

Contents

1	Setting the Stage: Myosin, Actin, Actomyosin and ATP	1
1.1	Introduction.....	1
1.2	Muscle Structure as Observed by Nineteenth Century Microscopy.....	2
1.3	Revolution in Muscle Physiology: The Pathway to ATP and the High Energy Phosphate Bond	4
1.3.1	Rise of Biochemistry.....	4
1.3.2	Lactic Acid Theory of Muscle Contraction.....	4
1.3.3	Studies on Muscle Contraction Without Formation of Lactic Acid.....	6
1.3.4	ATP and the High Energy Phosphate Bond	7
1.3.5	Meyerhof, Lundsgaard and Lohmann: The Later Years.....	9
1.4	Discovery of “Myosin” and Muscle Birefringence.....	10
1.5	Albert Szent-Gyorgyi: Myosin, Actin, Actomyosin and Role of ATP	11
1.6	Early Electron Microscopic Studies of Muscle Structure.....	19
1.7	Some Theories of Muscular Contraction Prior to 1954	21
1.8	Albert Szent-Gyorgyi: The Later Years.....	23
1.9	Thus the Stage Was Set	24
	References	24
2	Birth of the Sliding Filament Model of Muscular Contraction: Proposal	29
2.1	Introduction.....	29
2.2	The Investigators: Andrew Huxley and Rolf Niedergerke, Hugh Huxley and Jean Hanson	30
2.3	Overlapping Arrays of Filaments and the First Proposal of Sliding Filaments	38
2.4	Andrew Huxley and the Development of an Interference Microscope.....	40

2.5	Birth of Sliding Filaments: Nature, Volume 173, Pages 971–976, May 22, 1954	42
2.6	Interference Microscopy of Living Muscle Fibres by A. F. Huxley and Dr. R. Niedergerke. Nature. 173: 971–973, 1954	43
2.7	Changes in the Cross-Striations of Muscle During Contraction and Stretch and Their Structural Interpretations by Dr. Hugh Huxley and Dr. Jean Hanson. Nature. 173: 973–976, 1954	48
2.8	Scientific Reception of the Sliding Filament Model of Contraction	54
	References	55
3	Glory Days: Establishment of the Sliding Filament Model of Muscular Contraction in the 1950s and 1960s	59
3.1	Introduction	59
3.2	1957 Was a Very Good Year for the Sliding Filament Model of Muscle Contraction	60
3.2.1	Myosin Limited to the A band	60
3.2.2	Double Hexagonal Array of Filaments	60
3.2.3	A Hypothesis for the Mechanism of Contraction	65
3.3	Myosin, Actin, Thick and Thin Filaments	69
3.3.1	The Myosin Molecule	69
3.3.2	The Actin Molecule and Thin Filaments	77
3.3.3	Myosin and Actin Filaments and Filament Polarity	79
3.3.4	Cross-Bridge Orientation in Muscle at Rest and in Rigor	84
3.4	X-Ray Diffraction Studies of Muscles at Rest and During Contraction	85
3.5	Muscle Length Versus Isometric Force: A Critical Test of the Sliding Filament Hypothesis	89
3.5.1	“Creep” and Sarcomere Length Irregularity in Contracting Muscle	90
3.5.2	The Spot Follower Device and the Muscle Length Versus Isometric Force Relationship	92
3.6	Swinging-Tilting Cross-Bridge Model of Muscle Contraction	97
3.7	The Investigators: The Later Years	99
	References	101
4	Excitation-Contraction Coupling and the Role of Calcium in Contraction and Relaxation in the 1950s and 1960s	105
4.1	Introduction	105
4.2	Muscle Excitation and Onset of Contraction	106
4.3	Inward Spread of Muscle Activation	107
4.4	Sarcoplasmic Reticulum, Triads and Transverse Tubules	111

