Latent Transforming Growth Factor-β (TGF-β) Binding Proteins: Orchestrators of TGF-β Availability*

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Daniel B. Rifkin†

From the Departments of Cell Biology and Medicine, New York University School of Medicine, New York, New York 10016

The latent transforming growth factor-β (TGF-β) binding proteins (LTBP-1–4) are secreted multidomain glycoproteins, three of which are central to TGF-β regulation (1, 2). LTBP-1 is a component of the latent TGF-β complex that consists of TGF-β, the TGF-β propeptide, and LTBP (Fig. 1) (3). TGF-β is synthesized as a homodimeric proprotein, and the dimeric propeptide is cleaved intracellularly from the growth factor (4). Unlike most propeptides that have little affinity for the mature protein, the TGF-β propeptide strongly binds to TGF-β, and the proteins are secreted in complex (5). In this small latent complex (SLC), TGF-β cannot bind to its surface receptors. Therefore, the propeptide is called the latency-associated protein (LAP). The dissociation or activation of TGF-β from LAP is a critical regulatory event as all TGF-β is secreted in a latent form. The LAP dimer is usually disulfide-bonded to a second gene product, LTBP, and the trimolecular aggregate is called the large latent complex (LLC).

LTBP Molecular Biology

LTBP-1 cDNA has a predicted translation product of 1394 amino acids with a calculated \( M_r \) of 151,000 (6). The protein contains 17 epidermal growth factor (EGF)-like domains, 14 of which contain consensus Ca\(^{2+}\) binding sequences. In addition, there are four modules, each of ~70 amino acids with eight cysteines. These eight cysteine (8-Cys) domains are unique to the LTBPbs and the fibrillins (5). The most N-terminal 8-Cys domain, sometimes called a hybrid domain, has a more divergent sequence and may have derived from the use of separate promoters and alternative splicing between codons 145 and 146 of LTBP-1S (8).

Northern blotting revealed LTBP-1 transcripts of 5.2 and 7.0 kb (7). The shorter transcript corresponds to the initial cDNA isolate, LTBP-1S, whereas the larger transcript corresponds to a form of LTBP-1, LTBP-1L, that has an additional N-terminal 346 amino acids. This sequence encodes one EGF-like repeat and a four-cysteine module and is quite basic. LTBP-1S and LTBP-1L derive from the use of separate promoters and alternative splicing between codons 145 and 146 of LTBP-1S (8).

Subsequent cloning and expression experiments defined LTBP-2, -3, and -4 (9–12). The overall structures of these proteins are similar with four 8-Cys domains and multiple EGF-like modules (Fig. 2). All LTBPbs are expressed as two major transcripts, and the other LTBPb probably also have long and short forms. LTBP-1S and -1L show different distribution patterns; LTBP-1L is highly expressed in heart, kidney, lung, testes, and placenta, whereas LTBP-1S is broadly distributed (7). LTBP-2 mRNA is present at high levels in lung, placenta, and heart in addition to liver and muscle (10). LTBP-3 is abundant in heart, lung, and bone (12), whereas LTBP-4 is prominent in heart, aorta, uterus, and small intestine (11). Although LTBP distribution patterns correspond, in part, to the distribution of tissue phenotypes in mice with mutations in Ltbpb genes, cultured cells often produce multiple LTBP isoforms (13, 14).

LTBP Structural Motifs

Among the four LTBPbs, the hinge domain has the highest degree of sequence diversity. The hinge sequences of LTBP-1 and -2 are sensitive to proteolytic cleavage (15, 16), but LTBP-3 and -4 are not cleaved in this region (13). The LTBP-1 hinge contains a putative heparin binding sequence.

The central core of EGF-like domains is reminiscent of the tandem EGF-like repeats in the fibrillins (17). The repeating EGF-like modules may form a rigid sequence that extends the growth factor-binding C-terminal region away from the matrix-binding N-terminal domain (18) facilitating the interaction of latent TGF-β with its activators. However, removal of the EGF-like core from LTBP-1S does not impede latent TGF-β activation by the integrin αvβ3 (19). The EGF-like domains adjacent to 8-Cys domains may restrain 8-Cys (18, 20) domain motion and enhance interactions with matrix or fibrilar proteins as described for fibrillin (18, 21).

