SKELETAL MUSCLE REPAIR AND REGENERATION

Advances in Muscle Research

Volume 3

Series Editor

G.J.M. Stienen, *Vrije Universiteit, Amsterdam, The Netherlands*

Skeletal Muscle Repair and Regeneration

Edited by

Stefano Schiaffino
University of Padova and Venetian Institute of Molecular Medicine (VIMM), Padova, Italy

and

Terence Partridge
Center for Genetic Medicine, Washington, DC, USA

Springer

Library of Congress Control Number: 2008920295

ISBN 978-1-4020-6767-9 (HB)
ISBN 978-1-4020-6768-6 (e-book)

Published by Springer,
P.O. Box 17, 3300 AA Dordrecht, The Netherlands.

www.springer.com

Printed on acid-free paper

CONTENTS

PREFACE

Barring misfortune, there is a general expectation that our skeletal muscles will remain in effective service for our allotted 'three-score- years-and-ten' (Psalm 90, king James Bible, 1611) despite daily exposure to a variety of traumatic insults. It is now clear that this maintenance entails efficient operation of appropriate repair processes. To cover the whole spectrum of severity of muscle injury ranging from i) focal intracellular damage, such as plasma membrane rupture or myofibril disruption, to ii) segmental damage or necrosis involving the whole length of individual muscle fibers, to iii) injuries affecting whole muscle bundles, including blood vessels and interstitial tissues, requires that these repair processes be subtly tailored to cope appropriately (Sloper et al., 1978). So ingrained, currently, is the notion that skeletal muscle can repair itself, that it comes as somewhat of a shock to be reminded (Chapter 1) how recently this idea has come into general acceptance and of how hot was the debate as to the fundamental mechanisms behind this repair process.

By virtue of its mechanical function skeletal muscle is subject to continual mechanical stress caused by muscle contractions while its largely superficial distribution places it as the primary cushion against external physical impact. In consequence, some form of muscle damage and repair must occur on a continuous day-to-day basis. Muscle fibres are especially sensitive to eccentric (lengthening) contractions, such as downhill running, that produce focal membrane disruptions leading to influx of plasma proteins or tracers into the damaged fibers and efflux of muscle proteins, such as creatine kinase, into the blood (McNeil and Khakee, 1992). Such eccentric contractions appear to be especially damaging in muscular dystrophies caused by defects in components of the muscle fibre surface membrane. This is most conspicuous in Duchenne muscular dystrophy, the archetype of a number of inherited defects of the complex of proteins linking the internal cytoskeleton to the sarcolemma-extracellular matrix, absence or disturbance of which results in an increased membrane fragility (Rowland, 1980).

An important insight to emerge during the past few years, is that muscular dystrophy can result not only from diminished membrane resilience but also from deficiencies in the mechanisms that undertake repair of damaged muscle membranes. This notion is based on the discovery that a membrane protein called dysferlin is a major component of a specific membrane repair mechanism responsible for the maintenance of plasmalemmal integrity in many cells including skeletal muscle fibres (Bansal et al., 2003; Lennon et al., 2003). Following membrane damage dysferlin, together with other proteins, promotes a rapid membrane resealing through the Ca2+-dependent fusion of subsarcolemmal vescicles to the plasma

membrane. In humans, mutations in dysferlin result in limb-girdle muscular dystrophy 2B, as well as in other clinically distinct muscular dystrophies. Myofibrillar disruption and Z-disk streaming are also frequent sequelae of mechanical stress induced by eccentric contractions. Though generally considered as an expression of muscle damage and responsible for the force drop caused by eccentric contractions (Lieber and Friden, 2002), these changes have also been interpreted as an expression of myofibrillar remodeling, namely as part of the repair process that leads to formation of new myofibrils and to muscle hypertrophy (Yu et al., 2004).

More severe muscle damage characteristically provokes segmental or global muscle fiber necrosis which in turn triggers the typical response of muscle regeneration, mediated largely, if not entirely under normal circumstances, by a specific type of stem cell, the muscle satellite cell (Sherwood et al., 2004; Collins et al., 2005). Satellite cells undergo proliferation after muscle injury, followed by differentiation accompanied by fusion with one another into myotubes as well as with undamaged portions of the fibre, prior to their transformation into mature myofibre. Even when the injury is restricted to the muscle fibre, with maintenance of an intact basal lamina, this process requires the active participation of other cell types. In particular, macrophages, derived from blood monocytes, are attracted to the site of muscle injury and play an important role not only by clearing the necrotic debris, but also by releasing growth factors that promote myogenic cell proliferation and differentiation (Arnold et al., 2007). Finally, functional recovery requires re-establishment of any lost motor innervation to the regenerated fibers as well as formation of new myotendinous junctions to restitute mechanical linkage.

