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CYTOSKELETON

N-WASP 'muscles in' on actin nucleation

Muscle maturation and hypertrophy require the activation of protein synthesis and myofibrillogenesis. Takano *et al.* now show that insulin-like growth factor 1 (IGF1) can mediate myofibrillogenesis through a pathway involving neural Wiskott–Aldrich syndrome protein (N-WASP) and the sarcomeric protein nebulin.

Muscle cells are made up of arrays of myofibrils (made during myofibrillogenesis), which consist of actin and myosin filaments. However, it was unclear which proteins induce actin polymerization in these structures. Because N-WASP induces actin polymerization in non-muscle cells, the authors examined whether it might also do so in myofibrils. They observed that, during muscle regeneration, N-WASP localized specifically in Z disks (where actin filaments anchor) in response to IGF1. It colocalized here with α-actinin, which anchors actin filaments. This correlated with actin filament formation, indicating that the IGF1-mediated recruitment of N-WASP to Z disks might induce actin polymerization.

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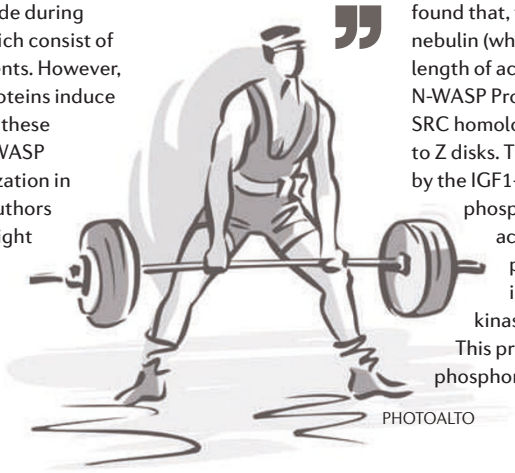

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Next, the authors examined how N-WASP is recruited to Z disks. They found that, following IGF1 treatment, nebulin (which spans almost the entire length of actin filaments) binds to the N-WASP Pro-rich region through its SRC homology 3 domain to recruit it to Z disks. This interaction is mediated by the IGF1-induced activation of phosphoinositide 3-kinase, which activates the kinase AKT to phosphorylate, and thus inhibit, glycogen synthase kinase 3β (GSK3β). This prevents the GSK3β-mediated phosphorylation of nebulin, which allows nebulin to associate with N-WASP and recruit it to Z disks.

So how does N-WASP induce actin filament formation in myofibrils? As the actin nucleator actin-related protein 2/3 (ARP2/3) was not associated with myofibrils, another mechanism must operate. Indeed, the authors showed that N-WASP and nebulin cooperate to polymerize actin through the two WASP homology 2 domains of N-WASP and the actin monomer-binding motifs of nebulin.

Therefore, it seems that in myofibrils, N-WASP and nebulin induce actin polymerization independently of ARP2/3. The resultant formation of actin filaments, together with myosin filament assembly, induces myofibrillogenesis.

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ORIGINAL RESEARCH PAPER Takano, K. *et al.* Nebulin and N-WASP cooperate to cause IGF-1-induced sarcomeric actin filament formation. *Science* **330**, 1536–1540 (2010)
FURTHER READING Sparrow, J. C. & Schöck, F. The initial steps of myofibril assembly: integrins pave the way. *Nature Rev. Mol. Cell Biol.* **10**, 293–298 (2009)