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Review

TGFBIp/βig-h3 protein: A versatile matrix molecule induced by TGF-β

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Abstract

TGFBIp/βig-h3 protein is an extracellular matrix molecule initially cloned from human adenocarcinoma cells treated with TGF-β. Its precise function remains obscure but a number of studies have demonstrated it to be an intriguingly versatile molecule role in a wide range of physiological and pathological conditions. To date, the most extensively studied and reported action of TGFBIp/βig-h3 protein is in corneal dystrophy and several excellent reviews are available on this. Work from various laboratories on this molecule has compiled a tremendous amount of information over the past decade and a half. Here we review the current understanding on TGFBIp/βig-h3 protein and its functions in morphogenesis, extracellular matrix interactions, adhesion/migration, corneal dystrophy, tumorigenesis, angiogenesis, nephropathies, osteogenesis, wound healing and inflammation.

Keywords: TGFBI; βig-h3; FAS1 domain; Integrin; Cell adhesion; Tumorigenesis; Angiogenesis; Inflammation; Osteogenesis; Nephropathy; Wound healing

Contents

Abbreviations: TGF-β, transforming growth factor-beta; EMI, N-terminal cystein-rich; FAS1, fasciclin I domain; IL-4, interleukin-4; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha; ECM, extracellular matrix; RGD, Arg-Gly-Asp; NKDIL, Asn-Lys-Asp-Ileu-leu; EPDIM, Glu-Pro-Asp-Ile-Met; PI3K, phosphatidyl inositide-3 kinase; FAK, focal adhesion kinase; Erk, extracellular signal regulated kinase; SPARC, secreted protein, acidic and rich in cystein; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor

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1. Introduction: gene and protein structure

The gene transforming growth factor beta induced (TGFBI) was originally named βig-h3. The name βig-h3 was derived from its original identification and cloning as a major TGF-β-responsive gene in the lung adenocarcinoma cell line A549: TGF-β-induced gene-human clone 3, abbreviated to βig-h3 (Skonier et al., 1992). However, TGFBI appropriately can indicate this gene in different species. Molecules identical or closely related to the TGFBI protein (TGFBIp) identified by subsequent workers have been named MP78/70 (Gibson, Kumaratilake, & Clearly, 1997), collagen fiber-associated protein (RGD-CAP) (Hashimoto et al., 1997) and keratoepithelin (Munier et al., 1997). For consistency, we prefer to use the terms TGFBI for gene and TGFBIp for protein throughout this manuscript. The human TGFBI maps to chromosome 5 in the region 5q31 and consists of 17 exons of almost similar sizes that span approximately 34 kb (Skonier et al., 1994) (Fig. 1A). A comparative analysis of TGFBIp among human, pig, mouse, chicken and zebrafish reveals about 53% amino acid conservation (Supplementary Fig. 1). No invertebrate homologues for this gene have been reported.

The human TGFBIp comprises 683 amino acids with a predicted molecular mass of 68 kDa in its secreted form. It contains a secretory signal (1–24 amino acids at the N-terminus), an EMI domain, four tandem repeats of FAS1 domains and a carboxy-terminal RGD sequence. The FAS1 domain represents an ancient cell adhesion domain homologous to fasciclin I protein in *Drosophila*. Since the identification of the prototypic *Drosophila* protein fasciclin I (Bastiani, Harrelson, Snow, & Goodman, 1987), many proteins containing FAS1 domains have now been identified in different organisms. Human proteins identified so far are TGFBIp, periostin, stabilin-1 and stabilin-2 (Fig. 1B). To date, no isoforms have been reported for TGFBIp and it is encoded by a single gene (Schorderet et al., 2000). The crystal structure of FAS1 domains 3 and 4 from *Drosophila* fasciclin I shows seven-stranded beta structures surrounded by a number of alpha helices (Clout, Tisi, & Hohenester, 2003).

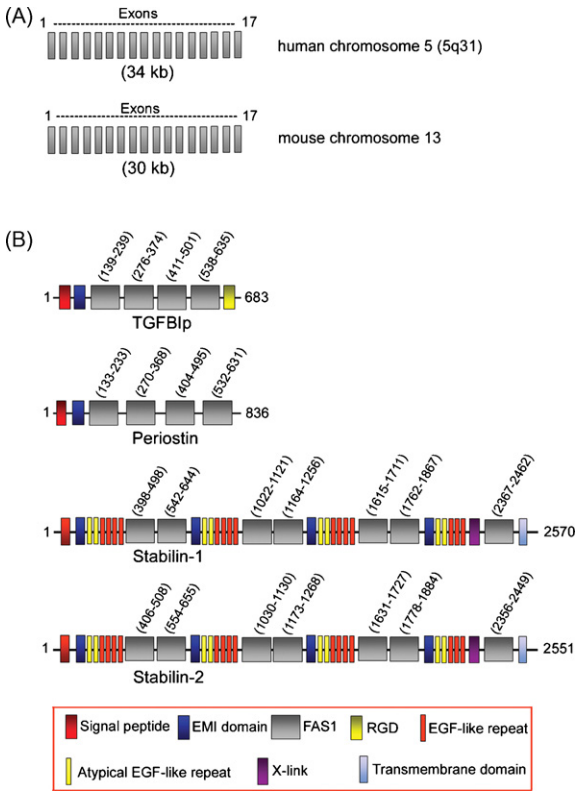

Fig. 1. (A) TGFBI is encoded by 17 exons of almost similar size that spans ~35 kb in human and ~30 kb in mouse (adapted from Schorderet et al., 2000). Human TGFBI maps to chromosome 5 in the region 5q31 whereas mouse TGFBI to mouse chromosome 13 region B to C1. (B) Schematic representations of FAS1 domain containing human proteins (TGFBIp, periostin, stabilin-1 and stabilin-2). TGFBIp contains N-terminal signal peptide immediately followed by EMI domain, four tandem repeats of FAS1 domain, and C-terminal RGD motif. Periostin contains EMI domain followed by four tandem repeats of FAS1 domain. Stabilin-1 and stabilin-2 contain seven FAS1 domains, clusters of EGF-like repeats, X-link domain followed by short cytoplasmic domain. However, EMI domains in stabilins are embedded in atypical EGF-like repeats. The domain architecture for TGFBIp (NM_000358), periostin (NM_006475), stabilin-1 (DQ786774) and stabilin-2 (AY311388) were analyzed by using SMART program. The numbers indicate the position of FAS1 domain in each protein.