Cellular Signalling 52 (2018) 112–120

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

TGF-β receptors: In and beyond TGF-β signaling

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ARTICLE INFO

Keywords:
Transforming growth factor β (TGF-β)
TGF-β receptor (TGFBR)
SMAD
Phosphorylation
Ubiquitination
Endocytosis

ABSTRACT

Transforming growth factor β (TGF-β) plays an important role in normal development and homeostasis. Dysregulation of TGF-β responsiveness and its downstream signaling pathways contribute to many diseases, including cancer initiation, progression, and metastasis. TGF-β ligands bind to three isoforms of the TGF-β receptor (TGFBR) with different affinities. TGFBR1 and 2 are both serine/threonine and tyrosine kinases, but TGFBR3 does not have any kinase activity. They are necessary for activating canonical or noncanonical signaling pathways, as well as for regulating the activation of other signaling pathways. Another prominent feature of TGF-β signaling is its context-dependent effects, temporally and spatially. The diverse effects and context dependency are either achieved by fine-tuning the downstream components or by regulating the expressions and activities of the ligands or receptors. Focusing on the receptors in events in and beyond TGF-β signaling, we review the membrane trafficking of TGFBRs, the kinase activity of TGFBR1 and 2, the direct interactions between TGFBR2 and other receptors, and the novel roles of TGFBR3.

1. Introduction

Transforming growth factor β (TGF-β) is expressed by all cells in the human body and plays an important role in normal development and homeostasis. There are three TGF-β forms (TGF-β1, 2, and 3), which are receptor ligands, have similar biological activity, and are important in processes such as regulating proliferation, migration, differentiation, and apoptosis. There are also three TGF-β receptors (TGFBR1, 2, and 3). Canonical TGF-β signaling occurs when one of the three ligands binds to TGFBR2, which then recruits and phosphorylates TGFBR1. In turn, phosphorylated TGFBR1 phosphorylates downstream SMAD2 and SMAD3 (mothers against decapentaplegic homolog 2 and 3), each on a serine residue at its carboxy terminus (pSmad2/3C), which then recruit SMAD4 and translocates to the nucleus where it regulates the transcription of TGF-β target genes [1–4].

On the other hand, SMAD7 could be recruited to the complex of activated TGFBRs or pSmad2/3C to initiate their degradation by SMAD-specific E3 ligase. Depending on the proteins recruited to the ligand–receptor complex, TGF-β binding its receptors can activate noncanonical TGF-β signaling by stimulating a variety of kinases, including the MAPKs, ERK, P38, JNK, phosphatidylinositol 3 kinase (PI3K)/PKB, or ROCK [5] (Fig. 1). These kinases are able to phosphorylate the linker regions of SMAD2/3, which is the region between the N-terminus Mad-homology 1 (MH1) and the C-terminus MH2 domains of a SMAD protein. Signaling based on such linker region phosphorylation has been defined as non-Smad (or Smad-independent) signaling [6,7]. The functions of linker region phosphorylation are not well understood. To avoid confusion, we will use “canonical signaling” for SMAD C-terminus phosphorylation and “noncanonical signaling” for the other TGF-β downstream pathways.

TGF-β signaling is a crucial regulator of normal inflammatory response, as demonstrated by homozygous TGF-β1–null mice that develop multifocal inflammatory syndrome soon after weaning [8,9]. Furthermore, TGF-β signaling plays pivotal roles in cancer, having both suppressor and promoter activity [10,11]. Since the discovery and purification of TGF-β, many researchers have been drawn to study its multiple roles in cancer. It is generally accepted that TGF-β signaling has a tumor-suppressive role in normal cells but a tumor-promoting role in malignant cells. Targeting TGF-β and its downstream signaling components have been effective against many cancers in preclinical animal models, but not clinically. Therefore, there is a crucial need for further understanding the TGF-β signaling and its regulation. Major advances have been made in dissecting the regulation of and identifying downstream targets of TGF-β signaling; these have been extensively reviewed [9–15]. In this review, we focus on the three TGFBRs and their kinase activities, their interactions with other proteins, and the dynamic of their presence at the plasma membrane, in and beyond the divergent TGF-β signaling effects.

