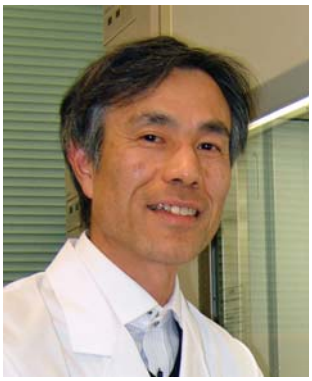
Biology

Molecular mechanisms of actin filament formation responsible for muscle contraction, regeneration, and hypertrophy



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Background of Research

Contraction of the skeletal and cardiac muscles is required not only for the movement of every part of the body but also for breathing, swallowing, and heartbeat. Therefore muscle contraction is an essential action directly linked to our life. Myofibrils, which consist mainly of actin and myosin filaments, are responsible for muscle contraction. In addition, myofibrils are one of the most ordered structures within a cell. Thus, many researchers have looked into the question of how myofibrils are created. To date, however, the molecular mechanisms of myofibril formation have remained uncertain.

Achievements of Research

Insulin-like growth factor-1 (IGF-1) causes muscle regeneration and enlargement (hypertrophy), during which myofibrils are formed. For this reason, we postulated that a series of signaling flows among particular proteins in cells (signal transduction) generated by IGF-1 stimulation is responsible for the formation of myofibrillar actin and myosin filaments. Thus, we investigated the molecular mechanisms of actin filament formation by this signal transduction. We found that IGF-1-induced signal transduction causes the binding of a protein N-WASP to a myofibrillar protein nebulin and that they cooperate to form actin filaments (Figure).

So far, N-WASP has been known to activate a protein complex to generate branched actin filaments in cells other than muscle cells. However, myofibrillar actin filaments are linear and unbranched. Accordingly, it is an unexpected finding that N-WASP acts in the formation of unbranched actin filaments. Experiments using mice showed that these mechanisms of myofibrillar actin filament formation are required for muscle regeneration and hypertrophy.

Prospects of Research

Because nebulin gene mutations lead to nemaline myopathy, a congenital skeletal muscle disease, this research may shed light on the pathological mechanisms of nemaline myopathy. On the other hand, a protein nebulette is present in cardiac muscle instead of nebulin. Recently, nebulette gene mutations have been reported to cause some dilated cardiomyopathy. Thus, this research might also lead to an understanding of the pathological mechanisms of cardiomyopathy.

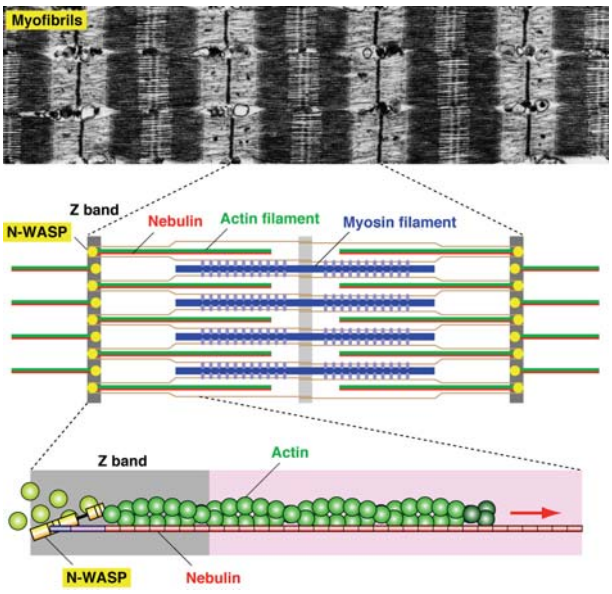

Figure: The structure of myofibrils and the mechanism of actin filament formation