The 8-Cys3 domain of LTBP-1, -2, and -4 binds the SLC (20, 22). LAP binds via its unpaired most N-terminal cysteines. The remaining 8-Cys motifs in LTBP-1, -3, and -4, as well as all of the 8-Cys domains in LTBP-2 and the fibrillins, do not bind SLC. The basis for the differential binding of LAP to 8-Cys3 domains was suggested by Saharinen and Keski-Oja (23), who pointed out that the three LAP-binding 8-Cys domains have a dipeptide insertion between cysteines 6 and 7 compared with the sequences of the non-LAP-binding 8-Cys. The structural basis for LLC complex formation was clarified with the elucidation of the solution structure of the LTBP-1 8-Cys3 domain (24) and comparison of this structure to the structure of the fibrillin-1 non-LAP-binding 8-Cys6. The 8-Cys fold is globular with six β-strands and two α-helices. The pairing of the eight cysteines is 1–3, 2–6, 4–7, and 5–8, creating a fairly rigid structure. Whereas the general structures of the TGF-β-binding and non-binding 8-Cys domains are similar, the Phe-Pro insertion between cysteines 6 and 7 projects a 2–6 disulfide bond permitting covalent attachment to the pair of cysteine 33 residues in TGF-β 1 LAP. The NMR structure also revealed a “ring” of five negatively charged amino acids surrounding the 2–6 disulfide, suggesting that electrostatic interactions between LAP and the LTBP-1 8-Cys3 domain initiate complex formation. LAP and 8-Cys3 electrostatic interactions, also demonstrated by fluorescence resonance energy transfer experiments, imply that non-covalent protein-protein associations are possible with 8-Cys domains. Covalent bonding may be only one end of a spectrum of 8-Cys domain binding interactions that might include propedites of other members of the TGF-β superfamily (25, 26), thereby expanding the binding repertoire of the LTBPbs.

An interesting question is whether the LTBPbs have distinct binding specificities for TGF-β isoforms. Saharinen and Keski-Oja (23) reported that in coexpression experiments the LTBP-1 and -3 8-Cys3 domains bound all three TGF-β isoforms well, but the...
onstration of a transglutaminase site in 8-Cys2 (27) suggest that the factor is a transglutaminase. The C-terminal domains of LTBP-1 and -4 interact with fibrillin-1 (29). The LTBP-1L N-terminal extension contains sequences that facilitate matrix incorporation as LTBP-1L associates more readily with ECM than does LTBP-1S (30). It is interesting that whereas LTBP-1 and -4 are effectively incorporated into the ECM, LTBP-3 is not (13). Forms of LTBP-1 that contain only the LAP-binding domains (8-Cys3) fail to target TGF-β to the ECM and yield animals with excess active TGF-β.4 LTBP-1 matrix binding may initiate utilizing sequences at either end of the protein, but ECM incorporation may require strong binding by the N-terminal domains followed by transglutaminase cross-linking.

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LTBP-1 and -4 also interact with the N-terminal sequence of fibrillin-1. The interaction of LTBP-1 with fibrillin-1 may affect tissue homeostasis as Neptune et al. (32) reported increased activation of latent TGF-β within the lungs of fibrillin-1 hypomorphic mice. The decreased amounts of fibrillin-1 in the mutant mice may result in excess LLC unable to interact with fibrillin-1 microfibrils. Free LLC then interacts with latent TGF-β activators normally separated from sequestered LLC. This provocative interpretation of the mouse phenotype suggests that defects in structural proteins, such as fibrillin-1, alter growth factor action. Thus, the etiologies of certain connective tissue diseases may result not from architectural functions of the mutant proteins but from an inability to control signaling molecules.