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https://doi.org/10.1016/j.cellsig.2018.09.002
Received 14 May 2018; Received in revised form 7 August 2018; Accepted 1 September 2018
Available online 07 September 2018
0898-6568/

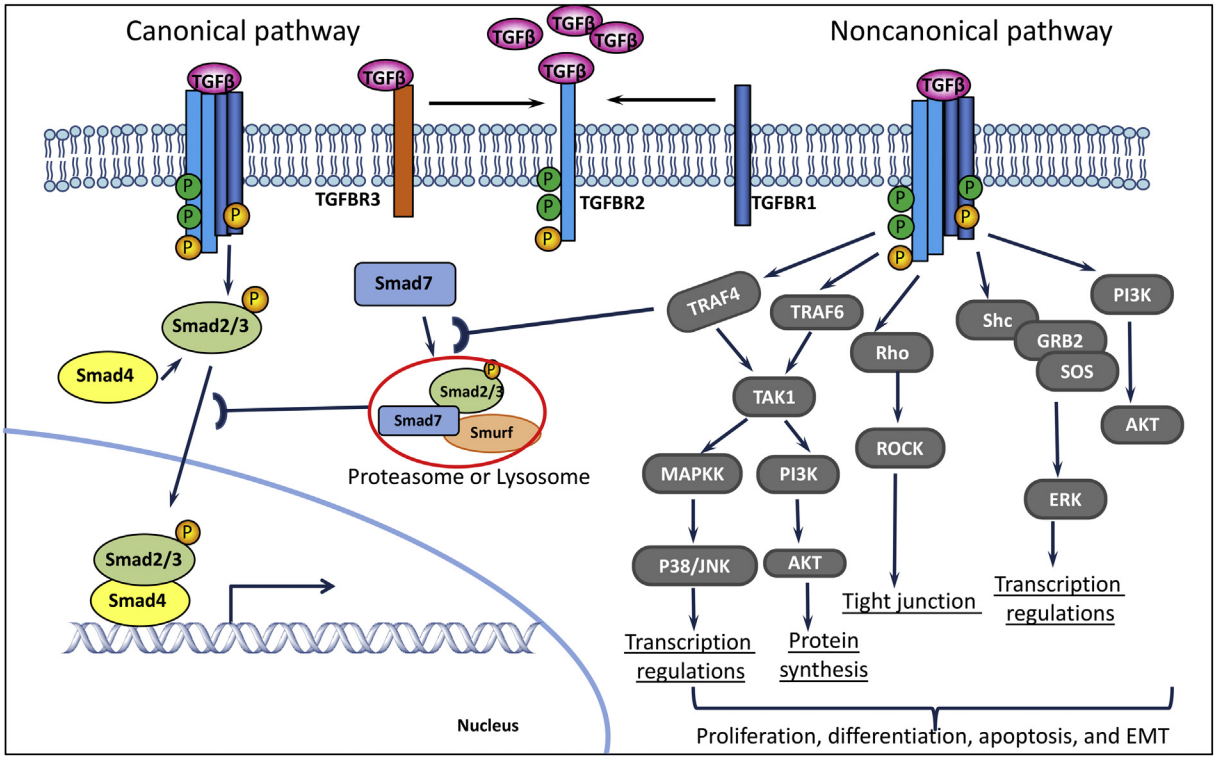

Fig. 1. TGF-β canonical and noncanonical signaling. Signaling starts with TGF-β binding to TGFBR2, a constitutively activated kinase, which phosphorylates TGFBR1 and activates its kinase activity, which then phosphorylates SMAD2/3 or noncanonical downstream components. EMT, epithelial–mesenchymal transition; Ⓟ in green circle, tyrosine kinase phosphorylation; Ⓟ in orange circle, serine/threonine kinase phosphorylation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Endocytosis of TGFBRs in signaling activation, receptor trafficking, and degradation

At the plasma membrane, TGFBRs reside in both lipid raft and non-raft membrane domains. All three TGFBRs have a rapid turnover from the cell membrane. By using an ^{125}I-TGF-β1 binding assay, it was shown that a 2-h cycloheximide treatment blocking new protein synthesis resulted in decreased TGF-β1 binding to both TGFBR1 or TGFBR2 (down to 50% of the initial level), and their activity was negligible after 24 h. TGFBR3 binding was reduced to 50% after 6 h of cycloheximide treatment [16]. In addition, ligand-independent recycling of TGFBRs has been observed [17], and ligand stimulation has no effect on the rates of internalization or receptor recycling [16].

One possible mechanism for the rapid TGFBR turnover might be linked to endocytosis, which is an important regulatory event in signal transduction. TGFBRs internalize into both caveolin– and clathrin–positive vesicles. Clathrin-dependent internalization into an early endosome antigen (EEA)-1-positive endosome promotes canonical signaling [18], by increasing SMAD2 nuclear translocation and thereby the activation of downstream signaling [19,20]. In contrast, the lipid raft-caveolar internalization pathway involves the SMAD7-SMURF1/2-bound receptor and is required for receptor turnover [18] (Fig. 2). The mechanism that directs the internalization of activated receptors for signaling turnover or signaling activation is unknown.