4.5	Mechanism of Inward Spread of Activation	113
4.5.1	Are the Transverse Tubules Open to the Surface?	114
4.5.2	Is the Spread of Activation into the T System Active or Passive?	120
4.6	Ca ²⁺ and Contractility: The Early Studies on Muscles.....	121
4.7	Ca ²⁺ and Contractility: Observations on Model Systems.....	125
4.8	Discovery of the Ca ²⁺ Receptor in Muscle Activation: Troponin	131
4.9	Mechanism of Relaxation: The Mysterious “Relaxing Factor”	135
4.10	The Ca ²⁺ Transient: Contraction and Relaxation in Muscles.....	142
4.11	The Later Years: Setsuro Ebashi	147
	References.....	148
5	Mechanics and Energetics of Muscular Contraction:	
	Before Sliding Filaments and into the Modern Era	155
5.1	Introduction.....	155
5.2	Mechanics of Muscular Contraction: The Classical Approach.....	157
5.2.1	The Visco-Elastic Model of Muscle Contraction.....	157
5.2.2	The Fenn Effect	158
5.2.3	Hill’s Two Component Model of Muscle Contraction	160
5.3	Mechanics of Muscular Contraction: The Contemporary Approach 162	
5.3.1	Velocity Transients.....	162
5.3.2	Tension Transients	163
5.3.3	Huxley-Simmons Model of Cross-Bridge Action	169
5.4	Energetics of Muscular Contraction	172
5.4.1	Archibald Vivian Hill: Scientist, Humanitarian, Public Servant	172
5.4.2	Energetics of Muscular Contraction: Establishing the Basic Framework	176
5.4.3	Chemistry of Muscular Contraction	179
5.4.4	Energy Balance Experiments and Unexplained Energy	181
5.4.5	Efficiency and Economy of Muscular Contraction.....	192
5.4.6	Energy Liberation and ATP Cleavage During Stretch of Active Muscle	195
5.5	Mechanism of Actomyosin ATPase: Relationship to Cross-Bridge Cycle.....	198
	References.....	204
6	1972 Cold Spring Harbor Symposia on Quantitative Biology:	
	The Mechanism of Muscle Contraction—Problem Solved??	211
6.1	Introduction.....	211
6.2	Sequence, Subunits and Assembly of Muscle Proteins.....	213
6.2.1	Amino Acid Sequence of Actin	213
6.2.2	Myosin Light Chains: Structure and Function.....	213
6.2.3	C-protein (Myosin Binding Protein C, MyBP-C): Discovery, Characterization and Localization	217

6.2.4	Structure and Assembly of Thick Filaments	222
6.2.5	Arrangement of Cross-bridges on the Thick Filament Surface	222
6.2.6	Packing of Myosin Molecules in a Thick Filament	225
6.2.7	Mechanism of Assembly of a Thick Filament	228
6.3	Muscle Regulatory Systems	231
6.3.1	Troponin	231
6.3.2	Parvalbumin: Structure of a Calcium Binding Protein	233
6.3.3	Tropomyosin	236
6.4	Muscle Structure	239
6.4.1	The Steric Blocking Model of Muscle Activation	239
6.4.2	Demise of the Steric Blocking Model?	245
6.4.3	Time Resolved X-ray Diffraction Evidence During Muscle Contraction Supports the Steric Blocking Model	248
6.4.4	Dynamic Equilibrium: Three State Model of Actomyosin ATPase Activation	249
6.4.5	Where is Tropomyosin on the Actin Filament? Is its Position Calcium and Cross-bridge Dependent?	252
6.4.6	Sarcoplasmic Reticulum, Transverse Tubules and Excitation-Contraction Coupling	256
6.4.7	Calcium Pump of the Sarcoplasmic Reticulum	258
6.4.8	Ryanodine Receptor: Calcium Release Channel of Sarcoplasmic Reticulum	261
6.4.9	Dihydropyridine Receptor: Voltage Sensor and Calcium Channel in Transverse Tubules	264
6.5	Contractile Proteins in Non-Muscle Tissue	268
6.6	ATPase and Contraction: Energetics and Mechanical Properties	272
6.7	Muscle 1972: Progress and Problems	273
	References	274
7	Endosarcomeric and Exosarcomeric Cytoskeleton:	
	Emergence of Cell and Molecular Biology in the Muscle Field	285
7.1	Introduction	285
7.2	Passive Force and the Third Filament of the Sarcomere: Titin First Discovered as Connectin	286
7.2.1	Introduction	286
7.2.2	Early Electron Microscopic Evidence for a Third Filament and Its Skeptical Reception	287
7.2.3	A Breakthrough: Protein Nature of a Putative Third Filament	289
7.2.4	What's in a Name: Connectin or Titin?	292
7.2.5	First Comprehensive Model of Titin and Nebulin Location and Function	292
7.2.6	Physiological Role of Titin in Muscle Fibers	294
7.2.7	Sarcomeric Organization of Titin Molecules	297
7.2.8	Elasticity of the Titin Molecule	299
7.2.9	Titin and the Molecular Ruler Hypothesis	304

- 7.2.10 Number of Titin Molecules per Half Thick Filament and the Sarcomere Symmetry Paradox 304
- 7.2.11 Titin Isoforms and the Passive Mechanical Properties of Muscle 305
- 7.2.12 Beyond the “Classical” Functions of the Titin molecule: Titin as a Mechanosensor and Integrator of Myocyte Signaling Pathways 306
- 7.3 A Fourth Sarcomeric Filament: Nebulin, Structure and Function..... 307
 - 7.3.1 Nebulin as a Molecular Ruler 308
 - 7.3.2 Beyond the Molecular Ruler and/or Actin Stabilizer: Possible Roles of Nebulin in Muscle Contraction..... 309
 - 7.3.3 Nebulin and Human Disease..... 310
- 7.4 Sarcomeric Organization: M Band and Z Disc Structure and Function..... 310
 - 7.4.1 M Band Structure..... 310
 - 7.4.2 Protein Content of the M Band 314
 - 7.4.3 Integrating M Band Proteins with M Band Structure: A Molecular Model..... 314
 - 7.4.4 Z Disc Structure 316
 - 7.4.5 Protein Content of the Z Disc 320
- 7.5 Intermediate Filaments: Desmin and the Exosarcomeric Cytoskeleton 322
- References..... 327