**LTBP Function: In Vitro Approaches**

In vitro approaches to LTBP function have indicated an association between LTBP and TGF-β activity. LTBP enhances SLC secretion in cultured HEL cells (33). Co-expression of LTBP-1 and SLC also yields complexes with the correct disulfide binding pattern. In the absence of LTBP-1, mixed disulfide bonds are formed. These aberrantly folded proteins may be recognized by endoplasmic reticulum quality control mechanisms and eliminated, thereby impairing the rate and degree of secretion. Bonding to the 8-Cys3 domain ensures correct SLC folding and disulfide bonding, thereby accelerating secretion. In this scenario, LTBP acts as chaperone for SLC, a concept reinforced by the observation that replacement of the LTBP-binding cysteines in LAP with serines promotes SLC secretion (19).

A number of LTBP-1 functions have been elucidated by perturbing cellular activities in culture with antibodies. Fluumenhaart et al. (34) reported that a polyclonal antibody to LTBP-1 blocked latent TGF-β activation in endothelial and smooth muscle cell co-cultures. This result indicated a requirement for LTBP-mediated targeting of LLC to the ECM for TGF-β liberation and was consistent with the report that the inhibition of transglutaminase cross-linking of LLC to the ECM blocked latent cytokine activation (27). Nakajima et al. (35) reported an LTBP-1 requirement for endothelial-mesenchymal transformation during mouse heart endocardial cushion formation, a process known to require TGF-β (36). Antibodies to LTBP-1 blocked endothelial-mesenchymal transformation of atrioventricular endocardial cells co-cultured with myocardium, and this effect was overcome by excess TGF-β. Again, the results suggest that most TGF-β is localized to the matrix by LTBP-1. Guanlandris et al. (37) provided further evidence that LTBP-1 is part of the regulatory network for TGF-β presentation. When embryonic stem cells differentiated in the presence of either an antibody to LTBP-1 or LAP, which recombines with and neutralizes free TGF-β, the numbers and organization of cells expressing endothelial cell markers were decreased. Conversely, added TGF-β increased endothelial cell numbers and tubelike structures. These data indicate that interference with LTBP-1 affects the maturation of endothelial cells in a TGF-β-dependent manner. Thus, all three

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4 R. Mazzieri, V. Jurukovskis, H. Obata, J. Sung, A. Platt, E. Annes, N. Karanam-Jurukovsk, P. E. Gleizes, and D. B. Rifkin, submitted for publication.

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**LTBP Interactions with Matrix**

LTBP-1S interacts with the matrix through both N- and C-terminal motifs (27, 28). Peptides containing either the first, second, or fourth 8-Cys domains of LTBP-1S associate with the ECM, with the 8-Cys2 region showing the most rapid and extensive incorporation (27). Matrix binding was enhanced by cell-conditioned medium. The association of the N-terminal sequence with the ECM, the requirement for a cell-derived factor, and the demonstration of a transglutaminase site in 8-Cys2 (27) suggest that the factor is a transglutaminase. The C-terminal domains of LTBP-1 and -4 interact with fibrillin-1 (29). The LTBP-1L N-terminal extension contains sequences that facilitate matrix incorporation as LTBP-1L associates more readily with ECM than does LTBP-1S (30). It is interesting that whereas LTBP-1 and -4 are effectively incorporated into the ECM, LTBP-3 is not (13). Forms of LTBP-1 that contain only the LAP-binding domains (8-Cys3) fail to target TGF-β to the ECM and yield animals with excess active TGF-β.4 LTBP-1 matrix binding may initiate utilizing sequences at either end of the protein, but ECM incorporation may require strong binding by the N-terminal domains followed by transglutaminase cross-linking.

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reports indicate an association of LTBP-1 and TGF-β activity. Not all of the experimental results obtained by treating cells with an antibody to LTBP have been interpreted as affecting TGF-β action. Dallas et al. (38) published that antibodies to LTBP-1 blocked development of mineralized foci by rat cancellous cells. The antibody effect was not suppressed by addition of active TGF-β but was replicated by treatment with an LTBP-1 antisense oligonucleotide. The description of an LTBP-2 adhesive activity (39) for melanoma cells indicates that LTBP-2 can have non-TGF-β-dependent activities. However, interpretation of the results of Dallas et al. (38) as demonstrating a direct effect of LTBP-1 can be criticized based upon lack of evidence that added TGF-β reached the target cells.

