Red Cell Membrane Transport in Health and Disease

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I. Bernhardt · J. C. Ellory (Eds.)

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Professor Dr. INGOLF BERNHARDT
Universität des Saarlandes
Naturwissenschaftlich-Technische Fakultät III
Arbeitsgruppe Biophysik
P.O.Box 151150
66041 Saarbrücken
Germany

Professor Dr. J. CLIVE ELLORY
University of Oxford
Laboratory of Physiology
Parks Road
Oxford OX1 3PT
United Kingdom

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Preface

The red cell has been a focus for scientific and medical investigation since the earliest times. A higher erythrocyte sedimentation rate was associated with diseases (usually pyrexias) before the thermometer was invented. Furthermore, ever since the early observers Swammerdam and Leeuvenhoek saw discrete corpuscles in samples of blood using the first microscopes, there has been a significant scientific interest in the structure and function of red blood cells. The later discovery that red cells were not spherical, but biconcave discs introduced a scientific puzzle which is still not completely resolved today, and identified the need for a detailed knowledge of the plasma membrane composition and structure, and its interaction with the cytoskeleton. Important concepts like the lipid bilayer, together with its more recent refinement as asymmetric in phospholipid composition led to the identification of translocases involved in actively maintaining its composition. Understanding the mechanics of red cell deformation as these biconcave discs traverse capillaries was advanced by the pioneering work of Rand and Burton in the Sixties, and progressed by Evans, Skalak and others. Based on the bilayer-couple hypothesis, the shape changes that are possible for a human red cell from echinocyte to stomatocyte were described by Sheetz and Singer in the Seventies in terms of alterations in the individual halves of the bilayer. Certain clinical conditions are associated with obvious changes in red cell morphology. Although alterations in membrane lipid or protein can be responsible, mutant haemoglobins (Hb SS), or changes in other cytoplasmic constituents can also be responsible for dramatic alterations in red cell shape, size and lifetime. Another area of importance which has attracted much recent attention is the intraerythrocytic life of malaria, and the way *Plasmodium falciparum* affects red cell contents, function and membrane transport.

In fact red cell contents, and in particular the intracellular concentrations of cations and anions represents an enduring topic of scientific interest. Over a hundred years ago, Abderhalden made meticulous chemical analyses of red cell ionic composition, and established two important concepts. He identified the fundamental principle of a non-equilibrium distribution of ions across the membrane, i.e. a low intracellular sodium and high intracellular potassium concentration. He also identified differences in internal cation levels between species' red cells, a finding taken further in classical work on HK and LK sheep red cells by Kerr, then Evans and later Tosteson and Hoffman and in the work on carnivore red cells leading to the seminal work of Parker with dog red cells.

The obvious conclusion from the finding of non-equilibrium ion distribution across the red cell membrane was that the cell membrane was impermeable (e.g. Gürber 1895). However, van Slyke et al. in the Twenties showed that the red cell membrane has a very high chloride permeability, whilst amongst others Dean et al. and Eisenmann in the early Forties demonstrated a significant sodium and potassium permeability in the red cells of various species. With this information, and the consequent interest in membrane properties and intracellular composition, it was realised that the red cell represents a convenient model for studying membrane transport processes, since it was assumed to be an easily accessible homo-

geneous population of isolated cells. The further discovery of the resealed red cell ghost allowed the incorporation of selected molecules, and the alteration of ion concentrations. This allowed red cells to be used to investigate the stoichiometry and energetics of the Na^+/K^+ pump and for radioisotope flux studies to characterise a variety of transporters including glucose and amino acid carriers as well as KCC and NKCC, the Ca^{2+}-activated K^+ channel and band 3-mediated anion transport.

The enormous impact of molecular biology on cell physiology was initially less applicable for studying mammalian red cells which lack intracellular organelles, including a nucleus. However, using progenitor cells, or reticulocytes has allowed a molecular biological approach to red cells, and further, the value of the transgenic mouse in answering haematological questions will continue to grow. In this context, the variety of diseases causing anaemias, resulting from unstable haemoglobins, or metabolic alterations involving particular enzymes and pathways continue to attract considerable research effort and attention.

The rationale for the present volume evolved partially from the meetings of the respective Red Cell Clubs in Europe and the USA. Many of the doyens of the red cell world who have contributed to this volume represent a lifetime of knowledge and authority in the field. Additionally there are contributions from the younger generation of scientists who are mapping significant areas of knowledge and contributing new techniques and developments. As always it is difficult to be comprehensive in coverage with such a volume, but we are pleased with the breadth of contributions, and feel that significant ground has been covered. In terms of editorial input, we have exercised a light touch, which means there are differences in style and density between the various contributions. There are also some inconsistencies between American and Oxford English, and some elements of non-native English style may still exist. The editors have tried to produce a book which is consistent within its scientific content. One of us (IB), in addition, has laboured long and hard, and wrestled with the publishing template to achieve homogeneity as far as possible. In this task he has been assisted by Erwin Weiss in Saarbrücken, and by Maureen Paler in Oxford.