8 Excitation-Contraction Coupling and Regulation of Contraction in Skeletal Muscle: The Modern Synthesis..... 333

- 8.1 Introduction..... 333
- 8.2 Molecular Basis of Excitation-Contraction Coupling..... 334
 - 8.2.1 Transverse Tubule-Sarcoplasmic Reticulum Communication..... 334
 - 8.2.2 Calcium Release Channel of Sarcoplasmic Reticulum: Structure, Function and Regulation 342
 - 8.2.3 The Calcium Transient..... 350
- 8.3 Regulation of Contraction in Striated Muscle 354
 - 8.3.1 The Troponin Complex and Protein-Protein Interaction in Regulation of Contraction..... 354
 - 8.3.2 Regulation of Muscle Force and Kinetics of Contraction by Calcium and Strongly Bound Cross-Bridges..... 363
 - 8.3.3 Myosin Light Chains and Muscle Function..... 371
- 8.4 Molecular Mechanism of Skeletal Muscle Relaxation 374
 - 8.4.1 Introduction..... 374
 - 8.4.2 Tertiary Structures of the Sarcoplasmic Reticulum Calcium Pump and Mechanism of Calcium Transport..... 375
 - 8.4.3 Other Factors Influencing the Time Course of Skeletal Muscle Relaxation 383
- 8.5 Conclusion 385
- References..... 386

9 Molecular Mechanism of Force Production: From the Difficult 1980s to the Supercharged 1990s and Beyond..... 395

9.1 Introduction..... 395

9.2 Kinetics of Actomyosin ATPase in Muscle Fibers: Relationship to the Cross-Bridge Cycle..... 396

9.2.1 Generation of Caged ATP 397

9.2.2 Transient Kinetic Studies of Actomyosin ATPase in Muscle Fibers..... 399

9.3 Testing the Swinging-Tilting Cross-Bridge Model of Muscle Contraction: The Difficult Early 1980s..... 406

9.3.1 Probes of Cross-Bridge Movement: Structural Techniques Designed to Sense Cross-Bridge Movement During Muscle Contraction..... 406

9.3.2 A Fundamental Problem: Asynchronous Cross-Bridge Movement 410

9.3.3 A Refined Cross-Bridge Model: Some Innocence of the Original Model Was Lost..... 412

9.3.4 More Complications for the Sliding Filament Model..... 412

9.4 In Vitro Motility Assays: Myosin Generated Movement and Force Production In Vitro..... 415

9.4.1 Myosin Generated Movement In Vitro 415

9.4.2 Single Mechanoenzyme Mechanics: Laser Traps and Optical Tweezers 420

9.4.3 Single Myosin Molecule Mechanics: Measurement of Force and Step Size..... 422

9.5 Muscle Enters the Atomic Age: Atomic Structures of Actin and Myosin..... 424

9.5.1 Atomic Structure of Actin..... 424

9.5.2 Atomic Model of an Actin Filament 426

9.5.3 Atomic Structure of Myosin and the Actin-Myosin Complex: Introduction 429

9.5.4 Three-Dimensional Structure of Myosin Subfragment-1: A Molecular Motor 431

9.5.5 Structure of the Actin-Myosin Complex and Implications for Muscle Contraction 433

9.5.6 Structure of the Myosin Motor Domain in the Presence of Nucleotide Analogs: Post Rigor and Pre-powerstroke States..... 436

9.5.7 Swinging Lever Arm Hypothesis of Cross-Bridge Action: Integration of Structural Biology, Molecular Genetics and In Vitro Motility Assays..... 437

9.5.8 Nucleotide Free Myosin V as a Model of the Rigor State..... 439

9.5.9 What Causes the Lever Arm to Move? Communication Between the Nucleotide Binding Site, the Actin Binding Domain and the Lever Arm..... 440

- 9.6 Engineering the Myosin Motor Domain: Structure/Function Relationships..... 442
 - 9.6.1 Structure/Function Studies of Myosin: Kinetic Tuning of Myosin via Surface Loops..... 443
- 9.7 Cross-Bridge Structural Changes During Contraction In Situ..... 447
 - 9.7.1 Fluorescence Probes Re-visited 447
 - 9.7.2 X-Ray Diffraction and Mechanical Studies of Cross-Bridge Conformation and Motion..... 451
 - 9.7.3 Myosin Head Conformations During and After Rapid Changes in Muscle Length..... 452
 - 9.7.4 X-Ray Interference and Axial Motions of Myosin Heads 454
- 9.8 Conclusion 459
- References..... 459

- Index..... 467**



<http://www.springer.com/978-1-4939-2006-8>

Mechanism of Muscular Contraction

Rall, J.A.

2014, XIII, 471 p. 179 illus., 34 illus. in color., Hardcover

ISBN: 978-1-4939-2006-8