METHODS IN MOLECULAR BIOLOGY™

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Tissue-Protective Cytokines

Methods and Protocols

Edited by

Pietro Ghezzi

Brighton and Sussex Medical School, Falmer, UK

Anthony Cerami

Leiden University Medical Center, Leiden, The Netherlands

Humana Press

Editors
Pietro Ghezzi
Brighton and Sussex Medical School
Falmer, UK

Anthony Cerami
Leiden University Medical Center
Leiden, The Netherlands

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Preface

In 2004, Pietro Ghezzi asked me to write a short introductory chapter for a book on TNF he was putting together for this very same series. The focus of what I wrote then was on TNF as an inflammatory agent. In fact, our finding, in the 1980s, that cachexia associated with inflammatory and infectious diseases was due to TNF opened the way to the development of anti-TNF drugs that are now standard treatment for chronic inflammatory disease.

Now, I am asked again to write about the continuation of this saga. In 1998, with Mike Brines and Carla Hand, I started investigating why patients who receive EPO feel well soon after the first treatment. That led to the discovery, published in 2000, that systemically administered EPO is neuroprotective in animal models of ischemic and traumatic brain injury. That paper opened the field of the neuroprotective action of EPO. The protective action of EPO was soon demonstrated in other tissues, hence the use of the term "tissue-protective cytokine" (1). As in the case of TNF, we had to fight the commonplace that EPO has only erythropoietic actions, that its receptor is present only in erythroid progenitor cells, and that EPO is produced only by the kidney (2).

As in the case of TNF, originally identified for its antitumor activities, we had to work against the common belief that EPO is solely an erythropoietic cytokine acting solely on erythroid progenitors. Several investigators also documented the expression of EPO in the central nervous system and other tissues, against the common belief that only the kidney and the foetal liver produce EPO.

From the perspective of pharmacological use, the erythropoietic action of EPO, by increasing the haematocrit and activating platelets, has some undesired side effects as a tissue-protectant, and this led to the development of novel non-erythropoietic EPO-derived tissue-protective molecules some of which are described here.

I believe that tissue-protection will be a new field of interest of cytokine biology, both in discovering novel actions of known cytokines and in developing new drugs. In this context, this book is a valuable collection of methodological papers that describe in detail the key models that have been used to characterize the tissue-protective actions of EPO and derivatives and will, hopefully, be of use in the discovery of new tissue-protective molecules.

Leiden, The Netherlands *Anthony Cerami*

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Contributors

Alberto Auricchio • *Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy; Medical Genetics, Department of Medical Translational Science, Federico II University, Naples, Italy*

Myriam Bernaudin • *CERVOxy team "Hypoxia, cerebrovascular and tumoral pathophysiologies", UMR 6301-ISTCT, CNRS, CEA, Université de Caen Basse-Normandie, CYCERON, Caen, France*

Anne-Lise Bienvenu • *Malaria Research Unit, SMITH ICBMS UMR CNRS, UCBL, INSA Lyon, Lyon, France*

Anna Yu. Bogdanova • *Institute of Veterinary Physiology, Vetsuisse Faculty and Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich, Zurich, Switzerland*

Michael Brines • *Araim Pharmaceuticals, Inc., Ossining, NY, USA*

Porretta-Serapiglia Carla • *Neuromuscular Diseases Unit, IRCCS Foundation, "Carlo Besta" Neurological Institute, Milan, Italy*

Anthony Cerami • *Araim Pharmaceuticals, Ossining, NY, USA; Leiden University Medical Center, Leiden, The Netherlands*

Ilaria Cervellini • *Brighton & Sussex Medical School, Falmer, UK*

Pasqualina Colella • *Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy*

Darrell Conklin • *Department of Computer Science and Artificial Intelligence, University of the Basque Country UPV/EHU, San Sebastián, Spain; IKERBASQUE, Basque Foundation for Science, Bilbao, Spain*

Jovany Cruz • *Baylor College of Medicine, Houston, TX, USA*

Albert Dahan • *Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands*

Murat Digicaylioglu • *Departments of Neurosurgery and Physiology, University of Texas Health Science Center, San Antonio, TX, USA*

Andrew Dilley • *Brighton and Sussex Medical School, Falmer, UK*

Catharine H. Duman • *Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA*

Serhat Erbayraktar • *Department of Neurosurgery, School of Medicine, Dokuz Eylul University, İnciralti, İzmir, Turkey*

