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LTBPs in Biology and Medicine; LTBP Diseases

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Abstract

The latent transforming growth factor (TGF) β binding proteins (LTBP) are crucial mediators of TGF β function, as they control growth factor secretion, matrix deposition, presentation and activation. Deficiencies in specific LTBP isoforms yield discrete phenotypes representing defects in bone, lung and cardiovascular development mediated by loss of TGF β signaling. Additional phenotypes represent loss of unique TGF β -independent features of LTBP effects on elastogenesis and microfibril assembly. Thus, the LTBPs act as sensors for the regulation of both growth factor activity and matrix function.

Keywords

TGF β ; Latent TGF β binding proteins; Fibrillin; Marfan syndrome; TGF β activation; Aneurysm; Elastin maturation

1. Introduction

The latent TGF β binding proteins LTBPs act at the nexus of two vital matrix functions; they are crucial organizing elements for several important proteins and they are part of a mechanosensing hub that regulates signaling by TGF β , a molecule that is a critical regulator of the expression of extracellular matrix (ECM) proteins [1]. This review will briefly describe the history and biochemistry of the LTBPs and then focus on the functions of each of these four proteins with respect to disease contributions. It is interesting that the functions of LTBPs in humans were largely derived by searching human populations for phenotypes initially described in mice with null mutations in individual *LTBP* genes. Special emphasis will be placed on the involvement of the LTBPs in human homeostasis and pathology, as well as unresolved questions within this field of research. Several earlier reviews provide more extensive background on biochemistry and function [2–5]. Additional descriptions of

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LTBP interactions with specific EMC proteins can be found within several of the other reviews in this issue of Matrix Biology.

2. History and Biochemistry

Latent TGF β binding protein-1 (LTBP-1) was initially described as a component of a high molecular weight complex of TGF β released from human platelets. Cloning of the LTBP-1 gene permitted the identification of three additional LTBP (LTBP-2, -3, and -4) genes [6–11].

The LTBPs are matrix proteins and have multiple calcium-binding EGF-like domains. In addition, the LTBPs contain a domain unique to the LTBPs and the fibrillins; the eight cysteine (8-Cys) or TGF β -binding (TB) domain, which has four intra domain cysteine residues [12–14]. LTBP-1 and -4 are produced as both long and short forms via the use of separate promoters that generate proteins with unique sequences at their amino termini but with identical sequences in the central and carboxy-terminal regions [13, 15]. As with other matrix proteins, multiple splice variants have been described for each of the LTBPs [16, 17].

The high molecular weight form of TGF β associated with LTBP-1 consists of a tripartite complex composed of the mature TGF β dimer, the TGF β propeptide dimer (also referred to as LAP) and a single molecule of LTBP, forming the large latent complex (LLC) [7, 8]. This complex is formed intracellularly, and even after secretion the TGF β propeptide dimer remains associated with the mature TGF β by non-covalent bonds. This interaction with its propeptide prevents TGF β from binding to its high affinity receptor. Thus, all TGF β is secreted in a latent form bound to its propeptide. In order to signal, TGF β must first dissociate from its propeptide in a process called activation, which is mediated by specific integrins, proteases, and several other molecules [18, 19].

Biochemical studies by Saharinen et al. showed binding of all three TGF β isoforms (1, 2, and 3) to LTBP-1 and -3, binding of only TGF β 1 to LTBP-4, and no covalent interaction between any of the three TGF β isoforms and LTBP-2 [20]. (TGF β does not bind to any of the 8-Cys domains in fibrillin). 8-Cys domain 3 is the site of LAP binding to LTBPs [21, 22]. Structural studies of the 8-Cys domains of fibrillin and LTBP revealed that 8-Cys domains that bind TGF β all contain a dipeptide insertion that is absent in the unreactive 8-Cys domains. The presence of this dipeptide forces cysteine residues 2 and 6 of 8-Cys domain 3 to the surface of the structure where they can pair with each other or bond with the free cysteines in LAP. The weaker binding of LTBP-4 to LAP may be explained by the replacement of three negatively charged amino acid residues in the 8-Cys domains of LTBP-1 and -3 with either uncharged or negatively charged amino acids surrounding the vital surface cysteines. Thus, docking of LAP with the 8-Cys 3 is a crucial first step in disulfide exchange. However, an important unanswered question is whether there is differential binding of to specific LTBPs. The initial experiments by Saharinen and Keski-Oja indicated a lack of TGF β isoform binding specificity for LTBPs –1 and –3 [20]. However, as these data were derived from over-expression experiments, specificity amongst TGF β isoform binding might exist at limiting reactant concentrations. Such selectivity might explain the specificity of certain LTBP-driven phenotypes. The reported binding of TGF β isoforms and

a variety of other molecules to the LTBP is depicted graphically in figure 1. In this figure the binding region on the LTBP of the protein illustrated is given in green, i.e. the green dash indicates the sequence within the LTBP where binding occurs.

Beside TGF β isoforms a number of other matrix constituents bind to the LTBPs (Fig. 1) These include fibronectin [23, 24] [25], fibrillin-1 [25–27], heparin sulfate and heparin [28], fibulin 4 and 5 [29, 30], and AdamTSL2 [26, 31]. Both myostatin and FGF-2 associate non-covalently with LTBP-3 and LTBP-2, respectively [32, 33]. However, the *in vivo* relevance of these interactions remains unknown.

LTBP Function

Early studies showed that LTBP-1 facilitates the secretion of latent TGF β . This is due to the fact that, if not bound to an LTBP, the two free SH groups in the TGF β propeptide form improper disulfide bonds resulting in intracellular protein degradation [34]. Once secreted, the LLC associates with the ECM via LTBP [27]. This matrix interaction potentially provides a reservoir of latent TGF β that can be rapidly mobilized. Binding initially occurs to fibronectin and over time LTBP-1 molecules, as visualized by immunofluorescence, realign with fibrillin fibers [35, 36].

Binding of the LTBP-1 TGF β complex to the ECM is necessary for latent TGF β activation by integrins (Figure 1A, Left). Work by the Munger and the Sheppard labs clearly demonstrated that for TGF β 1 and 3, each of which has an integrin binding arginylglycylaspartic acid (RGD) sequence in the propeptide, the RGD is required for integrin-mediated activation of the latent complex [37, 38]. Mice in which TGF β 1 RGD sequence was replaced by RGE had a phenotype identical to TGF β 1 null animals. In addition mice with a TGF β 1 gene mutation in which the propeptide cysteine that binds to LTBP was mutated to serine (precluding LLC formation) had a TGF β 1 null-like phenotype [39]. This indicates that not only is integrin binding to the propeptide necessary for activation, but the latent TGF β also must be bound to an LTBP, presumably so that the force applied by the integrin is countered by the tension from the LTBP being affixed to the ECM [18, 40, 41]. These data are in agreement with earlier work indicating that LTBP is cross-linked into the ECM by transglutaminase [42]. Analysis of the region of LTBP-1 required for ECM association and integrin-mediated activation revealed that a 55 amino acid stretch in an unstructured region is required and that this sequence binds to fibronectin [43]. LLC can also be activated by proteases, thrombospondin, and high pH. The requirements for activation of latent TGF β isoforms 1 and 3 when bound to LTBP-3 have not been examined nor have the mechanisms for activation of TGF β 2, which does not have an RGD sequence. Proteases can also activate latent TGF β bound to an LTBP (Figure 2A, Right) [4].

