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CURRENT CONCEPTS OF MUSCLE ULTRASTRUCTURE WITH EMPHASIS ON Z-LINE ARCHITECTURE

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Abstract

In vertebrate striated muscle, the Z-line, which defines the sarcomere length, presents diverse structural patterns both in cross section and in longitudinal section. Conflicting models have been proposed to explain the microscopic observations. The protein composition of the Z-line structure is unresolved. α-Actinin is widely accepted as a Z-line component, and actin filaments extend into wide Z-lines. Based on recent findings from our laboratory and others, we developed a new model applicable to wide and narrow Z-lines. The model allowed the observed ultrastructural patterns of Z-lines to be simulated. Improved electron microscopic techniques should allow further progress to be made in Z-line research, an area of interest both because of the degradation of the Z-line in meat storage and the abnormalities of Z-lines that characterize a wide range of muscle disorders.

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Introduction

In the past 30 years electron microscopy has played a major role in showing the several bands that comprise the vertebrate sarcomere in longitudinal section and elucidating the orientations and spacing of filaments in muscle. Clarification of the array of muscle fibers provided a framework for biochemical and physiological research and contributed to our understanding of muscle contraction. Most of the early ultrastructural studies were performed with vertebrate striated muscle, which, because it is the primary source of muscle for food, will be the focus of this paper. Current understanding of muscle ultrastructure will be summarized briefly, as the subject has been extensively reviewed. For detailed information the reader is referred to the excellent contributions of Schmalbruch, (1986); Squire, (1981); Ishikawa et al., (1983); Peachey and Franzini-Armstrong (1983); Eisenberg (1983); Pepe (1983); Haselgrove (1983). A comprehensive discussion of Z-lines then will be provided. Post-mortem degradation of the Z-line is evident in ultrastructural examination of stored meat (Goll, et al., 1970), and because of the importance of the Z-line in maintaining the integrity of the myofibril, the Z-line is of interest with regard to meat processing and tenderness. Finally, advances in methodology for electron microscopic study of muscle are considered.

Vertebrate Striated Muscle

Striated muscle, which includes skeletal and cardiac muscle, is distinguishable from smooth muscle on the basis of its striped appearance under the microscope. Skeletal muscle consists of bundles of fibers. Fibers vary greatly in size, and each contains approximately one thousand myofibrils.

Within myofibrils, repeating units called sarcomeres extend between the electron-dense Z-lines. In longitudinal section the sarcomere shows a central protein-dense region, the A-band. Between A-bands isotropic I-bands are found, each with a Z-line at the center. The contractile apparatus in striated muscle is composed of a double array of interdigitating thick and thin protein filaments (Huxley, 1969). Thin filaments are anchored at one end of the transverse Z-line and extend between the thick filaments at the other end. Thick filaments are composed primarily of myosin, with a small amount of C-protein localized in A-bands (Offer et al., 1973), 43 nm apart, on each side of the bipolar filament, which may help to hold the thick filament in its circular shape during tension development. Another thick filament protein, X-protein, contaminates C-protein preparations (Starr and Offer, 1983); its shape and molecular interactions have been examined recently by

electron microscopy (Bennet et al., 1985). An M-line containing poorly defined M-protein(s) crosslinks adjacent thick filaments into the proper three-dimensional structure. Thin filaments are thought to be composed of tropomyosin and the troponin complex bound to an actin backbone (Ebashi et al., 1969), with each thin filament having two strands of actin filaments coiled in a helix. Thin filaments undergo a structural rearrangement from a hexagonal pattern near the A-band to a square net pattern near the Z-line. Thin filaments extend into the A-band as far as the paler H-zone and increase in density; the M-line is in the center of the H-zone. Variation in I-filament length has been demonstrated with serial cross sections (Robinson & Winegrad, 1977; Traeger & Goldstein, 1983). In addition to thick and thin filaments, elastic components denoted as gap filaments have been reported (Locker and Leet, 1975; 1976a,b; Locker and Daines, 1980). According to these investigators, gap filaments are very extendible, spanning gaps up to 12 μm in stretched muscle, and appear as thin (2-6 nm) extensions at the ends of the thick filaments. Elastic components are constituted of high-molecular-weight proteins. Titin and nebulin (Wang and Ramirez-Mitchell 1979, Wang et al., 1979; Wang, 1981, 1985) and connectin (Maruyama, 1976 Maruyama et al., 1976, 1977a,b, 1981a,b, 1985) have high molecular weights, but they have not been demonstrated conclusively to be gap filament components.

