Molecules in focus

Tensin

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Abstract

Tensin is a cytoplasmic phosphoprotein that localized to integrin-mediated focal adhesions. It binds to actin filaments and contains a phosphotyrosine-binding (PTB) domain, which interacts with the cytoplasmic tails of β integrin. These interactions allow tensin to link actin filaments to integrin receptors. In addition, tensin has an Src Homology 2 (SH2) domain capable of interacting with tyrosine-phosphorylated proteins. Furthermore, several factors induce tyrosine phosphorylation of tensin. Thus, tensin functions as a platform for dis/assembly of signaling complexes at focal adhesions by recruiting tyrosine-phosphorylated signaling molecules through the SH2 domain, and also by providing interaction sites for other SH2-containing proteins. Analysis of knockout mice has demonstrated critical roles of tensin in renal function, muscle regeneration, and cell migration. Therefore, tensin and its downstream signaling molecules may be targets for therapeutic interventions in renal disease, wound healing and cancer.
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1. Introduction

Tensin is a 220 kDa protein localized to the specialized regions of plasma membrane called focal adhesions (Lo, An, & Bao, et al., 1994), which are formed around a transmembrane core of an αβ integrin heterodimer. The integrin extracellular domain binds to a component of the ECM, and its cytoplasmic tail constitutes the site of anchorage of the actin filaments (Hynes, 1992). Tensin is rapidly translocated to the assembling focal adhesion sites upon integrin ligation (Miyamoto, Akiyama, & Yamada, 1995). The first tensin cDNA sequence was isolated from chicken by Davis et al. in 1991 (Davis, Lu, & Lo, et al., 1991). It allowed the characterization of the encoded protein's

structure and function. Evidence is now emerging to suggest tensin is an important component linking the ECM, the actin cytoskeleton, and signal transduction.

2. Structure

The structure of the tensin molecule has been characterized by light scattering, electron microscopy, and gel filtration. The results indicated that tensin can form a dimer (Lo et al., 1994). Native and recombinant tensin protein migrated around 220 kDa on SDS gels, although the predicted molecular mass was 185 kDa. The discrepancy is due to an unusually slow migration property of the central region (Chen, Ishii, Wong, Chen, & Lo, 2000).

Tensin is a multi-domain protein capable of binding to several structural and signaling molecules

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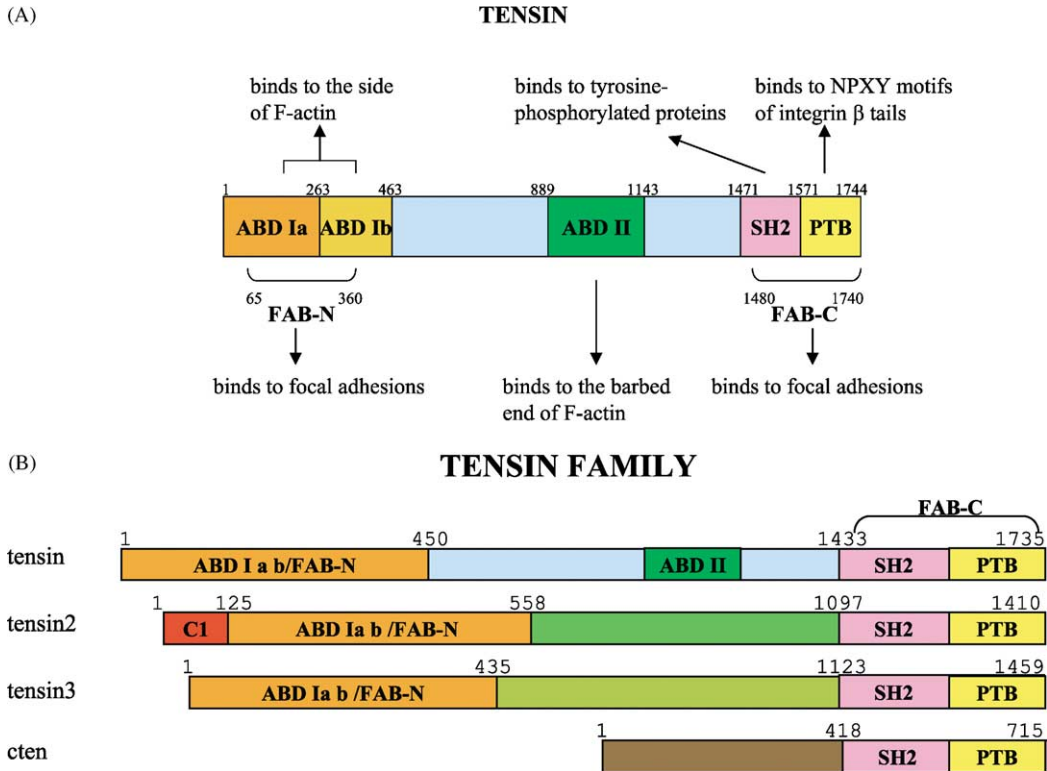*E-mail address:* shlo@ucdavis.edu (S.H. Lo).