A number of articles in this volume identify and characterize the players in this regeneration process; Chapter 2 describing the origin of the satellite cell and Chapter 3 giving a detailed description of it, insofar as that is possible with what appears increasingly to be a heterogeneous category united principally by its anatomical definition. This reassessment of the satellite cell has been provoked in large part by evidence from a variety of studies as presented in Chapter 4, that cells from other sources can, under some circumstances, participate in regeneration of skeletal muscle (Ferrari et al., 1998; Gussoni et al., 1999). The mechanisms that control the activities of myogenic cells during regeneration must be finely tuned if we are to end up with appropriate amounts of muscle and of reserve myogenic cells to cope with future bouts of degeneration. This issue is considered both from the viewpoint of the regulation of the activation and proliferation of the myogenic cells themselves (Chapter 6) and of the factors influencing their entry into the actual formation of new muscle fibres (Chapter 7). Both of these would appear to play important roles in regulating the amount of muscle formed and the size of the regenerated fibres, which, although more variable than that of uninjured muscle is still remarkably constant. Increasingly too, we have come to understand that the inflammatory cells that enter muscle lesions do not simply clean up the debris but also play a central role in coordinating the various stages of the regeneration process (Chapter 12) and are heavily implicated in determining the balance between muscle fibres and interstitial connective tissue.

While muscle fibre necrosis that leaves the basal lamina intact can be repaired by muscle regeneration with complete restitutio ad integrum, the problem becomes more complicated when entire muscle fibre bundles are damaged by major mechanical traumas or by muscle strain injuries in athletes. In this case, more extensive remodeling of muscle ensues (Chapter 8), often accompanied by formation of a scar of fibrous tissue. This latter tends to disturb muscle micro-anatomy, an effect which is to some extent coped with by development of insertions of the newly regenerated muscle fibers via new-formed myotendinous junctions onto disruptive collagenous sheets (see Chapter 11 Kalimo). An often unrecognized participant in this process is the intercellular matrix (Chapter 13) whose prompt and apposite restitution is clearly important in a tissue whose chief function is mechanical, but which also plays an integral part in the complex of cell signaling events that underlie control of the restoration of this tissue. Similarly, the matter of effectively re-innervating a muscle that is regenerating is essential for restoration of function (Chapter 14). This interaction between muscle and motor nerve is one of the most extensively and intensively studied archetypes of ectodermal/mesodermal interaction and is a clear example of the need for dynamic control mechanisms in so responsive a system as that which provides our locomotion. Much of our practical interest in muscle regeneration is focused on this more severe end of the spectrum of damage, in good part in the belief that a better understanding of the sequence of events involved in this complex process is likely to improve our prospects of optimizing its outcome. This partiality of interest is strongly reflected in the balance of research and hence in the selection of articles in this volume, which are concerned predominantly with regeneration on this larger scale.

Over the years, histopathological diagnostics has, by analysis of muscle obtained from various human diseases, evolved a sophisticated classification of the patterns of necrosis and regeneration associated with individual disease conditions and this (Chapter 10) remains as a critical basis of reference for all of the animal models of muscle disease and regeneration that have been developed. In recent years, it has become possible to view these histopathological processes from a quite different angle, in terms of the patterns of gene expression that characterize the variety of disease phenotypes (Chapter 5). Combination of these two descriptive dimensions looks set to provide a more coherent and comprehensive picture of the mechanisms involved and of the influence on overall pathology of changes in balance between the cellular and biochemical components. Of the animal models, perhaps the most informative have been based on muscle transplantation or other forms of major physical traumatic damage in mammalian muscle (Chapter 8). These were among the first to indicate the robustness of muscle regeneration and to give some hope that it was a process that might be managed to advantage. A still more startling instance of the astonishing potential for regeneration is that seen in urodele amphibians, where there is complete restitution of entire limbs, including the muscle tissue (Chapter 9). As an extreme example of the possibilities of reorganizing tissues in the adult, this phenomenon has long-attracted those seeking to elucidate the fundamental mechanisms that might, one day, be exploited in man.