Recent structural, biochemical, and immunocytochemical studies indicate that intermediate filaments (desmin) are major components which link adjacent myofibrils together at the Z-line region and serve as important cytoskeletal elements (Lazarides and Hubbard, 1976; Robson et al., 1981).

Z-line structure

The Z-line, besides defining sarcomere length, is of interest because of its dual properties: it is the muscle structure most resistant to physical forces but most susceptible to proteases (Fukazawa and Yasui, 1967; Busch et al., 1972; Okitani et al., 1980); thus, it is the initial target during muscle degradation and protein turnover.

The molecular architecture of the Z-line has been extensively studied, and conflicting structural views have been reported. The Z-line as viewed in cross section at electron microscope magnification is made up of filaments that give it the appearance of a well-ordered structure (Yamaguchi et al., 1983a,b) with at least three different patterns: (1) an angled large woven (basket-weave) pattern (Reedy, 1964), (2) an angled square pattern (diagonal square net) with 15.5-nm periodicity (Knappeis and Carlsen, 1962; Franzini-Armstrong, 1973), and (3) a small square lattice with 11-nm periodicity (Landon, 1970). A large woven or square net pattern (22-nm square) arises from four of the small squares. In addition to the structural diversity in section (Figure 1), the electron-dense covering of Z-lines impedes structural studies.

The first model for the Z-line was proposed by Knappeis and Carlsen (1962), who suggested that each thin filament inserts at four Z-filaments which run obliquely through the Z-line, deviating 10° from the direction of the fiber axis, and connects to four thin filaments from the opposite side. In cross sections the array of Z-filaments is tilted by 45° with respect to the squares formed by the I-filaments. Hence, cross sections through the Z-line show an angled tetragonal lattice with 15.5 nm periodicity. Franzini-Armstrong and Porter (1964) stated that thin filaments of adjacent sarcomeres are connected by lamina stretched into opposite directions by inserting thin filaments to give rise to a zigzag appearance in longitudinal sections from an array of oblique Z-filaments and to produce an angled tetragonal lattice in cross sections. Reedy (1964) hypothesized that each thin filament untwists and frays into four Z-filaments, the sense of twist being the same in all filaments approaching the Z-line from one side, and opposite sarcomeres, so that a basket-weave pattern results. Kelly (1967) assumed that two subfilaments arise from each I-filament, run through the Z-line, interlink with the subfilaments of opposite thin filaments, then return to the side of origin, and again enter the double helix of a thin filament. At each thin filament tip one would see two originating Z-filaments and both parts of a loop, giving the appearance of four Z-filaments in all. Rowe (1971) proposed a model in which 4 subfilaments (2 actin strands and 2 tropomyosin strands) arise from each thin filament, loop, and return to insert at the same side of the Z-line in other thin filaments.

Landon (1970) and MacDonald and Engel (1971) found that the image depends on the method of fixation, with glutaraldehyde producing an 11-nm square lattice pattern. According to MacDonald and Engel (1971) only an image observed by Landon (SS & LS, see later section) is compatible with the image after glutaraldehyde fixation, whereas the Knappeis - Carlsen model only accounts for the osmium tetroxide image. Landon (1982) explained the 11-nm square lattice pattern by a non-looping model in which the thin filaments of adjacent sarcomeres overlap, and their ends are cross-linked by transverse filaments. Ullrick et al. (1977) thought that three Z-filaments attach to each thin filament and loop without cross-linking so that filaments can easily separate or split in two directions to join adjacent thin filaments of the same sarcomere, whereas Katchburian et al. (1973) contended that four Z-filaments bound to thin filaments from one sarcomere directly connect to thin filaments of the opposite sarcomere.

