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Molecules in focus

C-terminal tensin-like (CTEN): A promising biomarker and target for cancer

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ABSTRACT

C-terminal tensin-like (cten, also known as tensin4, TNS4) is a member of the tensin family. Cten protein, like the other three tensin family members, localizes to focal adhesion sites but only shares sequence homology with other tensins at its C-terminal region, which contains the SH2 and PTB domains. Cten is abundantly expressed in normal prostate and placenta and is down-regulated in prostate cancer. However, overexpression of cten frequently associates with tumors derived from breast, colon, lung, stomach, skin and pancreas. A variety of cancer-associated growth factors and cytokines induce cten expression. Up-regulated cten promotes cell motility, prolongs epidermal growth factor receptor signaling, and enhances tumorigenicity. Emerging findings suggest that cten is a promising biomarker and therapeutic target for various cancers.

1. Introduction

Cten (C-terminal tensin-like, aka tensin4, TNS4) was identified as a distant member of the tensin focal adhesion family (Lo and Lo, 2002). It is a much smaller protein compared to other tensins and only shares the SH2 (Src homology 2) and PTB (phosphotyrosine binding) domains found at the C-terminal ends of all other tensins (Lo, 2004) (Fig. 1). It was included in the tensin family due to the following reasons. (1) The tensin family is the only family which contains an SH2 domain immediately followed by a PTB domain. (2) The genomic structures encoding the SH2 and PTB regions of tensins are almost identical. (3) Cten like other tensins mainly localizes to focal adhesions. Many lines of evidence have demonstrated that cten's critical roles in cell motility, apoptosis and growth factor receptor homeostasis may contribute to the development of various cancers.

2. Structure

Human cten is a 715-residue polypeptide which contains two conserved domains: the SH2 domain and PTB domain (Lo and Lo, 2002) (Fig. 1). Both were originally identified as binding modules for phosphotyrosine-containing peptides. PTB domain binding specificity is conferred by residues N-terminal to the phosphotyrosine residue. It was soon discovered that many PTB domains bind to tyrosine residues regardless of their phosphorylation status. Cten's PTB domain binds to the NPXY motif of the integrin β1 tail (Katz et al., 2007) and the assay conditions strongly suggested that this interaction does not require tyrosine phosphorylation. Together with studies on PTB domains of tensin1 and tensin2, it is believed that the interaction of integrin β tails with PTB domains of cten and other tensins is independent of tyrosine phosphorylation (Chen and Lo, 2003; Calderwood et al., 2003). In contrast to PTB domains, SH2 domains recognize an essential phosphotyrosine and adjacent C-terminal residues. Nonetheless, there are a few exceptions, including the SH2 domains of SLAM-associated protein (aka SAP, SH2D1A) and cten, in which the binding requires the tyrosine but regardless of its phosphorylation status. SH2 domains of cten and other tensins bind to the SIY^{442}DNV site on DLC1 (Deleted in Liver Cancer 1) and phosphorylation of the tyrosine is not required (Liao et al., 2007; Dai et al., 2011). This interaction recruits DLC1, a tumor suppressor, to focal adhesions (Liao et al., 2007). The SH2 domain of cten still interacts with phosphotyrosine-containing proteins. For example, it binds to pY^{744}DVPK site on c-Cbl and this interaction is critical in regulating homeostasis of EGFR (epidermal growth factor receptor) (Hong et al., 2013).

3. Expression, activation and turnover

Cten shows a relatively unique and restricted expression pattern in normal tissues. It is readily detected in normal prostate

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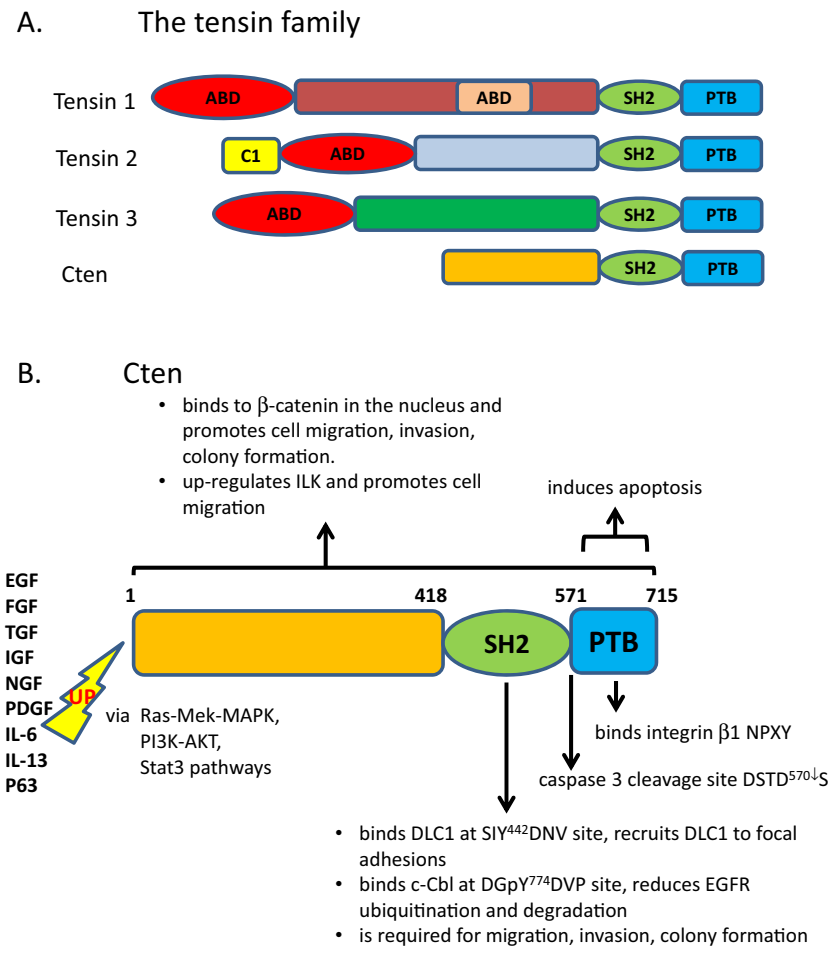

