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Recent Advances in Muscle Research

Jean M. Sanger and Joseph W. Sanger

Department of Cell and Developmental Biology, SUNY Upstate Medical University, Syracuse, NY 13210

Muscle, a tissue that accounts for about forty per cent of the weight of the human body, has been studied from the gross anatomical level down to the atomic level. Sir William Bowman, a pioneer in early muscle studies, summed up some of the difficulties in studying skeletal muscle cells in 1843 in his famous text book entitled **The Physiological Anatomy and Physiology of Man**: “The beautiful cross-markings of the voluntary fibre have been

Corresponding Author: Dr. Joseph W. Sanger, Department of Cell and Developmental Biology, SUNY Upstate Medical University, Syracuse, NY 13210 Tel: 1-315-464-8538 FAX: 1-315-464-8535 sangerjo@upstate.edu.

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Uwe Wolfrum, University of Mainz, Germany

Xu, Mayo Clinic, USA

Zhe Yang, City University New York, USA

known from the early days of microscopical research, and have given occasion to a variety of hypothetical and generally mechanical solutions of the problem of contraction; which by warping the minds of observers, have had the effects of greatly complicating an already difficult subject, that of the internal anatomy of the fibre, which can only be determined by pure observation.” Many technological advances since then have provided a detailed view of muscle structure and function. Recent progress in these areas is reviewed in this special issue of *The Anatomical Record*. The topics cover, in addition to vertebrate muscles, also those of model organisms, e. g., the worm or nematode *Caenorhabditis elegans*, and the fly *Drosophila melanogaster*. The zebrafish, *Danio rerio*, more recently has become a model vertebrate organism for muscle studies as well. In 1977, Francis Crick stated in an article for **The Encyclopedia of Ignorance**: “And how does a muscle fibre assemble all its components to produce a highly ordered contractile machine? The answer may come from studies on the fibrillar molecules themselves and how they interact or it may involve some other principals.” We are still uncertain how myofibrils are assembled *de novo*, and how their integrity is maintained over the life spans of animals (Sanger et al. 2005; 2010). Contributions in this special issue are focused on myofibrillar proteins, their interactions, and their involvement in myopathies, as well as on aspects of muscle structure and function and progress in understanding the requirements for the assembly and maintenance of muscle.

from 1999 to 2013 a Muscle Special Interest Group has been held as one of the member-organized Special Interest Subgroup sessions that are scheduled on the Saturday afternoon before the official start of the annual meeting of the American Society for Cell Biology (ASCB). The first Special Interest Muscle Session was organized by Professors Thomas Borg and Joseph W. Sanger because they felt that muscle cells biologists needed a venue at the annual meetings where they could present their latest advances in their fields. Drs. Borg and Sanger decided for this first session that the presentations should be of such a length that new data could be thoughtfully presented, and that audience participation could take place. The resultant successful format consisted of a short Introduction followed by eight to nine lectures, each lasting 25 minutes immediately followed by a five minute question or comment period. The *Anatomical Record* under the editorship of Professor Kurt Albertine sponsored one of the Muscle Special Interest Sessions, and suggested to the two current organizers that the *Anatomical Record* sponsor a Special Issue on muscle in the journal. All but three of the 22 present authors have presented aspects of their work at some of these 15 annual ASCB Muscle Special Interest Sessions.

Contributions in this issue

In memoriam

Professor Clara Franzini-Armstrong (2014) has submitted a contribution as tribute to the life and scientific achievements of Professor Annemarie Weber who died in 2012. Professor Weber made seminal contributions to our understanding of the role of calcium ions in muscle contraction and relaxation, on the role of sarcoplasmic reticulum in sequestering calcium ions in muscle relaxation, and on the roles of actin, troponins, and tropomyosins in muscle function.

Actin Associated Proteins

Actin is one of the most abundant proteins in animals, and a central protein in myofibrils of striated and smooth muscles. Five contributions highlight this protein. Professor Shoichiro Ono (2014) uses the model organism *Caenorhabditis elegans* to review the formation and role of actin filaments in striated muscles. Dr. Elisabeth Ehler and her colleagues (Dwyer et al., 2014) examine the role of the formin protein, FHOD1, in the formation of actin filaments in the myofibrils in cultured rat neonatal cardiomyocytes. Evidence for a three step sequence myofibril assembly through premyofibrils, nascent myofibrils and mature myofibrils is described in cultured primary mouse muscle cells in the article by White et al (2014) in which changes in distribution of actin and actin-binding proteins, alpha-actinin, non-muscle myosin II, and muscle myosin II, are documented during myofibrillogenesis in cultured mouse skeletal muscle cells formed from the fusion of primary myoblasts. Their results support and extend the original premyofibril model of myofibrillogenesis first proposed in 1994 by Rhee et al. using cultured embryonic avian cardiomyocytes. In the two papers by Dube et al. (2014 a, b), analyses of two additional actin-binding proteins (tropomyosin and myotilin) are described during muscle formation in skeletal and cardiac muscles.

Titin and MARP

Titin is the largest vertebrate protein, and has been suggested to play an important role in the formation and function of cardiac and skeletal muscles (Sanger et al., 2005; Kontogianni-Konstantopoulos et al., 2009; Meyer and Wright, 2013). Drs. Myre and Pilgrim (2014) in their review discuss roles of titin in cross-striated muscles of the zebrafish, a popular and advantageous model organism used in both cardiac and skeletal muscle studies. At a molecular weight of about three million Daltons, it is not surprising that titin can readily interact with a host of proteins in myofibrils. Drs. Lange and colleagues (Lun et al., 2014) report on the roles of one family of titin binding proteins, muscle ankyrin-repeat proteins (MARPs). MARPs are involved in myofibril assembly, but even more remarkably these proteins can diffuse from the myofibrils into the nuclei of muscle cells, where they modulate the activities of some transcription factors. MARPs join a growing list of proteins that can diffuse from myofibrils into nuclei (Sanger and Sanger, 2008).