In longitudinal sections vertebrate Z-lines show four main patterns: interdigitation of thin filaments (Fawcett and McNutt, 1969; Ovalle, 1972; Rowe, 1973), a zigzag arrowhead-like pattern (Rowe, 1973), thick (11 nm) lines with no interdigitation (Ovalle, 1972) and an amorphous appearance (Katchburian et al., 1973). The different images observed in longitudinal sections were explained by different levels of sectioning and by mismatch between the plane of sectioning and the square lattice (Katchburian et al. 1973). Rowe (1973) claimed that his 4-strand looping model applies to all types of Z-lines, and that the different width of the Z-line is due to the fact that in white fibers all loops from one side of the Z-line are in the same plane. In red fibers, where the Z-line is thicker than in white fibers, loops are in three planes, and in intermediate fibers in two planes.

Z-line width varies widely (Figure 2): Z-lines in fish are 30 nm wide (Franzini-Armstrong, 1973); mammalian white muscle Z-lines, 40 nm and mammalian red muscle Z-lines, 60 nm; mammalian cardiac muscle Z-lines, 100 nm (Fawcett and McNutt, 1969).

The width of the Z-line can be used to determine fiber types (Gauthier, 1969, 1970). Fast-twitch muscle fibers subjected to long-term stimulation and exercise undergo ultrastructural transformation and the Z-line width increases relative to that of slow-twitch muscle fibers. Thus, Z-line width seems to be related to muscle function.

Protein Constituents of Z-line Structures

The entire protein composition of the Z-line

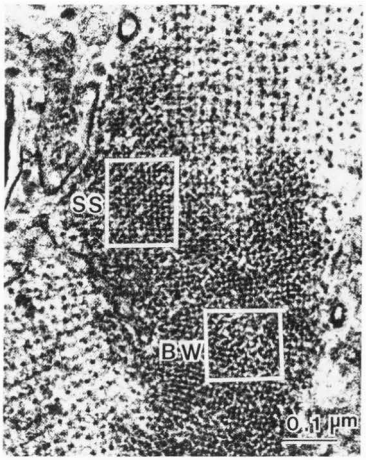

Figure 1. Cross sectional view of canine cardiac muscle Z-line. Z-line displays various patterns including small square net (SS), and basket weave (BW) structure. Structural diversity of Z-line cross section is very common in both skeletal and cardiac muscles. This specific electron micrograph shows the SS form together with the BW form.

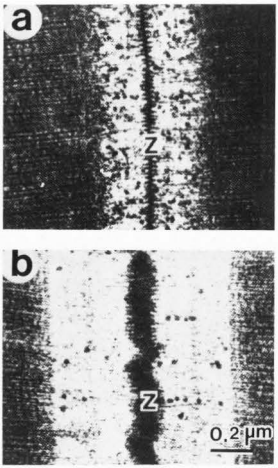

Figure 2. Difference in Z-line width. Fish (guppy) White skeletal muscle (a) and dog cardiac muscle (b) Z-line widths are compared in longitudinal section. The great variation in width between the two Z-lines is obvious. The width of Z-line is probably related to muscle function.

structure which holds the thin filaments in their proper juxtaposition is not known, although evidence for the involvement of α-actinin has accumulated (Masaki et al., 1967; Robson et al., 1970; Goll et al., 1972; Stromer and Goll, 1972; Suzuki et al., 1976; Chowrashi and Pepe, 1982).

By dissection of Z-lines and hypertrophic Z-lines or Z-rods with CAF, Yamaguchi et al., (1983a, b, 1985a) have obtained evidence that suggests the width of all wide Z-line structures is determined by the amount of overlap of antipolar actin filaments from adjacent sarcomeres. This new finding means that actin filaments from I-filament continuously extend into the Z-line and are involved as a structural component of wide Z-lines.

The Z-line lattice differs from the crystal lattice of tropomyosin (Stromer et al., 1969), and crude muscle extracts not containing tropomyosin are able to reconstitute solubilized Z-lines (Stromer et al., 1967, 1969). However, tropomyosin is likely to be associated with actin filaments at a Z-line in the same manner as with thin filaments (actin) in the myofibril, because of the continuity of thin filaments with actin filaments at the Z-line and because of the size of actin filaments at the Z-line is the same as that of myofibrillar thin filaments (Yamaguchi et al., 1983a).