Fig. 1. Functional and structural domains of tensins. (A) Tensin can be divided into three regions that are each involved in mediating protein-protein interactions. The N-terminus contains actin-binding domain (ABD) Ia and Ib that interact with actin filaments. This region also contains a focal adhesion-binding (FAB) activity and the PTEN homologous sequence. The center region of tensin contains the ABD II that retards the actin polymerization rate. The C-terminus contains a SH2 domain, PTB domain, and another FAB site. The SH2 domain binds to tyrosinephosphorylated PI3 kinase, FAK, and p130Cas. The PTB domain interacts with integrin tails of $\beta 1$, 3, 5, and 7. Amino acid numbers are based on chicken tensin sequence. (B) Human tensin, tensin2, tensin3, and cten are highly conserved at N- and C-terminal regions. A C1 domain (protein kinase C conserved region 1) is found in tensin2 only. The center regions of tensin members show no sequence homology.

(Fig. 1). It interacts with actin filaments at multiple sites, enabling tensin both to cap the barbed ends and to cross-link actin filaments (Lo, Janmey, Hartwig, & Chen, 1994). Tensin contains an Src Homology 2 (SH2) domain, which allows it to bind to tyrosine-phosphorylated proteins including PI3 kinase, p130Cas, and FAK (Auger, Songyang, & Lo, et al., 1996; Davis et al., 1991). Tensin also has a phosphotyrosine-binding (PTB) domain, which was originally identified as another binding motif for tyrosine-phosphorylated peptides. However, many PTB domains bind to proteins in a nonphosphorylated fashion. Tensin's PTB domain does not interact with tyrosine-phosphorylated proteins (Chen & Lo, 2003). Instead, it binds to the NPXY motifs in the β integrin

cytoplasmic tails (Calderwood, Fujioka, & de Pereda, et al., 2003). Since tensin fragments were originally co-purified with vinculin from chicken gizzards, it was proposed to bind to vinculin. However, no published report demonstrated the interaction exists. Two focal adhesion-binding (FAB) sites were found in the N- and C-terminal regions of tensin. Both FAB sites are critical for tensin's biological functions such as cell migration (Chen & Lo, 2003). Tensin is phosphorylated on tyrosine, serine, and threonine residues. The tyrosine phosphorylation of tensin is enhanced by treating cells with the ECMs, PDGF, thrombin, and angiotensin, as well as by oncogenes including Src, BCR/ABL (Bockholt & Burridge, 1993; Davis et al., 1991; Ishida, Ishida, Suero, Takahashi, & Berk, 1999;

Jiang, Yamamura, & Nelson, et al., 1996). Tensin also shares sequence homology with PTEN, auxilin, and GAK. However, the significance of this similarity is not known.

