Protein α-N-terminal acetylation regulates actin cytoskeleton structure, cellular motility and proliferation.

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Keywords: *NatB, actin, tropomyosin, cellular motility, cellular proliferation.*

Abstract

Protein alpha-aminoterminal acetylation (Nt-acetylation) is an important mediator of protein function, stability, sorting, and localization. This modification is catalyzed by N-terminal acetyltransferase enzymes (NATs), being an omnipresent protein modification that affects majority of eukaryotic proteins. NATs are a group of enzymatic complexes, NatA–F, that differ both in subunit composition as well as in substrate specificity. NatB, which targets Met-Glu-, Met-Asp-, Met-Gln-, and Met-Asn-starting protein N termini, is presumed to Nt-acetylate 20.6% of all human proteins. We have observed that NatB activity is required for maintaining the structure and function of actomyosin fibers and focal adhesions in mammalian cells. Therefore, NatB downregulation reduces cellular traction force and consequently cellular migration. In yeast, NatB knockout impairs actin filaments and cables stabilization, mainly as a result of a deficient tropomyosin-1 N-terminal acetylation. According to the observations made in yeast, expression of tropomyosin-1 restores the altered focal adhesions and cellular migration defects observed in hNatB-depleted HeLa cells, indicative for the conserved link between NatB, tropomyosin, and actin cable function from yeast to human.

Additionally, NatB downregulation mediated actin cytoskeleton disruption is associated with compromised cellular proliferation. This antiproliferative effect is induced by a reduced YAP/TAZ activity and is reflected in an impaired tumor engraftment and progression in a xenograft mouse model.