The extract obtained by solubilizing the Z-lines, contains α-actinin (Briskey et al., 1967; Goll et al., 1969), a protein that cross-links actin polymers (Ebashi and Kodama, 1965). α-Actinin amounts to about 50% of the mass of the Z-line (Suzuki et al., 1976). When actin filaments of muscle or nonmuscle cells are decorated with heavy meromyosin (HMM) SI subfragments, the arrowheads formed point away from the Z-lines (Ishikawa et al., 1969). It is conceivable that α-actinin is involved in the organization of the actin filaments, and that it is responsible for the polarization of thin filaments within the sarcomeres of muscle fibers (Huxley, 1963; Goll et al., 1972) and may constitute Z-filaments (Chowrashi & Pepe, 1982; Yamaguchi, 1983a,b 1985a). Other proteins suggested to be present in Z-filaments include actin (Reedy, 1964), tropomyosin (Reedy, 1964, Goldstein et al., 1979), and Z-protein (55,000 MW, Ohashi & Maruyama, 1979; Ohashi et al., 1982). Other possible Z-line components include amorphin (Chowrashi and Pepe, 1982), Eu-actinin (Kuroda et al., 1981), Z-nin (Suzuki et al., 1981), Filamin (Bechtel 1979, Wang et al., 1975), Zeugmatin (Maher et al., 1985) and 220,000 dalton protein (Muguruma et al., 1978, 1981).

Z-line abnormalities

Anomalous Z-line structures, including rod bodies, are associated with many diseases including nemaline myopathy (Shy et al., 1963; Conen et al., 1963), chronic alcoholism (Martinez et al., 1973), schizophrenia (Meltzer et al., 1973). Anomalous Z-lines also occur in aging cardiac muscle (Munnel and Getty, 1968; Fawcett, 1968) and rheumatic heart disease (Roy and Morin, 1971) and can be induced through tenotomy (Resnick et al., 1968; Yamaguchi et al., 1983b) and through injection of neostigmine methyl sulfate, which inhibits cholinesterase (Osame et al., 1975). How closely these structures are related to Z-lines is debated, but several recent studies (Stromer et al., 1976; Goldstein et al., 1977, 1980, 1982;

Yamaguchi et al., 1978; 1983a, b) suggest the basic backbone structure of the rod bodies is very similar if not identical to what would be seen if lateral Z-line polymers were formed. Nemaline rod bodies are rather electron-dense, develop in association with the Z-lines, and display a crystalline structure. In one plane they resemble cross sections through Z-lines showing the small square lattice; in others they reveal parallel filaments with a transverse periodicity of 12 to 20 nm (Engel and Gomez, 1967). HMM-SI binds to the filaments within the rods; thus, they contain actin (Yamaguchi et al., 1978), and antibody staining reveals that the rods contain α-actinin as well. A calcium-ion- activated protease which is known to dissolve selectively the Z-lines of muscle fibers (Busch et al., 1972) dissolves the matrix of the rods but leaves the actin filament lattice intact (Stromer et al., 1976).

New model of muscle Z-lines

Yamaguchi et al., (1985a, b) introduced a new model, which is applicable to both narrow and wide Z-lines, supported by evidence from electron microscopic studies. The model is based on a pair of Z-filaments (Figure 3) (termed a Z-unit), which are linked near their centers at 90° angle and form bridges between neighboring antipolar thin (actin) filaments.

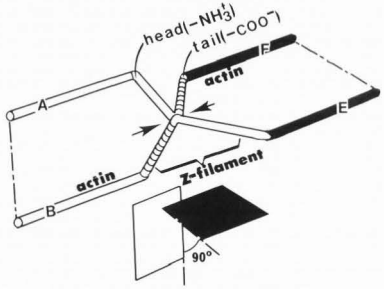

Figure 3. Z-filament assembly in Z-unit. A proposed model of Z-filament geometry shows a pair of Z-filaments (the pair comprises a Z-unit) bound at their centers (arrows) at an angle of 90°. Assumed polarity of Z-filaments is indicated by the white (head) and cross-marked (tail) portions. The planes defined by the two thin filaments on the left (white; thin filaments A & B)) and the two thin filaments on the right (black; thin filaments E & F) are shown below the Z-unit. Note that the thin filaments denoted by A, B, E, and F in Fig. 3 are labeled with the corresponding letters in Fig. 4. The Z-filament/Z-filament binding region is indicated by two arrows in Figs. 3 and 4. The Z-filament connected to thin filament A is connected to thin filament F, and the Z-filament connected to thin filament B is connected to thin filament E. (shown by permission of Academic Press, Yamaguchi et al., 1985a,b)

A square lattice of four Z-filament pairs (Figure 4) (the basic structure of the Z-line termed a Z-line unit) defines the geometrical position of the I-square unit.

