). UPR has been shown to have a cytoprotective role in a number of systems. Our current hypothesis is that UPR is also of importance in development of myocardial tolerance to ischemia/reperfusion injury. In particular, we presently focus on Ca²⁺-binding chaperones GRP78 and GRP94. These proteins are studied in our in vitro ischemia model, and the conditions of their upregulation along with their effects on cell survival are evaluated. We intend to extend these studies to include the S/ER Ca²⁺ pump, SERCA2, which we have shown to be one of the UPR-regulated proteins.

The perspective of this project is an identification of the pharmacologically accessible signaling pathways enabling an activation of cardioprotective gene responses.

Recent publications:

C. Caspersen, P.S. Pedersen and M. Treiman 2000 The sarco-endoplasmic reticulum calcium ATPase 2b is an endoplasmic reticulum stress-inducible protein J. Biol.Chem. 275, 22363-22372

A.H. Larsen, Aa. Frandsen and M. Treiman 2001 Upregulation of the SERCA type Ca^{2+} pump activity in response to endoplasmic reticulum stress in PC12 cells BMC Biochemistry 2, 4
M. Treiman 2002 Regulation of the endoplasmic reticulum calcium storage during the Unfolded Protein Response – significance in tissue ischemia? Trends Cardiovasc Med 12, 53-58.