Some insights have been gained by using a chimeric receptor model. The findings included that TGFBRs constantly recycle in the absence of ligands, and that ligand binding directs only heteromeric receptors (TGFBR1/TGFBR2) for degradation, whereas the homomeric receptors (TGFBR1/TGFBR1 or TGFBR2/TGFBR2) are recycled back to the plasma membrane [21]. More interestingly, in epithelial Mv1Lu cells, ligand-bound heteromeric receptors were all shuttled to the degradation pathway [21]. On the other hand, certain point mutations in TGFBR1 or TGFBR2 keep the heteromeric receptors in the recycling pathway in NIH-3 T3 fibroblasts [21]. These observations raised more questions. For example, is this mechanism applicable to a wide range of epithelial cells and fibroblasts? Is this the direction to pursue for uncovering the cell-specific effects of TGF-β signaling? And, what are the mechanisms of membrane trafficking of TGFBRs in other types of cells?

3. TGFBR1 in TGF-β signaling

TGFBR1 is the key component in passing extracellular stimulation to the downstream TGF-β signaling pathway. TGFBR1 can be phosphorylated at multiple sites, and it phosphorylates either downstream SMAD2/3 at the C-terminus, or kinases that activate noncanonical pathways. TGFBR1 is tightly controlled through ubiquitination, which regulates the amount of TGFBR1 protein and also mediates its activation of noncanonical signaling. TGFBR1 is important in the normal development of mice: homozygous *Tgfbr1*–null mice die at mid-gestation with a lack of circulating erythrocytes and defects in the yolk sac and placenta [22].

3.1. TGFBR1 phosphorylation in canonical and noncanonical signaling pathways

TGFBR1 is recruited and phosphorylated by ligand-bound TGFBR2. The phosphorylation occurs on serine and threonine residues in an extremely conserved glycine-serine-rich (GS) domain, TTSGSGSG. Mutation of two or more of these residues impairs TGFBR1 kinase activity, but replacement of the non-phosphorylation residue Thr204 by aspartic acid leads to partial activation of the TGFBR1 kinase independent of ligand binding [23 and references in]. Both the TGFBR1 and TGFBR2 receptors are required for any downstream canonical or noncanonical signaling response. TGFBR1 can phosphorylate only its downstream factors such as SMAD2/3; it cannot autophosphorylate or phosphorylate TGFBR2. Studies have shown that the noncanonical

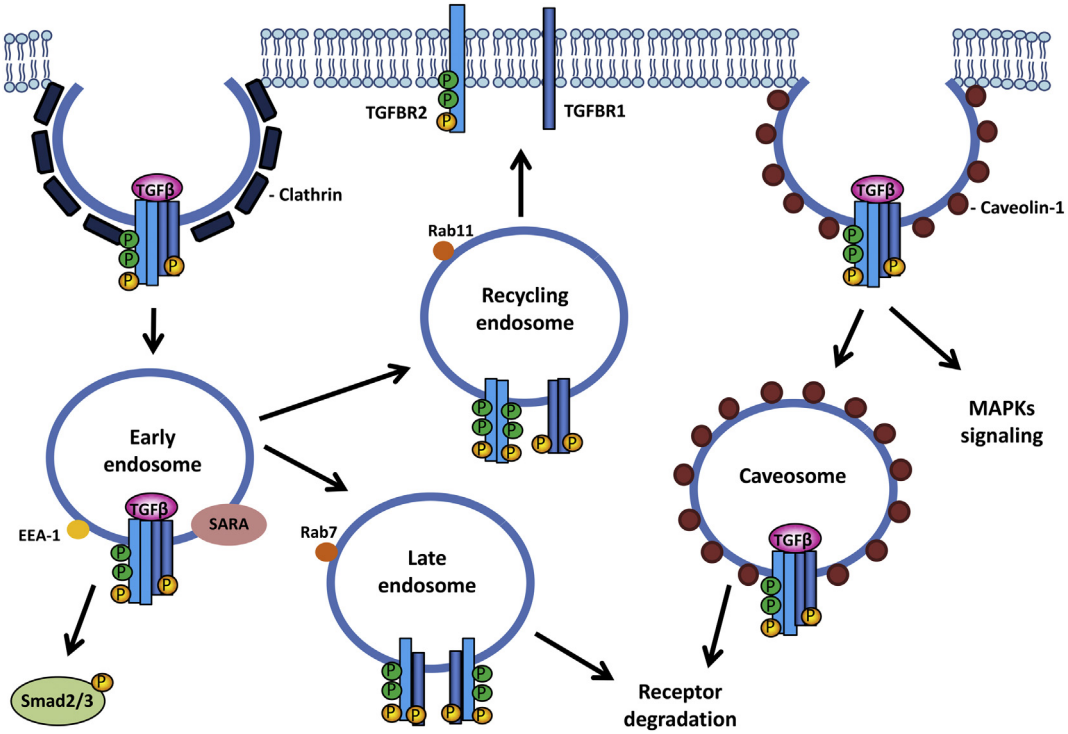

Fig. 2. Membrane trafficking of TGFBRs. TGFBRs on the plasma membrane are rapidly turned over through clathrin- or caveolin-mediated endocytosis. Endocytosis not only directs the degradation or recycling of TGFBRs, but it is also necessary for activation of downstream TGF-β canonical or noncanonical signaling.