In this native state of the Z-line, small square (SS) and large square (LS) net forms appear in cross section. Other cross-sectional patterns of Z-lines, including basket-weave (BW) and diagonal-square net (DS) patterns, can be explained by detachment of the Z-filament-to-Z-filament binding region within each Z-filament pair due to chemical or physical stress. Dissection of Z-lines and Z-line analogs with calcium-activated neutral protease provides evidence that the width of all wide Z-line structures is determined by the amount of overlap of antipolar thin filaments from adjacent sarcomeres. Longitudinal patterns of narrow and wide Z-lines also can be explained in relation to the model. To test the proposed model, the dynamics of the Z-line unit structure was computer simulated.

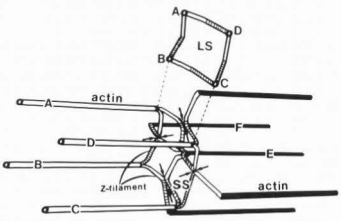

Figure 4. Structure of basic Z-line unit. The determination of the thin filament square net by assembly of four Z-units (i.e., four pairs of Z-filaments) into a basic Z-line unit is represented schematically. The LS (22 nm, see top) or SS (11 nm, see four SS forms) form would appear in cross section depending on sectioning position (i.e., the LS pattern would only be observed at the very outside edge of the Z-line, which includes the four Z-filament/Z-filament binding regions indicated by arrows). In this figure four Z-filaments, each connected to thin filaments A, B, C, and D, bind to the thin filament E of opposite polarity. (shown by permission of Academic Press, Yamaguchi et al., 1985a,b)

The computer simulations demonstrated that the structural transitions among the SS, and therefore LS net, as well as BW and DS forms seen in cross sections could be caused by movements of thin filaments less than 10 nm in any direction. Figure 5 shows the model of narrow Z-line structure. Stretching Z-filaments to the maximum extent in the longitudinal direction of the myofibril would convert the model to that of Knappeis and Carlsen (1962). Z-filament stretching could result from the combined effect of thin filament lattice expansion within the plane of the Z-line as well as Z-filament-Z-filament (Z-unit) detachment, and would result in the DS form in cross section.

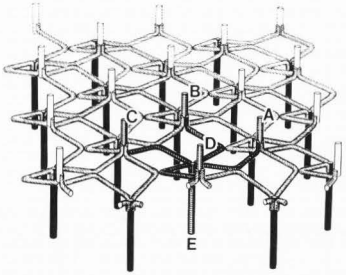

Figure 5. Proposed model of narrow Z-line. The assembly of Z-line units that comprise the narrow Z-line are schematically represented in the figure. Four pair of Z-units form a Z-line unit (emphasized lines) and dictate the position of thin (actin) filaments in the I-square net (A,B,C,D corresponding to alphabetical notation in Fig. 4). Stretching Z-filaments to the maximum extent in the longitudinal direction of myofibril would convert the model to that of Knappeis and Carlsen (1962). Z-filament stretching also could result from the combined effect of thin filament lattice expansion as well as Z-filament - Z-filament (Z-unit) detachment, and would result in the DS form in cross section. A lesser degree of stretching of Z-filaments would result in the BW form first described by Reedy (1964). (shown by permission of Academic Press, Yamaguchi et al., 1985a,b)

