UKE Paper of the Month July 2026

Evolutionarily conserved short linear motifs drive actin filament binding

Themistoklis Paraschiakos*, Biao Yuan*, Michael Hecht-Bucher, Kostiantyn Sopelniak, Pasquale Cervero, Lisa Simon, Ksenija Zonjic, Dominic Eggers, Franziska Selle, Jing Li, Ali Biabani, Stefan Linder, Thomas C. Marlovits & Sabine Windhorst

**contributed equally*

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ABSTRACT:

Regulation of the actin cytoskeleton by actin-binding proteins is essential for cellular homeostasis, and the mode of actin binding determines the activity of actin-binding proteins. Here we identify a 'short linear actin filament-binding motif' (SFM) based on the cryo-electron microscopy structure of the ITPKA-actin filament complex. Using the computational pipeline SLiMFold, we discovered 103 human proteins containing SFMs with diverse cellular roles. Phylogenetic analysis suggests that SFMs arose de novo and are conserved across eukaryotes, exhibiting actin filament-binding affinities of 2-12 µM. Critical residues mediating binding and modulating affinity were defined, and the cryo-electron microscopy structures of two SFM-actin filament complexes revealed that SFM binding decreases actin-filament stiffness. These findings indicate that SFMs regulate actin-filament conformation and serve as anchoring modules that connect actin dynamics to a broad variety of cellular functions, providing a framework for understanding the actin-associated roles of numerous proteins.

STATEMENT

"For the first time, we describe a short, evolutionarily conserved sequence motif, the 'short linear actin filament-binding motif' (SFM), that acts as a universal molecular anchor onto actin filaments, the dynamic scaffold that shapes and moves every human cell. Combining SLiMFold, a new computational pipeline we developed, with cryo-electron microscopy, biochemistry, cell biology and evolutionary analysis, we identify this motif in 103 human proteins of highly diverse function, thereby defining an entirely new and unexpectedly large class of human actin-binding proteins. Notably, the same motif is the shared structural basis of LifeAct and F-tractin, two of the most widely used probes for imaging actin in living cells worldwide. Because actin-binding proteins govern cell division, migration and neuronal function — and their dysregulation drives cancer as well as neurological and immune disorders — our findings provide a broadly applicable framework for interpreting the actin-associated roles of numerous, still uncharacterized proteins. The study is genuinely interdisciplinary, uniting four UKE institutes (Biochemistry and Signal Transduction; Medical Microbiology, Virology and Hygiene; Institute of Microbial and Molecular Sciences; and Mass Spectrometric Proteomics) across bioinformatics, structural biology, mass spectrometry and cell biology, and is published in Nature Cell Biology, a leading journal in the field."

BACKGROUND:

This was part of the MD PhD thesis of first author Themistoklis Paraschiakos in the group of Prof. Sabine Windhorst at the UKE (Biochemistry and Signal Transduction), which carried out the in silico prediction, protein purification and cell-based assays (together with M. Hecht-Bucher, L. Simon, K. Zonjic, D. Eggers, F. Selle, J. Li). Co-first author Biao Yuan performed the cryo-EM (Prof. Thomas C. Marlovits, Institute of Microbial and Molecular Sciences/CSSB); the group of Prof. Stefan Linder (Medical Microbiology, Virology and Hygiene; K. Sopelniak, P. Cervero) contributed macrophage experiments, with mass-spectrometry support from A. Biabani (Prof. Hartmut Schlüter). Funding: Roggenbuck-Stiftung to S.W./T.P., DFG RTG2771/P4 to S.L., and UKE open-access funding