Our ultimate aim in medical research is to develop ideas that may become of clinical use. In the case of skeletal muscle, the main interest is in conserving muscle mass and strength in the faceof affliction by genetic or acquired disease of skeletal muscle and in combating the profoundly debilitating loss of muscle mass and strength that accompanies disease of other systems, e.g. cachexia associated with cancer or chronic cardio-pulmonary disease. This search has led to a particular interest in the mechanisms of action of a variety of factors that have been shown to possess potent growth-promoting or growth-inhibiting activities on skeletal muscle (Chapter 15).

Finally, the fantasy of eternal youth leads us to wonder why only 'three-score-years-and-ten'? What goes wrong to prevent us maintaining our muscle bulk and strength (Chapter 16). It is with some surprise and stirrings of hope that we learn that muscle itself is probably not the main culprit.

Stefano Schiaffino
University of Padova, Italy

Partridge Terence
Center for Genetic Medicine, Washington, DC, USA

REFERENCES

Arnold L, Henry A, Poron F, Baba-Amer Y, van Rooijen N, Plonquet A, Gherardi RK, Chazaud B (2007) Inflammatory monocytes recruited after skeletal muscle injury switch into antiinflammatory macrophages to support myogenesis. J Exp Med 204:1057–1069

Bansal D et al (2003) Defective membrane repair in dysferlin-deficient muscular dystrophy. Nature 423:168–172

Collins CA, Olsen I, Zammit PS, Heslop L, Petrie A, Partridge TA, Morgan JE (2005) Stem cell function, self-renewal, and behavioral heterogeneity of cells from the adult muscle satellite cell niche. Cell 122:289–301

Ferrari G, Angelis C, Coletta M, Paolucci E, Stornaiuolo A, Cossu G, Mavilio F (1998) Muscle Regeneration by bone marrow derived myogenic progenitors. Science 279:1528–1530

Gussoni E, Soneoka Y, Strickland CD, Buzney EA, Khan MK, Flint AF, Kunkel LM, Mulligan RC (1999) Dystrophin expression in the mdx mouse restored by stem cell transplantation. Nature 401:390–394

Lennon NJ, Kho A, Bacskai BJ, Perlmutter SL, Hyman BT, Brown RH Jr (2003) Dysferlin interacts with annexins A1 and A2 and mediates sarcolemmal wound-healing. J Biol Chem 278:50466–50473

Lieber RL, Friden J (2002) Mechanisms of muscle injury gleaned from animal models. Am J Phys Med Rehabil 81(11 Suppl):S70–S79

McNeil PL, Khakee R (1992) Disruptions of muscle fiber plasma membranes. Role in exercise-induced damage. Am J Pathol 140:1097–1109

Rowland LP (1980) Biochemistry of muscle membranes in Duchenne muscular dystrophy. Muscle Nerve 3:3–20

Sherwood RI, Christensen JL, Conboy IM, Conboy MJ, Rando TA, Weissman IL,Wagers AJ (2004) Isolation of adult mouse myogenic progenitors: functional heterogeneity of cells within and engrafting skeletal muscle. Cell 119:543–554

Sloper JC, Barrett MC, Partridge TA (1978) The muscle cell. J Clin Pathol Suppl R Coll Pathol 12:25–43

Yu JG, Carlsson L, Thornell LE (2004) Evidence for myofibril remodeling as opposed to myofibril damage in human muscle with DOMS: an ultrastructural and immunoelectron microscopic study. Histochem Cell Biol 121(3):219–227

CONTRIBUTORS

Ville Äärimaa Department of Orthopedic Surgery, University and University Central Hospital of Turku, Turku, Finland
E-mail: ville.aarimaa@utu.fi

Andrew S. Brack Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305-5235, USA
E-mail: asbrack@stanford.edu

Margaret Buckingham Department of Developmental Biology, URA CNRS 2578, Institut Pasteur, 25 rue du Dr. Roux, 75015 Paris, France
E-mail: margab@pasteur.fr

Bruce M. Carlson Institute of Gerontology, 300 North Ingalls Building, University of Michigan, Ann Arbor MI 48109, USA
E-mail: brcarl@umich.edu

Giulio Cossu Stem Cell Research Institute, Dibit, H. San Raffaele, via Olgettina 58, 20132, Milan, Italy
E-mail: cossu.giulio@hsr.it

Graziella Messina Stem Cell Research Institute, Dibit, H. San Raffaele, via Olgettina 58, 20132, Milan, Italy
E-mail: messina.graziella@hsr.it

Stefano Biressi Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305-5235, USA
E-mail: sbiressi@stanford.edu

Miranda Grounds School of Anatomy & Human Biology, The University of Western Australia, 35 Stirling Hwy Crawley, Western Australia, Australia 6009
E-mail: mgrounds@anhb.uwa.edu.au