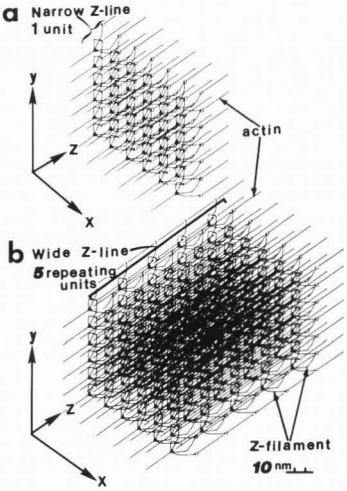

Figure 6. Computer simulated narrow (a) and wide (b) Z-lines. Three-dimensional reconstitution of computer simulated patterns of narrow (one Z-line unit) and wide (five repeating Z-line units) Z-lines in the BW form. The x-, y- and z- axes are indicated by arrows. Because of their structural simplicity, narrow Z-lines would probably be more susceptible to changes caused by thin filament and Z-filament movement than wide Z-lines would be. In wide Z-lines containing multiple Z-line units, the structure would be more rigid because greater overlap of thin (actin) filaments and the more numerous attached Z-filaments would contribute to structural stability.

A lesser degree of stretching of Z-filaments would result in the BW form first described by Reedy (1964). The paradoxes in Z-filament behavior and structural diversity of Z-lines reported in the literature (e.g., Knappeis and Carlsen, 1962; Huxley, 1963; Reedy, 1964; Landon, 1970; MacDonald and Engel, 1971; Rowe, 1971; Kelly and Cahill, 1972; Franzini-Armstrong, 1973; Rowe, 1973; Ullrick et al., 1977) were explained by computer-assisted simulation of this model (Figure 6, unpublished result).

Improved electron microscopic techniques of interest for study of muscle

Sawada et al., (1978) have combined improved preparative methods with high-resolution scanning electron microscopy to provide a detailed look at the surface of frog skeletal muscle; these authors discuss the usefulness and limitations of SEM.

The immunogold staining method (Faulk and Taylor, 1971; Geoghegan and Ackerman, 1977) provides excellent detail in immunocytochemistry and may be useful in identification and localization of myofibrillar proteins.

Heuser et al., (1979) introduced a revolutionary procedure for preparing biological samples for transmission electron microscopy. The method is called quick-freeze, deep-etch, rotary-replication (QDR). QDR should be extremely useful for muscle studies because it can resolve protein-protein interactions. In addition, no chemical fixatives or dehydrating agents are used. Tissues in the living state are frozen quickly enough (0.2 msec-1msec) to avoid ice crystal formation at the onset, whereas with previous freezing techniques sizable ice crystals could grow and physically distort the sample. Advantages to QDR are that the need for cryoprotectants is eliminated and a remarkable degree of three-dimensional structure is preserved. Freeze-drying is limited to a brief deep-etching period at low temperature after freeze-fracture. QDR has been effective in visualizing cellular structures of 10 to 100 nm (i.e., the size of macromolecular assemblies) in situ and in vitro. QDR was used to study actin-myosin interaction (Heuser and Cooke, 1983), and Tsukita and Yano (1985) applied similar methodology to obtain the first clear micrographs of myosin cross-bridges in contracting muscle preserved under physiological conditions.

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Discussion with Reviewer

Peter J. Bechtel:

Would you speculate on where other Z-line proteins are found in the proposed model?

Yamaguchi:

Neither I nor any other researcher has demonstrated unequivocally the exact location of protein components of the Z-line. Gap filaments are associated with the Z-line; however, the number of gap filaments is much lower than the number of actin filaments. Because the high-molecular-weight gap filaments are highly susceptible to proteases, some of the proteins identified as Z-line constituents may be degradation products from gap filaments. These components may occur on the periphery of the Z-line and/or may be integral Z-line components.

Peter J. Bechtel:

What specific molecular changes may account for the "Z-line abnormalities"?

Yamaguchi:

Excessive α-actinin production may be one cause of abnormal Z-lines, because α-actinin seems to be a major component of hypertrophic Z-rods. Z-rods contain unusually long filaments,suggests there may be problem in regulation of actin filament length in the hypertrophic Z-line. Hypertrophic Z-lines are almost devoid of myosin; thus, the disorder also may result from impaired myosin filament assembly or rapid myosin degradation; more likely myosin may not be formed proportionally to other myofibrillar proteins used in sarcomere assembly in hypertrophic Z-lines.