Edited by Valdur Saks

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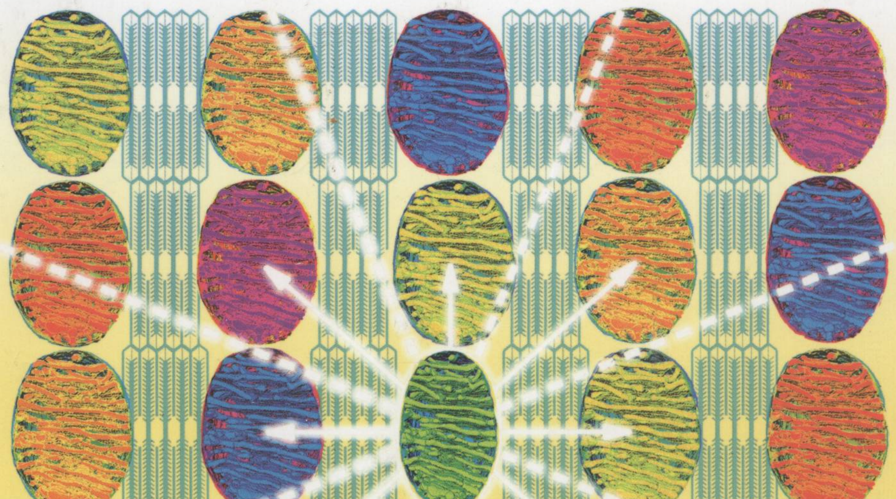
Molecular System Bioenergetics

Energy for Life



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The Editor

Prof. Valdur Saks
J. Fourier University
Laboratory of Bioenergetics
2280 rue de la Piscine
38041 Grenoble Cedex 9
France

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Preface

When Thucydides wrote his famous book *The History of the Peloponnesian War* in Athens in 460–400 BC, he supplied it with the following commentary: "My work is not a piece of writing designed to meet the taste of an immediate public, but was done to last forever." We could borrow this comment for our book, whose intention is to survey the results of more than 200 years of research in cellular bioenergetics, from the discovery that respiration is a process of biological oxidation by Lavoisier and Laplace in the 18^{th} century, to the latest achievements of molecular system bioenergetics in explaining the mechanistic basis of its regulation. Respiration is *la raison de être* of cells, and a knowledge of the mechanisms associated with biological oxidation, free energy transduction, and regulation of cellular respiration implies understanding how cells obtain energy for life. The scope of cellular energetics, however, is much broader than studying the mechanisms involved in respiratory regulation, because all biochemical processes are inseparable from free energy transduction, thus including the whole metabolism and the description of all kinds of work performed by cells.

At present, the biological sciences are witnessing a radical change in paradigms. Reductionism – which used to be the philosophical basis of biochemistry and molecular biology, when everything from genes to proteins and organelles were studied in their isolated state – is making way for systems biology, which favors the study of integrated systems at all levels: cellular, organ, organism, and population. Reductionism was justified in the initial stages of biological research, giving a wealth of information on system components. It is timely to put them together and analyze them in interaction, to understand the principles of functioning of the whole. These paradigmatic changes also concern bioenergetics. Unraveling the mechanisms of regulation of cellular energetics only appears to be possible by using an integrated approach based on computational models, which we call molecular system bioenergetics.

Not everybody, however, was taken by surprise following these paradigmatic changes. There have been pioneers in the systemic approach to biochemistry and metabolism. The roots of systems biology can be traced back to the works of Pasteur, Claude Bernard, Meyerhof, Cori, and Krebs, among others, and its theoretical basis can be found in the work of Norbert Wiener, the founder of cybernetics. Regarding cellular energetics, an important line of research of metabolic

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networks, energy transfer, and metabolic regulation has always existed, particularly emphasizing the significance of structure–function relationships for the integrated regulation of metabolic networks.

The aim of this book is to describe the "state of the art" of these investigations by the authors who have been most actively committed to developing integrated approaches to studying energy metabolism. In our pursuit we follow the historical unfolding of these developments, emphasizing the most important achievements in the area during the last 100 years. We begin with basic information about mitochondrial structure and function and a general description of the theoretical bases of cellular metabolism and bioenergetics in open thermodynamic systems, including Schrödinger's principle of negentropy. This is followed by an analysis of mitochondrial behavior and processes in cells, taking into account macromolecular crowding and compartmentation phenomena. The most important part of the book is devoted to the description of compartmentalized energy transfer in muscle and brain cells. The experimental data gathered during the last several decades in many laboratories allow us to explain the mechanistic bases of two highly significant phenomena for physiological energetics: the Frank–Starling law of the heart, related to the regulation of respiration, and acute ischemic cardiac contractile failure. This approach explains the regulation of substrate supply in the heart as well.

