Distinct actin filament populations regulate different signalling pathways

P. Gunning[1]*, G. Schevzov[1], A. Kee[1], J. Hook[1], B. Wang[1], C. Lucas[1], C. Tonthat[1], T. Fath[1,] J. Stehn[1], I. Pleines[2], R. Seger[3], B. Kile[2], E. C. Hardeman[1]

[1]School of Medical Sciences, UNSW Australia, Sydney, NSW, 2052, Australia; [2]Walter and Eliza Hall Institute, Melbourne, Victoria, 3000, Australia; [3]The Weizmann Institute of Science, Rehovot, 76100, Israel. p.gunning@unsw.edu.au

* Corresponding Author

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Abstract

The actin cytoskeleton has been implicated in the regulation of cell signalling pathways but elucidating specific mechanisms has been difficult because actin inhibitors profoundly compromise cell structure and do not discriminate between different actin filament populations. Most actin filaments in animal cells are composed of a co-polymer of actin and tropomyosin (Tm). The Tm isoform associated with a filament defines its functional characteristics by regulating its interaction with actin binding proteins and myosin motors. We have used both gain- and loss-of-function mouse models, and anti-Tm drug approaches to identify the physiological function of actin filament populations containing different Tms. The cancer-associated Tm, Tm5NM1, was found to impact organ and tissue size by regulating cell proliferation in Tm5NM1 overexpressing transgenic and knockout mice. RNA array and Kinexus pathway analyses indicated that Tm5NM1 regulates cell proliferation via the ERK1/2 (ERK) pathway. Studies using mouse embryo fibroblast cultures (MEFs) isolated from the mice confirmed that pERK-mediated cell proliferation is dependent on the presence of Tm5NM1. MEFs devoid of Tm5NM1 are completely refractory to ERK2 and Casein Kinase 2 inhibition indicating that pERK nuclear translocation is dependent on Tm5NM1. Serum stimulation revealed that the interaction between pERK and Tm5NM1 is growth factor dependent, and that the interaction of pERK with the nuclear transporter importin 7 is Tm5NM1 dependent. We conclude that the interaction between pERK and importin 7 which results in the translocation of pERK into the nucleus requires Tm5NM1-containing actin filaments. In contrast, studies using MEFs isolated from knockout mice of a different Tm isoform, Tm4, revealed that they can readily escape senescence and display dysregulation of PKC and STAT isoforms. Taken together these findings indicate that different signalling cascades may be regulated in cellular space and time via different actin filament networks defined by specific Tm isoforms.