

TGF β 1 as a Good and Bad Biological Molecule: Structure and Function

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ABSTRACT

Transforming Growth Factor (TGF- β 1) is a multifunctional cytokine belonging to the Transforming Growth Factor superfamily. It can be secreted by many cell types and has main role in cell proliferation and differentiation. In this mini review, TGF β 1 was addressed.

Introduction

Work over the past decades has revealed significant insight into the Transforming Growth Factor- β (TGF- β) signal transduction network. TGF- β is a multifunctional ubiquitous polypeptide cytokine that binds and activates a membrane receptor serine/threonine kinase complex. On TGF- β binding, the receptor complex phosphorylates the transcription factors Smad2 and Smad3, which then bind to Smad4 and accumulate in the nucleus, where they regulate transcription of target genes [1,2]. The physiological disorder of the TGF- β pathway has been discovered in many human diseases, including solid and hematopoietic tumors. Additionally, TGF- β acts as a tumor suppressor; however, in tumor cells, TGF- β loses anti-proliferative response and become an oncogenic factor helping cancer cells to be more invasiveness and metastasis [3].

Many previous reports revealed that TGF- β pathway has been mutated in cancer patients, in this case, the development of therapeutic substances seems to be evident. In fact, there are different reasons why the inhibition of the TGF- β pathway might be a promising target for anticancer therapies. First, the direct effect on tumor cells must be stressed. Second condition, the TGF- β pathway plays an important role in endothelial cell behavior and therefore in angiogenesis. Anti-angiogenic therapies belong to the most promising therapeutic cures that are currently under development. Thirdly, TGF- β is one of the most potent naturally immune-suppressors [4]. Various studies in vitro and in vivo have been reported, accounting for these different strategies to inhibit tumor growth and to target various components within the TGF- β

pathway including ligands, receptors and even downstream signals. More recently, many TGF- β inhibitors have been encapsulated to block TGF β signaling pathways. TGF- β family. The cell growth is controlled by polypeptide autocrine secretion called Transforming Growth Factor- α (TGF- α) and Transforming Growth Factor- β (TGF- β) [5-7]. TGF- β was further described by Roberts and Sporn as a secreted polypeptide capable of inducing fibroblast growth and collagen production [8]. TGF β family is homodimeric or heterodimeric polypeptides with multiple regulatory properties depending on cell type, growth conditions and presence of other polypeptide growth factors.

Since their expression is also controlled by distinct promoters, their secretion is temporal and tissue specific [9]. The TGF- β family contains a large group of proteins, including the activin/inhibin family, Bone Morphogenetic Proteins (BMPs), Growth Differentiation Factors (GDFs), the TGF- β subfamily and the Glial Cell Line Derived Neurotrophic Factor (GDNF) family [10].

Synthesis of TGF β

The structure of mature form of TGF- β , composed of two monomers stabilized by hydrophobic interactions and Disulphide Bridge, initiates intracellular signaling [11]. TGF- β initiated its structure as pro-proteins (pro-TGF- β s) with large amino-terminal pro-domains (called latency associated proteins - LAPs), which are required for proper folding and dimerization of carboxy-terminal growth-factor domain (mature peptide) [12]. This complex is called 'Small Latent Complex' (SLC). In trans-Golgi apparatus, TGF can be

cleaved by furin type enzymes; however, it remains associated with its pro-peptide through noncovalent interactions, creating 'Large Latent Complex' (LLC). Most cultured cell types release latent TGF- β into extracellular matrix as LLC which in addition includes a 120–240 kDa glycoprotein called latent TGF- β binding protein (LTBP) [13]. LTBP participates in the regulation of latent TGF- β bioavailability by addressing it to the Extracellular Matrix (ECM) [14].

TGF Complex Structure

Ligand: TGF- β s (bio active form) are dimers conjugated by hydrophobic interactions and, in most cases, by an intersubunit disulfide bond as well. The chemical structure of these ligands suggests that they function by bringing together pairs of type I and II receptors, forming heterotetrameric receptor complexes [15].