The requirement for latent TGF β to be bound to an LTBP and for that LTBP to be incorporated into the ECM has profound implications for the role of LTBP-TGF β complexes in matrix biology. If the TGF β LLC is not bound to the ECM, lower levels of active TGF β will be generated. Thus, in conditions, such as Marfan syndrome (MFS), in which decreased amounts of LTBP are found incorporated in the ECM as a result of defective fibrillin fibers, the initial result should be a **decrease**, not an increase, in active TGF β because activation of

latent TGF β is impaired. The increased levels of TGF β reported in some situations are probably a compensatory response by the cells to the initial decrease in TGF β . This implies that in the matrix there is a constitutive level of TGF β signaling that maintains homeostasis. Mutations that affect the ability to maintain the basal level of active TGF β will result in temporary decreases followed by attempts by the cells to readjust the TGF β level to normal.

LTBP Physiology and Pathology

LTBP-1 Physiology

The use of LTBP-1 neutralizing antibodies or siRNA knock down has revealed multiple in vitro LTBP-1 functions. The first described was the ability of antibodies to LTBP-1 to block the activation of latent TGF β in cocultures of endothelial cells and smooth muscle cells. LTBP-1 blocking antibody also inhibited the differentiation of embryonic stem (ES) cells to endothelial cells, an effect coincident with decreased levels of TGF β in the treated cultures[44]. Nakajima et al. performed an elegant study in which antibody to LTBP-1 inhibited the endothelial-mesenchymal transformation (ETM) of mouse atrio-ventricular endocardial cells [45]. The normal process is TGF β dependent and the addition of TGF β in the presence of the antibody overcame the EMT blockage. These data are of particular relevance in light of the aortic phenotype of LTBP-1 knockout in mice.

Pathology

The initial mouse LTBP-1 null mutation targeted only the long form of the protein; thus synthesis of the short form, Ltbp-1S was undisturbed. Ltbp-1L $^{-/-}$ mice die at birth from persistent truncus arteriosus and interrupted aortic arch [46]. A similar phenotype presents when the TGF beta receptor is knocked out in cardiac neural crest cells, precursors of aortic smooth muscle cells, consistent with loss of LTBP-1L yielding decreased levels of TGF beta signaling [47]. More recent experiments revealed that the complete loss of LTBP-1 (L and S) produces a phenotype similar to loss of LTBP-1L [48]. The limited phenotypes observed in LTBP-1 null animals is surprising given the ubiquity of LTBP-1 expression and the phenotypic modifications observed with in vitro LTBP-1 suppression. The recent availability of a conditional null allele for LTBP-1 should clarify this question with the timed loss of the protein after birth and in specific tissues. Humans with loss of LTBP-1 have not been described, but this is likely an issue of appropriate screening, as the phenotypes of the other LTBP mouse mutants are replicated in human counterparts (See below).

LTBP-2 Physiology

As with the other LTBPs, LTBP-2 binds to the matrix in a fibrillin-dependent manner [49, 50]. In addition to binding to fibrillin, LTBP-2 binds to fibulin-5 and this interaction provides an important elastin fiber assembly regulatory function for LTBP-2 [29]. Although LTBP-2 was thought to be required for early mouse development [51], recent work indicates that LTBP-2 is not required for development but is necessary for the formation of microfibril bundles in the ciliary zonules [52]. In this sense LTBP-2 functions similarly to LTBP-4 (See below).

Pathology

In humans, loss of LTBP-2 results in primary congenital glaucoma with defects in the trabecular network [53, 54]. It is interesting that phenotypes in LTBP-2 null individuals and mice appears to be confined to the eye even though the protein is ubiquitous in the vascular system and multiple other tissues. One possible explanation is that LTBP-4 compensates for the loss in these other sites.

LTBP-3 Physiology

LTBP-3 has several unique features. LTBP-3 interacts with the ECM much more slowly than does LTBP-1 and LTBP-3 is secreted very poorly if not bound to latent TGF beta [55, 56]. The reason for this latter property is unknown, but unlike other LTBPs, the 2:6 cysteines in LTBP-3 that bind to LAP may be more reactive than those in the other isoforms. Without binding to LAP, these cysteines may form abnormal disulfide bonds that induce the unfolded protein response and the subsequent degradation of the misfolded LTBP-3. Therefore, both LAP and LTBP-3 may act as chaperones for each other by inducing proper disulfide bond pairing in their companion protein.

Pathology

LTBP-3 null mice and humans share similar phenotypes with short stature, spinal curvature, cranio-facial malformations, increased bone mass, and dental abnormalities, including reduced enamel production and alterations in both the mandible and maxilla [57–59]. The craniofacial dysmorphism is caused by premature ossification of the cranial synchondroses resulting in decreased anterior elongation of the face, as well as swelling of the cranial vault to accommodate the increasing size of the brain. The precocious ossification is mediated by decreased TGF beta resulting in insufficient PTHrP expression [58, 60]. The increased bone mass in LTBP-3 null mice is caused by a defect in bone resorption [59]. In some patients LTBP-3 mutations also present with acromicric and geleophysic dysplasia consistent with a role of LTBP-3 in long bone growth and lung septation [61]. LTBP-3 mice have a mild defect in the development of pulmonary alveoli during the septation phase, in addition to spleen and thymus involution [62, 63].

Further studies with LTBP-3 null mice have revealed a role of LTBP-3 in the aortic dilation and dissection observed in Marfan syndrome (MFS). Increased levels of TGF β are found in the aortas of MFS patients and mice and antagonism of TGF beta reduces the degree of aortic dilation in MFS [64]. Consistent with a causative role of TGF beta in vessel dilation is the observation that deletion of LTBP-3 in mice with a rapidly progressing form of MFS yielded animals with normal-appearing aortas, as well as mRNA expression profiles [65]. The role of LTBP-3 in the aorta is probably more complex than simply regulating TGF β levels, however, as a recent study from the Ramirez group indicated that inhibition of the cytokine with a pan specific antibody had little effect on vessel dilation in mice with a rapidly progressing form of MFS [66]. The apparent discrepancy between these two studies may indicate the complex nature of TGF β , which is mediated by growth factor isoform, LTBP binding isoform, cell of origin, and probably the availability of other signaling molecules. LTBP-3 also may have a role in mesenchymal stem cell (MSC) differentiation, as MSC differentiation to bone is inhibited when LTBP-3 is knocked down with small

interfering (si) RNA [67]. This may reflect a role of TGF beta in the process, but it is also possible that LTBP-3 has a function independent of binding to LAP. Interestingly, the authors found that LTBP-1 expression is high, even as TGF beta levels decrease, indicating that the enhanced production of LTBP-1 does not supply TGF beta. These observations on a potential role of LTBPs and TGFβ in MSC differentiation is consistent with the observations of Smaldome et al. on the effects of fibrillin-1 loss and the modulation of stem cell niche associated changes in TGFβ [68].