Eric Hoffman Research Center for Genetic Medicine, Children's National Medical Center, 111 Michigan Ave NW, Washington DC 20010, USA
E-mail: EHoffman@cnmcresearch.org

Markku Järvinen Medical School, University of Tampere, Tampere, Finland; and Departments of Orthopaedic and Plastic Surgery, Tampere University Hospital, Tampere, Finland
E-mail: Markku.Jarvinen@uta.fi

Tero A.H. Järvinen Medical School, University of Tampere, Tampere, Finland; and Departments of Orthopaedic and Plastic Surgery, Tampere University Hospital, Tampere, Finland
E-mmail: Tero.AH.Jarvinen@uta.fi

George Karpati Neuromuscular Research Group, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada, H3A 2B4
E-mail: George.Karpati@mcgill.ca

Hannu Kalimo, MD Department of Pathology, University and University Hospital of Helsinki, P.O.Box 21, FI-00014, Helsinki, Finland
E-mail: hannu.kalimo@helsinki.fi

Minna Kääriäinen Medical School, University of Tampere, Tampere, Finland; and Departments of Orthopaedic and Plastic Surgery, Tampere University Hospital, Tampere, Finland
E-mail: minna.t.kaariainen@gmail.com

Maria J. Molnar Neuromuscular Research Group, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada; Molecular Medicine Division, National Institute of Psychiatry and Neurology, Budapest
E.mail: molnarm@opni.hu

Didier Montarras Department of Developmental Biology, URA CNRS 2578, Institut Pasteur, 25 rue du Dr. Roux, 75015 Paris, France
E-mail: dmontarr@pasteur.fr

Tommaso Nastasi EMBL – Mouse Biology Unit, Campus A. Buzzati-Traverso, Via Ramarini, 32, 00015, Monterotondo Scalo (RM), Italy
E-mail: nastasi@embl.it

Roddy S. O'Connor Graduate Program in Molecular and Systems Pharmacology, Department of Pharmacology, Emory University, School of Medicine, Atlanta, GA 30322-4218, USA
E-mail: rsoconn@emory.edu

Terence Partridge Center for Genetic Medicine Research, Children's National Medical Center, 111 Michigan Ave NW, Washington DC 20010, USA
E-mail: tpartridge@cnmcresearch.org

Grace K. Pavlath Emory University School of Medicine, Deptartment of pharmacology, Room 5027, O.W. Rollins Research Building, Atlanta, GA 30322-3090, USA
E-mail: gpavlat@emory.edu

Tom Rando Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305-5235, USA
E-mail: rando@stanford.edu

Nadia Rosenthal EMBL-Monterotondo Outstation, European Molecular Biology Laboratory, Campus "A. Buzzati-Traverso", Italy
E-mail: rosenthal@embl-monterotondo.it

Stefano Schiaffino Department of Biomedical Sciences, University of Padova, and Venetian Institute of Molecular Medicine (VIMM), Padova, Italy
E-mail: stefano.schiaffino@unipd.it

Gabi Shefer Department Cell and Developmental Biology, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
E-mail: gabise@post.tau.ac.il

Clarke R. Slater School of Neurology, Neurobiology & Psychiatry, Faculty of Medical Sciences, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK
E-mail: C.R.Slater@newcastle.ac.uk

Frank E. Stockdale Maureen Lyles D'Ambrogio Professor of Medicine, Emeritus, Stanford University, Stanford School of Medicine, Cancer Center Room 2238 Stanford, CA 94305-5826
E-mail: Stockdale@Stanford.edu

Elly M. Tanaka Max-Planck Institute of Molecular Cell Biology and Genetics, Pfotenhauerstrasse 108, 01307 Dresden, Germany
E-mail: tanaka@mpi-cbg.de

James G. Tidball Department of Physiological Science, University of California. Los Angeles, Los Angeles CA 90095-1606, USA
E-mail: jtidball@physci.ucla.edu

Zipora Yablonka-Reuveni Deptartment of Biological Structure, Box 357420, Warren B. Magneson HSB-G514, University of Washington, Seattle, WA, 98195, USA
E-mail: reuveni@u.washington.edu

Peter S. Zammit Randall Division of Cell and Molecular Biophysics, King's College London, New Hunt's House, Guy's Campus, London, SE1 1UL, England
E-mail: peter.zammit@kcl.ac.uk

Po Zhao Research Center for Genetic Medicine, Children's National Medical Center, 111 Michigan Ave NW, Washington DC 20010, USA
E-mail: pzhao@cnmcresearch.org