The last part of the book analyzes the applied aspects of cellular bioenergetics – the problems of mitochondrial pathology, exercise physiology, cancer research, and a new important area of research, the "metabolic syndrome" – related to the medical and socioeconomic problems of modern societies. Because these diseases, which are related to cellular and whole-body derailment of basic metabolism, are reaching epidemic proportions in the "civilized" world, the regulation of sugar and fat metabolism, once considered an old-fashioned discipline of physiological biochemistry, is back in the limelight again. Amazingly, these old disciplines and fields of metabolic regulation often are rediscovered and uncovered by young scientists, making it even more important to analyze the achievements of bioenergetics in historical perspective.

This effort intends to be a useful manual and valuable reference book for a large scientific audience, namely, in biology and medicine. We hope it will also be a resourceful tool for undergraduate and doctoral students, post-doctoral students, and research workers in bioenergetics, biophysics, biochemistry, cell biology, pharmacology, physiology, pathophysiology, and medicine.

Grenoble, May 2007

Valdur Saks

List of Contributors

Irina Agarkova
University Hospital of Zurich
Department of Cardiovascular
Surgery Research
Rämistrasse 100
8091 Zurich
Switzerland

Mayis K. Aliev
Cardiology Research Center
Institute of Experimental
Cardiology
Laboratory of Cardiac Pathology
3rd Cherepkovskaya Street 15A
121552 Moscow
Russia

Fabrizio Andreelli
Bichat Claude Bernard Hospital
Diabetology-Endocrinology-
Nutrion Department
46 Rue Henri Huchard
75877 Paris Cedex 18
France

Robert H. Andres
University of Bern
Department of Neurosurgery
Inselspital
Freiburgerstrasse 10
3010 Bern
Switzerland

Tiia Anmann
National Institute of Chemical and
Biological Physics
Laboratory of Bioenergetics
Akadeemia tee 23
12618 Tallinn
Estonia

Miguel A. Aon
Johns Hopkins University
Institute of Molecular Cardiobiology
720 Rutland Avenue
1059 Ross Building
Baltimore, MD 21205
USA

Stephan J.L. Bakker
University of Groningen and
University Medical Center Groningen
Department of Internal Medicine
Hanzeplein 1
9700 RB Groningen
The Netherlands

Cécile Batandier
Université Joseph Fourier
Bioénergétique Fondamentale et
Appliquée
INSERM E-0221
BP 53X
38041 Grenoble Cedex
France

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Dieter Brdiczka
University of Konstanz
Faculty of Biology
Untere Bohlstrasse 45
78465 Konstanz
Germany

Susan Chung
Mayo Clinic College of Medicine
Departments of Biochemistry and
Molecular Biology
200 First Street SW
Rochester, MN 559095
USA

Jolita Ciapaite
Vytautas Magnus University
Faculty of Nature Sciences
Centre of Environmental
Research
Vileikos 8
44404 Kaunas
Lithuania
and
VU University
Faculty of Earth and Life Sciences
Department of Molecular Cell
Physiology
Institute for Molecular Cell
Biology
De Boelelaan 1085
1081 HV Amsterdam
The Netherlands

Sonia Cortassa
Johns Hopkins University
Institute of Molecular
Cardiobiology
720 Rutland Avenue
1059 Ross Building
Baltimore, MD 21205
USA

Dominique Detaille
Université Joseph Fourier
Bioénergétique Fondamentale et
Appliquée
INSERM E-0221
BP 53X
38041 Grenoble Cedex
France

Anne Devin
Université de Bordeaux 2
Institut de Biochimie et de Génétique
Cellulaires du CNRS
1 Rue Camille Saint Saëns
33077 Bordeaux Cedex
France

Petras P. Dzeja
Mayo Clinic College of Medicine
Departments of Medicine, Molecular
Pharmacology, and Experimental
Therapeutics
Division of Cardiovascular Diseases
200 First Street SW
Rochester, MN 559095
USA

Jüri Engelbrecht
Tallinn University of Technology
Institute of Cybernetics
Centre for Nonlinear Studies
Akadeemia tee 21
12618 Tallinn
Estonia

Raquel F. Epand
McMaster University
Department of Biochemistry and
Biomedical Sciences
Health Science Centre
1200 Main Street West
Hamilton, Ontario, L8N 3Z5
Canada

