

Alpha-Smooth Muscle Actin (α -SMA)

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Abstract: Alpha-smooth muscle actin (alpha-SMA) is the actin isoform that predominates within vascular smooth-muscle cells and plays an important role in fibrogenesis. Myofibroblasts are metabolically and morphologically distinctive fibroblasts expressing alpha-SMA, and their activation plays a key role in development of the fibrotic response. In an activated state, myofibroblasts cease to proliferate and start to synthesize large amounts of extracellular component proteins. The expression of alpha-SMA correlates with the activation of myofibroblasts. In contrast, the expression of alpha-SMA in cells made quiescent by cell-cell contact was lower than that in cells made quiescent by serum starvation. [The Journal of American Science. 2008;4(2):1-3]. (ISSN 1545-1003).

Keywords: alpha-smooth muscle actin (alpha-SMA); fibrogenesis; myofibroblasts; proliferate; cell

Introduction

Alpha-smooth muscle actin (alpha-SMA) is the actin isoform that predominates within vascular smooth-muscle cells and plays an important role in fibrogenesis (Kawasaki, Imaizumi et al. 2008). alpha-SMA was recently shown to be present in mouse subcutaneous tissue fibroblasts in the absence of tissue injury (Storch, Taatjes et al. 2007). Myofibroblasts are metabolically and morphologically distinctive fibroblasts expressing alpha-SMA, and their activation plays a key role in development of the fibrotic response. In an activated state, myofibroblasts cease to proliferate and start to synthesize large amounts of extracellular component proteins. The expression of alpha-SMA correlates with the activation of myofibroblasts. In contrast, the expression of alpha-SMA in cells made quiescent by cell-cell contact was lower than that in cells made quiescent by serum starvation (Nakatani, Honda et al. 2008). This article gives a brief description of the alpha-SMA (Wikipedia, 2008).

Myofibroblasts are a form of fibroblast cell that has differentiated partially towards a smooth muscle phenotype (Elberg, Chen et al. 2008). It can contract by using some of the cytoskeletal proteins that are normally found in smooth muscle cells, in particular alpha-SMA (Jiroutova, Majdiakova et al. 2005). These cells are then capable of speeding wound repair by contracting the edges of the wound. Early work on wound healing showed that granulation tissue taken from a wound, could contract in vitro in a similar fashion to smooth muscle, when exposed to substances that cause smooth muscle to contract, such as adrenaline or angiotensin (Park, Bivona et al. 2007). After healing is complete, these cells are lost through apoptosis and it has been suggested that in several fibrotic diseases that this mechanism fails to work, leading to persistence of the myofibroblasts, and consequently expansion of the extracellular matrix and contraction (Darby and Hewitson 2007). It is generally accepted that fibroblast-to-myofibroblast differentiation represents a key event during wound healing and tissue repair. The high contractile force generated by myofibroblasts is beneficial for physiological tissue remodeling but detrimental for tissue function when it becomes excessive such as in hypertrophic scars, in virtually all fibrotic diseases and during stroma reaction to tumors. Specific molecular features as well as factors that control myofibroblast differentiation are potential targets to counteract its development, function, and survival. Such targets include alpha-smooth muscle actin and more recently discovered markers of the myofibroblast cytoskeleton, membrane surface proteins, and the extracellular matrix. Moreover, intervening with myofibroblast stress perception and transmission offers novel strategies to reduce tissue contracture; stress release leads to the instant loss of contraction and promotes apoptosis (Hinz 2007).

Actin is a globular structural protein that polymerizes in a helical fashion to form an actin filament. These form the cytoskeleton - a three-dimensional network inside an eukaryotic cell. Actin filaments provide mechanical support for the cell, determine the cell shape, enable cell movements. In muscle cells they play an essential role, along with myosin, in muscle contraction. In the cytosol, actin is

predominantly bound to ATP, but can also bind to ADP. An ATP-actin complex polymerizes faster and dissociates slower than an ADP-actin complex. Actin is one of the most abundant proteins in many eukaryotic cells, with concentrations of over 100 μM . It is also one of the most highly conserved proteins, differing by no more than 5% in species as diverse as algae and humans (Lambert, Perri et al. 2005).

