Biochimica et Biophysica Acta 1838 (2014) 579–588

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Review

Mechanisms of talin-dependent integrin signaling and crosstalk ☆

Mitali Das [1], Sujay Subbayya Ithychanda [1], Jun Qin *,[2], Edward F. Plow *,[2]

Department of Molecular Cardiology, Joseph J. Jacobs Center for Thrombosis and Vascular Biology, Lerner Research Institute, Cleveland Clinic, USA

ARTICLE INFO

Article history:
Received 26 February 2013
Received in revised form 3 July 2013
Accepted 15 July 2013
Available online 24 July 2013

Keywords:
Talin
Integrin
Actin
Crosstalk

ABSTRACT

Cells undergo dynamic remodeling of the cytoskeleton during adhesion and migration on various extracellular matrix (ECM) substrates in response to physiological and pathological cues. The major mediators of such cellular responses are the heterodimeric adhesion receptors, the integrins. Extracellular or intracellular signals emanating from different signaling cascades cause inside-out signaling of integrins via talin, a cytoskeletal protein that links integrins to the actin cytoskeleton. Various integrin subfamilies communicate with each other and growth factor receptors under diverse cellular contexts to facilitate or inhibit various integrin-mediated functions. Since talin is an essential mediator of integrin activation, much of the integrin crosstalk would therefore be influenced by talin. However, despite the existence of an extensive body of knowledge on the role of talin in integrin activation and as a stabilizer of ECM-actin linkage, information on its role in regulating inter-integrin communication is limited. This review will focus on the structure of talin, its regulation of integrin activation and discuss its potential role in integrin crosstalk. This article is part of a Special Issue entitled: Reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters. Guest Editor: Jean Claude Hervé.

Contents

1. Introduction

The communication of extracellular matrix (ECM) with intracellular cytoskeleton is crucial for regulating cell adhesion, cell shape change and cell migration. Such communication depends heavily on integrins, a large family of noncovalent heterodimeric (α/β) adhesion receptors [65,68]. Integrins function by engaging ECM ligands through their large extracellular domains and actin-binding proteins through their short cytoplasmic tails (CT), thereby linking ECM with the cytoskeleton (Fig. 1). Talin [19,24,63,82], the focus of the article, together with filamin [95] and α-actinin [77,127,160,139], are known to be the key players in this linkage, which can bind directly and simultaneously to both actin and integrin CTs. Numerous other intracellular proteins also connect integrins and the actin cytoskeleton but indirectly via shared binding partners. These extensive integrin-actin networks of protein–protein interactions coalesce to form discrete structures, focal adhesions, podosomes or analogous structures, that constitute dynamic hubs of adhesive and signaling activities [85,146,177].

☆ This article is part of a Special Issue entitled: Reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters. Guest Editor: Jean Claude Hervé.

* Corresponding authors at: Cleveland Clinic, 9500 Euclid Ave., NB-50, Cleveland, OH 44195, USA. Tel.: +1 216 445 8200; fax: +1 216 445 8204.
E-mail addresses: qinj@ccf.org (J. Qin), plowe@ccf.org (E.F. Plow).

[1] Equal contributors as first authors.
[2] Equal contributors as corresponding authors.

0005-2736/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbamem.2013.07.017

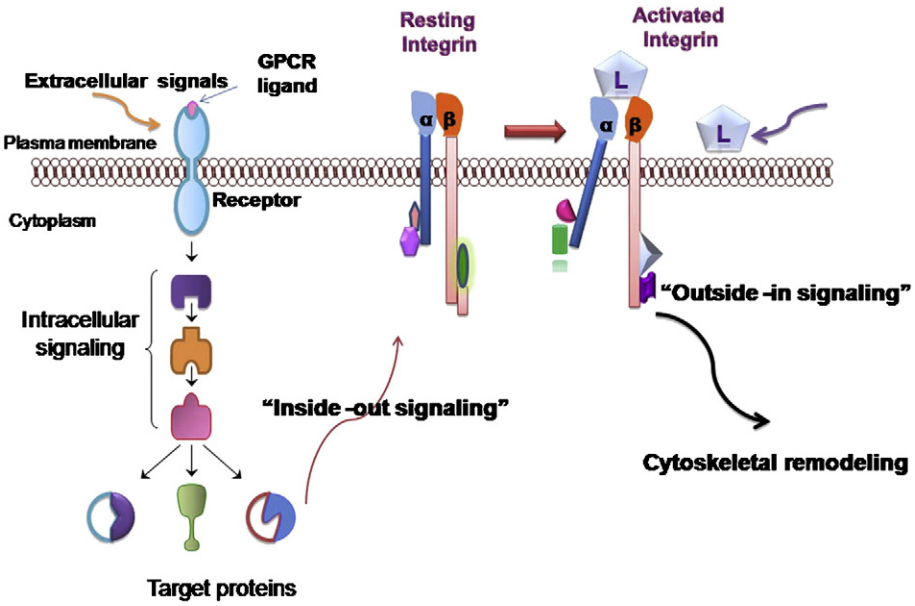

Fig. 1. Bidirectional signaling across integrins. Agonist stimulation, signaling via G protein coupled receptors (GPCRs) and/or growth factor receptors can lead to "inside-out" signaling of integrins. Extracellular domains of resting integrins open up to bind extracellular matrix ligands (L). This leads to "outside-in" signaling of integrins resulting in cytoskeletal remodeling and downstream signaling cascades.