The aim of the present authors is to produce a red cell book which will inform and provide cover of the major biophysical and cell physiological aspects of red cell function. We must thank all the contributors for their input, and also Dr. Rogaschweski (Humboldt University Berlin) for the photograph on the cover of the book. Springer-Verlag have been active in helping to edit and process the text, and we thank Mrs. Cuneus for her assistance.

Finally we hope that everyone will find something interesting or surprising in one or other chapters of this book. We hope it may encourage scientists to continue to work on red cells, and solve some of the mysteries still present. In his paper "Questions for red blood cell physiologists to ponder for the millennium" (Blood cell, molecules and diseases (2001) 27:57-61), Joseph Hoffman posed many fascinating and important questions still to be resolved in the field of red cell physiology. Although it must be admitted that the present volume may not answer them directly, it is by stimulating interest in the subject of red blood cells that we will produce the research and hopefully the answers to his millennium questions.

Saarbrücken and Oxford, March 2003 Ingolf Bernhardt and Clive Ellory

Contents

Contributing Authors

Arese, P., Prof. Dr.
Department of Genetics, Biology and Biochemistry, University of Torino, Medical School,
Via Santena 5 bis, 10126 Torino,
Italy

Baldwin, S. A., Prof. Dr.
School of Biochemistry and Molecular Biology, University of Leeds,
Leeds, LS2 9JT,
UK

Bennekou, P., Prof. Dr.
LCMF, The August Krogh Institute, University of Copenhagen,
Universitetsparken 13, 2100 Copenhagen Ø,
Denmark

Bernhardt, I., Prof. Dr.
Arbeitsgruppe Biophysik, Naturwissenschaftlich-Technische Fakultät III,
Universität des Saarlandes,
Gebäude 6, Postfach 151150, 66041 Saarbrücken,
Germany

Bookchin, R. M., Prof. Dr.
Department of Medicine, Albert Einstein College of Medicine,
Bronx, New York 10461,
USA

Borgese, F., Dr.
Laboratoire de physiologie des membranes cellulaires, Université de Nice-Sophia Antipolis, UMR 6078 CNRS, Bâtiment Jean Maetz,
284 chemin du Lazaret, 06230 Villefranche sur mer,
France

Brovelli, A., Prof. Dr.
Dipartimento di Biochimica "A. Castellani", Università di Pavia,
via Bassi 21, 27100 Pavia,
Italy

Browning, J., Dr.
Laboratory of Physiology, Oxford University,
Parks Road, Oxford, OX1 3PT,
UK

Brugnara, C., Prof. Dr.
Department of Laboratory Medicine, Children's Hospital Boston, Harvard Medical School,
300 Longwood Avenue, Boston, MA 02115,
USA

Brunini, T. M. C., Dr.
Departamento de Farmacologia e Psicobiologia, Instituto de Biologia,
Av. 28 de Setembro 87, CEP 20551-030, Rio de Janeiro,
Brazil

Cass, C. E., Prof. Dr.
Membrane Protein Research Group, Department of Oncology,
University of Alberta, and Cross Cancer Institute,
Edmonton, Alberta T6G 2H7,
Canada

Christophersen, P., Dr.
NeuroSearch A/S, Ballerup,
Pederstrupvej 93, 2750 Ballerup,
Denmark

Deuticke, B., Prof. Dr.
Institut für Physiologie, Universitätsklinikum der RWTH,
Pauwelsstrasse 30, 52057 Aachen,
Germany

Ellory, J. C., Prof. Dr.
Laboratory of Physiology, Oxford University,
Parks Road, Oxford OX1 3PT,
UK

Fischer, T. M., Dr.
Institut für Physiologie, Universitätsklinikum der RWTH,
Pauwelsstrasse 30, 52057 Aachen,
Germany

Flatman, P. W., Dr.
Membrane Biology Group, Division of Biomedical and Clinical Laboratory Sciences, The University of Edinburgh, Hugh Robson Building,
George Square, Edinburgh EH8 9XD, Scotland,
UK

Gibson, J. S., Dr.
Department of Clinical Veterinary Medicine, University of Cambridge,
Madingley Road, Cambridge CB3 0ES,
UK

Grosveld, F. G., Prof. Dr.
MGC Department of Cell Biology and Genetics, Faculty of Medicine, Erasmus University Medical Center Rotterdam,
PO Box 1738, 3000 DR, Rotterdam,
The Netherlands

Guizouarn, H., Dr.
Laboratoire de physiologie des membranes cellulaires, Université de Nice - Sophia Antipolis, UMR 6078 CNRS, Bâtiment Jean Maetz,
284 chemin du Lazaret, 06230 Villefranche sur mer,
France

Haest, C. W. M., Dr.
Institut für Physiologie, Universitätsklinikum der RWTH,
Pauwelsstrasse 30, 52057 Aachen,
Germany

Halestrap, A. P., Prof. Dr.
Department of Biochemistry, School of Medical Sciences,
University of Bristol,
Bristol BS8 1TD,
UK