Interest in LTBP-1, -3, and -4 derives largely from potential involvement in latent TGF-β activation. A number of mechanisms have been described for latent TGF-β activation including high heat, pH extremes, chaotropic agents, proteases, integrins, and thrombospondin 1, but only the integrin αvβ6 and thrombospondin 1 have been implicated in latent TGF-β activation by both in vitro and in vivo experiments (5). Although a role for LTBP-1 in latent TGF-β activation was suggested (34), the size of the antibody used in these experiments may have interfered nonspecifically with the activation process. Moreover, the fact that activation by the integrin αvβ6 requires the Arg-Gly-Asp within the LAP sequences of TGF-β1 or β2 LAP does not have an Arg-Gly-Asp (40) suggested that LTBP is not part of that activation pathway. However, LTBP-1 is required for latent TGF-β activation by αvβ6 (19). Unexpectedly cells expressing αvβ6 did not activate added or endogenously expressed SLC. This result suggested that LLC formation is crucial for αvβ6-mediated activation. Annes et al. (19) demonstrated that the region of LTBP-1 required for TGF-β activation is a 46-amino acid sequence within the hinge domain; neither the core of EGF-like repeats nor the N- or C-terminal 8-Cys domains are necessary. Latent TGF-β activation by αvβ6 can work in trans, as one cell can utilize the LLC produced by another cell. Interestingly, the LTBP-3 hinge sequence cannot substitute for LTBP-1 nor can the entire LTBP-3 promote activation. However, if the LTBP-1 hinge is substituted in LTBP-3, the chimeric LTBP supports activation. Thus, not all LTBP-2 (or even all LTBP hinge sequences) participate in αvβ6-mediated latent TGF-β activation. The results suggest a model in which αvβ6-mediated activation requires the generation of force, and force can only be applied if the latent complex is tethered to the matrix or cell surface. An important question is what is the hinge binding partner?

**LTBP Function: Genetic Approaches**

Null or hypomorphic mutations for three of the four LTBP have been described. Ltbp-2−/− mice die in early gestation (E3.5 and E6.5) (41). The reason for lethality is unknown, but there may be a defect in implantation. The recently described anti-adhesive (42) or pro-adhesive (39) functions of LTBP-2 may be crucial during this period of development. Alternatively, Ltbp-2 may bind another signaling molecule essential for successful development.

The Ltbp-3 null mouse has a number of abnormalities but is fertile and survives for over 2 years (43). Homozygous mutant animals have skeletal and craniofacial abnormalities, developmental emphysema, involvement of the spleen and thymus, and a reduction of CD4/CD8 double positive T cells (44). The skeletal defects are multiple (43); the mice have cranial doming, kyphosis, the long bones are short, and as the animals age, the long bones and vertebrae become osteoarthritic and osteoporotic. Both osteoarthritic and osteoporotic phenotypes occur in mice with impaired TGF-β signaling (45, 46). Thus, the Ltbp-3−/− phenotypes are consistent with decreased extracellular levels of TGF-β, but attempts to measure changes in TGF-β were unsuccessful. The craniofacial abnormalities result from the ossification of the synchondroses (growth zones) in the base of the skull. The increased rate of differentiation of the synchondroses results from a defect in a negative regulatory loop, involving Indian hedgehog (IHH) and parathyroid hormone-related protein (PTHRP) that mediates chondrocyte differentiation. The expression of IHH by the early hypertrophic chondrocytes stimulates the production of PTHrP by the perichondrium and resting chondrocytes (47). PTHrP interacts with its receptor, expressed by prehypertrophic chondrocytes, and slows the rate of chondrocyte differentiation. In Ltbp-3 null mice, PTHrP expression is decreased suggesting that TGF-β regulates PTHrP expression. The absence of Ltbp-3 mutant mice demonstrates a lack of active TGF-β in response to IHH, decreased TGF-β results in impaired expression of PTHrP, and low PTHrP yields accelerated chondrocyte differentiation. This model can be tested by determining if expression of constitutively active TGF-β or PTHrP by prehypertrophic chondrocytes in vivo, using the collagen type II promoter, rescues the Ltbp-3−/− phenotype.