Alpha-SMA molecular weight is 42 kD. The individual subunits of actin are known as globular actin, while the filamentous polymer composed of G-actin subunits (a microfilament), is called F-actin. The microfilaments are the thinnest component of the cytoskeleton, measuring only 7 nm in diameter. Much like the microtubules, actin filaments are polar, with a fast growing plus (+) or *barbed* end and a slow growing minus (-) or *pointed* end. ADP-actin dissociates from the minus end and the increase in ADP-actin stimulates the exchange of bound ADP for ATP, leading to more ATP-actin units. This rapid turnover is important for the cell's movement. Many cellular functions depend on rapid cytoskeletal rearrangements localized to specific cytoplasmic domains. End-capping proteins such as CapZ prevent the addition or loss of monomers at the filament end where actin turnover is unfavourable like in the muscle apparatus (DiNubile 1999).

Actin filaments are assembled in two general types of structures: bundles and networks. Actin-binding proteins dictate the formation of either structure since they cross-link actin filaments. Actin filaments have the appearance of a double-stranded helix. In non-muscle actin bundles, the filaments are held together such that they are parallel to each other by actin-bundling proteins and/or cationic species. Bundles play a role in many cellular processes such as cell division (cytokinesis) and cell movement. Actin, together with myosin filaments, form actomyosin, which provides the mechanism for muscle contraction. Muscular contraction uses ATP for energy. The ATP allows, through hydrolysis, the myosin head to extend up and bind with the actin filament. However ATP is not needed to the attachment of myosin (in muscle it is myosin II) onto the actin filament. The myosin head then releases after moving the actin filament in a relaxing or contracting movement by usage of ADP (Cooke, White et al. 1994).

In contractile bundles, the actin-bundling protein actinin separates each filament by 40 nm. This increase in distance allows the motor protein myosin to interact with the filament, enabling deformation or contraction. In the first case, one end of myosin is bound to the plasma membrane while the other end *walks* towards the plus end of the actin filament. This pulls the membrane into a different shape relative to the cell cortex. This results in the shortening, or contraction, of the actin bundle. This mechanism is responsible for muscle contraction and cytokinesis, the division of one cell into two (Lewalle, Steffen et al. 2008).

Actin filaments, along with many actin-binding proteins form a complex network at the cortical regions of the cell. Recent studies have also suggested that actin networks on the cell cortex serve as barriers for molecular diffusion within the plasmic membrane (He, Liu et al. 2007; Jaworski, Hoogenraad et al. 2008).

Principal interactions of structural proteins at cadherin-based adherens junction. Actin filaments are linked to α -actinin and to membrane through vinculin. The head domain of vinculin associates to E-cadherin via α -, β - and γ -catenins. The tail domain of vinculin binds to membrane lipids and to actin filaments (Miyake, Inoue et al. 2006).

Although most yeasts have only a single actin gene, higher eukaryotes generally express several isoforms of actin encoded by a family of related genes. Mammals have at least six actins, which are divided into three classes according to their isoelectric point. Alpha actins are generally found in muscle, whereas beta and gamma isoforms are prominent in non-muscle cells. Although there are small differences in sequence and properties between the isoforms, all (DeBiase, Lane et al. 2006; Lee, Dixelius et al. 2006).

All non-spherical prokaryotes appear to possess genes such as MreB which encode homologues of actin; these genes are required for the cell's shape to be maintained. The plasmid-derived gene ParM encodes an actin-like protein whose polymerised form is dynamically unstable, and appears to partition the plasmid DNA into the daughter cells during cell division by a mechanism analogous to that employed by microtubules in eukaryotic mitosis (Clerici, Mantiero et al. 2005; Stehle, Postberg et al. 2007).

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