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Conformational equilibrium of talin is regulated by anionic lipids

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Running Title: Talin conformational equilibrium

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ABSTRACT

A critical step in the activation of integrin receptors is the binding of talin to the cytoplasmic domain of the β subunits. This interaction leads to separation of the integrin α and β transmembrane domains and significant conformational changes in the extracellular domains, resulting in a dramatic increase in integrin's affinity for ligands. It has long been shown that the membrane bilayer also plays a critical role in the talin–integrin interaction. Anionic lipids are required for proper interaction, yet the specificity for specific anionic headgroups is not clear. In this report, we document talin–membrane interactions with bilayers of controlled composition using Nanodiscs and a FRET based binding and structural assay. We confirm that recruitment of the talin head domain to the membrane surface is governed by charge in the absence of other adapter proteins. In addition, measurement of the donor–acceptor distance is consistent with the hypothesis that anionic lipids promote a conformational change in the talin head domain allowing interaction of the F3 domain with the phospholipid bilayer. The magnitude of the F3 domain movement is altered by the identity of the phospholipid headgroup with phosphatidylinositides promoting the largest change. Our results suggest that phoshpatidylinositol-4,5-bisphosphate plays key a role in converting talin head domain to a conformation optimized for interactions with the bilayer and subsequently integrin cytoplasmic tails.

1. INTRODUCTION

Talin is a large adapter protein that plays a key role in connecting the actin cytoskeleton to the extracellular matrix (ECM)[1] via integrin receptors. Talin was discovered nearly 30 years ago and since that time many studies have shown that it is involved in the final step of integrin inside-out activation [1–3]. Talin is composed of a globular head domain (THD) that is homologous to the domain found in band 4.1/ezrin/radixin/moesin family of proteins (FERM domain). THD differs from a canonical FERM domain by the presence of an additional 85 amino acids at the C-terminus termed F0. In comparison to canonical FERM domains, THD adopts a linear configuration of F0-F3 as opposed to the standard cloverleaf structure seen in other FERM domains [4]. Talin also contains a large rod domain which consists of 13 helical bundles and a small dimerization helix [4,5]. Functionally, the head domain is critical for the activation of integrin through interactions with the cytoplasmic tails of β integrins and the cytoplasmic membrane surface, while the rod domain provides a link to the actin cytoskeleton via interactions with actin and other adapter proteins such as vinculin [6–9]. The rod domain also plays a role in the regulation of talin through a self-association with the head domain, thus creating an auto-inhibited form of talin [10,11]. A recent study has shown that talin exists as a dimer and adopts a complex donut–like structure in what would presumably be the auto-inhibited form [12]. Several mechanisms of talin activation have been

[1] Abbreviations: ECM, extracellular matrix; PIP2, phoshpaidylinositol-4,5-bisphosphate; PI4P, phoshpaidylinositol-4-phosphate; FERM, band 4.1/ezrin/radixin/moesin; THD, talin head domain; TM, transmembrane; OMC, outer membrane clasp; IMC, inner membrane clasp; MD, Molecular Dynamics; TAMRA, Tetramethylrhodamine-5-(and -6) C2 maleimide; MSP, Membrane Scaffold Protein; UA, Uniblue A;