3. Synthesis and degradation

Tensin is broadly expressed in human tissues including heart, skeletal muscle, kidney, lung, small intestine, liver, colon, prostate, testis, and ovary. Very low or no expression was found in brain, thymus, and circulating leukocytes (Chen et al., 2000).

Tensin is a substrate of at least two protease families: calpain and caspase. Activation of calpains occurs in response to a variety of physiological stimuli and is associated with proteolysis of a number of key cellular proteins. One member, calpain II, is found at focal adhesions and is able to cleave tensin into small fragments (Chen et al., 2000). Digestion of tensin and other focal adhesion molecules by calpain II appears to be important in maintaining cell morphology (Chen et al., 2000).

Tensin is cleaved during apoptosis, which is executed with a cascade of sequential activation of initiator and effector caspases. Effector caspases including caspase 3, 6, and 7 are responsible for the execution of apoptosis by cleaving selected proteins, thus governing the morphological changes that characterize the apoptotic phenotype. Tensin is one of the substrates for caspase 3, suggesting that cleavage of tensin is a critical step for disrupting the structure of focal adhesion during apoptosis.

4. Biological function

The targeted inactivation of the tensin gene revealed its functions in mice. While tensin-null mice developed normally and most tissues were persistently healthy, multiple cysts developed in the kidneys of older mice. The mice subsequently died from renal failure, demonstrating that tensin is required for the normal renal function (Lo, Yu, Degenstein, Chen, & Fuchs, 1997). In addition, a nine-fold increase of centrally nucleated (premature) skeletal muscle fibers was found in tensin-null mice (Ishii & Lo, 2001). By examining the regeneration process of ex-

perimentally damaged skeletal muscle in tensin-null mice, it was shown that the regeneration process was much slower in tensin-null than in wild-type skeletal muscle fibers, suggesting that tensin is involved in skeletal muscle regeneration. Analysis of fibroblasts isolated from mouse embryos has shown that tensin-null cells migrated significantly slower than their normal counterparts (Chen, Duncan, Bozorgchami, & Lo, 2002). Further characterization has demonstrated that the focal adhesion localization and the phosphotyrosine-binding activity of the SH2 domain are critical for tensin-regulated cell migration (Chen & Lo, 2003).

Three molecules (tensin2, tensin3, and cten) with extensive homology to tensin have recently been reported (Chen et al., 2002; Lo & Lo, 2002). Based on protein sequences and genomic structures, they clearly represent a single gene family. The most conserved areas are at the N- and C-terminal regions (Fig. 1). Since cten is a shorter polypeptide and lacks the N-terminal regions found in other tensins, homology is restricted to the C-terminus, which contains the SH2 and PTB domains. Given the high sequence similarities of both regions among tensins, it is likely that the actin-, phosphotyrosine- and integrin-binding activities are conserved in all family members with the exception that cten may not bind to actin filaments. Despite the high sequence similarities of tensins, the middle regions are highly divergent, suggesting that each tensin member may have acquired unique biological roles.

5. Possible medical applications

Several aspects of tensin function are of medical interest. The renal histology of tensin-null mice revealed the typical triad of human nephronophthisis with tubular membrane disruption, tubular ectasis, and interstitial inflammation. Therefore, tensin-null mouse could be used as an animal model for human nephronophthisis or similar renal diseases. Tensin contains trinucleotide (CAG) repeats (Chen et al., 2000). Expansion of CAG repeats has been detected in many proteins that are relevant to inherited diseases, such as Huntington's disease. The numbers of CAG repeats in chicken, human and bovine tensin are 2, 9, and 12, respectively, implying that the motif is unstable through

the course of evolution. It will be intriguing to know whether an expansion of tensin CAG repeats plays a role in the pathogenesis of human disease. Analysis of tensin expressions in human cancer patients and cell lines has led to speculate that the loss of tensin expression may be an early event involved in cell transformation (Chen et al., 2000). If so, tensin and its downstream signaling molecules could be biomarkers or targets for therapeutic interventions in cancer.

Acknowledgements

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