Another provocative study implicated LTBP-3 in TGFβ action in a mouse model of lupus. The authors found that a CD4+ T cell subset expressed the early growth response gene *Erg2*, and that *Erg2* controlled the production of TGFβ 3 that is essential for the lupus phenotype. Interestingly lack of *Egr2* did not affect the transcription of the TGF beta 3 gene; rather lack of *Erg2* prevented the expression of LTBP-3. Therefore, in this system, LTBP-3 levels govern extracellular TGF beta 3 activity [69]. LTBP-3 may also be important in cancer cell metastasis. The Hynes group evaluated the ECM protein content of several human tumors and found that LTBP-3 expression was increased in most of the tumors analyzed. LTBP-3 knock down in human breast cancer cells resulted in a loss of metastatic ability when injected into immunocompromised mice [70]. A recent report claims that knock down of LTBP-2 in thyroid carcinoma cells suppresses invasion [71]. Curiously the authors indicate that this effect is mediated by TGFβ even though LTBP-2 is not a carrier of TGFβ. Additional work is necessary to establish the generality of LTBP-3 support of metastasis as well as potential mechanisms, i. e. is metastasis regulated by LTBP-3 or by the TGFβ carried by LTBP-3. Although there is no direct evidence for a non-TGFβ-mediated function of LTBP-3, the fact that LTBP-2 and 4 have non-TGFβ activities indicates the potential for such a mechanism.

LTBP-4 Physiology

The biology of LTBP-4 is interesting, as both TGFβ-dependent and independent activities have been described. The initial LTBP-4 deficient mouse, which was a severe hypomorph of the short form of LTBP-4 (LTBP-4S), displayed defective elastogenesis in multiple organs including the lungs [72]. The elastin appears as globules adjacent to or on fibrillin fibrils and the ability of the elastin to envelope the microfibrils is defective. More recent studies using a complete LTBP-4 knock out replicated the findings from the LTBP-4S mouse but also indicated that LTBP-4L promotes the incorporation of fibulin 4 into the ECM [73] (Figure 2B). Experiments by Fujikawa et al. demonstrated that LTBP-2 and LTBP-4 have similar functions in the eye and that the ciliary zonules microfiber defect observed in LTBP-2 null mice can be prevented by ectopic expression of LTBP-4 [74].

Pathology

LTBP-4S null mice also develop cardiomyopathy and rectal-anal tumors, as well as increased cell proliferation in the affected tissues, which correlates with decreased TGFβ [72]. The tumor phenotype, however, appears to have been lost with successive breeding, as other labs been unable to reproduce this finding. Based upon the mouse phenotype, humans deficient in LTBP-4 were identified and displayed essentially the same features as the mouse LTBP-4 knockout [75]. The human mutant fibroblasts produce less TGF beta than normal

control cells consistent with loss of TGF beta-related phenotypes in other LTBP knock out mice and people. The mouse lung developmental abnormality occurs at the saccular phase, rather than at the developmentally later septation phase as observed with LTBP-3 loss. These results are consistent with the earlier expression of LTBP-4 in the lung when compared to that of LTBP-3 [76]. The defect is dependent on elevated TGF beta 2 signaling as LTBP-4; TGFβ 2 double null embryos display normal septation as measured by Mean Linear Intercept analysis [77]. However, the septation defect is not normalized with the loss of TGFβ 1 or 3, nor does the lung abnormality occur when the LTBP-4 is mutated such that latent TGF beta cannot bind nor be activated implying that it is the loss of LTBP-4 not TGFβ that is responsible for the initial defect [78]. LTBP-4; TGFβ 2 double null mice, however, continue to display abnormal elastogenesis implying that the TGFβ 2 defect is either secondary or parallel to the elastin abnormality. The lack of association of elastogenesis and TGFβ 2 signaling in LTBP-4 deficient mice is consistent with earlier observations that LTBP-4 binds to TGFβ 1 but not to TGFβ 2 [20]. Further genetic studies with LTBP-4S mice have shown that the elastin defect arises because LTBP-4 is essential for the binding of fibulin-5-elastin complexes to fibrillin microfibrils. Knockdown of LTBP-4 using siRNA resulted in decreased deposition of fibulin 5 onto microfibrils in cultures of dermal fibroblasts. However, the addition of purified LTBP-4 stripped of TGFβ restored and enhanced fibulin 5 deposition, as well as elastic fiber deposition further supporting the TGFβ independent role of LTBP-4 in elastogenesis [30]. Thus, LTBP-4 can be thought of as an extracellular chaperone for elastin.

Although LTBP-4 null mice do not appear to display aortic dilation or dissection, a report has appeared linking an association of LTBP-4 haplotypes and increased dilation rates in Abdominal Aortic Aneurysms (AAA) [79]. The association of this increased growth of AAA and LTBP-4 haplotypes is not understood but may be related to abnormalities in the elastin organization.

An interesting set of findings involving LTBP-4 was reported regarding its potential involvement in muscular dystrophy [80–82]. The authors initially found that an LTBP-4 allele with a 12 amino acid insertion in the hinge region correlated with more severe muscular dystrophy. The LTBP-4 hinge lacking the insertion was more sensitive to proteases than the extended form of LTBP-4 and both animals and humans with the shorter form of LTBP-4 presented with less severe forms of muscular dystrophy. The severity of the phenotype also appears to depend upon the level of extracellular TGFβ and inhibition of TGFβ reduces the severity of muscle wasting. Thus, the authors have suggested that in animals and people the shorter form of LTBP-4 allows more proteolytic release of TGFβ from LTBP and this TGFβ promotes the pathological phenotype.

These later results are exciting, but contradict earlier results indicating that the lung phenotype in LTBP-4 null mice is not dependent upon TGFβ binding to the LTBP. Rather, the heightened TGFβ 2 observed in these mice is secondary and related in an unknown way to the elastogenesis defect. Indeed, the question of whether LAP can bind to LTBP-4 is controversial. As mentioned, the initial reports described LTBP-4 as binding exclusively and only to TGFβ 1 LAP. Our attempts to show binding failed (unpublished data). However, the long form of LTBP-4 is reported to bind LAP very effectively, although the site of binding

was not described nor was the binding of LAP shown to produce a true LLC. The work of Chen et al. seemed to indicate that binding was very inefficient because of the charge change in the amino acids surrounding the LTBP-4 LAP binding 8-Cys domain [83]. Perhaps a way to resolve this conundrum would be to utilize the mutant LTBP-4 mice described by Dabovic et al. (2015) in which the cysteine pair that binds to LAP was mutated to serine thus precluding LTBP-4-LAP complex formation and to determine whether this affects the muscular phenotype.

Summary and Perspectives

Although the basic functions of the LTBPs have been elucidated and multiple phenotypes have been characterized (Table 1), much is not understood. As with other null mutations, it is likely that only the most obvious effects of loss of function have been described. The fact that LTBP-2 and 4 have TGF β -independent activities suggests that LTBP-1 and 3 may also exhibit functions independent of the cytokine (Table 2). Interestingly, the idea that LTBP-1 and 3 bind all three TGF β isoforms equivalently comes from in vitro over-expression experiments, which leaves open the possibility that there may be discrimination in TGF β isoform binding to individual LTBPs at lower in vivo concentrations of both ligands and LTBPs. This would yield specific LTBPs regulating individual TGF β isoform activities. The multiple splice variants of the LTBPs have not been explored in any meaningful way in vivo, but it is likely that these variants will modulate both LTBP and TGF β activities [16]. It also is possible that LTBP degradation products, like a degradation product of fibrillin-1, are biologically active [84]. Finally, although there have been several in vitro studies on the biomechanical properties of LTBP-1, the significance to these results has not been translated to a physiological setting. It is likely that certain pathologies will reflect defects in the mechanosensing properties of LTBPs.