Fig. 1. (A) Domain structures of tensins. ABD: actin-binding domain. C1: protein kinase C conserved regions. SH2: Src homology 2. PTB: phosphotyrosine binding. (B) Cten expression is induced by numerous growth factors and cytokines (listed in bold) through Ras-Mek-MAPK, PI3K-Akt, or Stat3 pathways. Up-regulated cten promotes cell migration, invasion and colony formation activities, which require the functional SH2 domain. The SH2 domain binds to DLC1 in a phosphorylation independent manner and recruits DLC1 to the focal adhesion site. The SH2 domain also interacts with tyrosine phosphorylated c-Cbl and reduces ligand-induced EGFR degradation. The PTB domain binds to β integrin NPXY sites. Caspase 3 cleaves cten between the SH2 and PTB domains. The resulting PTB domain fragment is able to promote apoptosis.

and placenta but is not detectable in other tissues by Northern blot assays (Lo and Lo, 2002). The tissue specific expression pattern has triggered the identification of CTEN promoter region. By promoter bashing, a 327-bp fragment around exon 1 was identified as the essential region of human CTEN promoter activity (Chen et al., 2013). It showed very strong promoter activities in human prostatic epithelial cell lines and significantly weaker activities in non-prostatic cells in reporter assays. When a Cre transgenic mouse line driven by this 327-bp human CTEN fragment was generated and crossed with R26R reporter mice, the β-galactosidase reporter signals were detected strongly in the prostate, brain, pancreas, lung and testis (Chen et al., 2013). These results suggest that the fragment does contain a functional promoter activity. However, it is not sufficient for regulating a very tight tissue specific expression pattern due to either missing critical regulatory elements and/or the discrepancy between human and mouse CTEN promoters. Interestingly, a p63 binding site within this 327-bp region was identified by the ChIP assay (Seo et al., 2012), indicating that CTEN is a target gene of p63. However, the biological relevance is currently unclear.

In human cancers, cten expression is reduced or absence in advanced prostate cancers (Chen et al., 2013; Lo and Lo, 2002; Li et al., 2010) (Table 1). Despite of its low expression in the normal kidney, cten is further downregulated in kidney cancers (Martuszewska et al., 2009). Although it may not be expressed in other normal tissues, cten expression has been found to increase significantly in many types of cancer including thymoma, gastric, colorectal, breast, lung, skin, and pancreatic cancer (Liao et al., 2009; Sasaki et al., 2003a,b; Katz et al., 2007; Albasri et al., 2011b,c; Al-Ghamdi et al., 2011, 2013; Sjoestroem et al., 2013; Li et al., 2010; Sakashita et al., 2008), suggesting that overexpression of cten in certain tissues may play a critical role in tumorigenesis.

Cten expression is up-regulated by EGF, FGF2 (fibroblast growth factor 2), TGF-β (transforming growth factor beta), NGF (nerve growth factor), PDGF (platelet-derived growth factor), IGF-1 (insulin-like growth factor 1), IL-6 (interleukin 6) and IL-13 (interleukin 13) (Hung et al., 2013) mainly through the RAS-Raf-Mek, PI3K-Akt and Stat3 pathways activated by these cancer associated growth factors and cytokines (Hung et al., 2013; Barbieri et al., 2010; Al-Ghamdi et al., 2011). This may partially explain how cten levels increase dramatically in various cancers.

MicroRNAs (miRs) are a class of noncoding RNAs that post-transcriptionally regulate gene expression in cells. These 21-23 nucleotide RNAs match to sites in the mRNAs of protein-coding genes and negatively regulate the targeted gene expressions. Cten expression is potentially regulated by many miRs based on sequence alignment predictions. However, only cten down-regulations by miR-1, miR-26b, miR-124, and miR-335 are supported by microarray data (Lim et al., 2005; Gennarino et al., 2009; Baek et al., 2008; Tavazoie et al., 2008). Interestingly, these four miRs play roles in preventing tumor formation and are