Zübeyde Erbayraktar • *Department of Medical Biochemistry, School of Medicine, Dokuz Eylul University, İnciralti, İzmir, Turkey*

Samson Kumar Gaddam • *Baylor College of Medicine, Houston, TX, USA*

Eithan Galun • *Goldyne Savad Inst. of Gene Therapy, Hadassah Hebrew University Hospital, Jerusalem, Israel*

Max Gassmann • *Institute of Veterinary Physiology, Vetsuisse Faculty and Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich, Zurich, Switzerland*

Pietro Ghezzi • *Brighton & Sussex Medical School, Falmer, UK*
Lauria Giuseppe • *Neuromuscular Diseases Unit, IRCCS Foundation, "Carlo Besta" Neurological Institute, Milan, Italy*
Necati Gokmen • *Department of Anesthesia and Reanimation, School of Medicine, Dokuz Eylul University, İnciralti, İzmir, Turkey*
Sandra E. Juul • *Division of Neonatology, Department of Pediatrics, University of Washington, Seattle, WA, USA*
Roberto Latini • *Department of Cardiovascular Research, Istituto Mario Negri, Milan, Italy*
Annelise Letourneur • *CERVOxy team "Hypoxia, cerebrovascular and tumoral pathophysiologies", UMR 6301-ISTCT, CNRS, CEA, Université de Caen Basse-Normandie, CYCERON, Caen, France*
Manuela Mengozzi • *Brighton & Sussex Medical School, Falmer, UK*
Samuel S. Newton • *Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA*
Marieke Niesters • *Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands*
Omolara O. Ogunshola • *Institute of Veterinary Physiology, Vetsuisse Faculty and Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich, Zurich, Switzerland*
Edwige Petit • *CERVOxy team "Hypoxia, cerebrovascular and tumoral pathophysiologies", UMR 6301-ISTCT, CNRS, CEA, Université de Caen Basse-Normandie, CYCERON, Caen, France*
Stephane Picot • *Malaria Research Unit, SMITH ICBMS UMR CNRS, UCBL, INSA Lyon, Lyon, France*
Lombardi Raffaella • *Neuromuscular Diseases Unit, IRCCS Foundation, "Carlo Besta" Neurological Institute, Milan, Italy*
Domenico Ribatti • *Department of Basic Medical Sciences, Neurosciences, and Sensory Organs, University of Bari Medical School, Bari, Italy*
Bianchi Roberto • *Neuromuscular Diseases Unit, IRCCS Foundation, "Carlo Besta" Neurological Institute, Milan, Italy*
Claudia Robertson • *Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA*
Stefan Rose-John • *Institut für Biochemie, Christian-Albrechts-Universität zu Kiel, Kiel, Germany*
Simon Roussel • *CERVOxy team "Hypoxia, cerebrovascular and tumoral pathophysiologies", UMR 6301-ISTCT, CNRS, CEA, Université de Caen Basse-Normandie, CYCERON, Caen, France*
Tommy Seaborn • *Faculty of Medicine, Department of Pediatrics, Centre de Recherche de l'Hôpital St-François d'Assise (CR-SFA), Centre Hospitalier Universitaire de Québec (CHUQ), Laval University, Québec, QC, Canada*
Jorge Soliz • *Faculty of Medicine, Department of Pediatrics, Centre de Recherche de l'Hôpital St-François d'Assise (CR-SFA), Centre Hospitalier Universitaire de Québec (CHUQ), Laval University, Québec, QC, Canada*
Maarten Swartjes • *Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands*

Mark I. Talan • *Laboratory of Cardiovascular Sciences, National Institute on Aging, NIH, Baltimore, MD, USA*

Omar Touzani • *CERVOxy team "Hypoxia, cerebrovascular and tumoral pathophysiologies", UMR 6301-ISTCT, CNRS, CEA, Université de Caen Basse-Normandie, CYCERON, Caen, France*

Christopher M. Traudt • *Division of Neonatology, Department of Pediatrics, University of Washington, Seattle, WA, USA*

Osman Yilmaz • *Animal Research Center, School of Medicine, Dokuz Eylul University, İnciralti, İzmir, Turkey*