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Abbreviations used

AAA	Aortic abdominal aneurysm
RGD	Arginylglycylaspartic Acid
8-Cys	Eight cysteine
EMT	Endothelial-mesenchymal transformation
ECM	Extracellular Matrix
ES	embryonic stem
FGF	Fibroblast growth factor
LLC	Large latent complex
LTBP	Latent TGF β binding protein

MFS	Marfan syndrome
MSC	Mesenchymal stem cell
Si	Small interfering
SH	Sulfhydryl
TB	TGF β binding
LAP	TGF β propeptide
TGF	Transforming growth factor

References

- Ramirez F, Rifkin DB. Cell signaling events: a view from the matrix. *Matrix biology: journal of the International Society for Matrix Biology*. 2003; 22(2):101–7. [PubMed: 12782137]
- Todorovic V, Rifkin DB. LTBP β s, more than just an escort service. *J Cell Biochem*. 2012; 113(2): 410–8. [PubMed: 22223425]
- Hyytiainen M, Penttinen C, Keski-Oja J. Latent TGF-beta binding proteins: extracellular matrix association and roles in TGF-beta activation. *Crit Rev Clin Lab Sci*. 2004; 41(3):233–64. [PubMed: 15307633]
- Rifkin DB. Latent transforming growth factor-beta (TGF-beta) binding proteins: orchestrators of TGF-beta availability. *J Biol Chem*. 2005; 280(9):7409–12. [PubMed: 15611103]
- Robertson IB, Horiguchi M, Zilberberg L, Dabovic B, Hadjiolova K, Rifkin DB. Latent TGF-beta-binding proteins. *Matrix biology: journal of the International Society for Matrix Biology*. 2015; 47:44–53. [PubMed: 25960419]
- Giltay R, Kostka G, Timpl R. Sequence and expression of a novel member (LTBP-4) of the family of latent transforming growth factor-beta binding proteins. *FEBS Lett*. 1997; 411(2–3):164–8. [PubMed: 9271198]
- Kanzaki T, Olofsson A, Moren A, Wernstedt C, Hellman U, Miyazono K, Claesson-Welsh L, Heldin CH. TGF-beta 1 binding protein: a component of the large latent complex of TGF-beta 1 with multiple repeat sequences. *Cell*. 1990; 61(6):1051–61. [PubMed: 2350783]
- Miyazono K, Hellman U, Wernstedt C, Heldin CH. Latent high molecular weight complex of transforming growth factor beta 1. Purification from human platelets and structural characterization. *J Biol Chem*. 1988; 263(13):6407–15. [PubMed: 3162913]
- Moren A, Olofsson A, Stenman G, Sahlin P, Kanzaki T, Claesson-Welsh L, ten Dijke P, Miyazono K, Heldin CH. Identification and characterization of LTBP-2, a novel latent transforming growth factor-beta-binding protein. *J Biol Chem*. 1994; 269(51):32469–78. [PubMed: 7798248]
- Saharinen J, Taipale J, Monni O, Keski-Oja J. Identification and characterization of a new latent transforming growth factor-beta-binding protein, LTBP-4. *J Biol Chem*. 1998; 273(29):18459–69. [PubMed: 9660815]
- Yin W, Smiley E, Germiller J, Mecham RP, Florer JB, Wenstrup RJ, Bonadio J. Isolation of a novel latent transforming growth factor-beta binding protein gene (LTBP-3). *J Biol Chem*. 1995; 270(17):10147–60. [PubMed: 7730318]
- Lack J, O'Leary JM, Knott V, Yuan X, Rifkin DB, Handford PA, Downing AK. Solution structure of the third TB domain from LTBP1 provides insight into assembly of the large latent complex that sequesters latent TGF-beta. *J Mol Biol*. 2003; 334(2):281–91. [PubMed: 14607119]
- Saharinen J, Hyytiainen M, Taipale J, Keski-Oja J. Latent transforming growth factor-beta binding proteins (LTBP β s)--structural extracellular matrix proteins for targeting TGF-beta action. *Cytokine Growth Factor Rev*. 1999; 10(2):99–117. [PubMed: 10743502]