Richard M. Epand
McMaster University
Department of Biochemistry and
Biomedical Sciences
Health Science Centre
1200 Main Street West
Hamilton, Ontario, L8N 3Z5
Canada

Roland Favier
Université Joseph Fourier
Bioénergétique Fondamentale et
Appliquée
INSERM U884
BP 53X
38041 Grenoble Cedex
France

Eric Fontaine
Université Joseph Fourier
Bioénergétique Fondamentale et
Appliquée
INSERM U884
BP 53X
38041 Grenoble Cedex
France

Frank Norbert Gellerich
KeyNeurotek AG
ZENIT – Technology Park
Magdeburg
Leipziger Strasse 44
39120 Magdeburg
Germany

Zemfira Gizatullina
KeyNeurotek AG
ZENIT – Technology Park
Magdeburg
Leipziger Strasse 44
39120 Magdeburg
Germany

Rita Guzun
Université Joseph Fourier
Bioénergétique Fondamentale et
Appliquée
INSERM U884
BP 53X
38041 Grenoble Cedex
France

D. Grahame Hardie
University of Dundee
College of Life Science
Division of Molecular Physiology
Sir James Black Centre
Dow Street
Dundee DD1 5EH
United Kingdom

Arend Heerschap
Radboud University Nijmegen
Medical Centre
Department of Radiology
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Robert J. Heine
VU University Medical Center
Department of Endocrinology
Institute for Cardiovascular Research
De Boelelaan 1117
1007 MB Amsterdam
The Netherlands

Thorsten Hornemann
University Hospital Zurich
Institute of Clinical Chemistry
Rämistrasse 100
8091 Zurich
Switzerland

René in 't Zandt
Radboud University Nijmegen
Medical Centre
Department of Radiology
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Hikari Jo
Kyoto University
Department of Physiology and
Biophysics
Graduate School of Medicine
Yoshida-Konoe, Sakyo-ku
Kyoto 606-8501
Japan

Caroline Jost
Radboud University Nijmegen
Medical Centre
Department of Cell Biology
NCMLS 283
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Klaas Krab
VU University
Faculty of Earth and Life Sciences
Department of Molecular Cell
Physiology
Institute for Molecular Cell
Biology
De Boelelaan 1085
1081 HV Amsterdam
The Netherlands

Jan Kuiper
Radboud University Nijmegen
Medical Centre
Department of Cell Biology
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Andrey V. Kuznetsov
Innsbruck Medical University
Department of General and Transplant
Surgery
Daniel-Swarovski Research Laboratory
Innrain 66
6020 Innsbruck
Austria

Masanori Kuzumoto
Discovery Research Laboratories
Shionogi & Co., Ltd.
12-4, Sagisu 5-chome
Fukushima-ku
Osaka 553-0002
Japan

Xavier M. Leverve
Université Joseph Fourier
Bioénergétique Fondamentale et
Appliquée
INSERM U884
BP 53X
38041 Grenoble Cedex
France

Satoshi Matsuoka
Kyoto University
Graduate School of Medicine
Department of Physiology and
Biophysics
Yoshida-Konoe, Sakyo-ku
Kyoto 606-8501
Japan

Sybille Mazurek
Institute of Biochemistry and
Endocrinology
Veterinary Faculty
University of Giessen
Frankfurter Strasse 100
35392 Giessen
Germany
and
ScheBo Biotech AG
Netanyastrasse 3
35394 Giessen
Germany

Claire Monge
Université Joseph Fourier
Bioénergétique Fondamentale et
Appliquée
INSERM U884
BP 53X
38041 Grenoble Cedex
France

Arnaud Mourier
Université de Bordeaux 2
Institut de Biochimie et de
Génétique
Cellulaires du CNRS
1 Rue Camille Saint Saëns
33077 Bordeaux Cedex
France

Dietbert Neumann
ETH Zurich
Hoenggerberg
Institute of Cell Biology
HPM-D24
Schafmattstrasse 18
8093 Zurich
Switzerland

Akinori Noma
Kyoto University
Graduate School Medicine
Department of Physiology and
Biophysics
Yoshida-Konoe, Sakyo-ku
Kyoto 606-8501
Japan

Frank Oerlemans
Radboud University Nijmegen
Medical Centre
Department of Cell Biology
NCMLS 283
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Brian O'Rourke
Johns Hopkins University
Institute of Molecular Cardiobiology
720 Rutland Avenue
1059 Ross Building
Baltimore, MD 21205
USA