Heberle, J., Dr.
Forschungszentrum Jülich, IBI-2: Strukturbiologie,
52425 Jülich,
Germany

Horn, N. M., Dr.
School of Biological Sciences, University of Southampton,
Bassett Crescent East, Southampton SO16 7PX,
UK

Jarolim, P., Dr.
Department of Pathology, Brigham and Women's Hospital, Harvard Medical School,
75 Francis Street, Boston MA 02115,
USA

Kirk, K., Prof. Dr.
School of Biochemistry and Molecular Biology, Faculty of Science, Australian National University,
Canberra A.C.T. Australia 0200,
Australia

Knauf, P. A., Prof. Dr.
Department of Biochemistry and Biophysics, University of Rochester Medical Center,
Rochester, NY 14642,
USA

Lauf, P. K., Prof. Dr.
Department of Physiology and Biophysics, Wright State University School of Medicine,
Dayton, OH 45435,
USA

Lepke, S.
Max Planck Institut für Biophysik,
Heinrich-Hoffmann-Str. 7, 60528 Frankfurt am Main,
Germany

Lew, V. L., Dr.
Physiological Laboratory, University of Cambridge,
Cambridge CB2 3EG,
UK

Lytle, C., Prof. Dr.
Division of Biomedical Sciences, University of California, Riverside,
Riverside, California, 92521,
USA

Mendes Ribeiro, A. C., Dr.
Departamento de Farmacologia e Psicobiologia, Instituto de Biologia,
Av. 28 de Setembro 87, CEP 20551-030, Rio de Janeiro,
Brazil

Minetti, G., Dr.
Dipartimento di Biochimica "A. Castellani", Università di Pavia,
via Bassi 21, 27100 Pavia,
Italy

Motais, R., Prof. Dr.
Laboratoire de physiologie des membranes cellulaires, Université de Nice - Sophia Antipolis, UMR 6078 CNRS, Bâtiment Jean Maetz,
284 chemin du Lazaret, 06230 Villefranche sur mer,
France

Naftalin, R. J., Prof. Dr.
Physiology Division, King's College London, Guy's Campus,
London SE1 1UL,
UK

Nikinmaa, M., Prof. Dr.
Department of Biology, University of Turku,
20014 Turku,
Finland

Oakley, F., Dr.
School of Biological Sciences, University of Southampton,
Bassett Crescent East, Southampton SO16 7PX,
UK

Orlov, S. N., Prof. Dr.
Laboratory of Pathophysiology of Ion Transport Disorders, Research Centre, University of Montreal Hospital, CHUM,
3850 rue St.-Urbain, Montreal, PQ, H2W 1T8,
Canada

Pal, P., M. Sc.
Department of Biochemistry and Biophysics, University of Rochester Medical Center,
Rochester, NY 14642,
USA

Passow, H., Prof. Dr.
Max Planck Institut für Biophysik,
Heinrich-Hoffmann-Str. 7, 60528 Frankfurt am Main, and
Institut für Biochemie und Biophysik, Friedrich Schiller Universität Jena,
Philosophenweg 12, 07743 Jena,
Germany

Patrinos, G. P., Dr.
MGC Department of Cell Biology and Genetics, Faculty of Medicine, Erasmus University Medical Center Rotterdam,
PO Box 1738, 3000 DR, Rotterdam,
The Netherlands

Sachs, J. R., Prof. Dr.
Department of Medicine, State University of New York at Stony Brook,
Stony Brook, NY, 11794-8151,
USA

Saliba, K. J., Dr.
School of Biochemistry and Molecular Biology, Faculty of Science, Australian National University,
Canberra A.C.T. Australia 0200,
Australia

Schwarzer, E., Dr.
Department of Genetics, Biology and Biochemistry, University of Torino, Medical School, Via Santena 5 bis, 10126 Torino,
Italy

Stewart, G. W., Prof. Dr.
Department of Medicine, Rayne Institute, University College London,
University Street, London WC1E 6JJ,
UK

Swietach, P.
Laboratory of Physiology, Oxford University,
Parks Road, Oxford OX1 3PT,
UK

Thomas, A. L., Dr.
School of Biological Sciences, University of Southampton,
Bassett Crescent East, Southampton SO16 7PX,
UK

Tiffert, T., Dr.
Physiological Laboratory, University of Cambridge,
Cambridge CB2 3EG,
UK

Weiss, E., Dipl.-Biophys.
Arbeitsgruppe Biophysik, Naturwissenschaftlich-Technische Fakultät III,
Universität des Saarlandes,
Gebäude 6, Postfach 151150, 66041 Saarbrücken,
Germany

Wilkins, R., Dr.
Laboratory of Physiology, Oxford University,
Parks Road, Oxford, OX1 3PT,
UK

Yao, S. Y. M., Dr.
Membrane Protein Research Group, Department of Physiology,
University of Alberta,
Edmonton, Alberta T6G 2H7,
Canada

Young, J. D., Prof. Dr.
Membrane Protein Research Group, Department of Physiology,
University of Alberta,
Edmonton, Alberta T6G 2H7,
Canada