Receptors: Three isoforms of TGF- β are now known including TGF- β 1, TGF- β 2 and TGF- β 3. They are expressed in mammalian tissues. Moreover, these isoforms contain highly conserved regions but diverge in several amino acid regions. T β RI and T β RII mediate signal transduction. Both receptors are transmembrane serine/threonine kinases, which associate in a homo- or heteromeric complex and act as tetramers. Additionally, these isoforms are organized sequentially into an N-terminal extracellular ligand-binding domain, a transmembrane region, and a C-terminal serine/threonine kinase domain. The type II receptors range from 85 to 110 kDa, while the type I receptors are smaller and their size ranges from 65 to 70 kDa. Moreover, T β RI contains a characteristic, highly conserved 30 amino acids long GS domain in the cytoplasmic part, which needs to be phosphorylated to fully activate T β RI [16]. TGF β (T β RII) contains 10 bp polyadenine repeat in the coding region of the extracellular domain. This region is frequently a target of changes leading to frameshift missense mutations or early protein terminations that result in truncated or inactive products [17].

Co-Receptors:

- a) **Betaglycan:** betaglycan, is the largest (250-350 kDa) and most abundant binding molecule. This cell-surface chondroitin sulfate / heparan sulfate, proteoglycan is expressed on both fetal and adult tissues and most cell types [18].
- b) **Endoglin:** Endoglin (CD105) was shown to act as type III receptor for TGF- β as well [19]. Endoglin is a membrane, an RGD-containing glycoprotein, which is expressed in a limited set of cell types, primarily vascular endothelial cells, several hematopoietic cell types, bone marrow stromal cells and chondrocytes. Its expression strongly increases in active vascular endothelial cells upon tumor angiogenesis [20]. In normal brain, it was reported to be expressed in the adventitia of arteries and arterioles, and it is expressed on several types of tumor cells, such as invasive breast cancers and cell lines or renal cell carcinoma [21,22]. However, betaglycan and endoglin are co-receptors, they are not directly involved in intracellular TGF- β signaling due to lack of kinase domain. They can control access of TGF- β to TGF- β receptors and consequently modulate intracellular TGF- β activity [23]. Betaglycan binds all three

isoforms of TGF- β , with higher affinity for TGF- β 2; however, endoglin binds TGF- β 1 and - β 3 with constant affinity and has only weak affinity for TGF- β 2 [24].

TGF Activation

TGF- β 1 becomes active when TGF- β 1 is liberated from the Latency-Associated Peptide (LAP) and dissociated from LTBP via proteolytic cleavage by plasmin, Matrix Metalloproteases MMP-2 and MMP-9, reactive oxygen species, thrombospondin-1 and acid [25].

TGF Signaling Pathway

It is now well established that the binding of TGF- β 1 to its receptor II (T β RII) can activate the TGF- β receptor type I (T β RI)-kinase, resulting in phosphorylation of Smad2 and Smad3, two receptor-associated Smads (R-Smads). Subsequently, phosphorylated Smad2 and Smad3 bind to the common Smad4 and form the Smad complex, which translocates into the nucleus to regulate the target gene transcription, including Smad7. Smad7 is an inhibitory Smad that negatively regulates Smad2 and Smad3 activation and functions by targeting the T β RI and Smads for degradation via the ubiquitin proteasome degradation mechanisms [26]. Recently, many studies involved TGF β 1 blockers as smart therapeutic molecules can inhibit TGF β 1 signaling pathway such as Activin like kinase (ALK1) [27] LY2157299 (LY) [28] siRNAs, shDNA, peptide 17 [29-30].

Conclusion

Transforming Growth Factor (TGF- β 1) as a smart molecule exhibited a good inhibition for cell proliferation in early stages of many malignancies. While in the late-stage tumors, TGF- β 1 promote cancer progression expressing on its bad face.

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