**TGFβ1 as a Good and Bad Biological Molecule: Structure and Function**

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**ARTICLE INFO**

Received: April 05, 2019
Published: April 18, 2019


**ABSTRACT**

Transforming Growth Factor (TGF-β1) 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, TGFβ1 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 TGFβ 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**

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-βs) 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-βs (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-β1, TGF-β2 and TGF-β3. They are expressed in mammalian tissues. Moreover, these isoforms contain highly conserved regions but diverge in several amino acid regions. TβRI and TβRII 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, TβRI contains a characteristic, highly conserved 30 amino acids long GS domain in the cytoplasmic part, from 65 to 70 kDa. Moreover, TGFRI and TGFRII contain 10 bp polyadenine repeat in the coding region of many malignancies. While in the late-stage tumors, TGF-β1 promote cancer progression expressing on its bad face.

**References**


ISSN: 2574-1241
DOI: 10.26717/BJSTR.2019.17.002966

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