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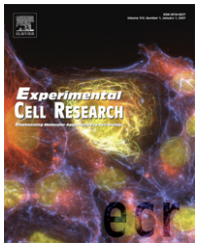

Review Article

Muscle intermediate filaments and their links to membranes and membranous organelles

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ABSTRACT

Intermediate filaments (IFs) play a key role in the integration of structure and function of striated muscle, primarily by mediating mechanochemical links between the contractile apparatus and mitochondria, myonuclei, the sarcolemma and potentially the vesicle trafficking apparatus. Linkage of all these membranous structures to the contractile apparatus, mainly through the Z-disks, supports the integration and coordination of growth and energy demands of the working myocyte, not only with force transmission, but also with de novo gene expression, energy production and efficient protein and lipid trafficking and targeting. Desmin, the most abundant and intensively studied muscle intermediate filament protein, is linked to proper costamere organization, myoblast and stem cell fusion and differentiation, nuclear shape and positioning, as well as mitochondrial shape, structure, positioning and function. Similar links have been established for lysosomes and lysosome-related organelles, consistent with the presence of widespread links between IFs and membranous structures and the regulation of their fusion, morphology and stabilization necessary for cell survival.

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Abbreviations: Ank, ankyrin; ANT, adenine nucleotide translocator; BLOC-1, biogenesis of lysosomes-related organelle complex-1; BMSC, bone marrow stem cells; CK, creatine kinase; CMT, Charcot–Marie–Tooth; DG, dystroglycan; EDMD, Emery–Dreyfuss muscular dystrophy; ER, endoplasmic reticulum; IFM, interfibrillar mitochondria; IFs, intermediate filament; IP3R, 1,4,5-triphosphate receptor; K, keratin; LMNA, lamin A; LINC, linker of the nucleoskeleton and the cytoskeleton; M, mitochondria; MAM, mitochondria-associated ER membrane; MAP, microtubule-associated protein; MLP, striated muscle-specific LIM protein; PLB, phospholamban; RyR, ryanodine receptor; SERCA, sarcoplasmic reticulum calcium ATPase; SG, sarcoglycan; SR, sarcoplasmic reticulum; SSM, subsarcolemmal mitochondria; VDAC, voltage-dependent anion channel

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Contents

Introduction

Striated muscle is highly organized, with direct links between morphology and function and effective mechanochemical signaling between the contractile apparatus to the nucleus and other organelles. Maintenance of this high level of integration requires a cell-wide system that has the potential to interact with all the key structures involved. A good candidate for such a system is the cytoskeletal network composed of intermediate filaments (IFs).

Initial morphological studies suggest that the IF-containing lattices interconnect the myofibrils through the Z-disks and link the contractile apparatus to the sarcolemmal cytoskeleton as well as to several cytoplasmic organelles and the nucleus [1,2]. The continuous network formed by IFs could be involved in diverse functions, including mechanical integration of all the contractile actions of a muscle fiber, cellular integrity, force transmission, mechanochemical signaling and integration of organelle structure and function [3,4] (see Fig. 1). Studies using different IF transgenic mouse models and related human

Fig. 1 – Schematic representation of the intermediate filament scaffold in cardiac muscle and its potential associations with different membranous compartments and organelles. In striated muscle, the IF lattice is composed predominantly of the muscle-specific IF protein desmin (yellow), which associates with other (*), non muscle-specific IF proteins, synemin, paranemin and syncoilin, and lesser amounts of keratins, K8 and K19, which organize independently. Desmin and associated proteins (yellow), as well as keratin filaments (not shown), surround the Z-disks, interconnecting them to each other and to the sarcolemma. Desmin filaments also link the entire contractile apparatus to different membranous compartments and organelles, including the nucleus, mitochondria (M), lysosomes and potentially the sarcoplasmic reticulum (SR), and, in cardiac muscle, to desmosomes at the intercalated disk (blow-up of blue box at lower left panel). With the possible exception of paranemin, all IFs extend and associate with costameres through dystrobrevin (synemin and syncoilin), dystrophin (synemin, keratin 19) and possibly myospryn. The only IFs localized around the M-lines are keratin filaments (K8/K19) (red-brown) and only near the cell surface, where they also link to costameres. Thus, the IF lattice connects all the major elements of the cytoplasm and cell surface of striated muscle cells. Maintenance of organelle proximity by IFs could allow efficient functional crosstalk (e.g., lipid and calcium traffic) between them, as is known for ER/SR and mitochondria (MAM and mitochondrial contact sites are shown in the red box and, at higher magnification, in the lower right panel; see text). The recently discovered association of desmin IFs with myospryn is shown around the nucleus, at costameres and intercalated disks, and indirectly with lysosomes. MAM: mitochondria-associated ER/SR membranes; Ank: ankyrin; ANT: adenine nucleotide translocator; CK: creatine kinase; DG: dystroglycan; ER: endoplasmic reticulum; IFs: intermediate filaments; IP3R; 1,4,5-triphosphate receptor; K: keratin; M: mitochondria; MAM: mitochondria-associated ER membrane; MLP: striated muscle-specific LIM protein; PLB: phospholamban; RyR: ryanodine receptor; serca: sarcoplasmic reticulum calcium ATPase; SG: sarcoglycan; SR: sarcoplasmic reticulum; VDAC: voltage-dependent anion channel.