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Abstract

Comparative Analyses of the Gelsolin Homology Domains of Gelsolin and Flightless-I †

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Abstract: Flightless-I is a unique member of the gelsolin superfamily alloying six gelsolin homology (GH) domains and leucine-rich repeats. Flightless-I is an established regulator of the actin cytoskeleton. However, its biochemical activities in actin dynamics regulation are still largely elusive. To better understand its biological functioning, we studied Flightless-I by in vitro fluorescence spectroscopy and single filament TIRF microscopy approaches. We found that Flightless-I inhibits actin assembly by high-affinity (~nM) filament barbed end capping, moderately facilitates nucleation by low-affinity (~μM) monomer binding and does not sever actin filaments in vitro. Flightless-I was found to interact with actin and affect actin dynamics in a calcium-independent fashion. Notably, our functional analyses indicate that GSN and Flightless-I respond to calcium differently implying different conformational characteristics of the GH domains in the two proteins. Bioinformatics analyses predict that the sequence elements responsible for calcium activation of GSN are not conserved in the GH domains of Flightless-I. Consistently, the use of the hydrophobic fluorescent dye (8-anilinonaphthalene-1-sulfonic acid; ANS) revealed that unlike that of GSN the conformational behavior of the GH domains Flightless-I was not significantly affected by calcium-binding. Altogether, our work reveals different calcium-response and predicts distinct modes of activation of GSN and Flightless-I.

Keywords: actin; Flightless-I; gelsolin; cytoskeleton; ANS

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