14. Yuan X, Downing AK, Knott V, Handford PA. Solution structure of the transforming growth factor beta-binding protein-like module, a domain associated with matrix fibrils. *The EMBO journal*. 1997; 16(22):6659–66. [PubMed: 9362480]
15. Koski C, Saharinen J, Keski-Oja J. Independent promoters regulate the expression of two amino terminally distinct forms of latent transforming growth factor-beta binding protein-1 (LTBP-1) in a cell type-specific manner. *J Biol Chem*. 1999; 274(46):32619–30. [PubMed: 10551816]
16. Koli K, Saharinen J, Karkkainen M, Keski-Oja J. Novel non-TGF-beta-binding splice variant of LTBP-4 in human cells and tissues provides means to decrease TGF-beta deposition. *Journal of cell science*. 2001; 114(Pt 15):2869–78. [PubMed: 11683420]
17. Oklu R, Hesketh R. The latent transforming growth factor beta binding protein (LTBP) family. *Biochem J*. 2000; 352(Pt3):601–10. [PubMed: 11104663]
18. Annes JP, Chen Y, Munger JS, Rifkin DB. Integrin alphaVbeta6-mediated activation of latent TGF-beta requires the latent TGF-beta binding protein-1. *J Cell Biol*. 2004; 165(5):723–34. [PubMed: 15184403]
19. Munger JS, Sheppard D. Cross talk among TGF-beta signaling pathways, integrins, and the extracellular matrix. *Cold Spring Harb Perspect Biol*. 2011; 3(11):a005017. [PubMed: 21900405]
20. Saharinen J, Keski-Oja J. Specific sequence motif of 8-Cys repeats of TGF-beta binding proteins, LTBPs, creates a hydrophobic interaction surface for binding of small latent TGF-beta. *Mol Biol Cell*. 2000; 11(8):2691–704. [PubMed: 10930463]
21. Gleizes PE, Beavis RC, Mazzieri R, Shen B, Rifkin DB. Identification and characterization of an eight-cysteine repeat of the latent transforming growth factor-beta binding protein-1 that mediates bonding to the latent transforming growth factor-beta1. *J Biol Chem*. 1996; 271(47):29891–6. [PubMed: 8939931]
22. Saharinen J, Taipale J, Keski-Oja J. Association of the small latent transforming growth factor-beta with an eight cysteine repeat of its binding protein LTBP-1. *The EMBO journal*. 1996; 15(2):245–53. [PubMed: 8617200]
23. Kantola AK, Keski-Oja J, Koli K. Fibronectin and heparin binding domains of latent TGF-beta binding protein (LTBP)-4 mediate matrix targeting and cell adhesion. *Exp Cell Res*. 2008; 314(13):2488–500. [PubMed: 18585707]
24. Massam-Wu T, Chiu M, Choudhury R, Chaudhry SS, Baldwin AK, McGovern A, Baldock C, Shuttleworth CA, Kiely CM. Assembly of fibrillin microfibrils governs extracellular deposition of latent TGF beta. *Journal of cell science*. 2010; 123(Pt 17):3006–18. [PubMed: 20699357]
25. Unsold C, Hyytiainen M, Bruckner-Tuderman L, Keski-Oja J. Latent TGF-beta binding protein LTBP-1 contains three potential extracellular matrix interacting domains. *Journal of cell science*. 2001; 114(Pt1):187–197. [PubMed: 11112702]
26. Sengle G, Tsutsui K, Keene DR, Tufa SF, Carlson EJ, Charbonneau NL, Ono RN, Sasaki T, Wirtz MK, Samples JR, Fessler LI, Fessler JH, Sekiguchi K, Hayflick SJ, Sakai LY. Microenvironmental regulation by fibrillin-1. *PLoS Genet*. 2012; 8(1):e1002425. [PubMed: 22242013]
27. Isogai Z, Ono RN, Ushiro S, Keene DR, Chen Y, Mazzieri R, Charbonneau NL, Reinhardt DP, Rifkin DB, Sakai LY. Latent transforming growth factor beta-binding protein 1 interacts with fibrillin and is a microfibril-associated protein. *J Biol Chem*. 2003; 278(4):2750–7. [PubMed: 12429738]
28. Parsi MK, Adams JR, Whitelock J, Gibson MA. LTBP-2 has multiple heparin/heparan sulfate binding sites. *Matrix biology: journal of the International Society for Matrix Biology*. 2010; 29(5):393–401. [PubMed: 20382221]
29. Hirai M, Horiguchi M, Ohbayashi T, Kita T, Chien KR, Nakamura T. Latent TGF-beta-binding protein 2 binds to DANCE/fibulin-5 and regulates elastic fiber assembly. *The EMBO journal*. 2007; 26(14):3283–95. [PubMed: 17581631]
30. Noda K, Dabovic B, Takagi K, Inoue T, Horiguchi M, Hirai M, Fujikawa Y, Akama TO, Kusumoto K, Zilberberg L, Sakai LY, Koli K, Naitoh M, von Melchner H, Suzuki S, Rifkin DB, Nakamura T. Latent TGF-beta binding protein 4 promotes elastic fiber assembly by interacting with fibulin-5. *Proc Natl Acad Sci U S A*. 2013; 110(8):2852–7. [PubMed: 23382201]
31. Le Goff C, Morice-Picard F, Dagoneau N, Wang LW, Perrot C, Crow YJ, Bauer F, Flori E, Prost-Squarcioni C, Krakow D, Ge G, Greenspan DS, Bonnet D, Le Merrer M, Munnich A, Apte SS,

- Cormier-Daire V. ADAMTSL2 mutations in geophytic dysplasia demonstrate a role for ADAMTS-like proteins in TGF-beta bioavailability regulation. *Nat Genet.* 2008; 40(9):1119–23. [PubMed: 18677313]
32. Anderson SB, Goldberg AL, Whitman M. Identification of a novel pool of extracellular pro-myoostatin in skeletal muscle. *J Biol Chem.* 2008; 283(11):7027–35. [PubMed: 18175804]
33. Menz C, Parsi MK, Adams JR, Sideek MA, Kopecki Z, Cowin AJ, Gibson MA. LTBP-2 Has a Single High-Affinity Binding Site for FGF-2 and Blocks FGF-2-Induced Cell Proliferation. *PLoS One.* 2015; 10(8):e0135577. [PubMed: 26263555]
34. Miyazono K, Olofsson A, Colosetti P, Heldin CH. A role of the latent TGF-beta 1-binding protein in the assembly and secretion of TGF-beta 1. *The EMBO journal.* 1991; 10(5):1091–101. [PubMed: 2022183]
35. Dallas SL, Sivakumar P, Jones CJ, Chen Q, Peters DM, Mosher DF, Humphries MJ, Kielty CM. Fibronectin regulates latent transforming growth factor-beta (TGF beta) by controlling matrix assembly of latent TGF beta-binding protein-1. *J Biol Chem.* 2005; 280(19):18871–80. [PubMed: 15677465]
36. Sivakumar P, Czirok A, Rongish BJ, Divakara VP, Wang YP, Dallas SL. New insights into extracellular matrix assembly and reorganization from dynamic imaging of extracellular matrix proteins in living osteoblasts. *Journal of cell science.* 2006; 119(Pt 7):1350–60. [PubMed: 16537652]
37. Munger JS, Huang X, Kawakatsu H, Griffiths MJ, Dalton SL, Wu J, Pittet JF, Kaminski N, Garat C, Matthey MA, Rifkin DB, Sheppard D. The integrin alpha v beta 6 binds and activates latent TGF beta 1: a mechanism for regulating pulmonary inflammation and fibrosis. *Cell.* 1999; 96(3): 319–28. [PubMed: 10025398]
38. Yang Z, Mu Z, Dabovic B, Jurukovski V, Yu D, Sung J, Xiong X, Munger JS. Absence of integrin-mediated TGFbeta1 activation in vivo recapitulates the phenotype of TGFbeta1-null mice. *J Cell Biol.* 2007; 176(6):787–93. [PubMed: 17353357]
39. Yoshinaga K, Obata H, Jurukovski V, Mazziari R, Chen Y, Zilberberg L, Huso D, Melamed J, Prijatelj P, Todorovic V, Dabovic B, Rifkin DB. Perturbation of transforming growth factor (TGF)-beta1 association with latent TGF-beta binding protein yields inflammation and tumors. *Proc Natl Acad Sci U S A.* 2008; 105(48):18758–63. [PubMed: 19022904]
40. Buscemi L, Ramonet D, Klingberg F, Formey A, Smith-Clerc J, Meister JJ, Hinz B. The single-molecule mechanics of the latent TGF-beta1 complex. *Curr Biol.* 2011; 21(24):2046–54. [PubMed: 22169532]
41. Wipff PJ, Rifkin DB, Meister JJ, Hinz B. Myofibroblast contraction activates latent TGF-beta1 from the extracellular matrix. *J Cell Biol.* 2007; 179(6):1311–23. [PubMed: 18086923]
42. Nunes I, Gleizes PE, Metz CN, Rifkin DB. Latent transforming growth factor-beta binding protein domains involved in activation and transglutaminase-dependent cross-linking of latent transforming growth factor-beta. *J Cell Biol.* 1997; 136(5):1151–63. [PubMed: 9060478]
43. Fontana L, Chen Y, Prijatelj P, Sakai T, Fassler R, Sakai LY, Rifkin DB. Fibronectin is required for integrin alphavbeta6-mediated activation of latent TGF-beta complexes containing LTBP-1. *FASEB J.* 2005; 19(13):1798–808. [PubMed: 16260650]
44. Gualandris A, Annes JP, Arese M, Noguera I, Jurukovski V, Rifkin DB. The latent transforming growth factor-beta-binding protein-1 promotes in vitro differentiation of embryonic stem cells into endothelium. *Mol Biol Cell.* 2000; 11(12):4295–308. [PubMed: 11102524]
45. Nakajima Y, Miyazono K, Kato M, Takase M, Yamagishi T, Nakamura H. Extracellular fibrillar structure of latent TGF beta binding protein-1: role in TGF beta-dependent endothelial-mesenchymal transformation during endocardial cushion tissue formation in mouse embryonic heart. *J Cell Biol.* 1997; 136(1):193–204. [PubMed: 9008713]
46. Todorovic V, Frendewey D, Gutstein DE, Chen Y, Freyer L, Finnegan E, Liu F, Murphy A, Valenzuela D, Yancopoulos G, Rifkin DB. Long form of latent TGF-beta binding protein 1 (Ltbp1L) is essential for cardiac outflow tract septation and remodeling. *Development.* 2007; 134(20):3723–32. [PubMed: 17804598]