The effects of talin on integrin function are broad. It transduces signals across integrins in both the inside-out and outside-in directions and it also influences the organization of the actin network and the composition of focal adhesions [1,28,45,75,76,110,147,178]. Much of the recent studies on talin have emphasized its unique role in the inside-out signaling of integrins; i.e., their transformation from their basal or "resting" state to a more "active" state in which they can engage their cognate ECM ligands more efficiently (integrin activation). Less emphasized but clearly documented is the influence of talin on integrin outside-in signaling (Fig. 1). Much less is known concerning the role of talin in the crosstalk between integrins of the same or different integrin subfamilies or with other signaling pathways. This review will summarize recent advance on talin structure and its control of integrin function and will touch upon its role in integrin crosstalk.

2. Talin expression, structure and subcellular distribution

Talin was discovered three decades ago as a protein highly enriched at cell adhesion sites [20]. The Tln gene and its orthologs can be traced from vertebrates back to protists [149]. Of the two mammalian isoforms of talin, Tln1 is ubiquitously expressed, being most abundant in the heart and scarce in the brain. Tln2 is enriched in the heart and brain with lower levels detected in the skeletal muscle, liver and lung [115]. Although the Tln1 and Tln2 isoforms in mammals share 74% identity, they do not fully compensate for each other. For example, in skeletal muscle or heart specific knockout models and during epithelial embryogenesis, when Tln1 is inactivated, Tln2 levels do not increase and existing levels do not compensate for Tln1 [29,101,108]. Moreover, Tln1 levels remain unelevated and do not compensate functionally for Tln2 in Tln2 deficient mice [29]. Gastrulation defects result in early embryonic lethality of Tln1 global knockout mice while Tln2 knockout mice are viable and fertile although early and severe myopathy in skeletal muscles is observed in the Tln2 knockout which is not prominent in the skeletal muscle specific Tln1 knockout [17,29]. Platelet or endothelial specific Tln1 deficiency results in severe phenotypes in mouse models [114,57,122,131], although some compensation could be demonstrated by exogenous Tln2 in endothelial cells and upregulated Tln2 expression was observed in undifferentiated embryonic stem cells [83,179]. The vital role of talin in integrin activation and cell adhesion has been established using multiple model organisms [17,30,31,115] as well as tissue-specific inactivation of the Tln1 gene [108,114,122].

The human talin (Q9Y490, UniProtKB) monomer is a 270 kDa protein composed of 2541 amino acids and consists of an N-terminal head of 433 amino acids (talin-H) followed by a much larger rod domain (talin-R) (Fig. 2). Talin-H contains four subdomains, F0, F1, F2 and F3 with F1–F3 being homologous to a typical FERM domain. The F0 and F1 subdomains exhibit ubiquitin-like folds [53] and form a

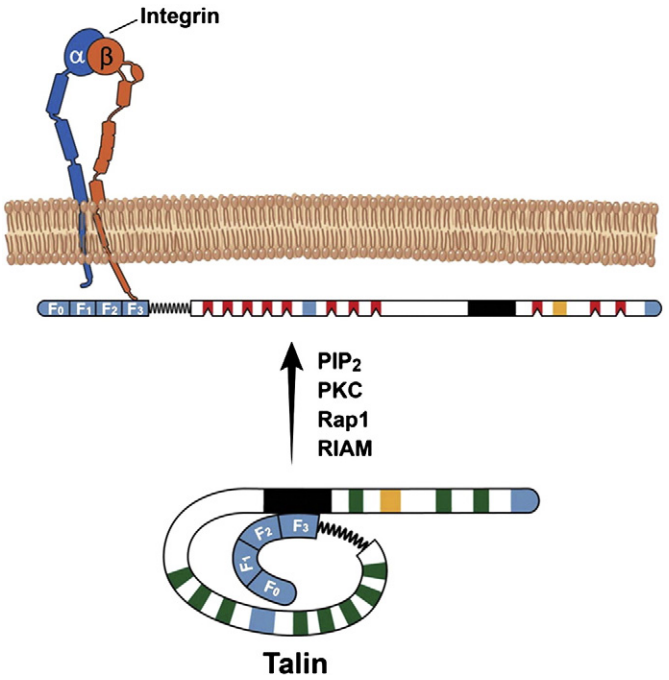

Fig. 2. Structure of talin. Talin can be subdivided into head (talin-H) and rod (talin-R) regions. Talin-H is comprised of F0, F1, F2 and F3 domains while the talin-R has ~11 vinculin- and 3 actin-binding sites (in blue). The vinculin binding sites are dormant (in green) and are likely mechanoactivated (in red). PIP2, PKC, Rap1 and or RIAM can relieve the autoinhibitory effect of talin-R (1654–2344aa; black region) on F3 domain, promoting talin binding to β CT. The secondary integrin binding site is in orange.