Ltbp-4 hypomorphic mice were produced as part of a gene trap screen (48). Mutant animals have undetectable levels of Ltbp-4 protein and less than 2% of the normal level of Ltbp-4 mRNA. The hypomorphic mice develop emphysema at the saccular stage, which is earlier than the emphysema observed in the Ltbp-3−/− mice. The lungs are characterized by decreased numbers of septae, larger air spaces, and fragmented elastic fibers. The mice develop carcinomas of the small intestine consistent with both the high expression of LTBP-4 in the small intestine (11) and the known tumor suppressive effect of TGF-β (49). Immunohistochemical analysis of lung and intestinal tissue from mutant animals revealed a lack of extracellular matrix-bound TGF-β coincident with normal intracellular staining of the growth factor. Thus, the major phenotypes relate to decreased extracellular levels of TGF-β.

The mechanism governing the Ltbp-4 hypomorphic phenotypes has been elucidated by Koli et al. (50), who demonstrated that cells derived from Ltbp-4 mutant mice have a defective matrix containing excessive amounts of fibronectin. The mutant cells have decreased levels of active extracellular TGF-β, increased expression of BMP-4, and decreased expression of the BMP-4 inhibitor gremlin. The matrix composition is reversed by overexpressing either gremlin or a dominant negative receptor for BMP-4. Increased BMP-4 and decreased gremlin expression were also observed in vivo. These studies demonstrate that the Ltbp-4 modulates extracellular TGF-β levels. Curiously, overexpression of Ltbp-1 in the mutant cells fails to rescue the phenotype.

**Conclusions and Perspectives**

The significance of LTBP in TGF-β biology is clear from the phenotypes of Ltbp mutant mice. Additional phenotypes will certainly be observed in these as well as in Ltbp−/− mice. Two important questions remain with regard to LTBP action. First, are there non-TGF-β related activities? Although the LTBP-2 may have non-TGF-β related activities, some animal data point to LTBP as modifiers of TGF-β action. It is also possible that LTBP-3 may participate in the action of other TGF-β superfamily members. Second, what are the functions of individual LTBP within the multicellular environment of a tissue where several different LTBP may be produced? The discrete phenotypes of the Ltbp-2, -3, and -4 mutant mice suggest unique cell or tissue activities, a situation in which tissue-specific expression would account for the function of individual family members. Yet, the results of Koli et al. (50) that Ltbp-1 overexpression fails to rescue the phenotype of Ltbp-4 hypomorphic cells demonstrate a lack of redundancy. Moreover, the observation that not all LLCs are activated by the integrin αvβ6 supports the view that individual LTBP have unique functions. However, overlap of function must exist as no LTBP mutation mimics any of the three TGF-β isoform null mutations. Within tissues a variety of LLCs differing in LTBP isoform or splice variants may be produced. These forms may localize differentially according to interactions with cell surface or matrix molecules. Activation of these latent complexes would depend upon the ability of specific activators, themselves uniquely organized in a spatiotemporal manner, associating with the LLC and generating active TGF-β. This scenario permits both specificity and redundancy as one activation mechanism may be favored, but a second mechanism may substitute with less favorable kinetic or thermodynamic constants.

An obvious question is why is there such a degree of complexity? Perhaps the answer lies in the complexity and ubiquity of TGF-β responses. The formation of TGF-β anywhere other than the correct location may produce an unwanted response. The LTBP add one more layer of specificity and control to TGF-β action.
Minireview: Latent TGF-β Binding Proteins

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