47. Choudhary B, Ito Y, Makita T, Sasaki T, Chai Y, Sucoy HM. Cardiovascular malformations with normal smooth muscle differentiation in neural crest-specific type II TGFbeta receptor (Tgfb2) mutant mice. *Dev Biol.* 2006; 289(2):420–9. [PubMed: 16332365]
48. Horiguchi M, Todorovic V, Hadjiolova K, Weiskirchen R, Rifkin DB. Abrogation of both short and long forms of latent transforming growth factor-beta binding protein-1 causes defective cardiovascular development and is perinatally lethal. *Matrix biology: journal of the International Society for Matrix Biology.* 2015; 43:61–70. [PubMed: 25805620]
49. Hyytiainen M, Taipale J, Heldin CH, Keski-Oja J. Recombinant latent transforming growth factor beta-binding protein 2 assembles to fibroblast extracellular matrix and is susceptible to proteolytic processing and release. *J Biol Chem.* 1998; 273(32):20669–76. [PubMed: 9685426]
50. Vehvilainen P, Hyytiainen M, Keski-Oja J. Matrix association of latent TGF-beta binding protein-2 (LTBP-2) is dependent on fibrillin-1. *J Cell Physiol.* 2009; 221(3):586–93. [PubMed: 19681046]
51. Shipley JM, Mecham RP, Maus E, Bonadio J, Rosenbloom J, McCarthy RT, Baumann ML, Frankfater C, Segade F, Shapiro SD. Developmental expression of latent transforming growth factor beta binding protein 2 and its requirement early in mouse development. *Mol Cell Biol.* 2000; 20(13):4879–87. [PubMed: 10848613]
52. Inoue T, Ohbayashi T, Fujikawa Y, Yoshida H, Akama TO, Noda K, Horiguchi M, Kameyama K, Hata Y, Takahashi K, Kusumoto K, Nakamura T. Latent TGF-beta binding protein-2 is essential for the development of ciliary zonule microfibrils. *Hum Mol Genet.* 2014; 23(21):5672–82. [PubMed: 24908666]
53. Narooie-Nejad M, Paylakhi SH, Shojaee S, Fazlali Z, Rezaei Kanavi M, Nilforushan N, Yazdani S, Babrzadeh F, Suri F, Ronaghi M, Elahi E, Paisan-Ruiz C. Loss of function mutations in the gene encoding latent transforming growth factor beta binding protein 2, LTBP2, cause primary congenital glaucoma. *Hum Mol Genet.* 2009; 18(20):3969–77. [PubMed: 19656777]
54. Ali M, McKibbin M, Booth A, Parry DA, Jain P, Riazuddin SA, Hejtmancik JF, Khan SN, Firasat S, Shires M, Gilmour DF, Towns K, Murphy AL, Azmanov D, Tournev I, Cherninkova S, Jafri H, Raashid Y, Toomes C, Craig J, Mackey DA, Kalaydjieva L, Riazuddin S, Inglehearn CF. Null mutations in LTBP2 cause primary congenital glaucoma. *Am J Hum Genet.* 2009; 84(5):664–71. [PubMed: 19361779]
55. Chen Y, Dabovic B, Annes JP, Rifkin DB. Latent TGF-beta binding protein-3 (LTBP-3) requires binding to TGF-beta for secretion. *FEBS Lett.* 2002; 517(1–3):277–80. [PubMed: 12062452]
56. Penttinen C, Saharinen J, Weikkolainen K, Hyytiainen M, Keski-Oja J. Secretion of human latent TGF-beta-binding protein-3 (LTBP-3) is dependent on co-expression of TGF-beta. *Journal of cell science.* 2002; 115(Pt 17):3457–68. [PubMed: 12154076]
57. Morkmued S, Hemmerle J, Mathieu E, Laugel-Haushalter V, Dabovic B, Rifkin DB, Dolle P, Niederreither K, Bloch-Zupan A. Enamel and dental anomalies in latent-transforming growth factor beta-binding protein 3 mutant mice. *Eur J Oral Sci.* 2017; 125(1):8–17. [PubMed: 28084688]
58. Dabovic B, Chen Y, Colarossi C, Zambuto L, Obata H, Rifkin DB. Bone defects in latent TGF-beta binding protein (Ltp)-3 null mice; a role for Ltp in TGF-beta presentation. *J Endocrinol.* 2002; 175(1):129–41. [PubMed: 12379497]
59. Dabovic B, Lévasséur R, Zambuto L, Chen Y, Karsenty G, Rifkin DB. Osteopetrosis-like phenotype in latent TGF-beta binding protein 3 deficient mice. *Bone.* 2005; 37(1):25–31. [PubMed: 15878314]
60. Dabovic B, Chen Y, Colarossi C, Obata H, Zambuto L, Perle MA, Rifkin DB. Bone abnormalities in latent TGF-[beta] binding protein (Ltp)-3-null mice indicate a role for Ltp-3 in modulating TGF-[beta] bioavailability. *J Cell Biol.* 2002; 156(2):227–32. [PubMed: 11790802]
61. McInerney-Leo AM, Le Goff C, Leo PJ, Kenna TJ, Keith P, Harris JE, Steer R, Bole-Feysot C, Nitschke P, Kielty C, Brown MA, Zankl A, Duncan EL, Cormier-Daire V. Mutations in LTBP3 cause acromicric dysplasia and geleophysic dysplasia. *J Med Genet.* 2016; 53(7):457–64. [PubMed: 27068007]
62. Colarossi C, Chen Y, Obata H, Jurukovski V, Fontana L, Dabovic B, Rifkin DB. Lung alveolar septation defects in Ltp-3-null mice. *Am J Pathol.* 2005; 167(2):419–28. [PubMed: 16049328]

