Co-polymers of actin and tropomyosin account for a major fraction of the human actin cytoskeleton

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The actin cytoskeleton is involved directly or indirectly in almost every process in the cell. Actin filaments are remarkably versatile and are used to build a diverse range of structures, however the composition and assembly of different actin structures is not yet fully understood. Our work focuses on the incorporation and organisation of the actin filament regulator, tropomyosin, in the actin cytoskeleton. Tropomyosin is a coiled-coil dimer that wraps around actin filaments and regulates their function by influencing filament stability, binding of actin binding proteins and myosin activity in an isoform dependent manner. For the first time, biochemical measurements were made of the quantity of tropomyosin in cultured human cells along with quantification of the association of different isoforms with actin filaments. These measurements indicated that co-polymers of actin and tropomyosin account for a major fraction of actin filaments in cultured human cells. Furthermore, Tpm3.1/3.2 was identified as the dominant isoform in transformed cells, which supports the strategy of targeting Tpm3.1/3.2 in cancer. Lastly, STED super resolution microscopy experiments revealed that tropomyosin isoforms localise to segregated micro-domains within contractile stress fibres, and that Tpm3.1/3.2 aligns with Myosin IIa/Iib heads. Our work highlights the importance of understanding the composition of specific actin structures, since based on estimated concentrations in cells, it seems unlikely that any given actin filament would be free of either tropomyosin or competing actin binding proteins. Given that the actin cytoskeleton is implicated in almost every function of the cell, we conclude that tropomyosin isoforms will impact a host of different areas of medical research.