Processes that Affect Assembly and Function of Myofibrils

One of the newly discovered methods of posttranslational alteration of proteins is arginylation. In the contribution by Professor Anna Kashina (2014), the role arginylation plays in the function of cardiac and skeletal muscle cells is reviewed. Professor Sanford Bernstein and his colleagues (Smith et al., 2014) review another form of protein modification: proper three-dimensional folding of proteins by molecular chaperones. The interactions of chaperones with proteins in the sarcomere are discussed with evidence for the roles of chaperones in myofibrillar assembly and maintenance. Professor Shaojun Du and his colleagues (2014) provide a detailed view of the family of Smyd proteins that may regulate some of these chaperones and other proteins in cardiac and skeletal muscle cells.

Cardiac and Skeletal Myopathies

Many muscle proteins have undergone mutations, truncations and deletions that lead to dysfunction or diseases in cardiac, skeletal and smooth muscles (Guo et al., 2009; Seidman and Seidman, 2011; Mercuri and Muntoni, 2013). Four contributions in this Anatomical Record are focused on the functional changes that result from expression of mutant myofibrillar proteins in cardiac muscles and in skeletal muscle cells. Drs. Thompson and Metzger (2014) illustrate the use of protein engineering to achieve stoichiometric replacement of mutant sarcomeric proteins in adult cardiomyocytes, and the therapeutic potential it could provide in reversing the pathogenic effect of cardiomyopathic proteins. Drs. Colegrave and Peckham (2014) review disease-causing point mutations in human cardiac β -myosin heavy chains with respect to their clustered localizations along the myosin sequence and their structural and functional effects. The contribution by Yang et al. (2014) provides a detailed review of genetic studies focused on sarcomere assembly and sarcomere-based cardiomyopathies in zebrafish. Techniques are described for producing loss-of-function mutants in fish, and the results gained from genetic studies of sarcomeric proteins illustrate the advantages of zebrafish as a model for studies of sarcomere formation and maintenance. A complex of glycoproteins that interact with dystrophin are required for normal function of striated muscle, and are associated with many forms of muscular dystrophy. Townsend's review (2014) of current knowledge of the components of the complex describes the proteolytic cleavages and assembly reactions involved in the formation and presents a model of the process.

One of the surprising results of cell biology is the discovery of proteins that share biochemical and biophysical properties of the first muscle myosin IIs, or what we now call conventional myosin IIs. These newly discovered myosin-like molecules are referred to as unconventional myosins. There are about twenty classes of these molecules (Krendel and Mooseker, 2005; Hartman and Spudich, 2012). Professor Maria Redowicz and her colleagues (Karolczak et al., 2014) review the distribution and roles of one of these unconventional myosins, Myosin VIA, in healthy and in diseased striated muscle cells.

Smooth Muscle

Smooth muscles, although also possessing thin, thick and intermediate filaments as found in striated muscle, do not have these elements in arrays that yield striations to the eye of the light microscopist. Thus, these nonstriated muscle cells are termed smooth muscle cells. Smooth muscle structure and functions are highlighted in four papers. Professor Marion Siegman (2014) reviews the interplay between smooth muscle cells and the extracellular matrix using ultrastructural images of extracellular matrix and muscle at myotendinous junctions and intramuscular junctions. Professor Thomas Eddinger (2014) presents his study of the translocation of vinculin and PKC in freshly isolated smooth muscle cells. Professor Kyoko Imanaka-Yoshida and her collaborators (2014) review the extracellular matrix glycoprotein, tenascin-C, secreted by smooth muscle cells, and its role in cardiovascular development and diseases. Drs. Ye, Nesmith and Parker (2014) review the mechanosensing and mechanotransduction in vascular smooth muscle cells that is coupled with the remodeling of cytoskeletal proteins and activation of signaling pathways that impact on physiological or pathological functions.

Lattices of Thick and Thin Filaments

The ultrastructural and light microscopy reports of Hugh Huxley and Jean Hanson in the 1950s and 1960's revolutionized our views of cross-striated muscles (Hanson and Huxley, 1953; Huxley, 1963; 2004). Professor George Kepner (2014) asks in his review whether the arrangements of thick and thin filaments in the sarcomere are optimal in their hexagonal pattern in cross-section considering the key factors of lattice geometry, ratio of thin and thick filaments, and their arrangements.

Nonmuscle Cell and an Unconventional Myosin

In the final contribution for this special issue of the *Anatomical Record*, we have included a report by Hodel et al. (2014), submitted directly to *The Anatomical Record*, that presents evidence that the unconventional myosin VIIA is localized in the accessory outer segment (AOS) in zebrafish cone photoreceptors. Both immunofluorescence and immunogold experiments indicate that Myosin VIIA is concentrated in the AOS. This paper is one of thousands inspired by muscle research accomplished over the last 50 years. The frontiers of muscle research continue to expand, especially into many different types of nonmuscle cells, e.g., the zebrafish photoreceptors. Movement is a central characteristic of life, and muscle related molecules are central to the movement of molecules inside cells, cells inside organisms, and organisms inside our universe.

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