Helma Pluk
Radboud University Nijmegen
Medical Centre
Department of Cell Biology
NCMLS 283
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Klaas Jan Renema
Radboud University Nijmegen
Medical Centre
Department of Radiology
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Mark H. Rider
Christian de Duve Institute of Cellular Pathology
Hormone and Metabolic Research Unit
Avenue Hippocrate 75
1200 Brussels
Belgium
and
University of Louvain
Medical School
1200 Brussels
Belgium

Michel Rigoulet
Université de Bordeaux 2
Institut de Biochimie et de Génétique
Cellulaires du CNRS
1 Rue Camille Saint Saëns
33077 Bordeaux Cedex
France

Kent Sahlin
GIH
Swedish School of Sport and Health Sciences
Department of Physiology and Pharmacology
Box 5626
11486 Stockholm
Sweden
and
University of Southern Denmark
Institute of Physiology and Clinical Biomechanics
5230 Odense
Denmark

Ryuta Saito
Discovery Technology Laboratory
Mitsubishi Pharma Corporation
1000, Kamoshida-cho, Aoba-ku
Yokohama 227-0033
Japan

Valdur Saks
Université Joseph Fourier
Bioénergétique Fondamentale et Appliquée
INSERM U884
BP 53X
38041 Grenoble Cedex
France
and
National Institute of Chemical and Biological Physics
Laboratory of Bioenergetics
Akadeemia tee 23
12618 Tallinn
Estonia

Uwe Schlattner
ETH Zurich
Hoenggerberg
Institute of Cell Biology
HPM-D24
8093 Zurich
Switzerland
and
Université Joseph Fourier
Laboratoire de Bioénergétique
Fondamentale et Appliquée
INSERM U884
BP 53X
38041 Grenoble Cedex
France

Enn Seppet
University of Tartu
Department of Pathophysiology
19 Ravila Street
50411 Tartu
Estonia

Femke Streijger
Radboud University Nijmegen
Medical Centre
Department of Cell Biology
NCMLS 283
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Frank Striggow
KeyNeurotek AG
ZENIT – Technology Park
Magdeburg
Leipziger Strasse 44
39120 Magdeburg
Germany

Ayako Takeuchi
Kyoto University
Graduate School of Medicine
Department of Physiology and
Biophysics
Yoshida-Konoe, Sakyo-ku
Kyoto 606-8501
Japan

Nellie Taleux
Université Joseph Fourier
Bioénergétique Fondamentale et
Appliquée
INSERM E-0221
BP 53X
38041 Grenoble Cedex
France

André Terzic
Mayo Clinic College of Medicine
Departments of Medicine,
Medicinal Genetics, Molecular
Pharmacology, and Experimental
Therapeutics
200 First Street SW
Rochester, MN 559095
USA

Malgorzata Tokarska-Schlattner
Université Joseph Fourier
Laboratoire de Bioénergétique
Fondamentale et Appliquée
INSERM U884
BP 53X
38041 Grenoble Cedex
France

Sonata Trumbeckaite
Kaunas University of Medicine
Institute for Biomedical Research
4 Eiveniu Street
50009 Kaunas
Lithuania

Ineke van der Zee
Radboud University Nijmegen
Medical Centre
Department of Cell Biology
NCMLS 283
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Marko Vendelin
Tallinn University of Technology
Institute of Cybernetics
Laboratory of Systems Biology
Centre for Nonlinear Studies
Akadeemia tee 21
12618 Tallinn
Estonia

Benoit Viollet
Université Paris 5
Department of Endocrinology,
Metabolism, and Cancer
Institut Cochin
INSERM U567, CNRS UMR 8104
24 Rue du Faubourg Saint-Jacques
75014 Paris
France

Theo Wallimann
ETH Zurich
Hoenggerberg
Institute of Cell Biology
HPM-D24
Schafmattstrasse 18
8093 Zurich
Switzerland

Hans V. Westerhoff
VU University
Faculty of Earth and Life Sciences
Department of Molecular Cell
Physiology
Institute for Molecular Cell
Biology
De Boelelaan 1085
1081 HV Amsterdam
The Netherlands
and
The University of Manchester
Manchester Centre for Integrative
Systems Biology, MIB
Sackville Street
Manchester M60 1QD
United Kingdom

Hans Rudolf Widmer
University of Bern
Department of Neurosurgery
Inselspital
Freiburgerstrasse 10
3010 Bern
Switzerland

Bé Wieringa
Radboud University Nijmegen
Medical Centre
Department of Cell Biology
NCMLS 283
P.O. Box 9101
6500 HB Nijmegen
The Netherlands

Stephan Zierz
Universität Halle/Wittenberg
Neurologische Klinik und Poliklinik
der Martin-Luther-Universität
06097 Halle/Saale
Germany

Contents

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