63. Chen Y, Dabovic B, Colarossi C, Santori FR, Lilic M, Vukmanovic S, Rifkin DB. Growth retardation as well as spleen and thymus involution in latent TGF-beta binding protein (Ltbp)-3 null mice. *J Cell Physiol.* 2003; 196(2):319–25. [PubMed: 12811825]
64. Doyle JJ, Gerber EE, Dietz HC. Matrix-dependent perturbation of TGFbeta signaling and disease. *FEBS Lett.* 2012; 586(14):2003–15. [PubMed: 22641039]
65. Zilberberg L, Phoon CK, Robertson I, Dabovic B, Ramirez F, Rifkin DB. Genetic analysis of the contribution of LTBP-3 to thoracic aneurysm in Marfan syndrome. *Proc Natl Acad Sci U S A.* 2015; 112(45):14012–7. [PubMed: 26494287]
66. Cook JR, Clayton NP, Carta L, Galatioto J, Chiu E, Smaldone S, Nelson CA, Cheng SH, Wentworth BM, Ramirez F. Dimorphic effects of transforming growth factor-beta signaling during aortic aneurysm progression in mice suggest a combinatorial therapy for Marfan syndrome. *Arterioscler Thromb Vasc Biol.* 2015; 35(4):911–7. [PubMed: 25614286]
67. Koli K, Ryyananen MJ, Keski-Oja J. Latent TGF-beta binding proteins (LTBPs)-1 and -3 coordinate proliferation and osteogenic differentiation of human mesenchymal stem cells. *Bone.* 2008; 43(4): 679–88. [PubMed: 18672106]
68. Smaldone S, Clayton NP, del Solar M, Pascual G, Cheng SH, Wentworth BM, Schaffler MB, Ramirez F. Fibrillin-1 Regulates Skeletal Stem Cell Differentiation by Modulating TGFbeta Activity Within the Marrow Niche. *J Bone Miner Res.* 2016; 31(1):86–97. [PubMed: 26189658]
69. Morita K, Okamura T, Inoue M, Komai T, Teruya S, Iwasaki Y, Sumitomo S, Shoda H, Yamamoto K, Fujio K. Egr2 and Egr3 in regulatory T cells cooperatively control systemic autoimmunity through Ltbp3-mediated TGF-beta3 production. *Proc Natl Acad Sci U S A.* 2016; 113(50):E8131–e8140. [PubMed: 27911796]
70. Naba A, Clauser KR, Lamar JM, Carr SA, Hynes RO. Extracellular matrix signatures of human mammary carcinoma identify novel metastasis promoters. *Elife.* 2014; 3:e01308. [PubMed: 24618895]
71. Wan F, Peng L, Zhu C, Zhang X, Chen F, Liu T. Knockdown of Latent Transforming Growth Factor-beta (TGF-beta)-Binding Protein 2 (LTBP2) Inhibits Invasion and Tumorigenesis in Thyroid Carcinoma Cells. *Oncol Res.* 2017; 25(4):503–510. [PubMed: 27712597]
72. Sterner-Kock A, Thorey IS, Koli K, Wempe F, Otte J, Bangsow T, Kuhlmeier K, Kirchner T, Jin S, Keski-Oja J, von Melchner H. Disruption of the gene encoding the latent transforming growth factor-beta binding protein 4 (LTBP-4) causes abnormal lung development, cardiomyopathy, and colorectal cancer. *Genes Dev.* 2002; 16(17):2264–73. [PubMed: 12208849]
73. Bultmann-Mellin I, Conradi A, Maul AC, Dinger K, Wempe F, Wohl AP, Imhof T, Wunderlich FT, Bunck AC, Nakamura T, Koli K, Bloch W, Ghanem A, Heinz A, von Melchner H, Sengle G, Sterner-Kock A. Modeling autosomal recessive cutis laxa type 1C in mice reveals distinct functions for Ltbp-4 isoforms. *Dis Model Mech.* 2015; 8(4):403–15. [PubMed: 25713297]
74. Fujikawa Y, Yoshida H, Inoue T, Ohbayashi T, Noda K, von Melchner H, Iwasaka T, Shiojima I, Akama TO, Nakamura T. Latent TGF-beta binding protein 2 and 4 have essential overlapping functions in microfibril development. *Sci Rep.* 2017; 7:43714. [PubMed: 28252045]
75. Urban Z, Huchtagowder V, Schurmann N, Todorovic V, Zilberberg L, Choi J, Sens C, Brown CW, Clark RD, Holland KE, Marble M, Sakai LY, Dabovic B, Rifkin DB, Davis EC. Mutations in LTBP4 cause a syndrome of impaired pulmonary, gastrointestinal, genitourinary, musculoskeletal, and dermal development. *Am J Hum Genet.* 2009; 85(5):593–605. [PubMed: 19836010]
76. Dabovic B, Chen Y, Choi J, Davis EC, Sakai LY, Todorovic V, Vassallo M, Zilberberg L, Singh A, Rifkin DB. Control of lung development by latent TGF-beta binding proteins. *J Cell Physiol.* 2011; 226(6):1499–509. [PubMed: 20945348]
77. Dabovic B, Chen Y, Choi J, Vassallo M, Dietz HC, Ramirez F, von Melchner H, Davis EC, Rifkin DB. Dual functions for LTBP in lung development: LTBP-4 independently modulates elastogenesis and TGF-beta activity. *J Cell Physiol.* 2009; 219(1):14–22. [PubMed: 19016471]
78. Dabovic B, Robertson IB, Zilberberg L, Vassallo M, Davis EC, Rifkin DB. Function of latent TGFbeta binding protein 4 and fibulin 5 in elastogenesis and lung development. *J Cell Physiol.* 2015; 230(1):226–36. [PubMed: 24962333]
79. Thompson AR, Cooper JA, Jones GT, Drenos F, van Bockxmeer FM, Biros E, Walker PJ, van Rij AM, Golledge J, Norman PE, Hafez H, Humphries SE. Assessment of the association between

- genetic polymorphisms in transforming growth factor beta, and its binding protein (LTBP), and the presence, and expansion, of Abdominal Aortic Aneurysm. *Atherosclerosis*. 2010; 209(2):367–73. [PubMed: 19897194]
80. Heydemann A, Ceco E, Lim JE, Hadhazy M, Ryder P, Moran JL, Beier DR, Palmer AA, McNally EM. Latent TGF-beta-binding protein 4 modifies muscular dystrophy in mice. *J Clin Invest*. 2009; 119(12):3703–12. [PubMed: 19884661]
81. Ceco E, Bogdanovich S, Gardner B, Miller T, DeJesus A, Earley JU, Hadhazy M, Smith LR, Barton ER, Molkentin JD, McNally EM. Targeting latent TGFbeta release in muscular dystrophy. *Sci Transl Med*. 2014; 6(259):259ra144.
82. Lamar KM, Bogdanovich S, Gardner BB, Gao QQ, Miller T, Earley JU, Hadhazy M, Vo AH, Wren L, Molkentin JD, McNally EM. Overexpression of Latent TGFbeta Binding Protein 4 in Muscle Ameliorates Muscular Dystrophy through Myostatin and TGFbeta. *PLoS Genet*. 2016; 12(5):e1006019. [PubMed: 27148972]
83. Chen Y, Ali T, Todorovic V, O'Leary M, Kristina Downing JA, Rifkin DB. Amino acid requirements for formation of the TGF-beta-latent TGF-beta binding protein complexes. *J Mol Biol*. 2005; 345(1):175–86. [PubMed: 15567420]
84. Romere C, Duerschmid C, Bournat J, Constable P, Jain M, Xia F, Saha PK, Del Solar M, Zhu B, York B, Sarkar P, Rendon DA, Gaber MW, LeMaire SA, Coselli JS, Milewicz DM, Sutton VR, Butte NF, Moore DD, Chopra AR. Asprosin, a Fasting-Induced Glucogenic Protein Hormone. *Cell*. 2016; 165(3):566–79. [PubMed: 27087445]

Highlights

The latent TGF beta binding proteins (LTBPs) are important matrix mediators of biological functions. The fact that these molecules are crucial components of the regulation of both TGF beta action and elastin organization makes them important mediators of a multitude of biological processes. This review describes the basic biology of the LTBPs and outlines the physiological and pathological consequences of LTBP activity or loss. Special attention is paid to in vivo analysis.

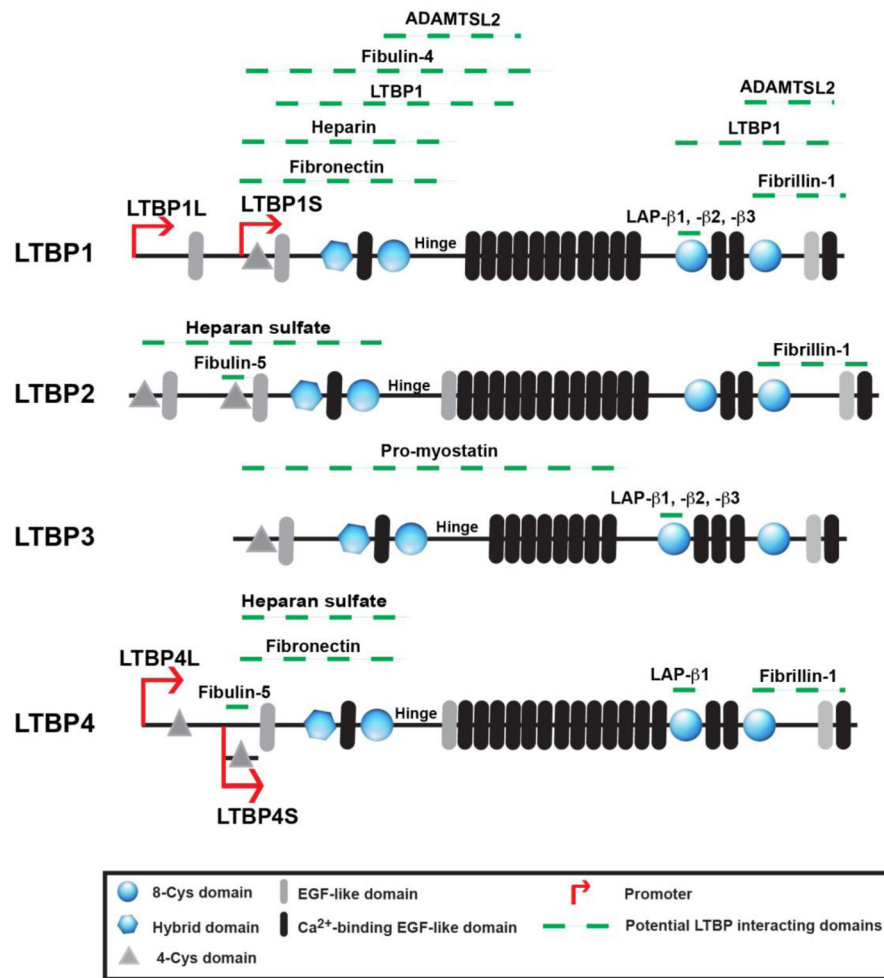


Figure 1. Graphic illustration of where on each of the four LTBPs a number of ECM proteins bind.

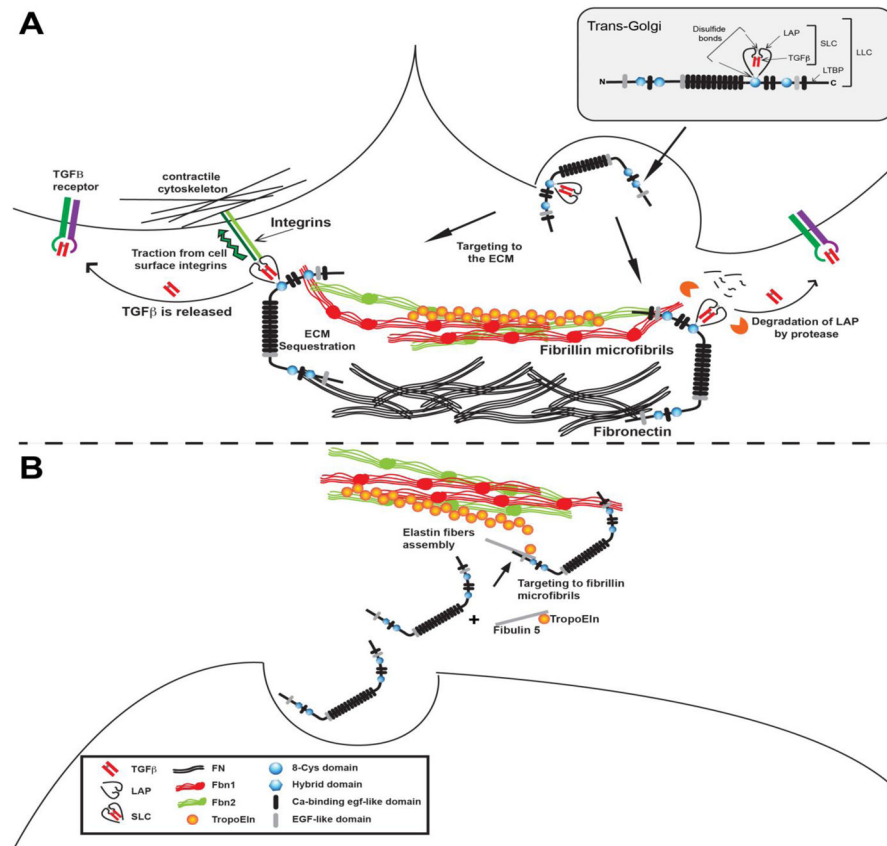


Figure 2. Illustration of synthesis, secretion, and activation of LTBP – TGF beta complexes.
 A. Synthesis, secretion and activation by integrins (left) or proteases (right) of latent TGF beta bound to an LTBP.
 B. Secretion of an LTBP interacting with matrix components in the assembly of elastin containing microfibrils.

Table 1

LTBP-Dependent Phenotypes

Name		Mouse		Human
LTBP-1	In Vivo	Persistent Truncus Arteriosis Interrupted aortic arch		Non reported
	In Vitro	Anti-LTBP-1 antibody blocks ES cell differentiation to endothelial cells		
LTBP-2		Lens Luxation	In Vivo	Primary Congenital glaucoma, Microspherophakia.
LTBP-3	In Vivo	Cranial facial and dental malformations. Premature cranial synchondroses ossification	In Vivo	Acromeric and geleophysic dysplasia. Enamel abnormalities
LTBP-4	In Vivo	Defective elastogenesis in lung, cardiomyopathy, impaired lung development at the secular phase Modulation of muscular dystrophy phenotype.	In Vivo	Loss associated with enhances AAA growth. Decrease alveolar septation in the alveolar phase. Certain alleles enhance or diminish muscular dystrophy Phenotype.

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Table 2Non-TGF β Mediated Functions of LTBP s

LTBP-1	Non-reported.
LTBP-2	Support of microfibril formation in the eye.
LTBP-3	Non-reported, possible contribution to metastasis.
LTBP-4	Support of elastogenesis in many tissues. Support of microfibril formation in the eye.

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