MAPK or ERK activations are associated with tyrosine kinase phosphorylation of TGFBRs [24].

Phosphorylation is a process which is reversed by protein phosphatases. Protein phosphatase 1 catalytic subunit gamma (PP1c) has been reported to dephosphorylate TGFBR1. TGF-β promotes a ternary complex formed by the PP1 regulatory subunit GADD34 (also known as PPP1R15A), SMAD7, and TGFBR1, leading to the recruitment of PP1c via SMAD7 and GADD34 to the receptor complexes. This serves as a negative feedback mechanism, decreasing TGF-β signaling through dephosphorylation of TGFBR1 [1,25–27]. It was also reported that in *Drosophila*, SARA can recruit PP1c to reduce the phosphorylation level of TGFBR1. In addition, PP2A is known to associate with TGFBRs, but there is no consistent evidence to conclude that PP2A direct dephosphorylates TGFBRs [1,25,26,28,29].

3.2. Ubiquitination in TGFBR1 degradation and signaling

Ubiquitination plays an important role in regulating and mediating TGF-β signaling. TGFBRs can undergo either ubiquitination-mediated or lysosomal degradation, depending on the proteins involved [23]. TGFBR1 is a ubiquitination target for either degradation or cleavage, thus down-regulating TGF-β signaling or stimulating target gene expression in the nucleus, respectively. Furthermore, activated TGFBR1 recruits specific ubiquitin E3 ligases, which regulate canonical and/or initiate noncanonical TGF-β signaling (Fig. 3).

TGFBR1 degradation requires an additional adaptor protein, SMAD7. SMAD7 interacts with activated TGFBR1 to recruit E3 ligases SMURF1, SMURF2, NEDD4–2, or WWP1, resulting TGFBR1 ubiquitination and degradation and a subsequent decrease in downstream signaling. Targeting protein in general for degradation is mediated by lysine-48 (K48) polyubiquitin. On the other hand, ubiquitination via a lysine at position 63 (K63) activates the target protein for signaling. TGF-β activates TGFBR1, which binds with TRAF6 and increases the auto-ubiquitination of TRAF6, which causes K63-polyubiquitylation of TAK1. This ubiquitination of TAK1 (a MAP kinase kinase kinase) in turn phosphorylates MAP kinase kinase, leading to activation of p38 and JNK signaling, which induces cellular apoptosis, epithelial–mesenchymal transition, and cancer cell invasion [30–33].In addition to direct activation of the PI3k/AKT pathway by TGFBR1, TGF-β can indirectly activate PI3K/AKT. This can occur through the interaction of TGFBR1 and TRAF6, which in turn polyubiquitinates p85a, the PI3K regulatory subunit in order to activate the PI3K/AKT pathway [34,35].

Interestingly, TRAF6 could also promote the proteolytic cleavage of the polyubiquitinated TGFBR1 by TNF-alpha converting enzyme (TACE) and presenilin-1, which would release the intracellular domain of TGFBR1 for translocation to the nucleus. The intracellular domain induces a set of genes, including Snail and MMP2, that promotes cancer cell invasiveness [36–38]. TRAF6 is necessary for noncanonical TGF-β signaling. In breast cancer cells, TRAF4 mediates noncanonical signaling in a TRAF6-independent manner, and also regulates canonical signaling by stabilizing the TGFBRs on the plasma membrane by ubiquitinating SMURF2 for degradation [39].

Other post-translational modifications of the receptors have been identified. For example, sumoylation, the covalent attachment of the small ubiquitin-like modifier (SUMO), is found in phosphorylated and activated TGFBR1. TGF-β ligand binding and TGFBR2 are required for TGFBR1 sumoylation, which enhances downstream canonical signaling [40]. Neddylation is another ubiquitin-like modification, in which NEDD8 is covalently conjugated to lysine residues of TGFBR2. Neddylation stabilizes TGFBR2 and promotes canonical TGF-β signaling [41]. Fucosylation of Ser and Thr on TGFBRs is required for TGFBRI phosphorylation and the activation of downstream signaling in the lungs, colorectal cancer cells, vascular smooth muscle cells, and renal cells [42–47]. N-linked glycosylation of TGFBR2 is necessary for its transportation to the plasma membrane in many types of cell [48].

4. Kinase activity of TGFBR2

TGFBR2 is the receptor that TGF-β binds directly, and thus it serves as a gatekeeper for the activation of downstream signaling. TGFBR2 is a constitutively active kinase independent of ligand binding, phosphorylating itself, TGFBR1, or other receptors. This feature is the basis of the

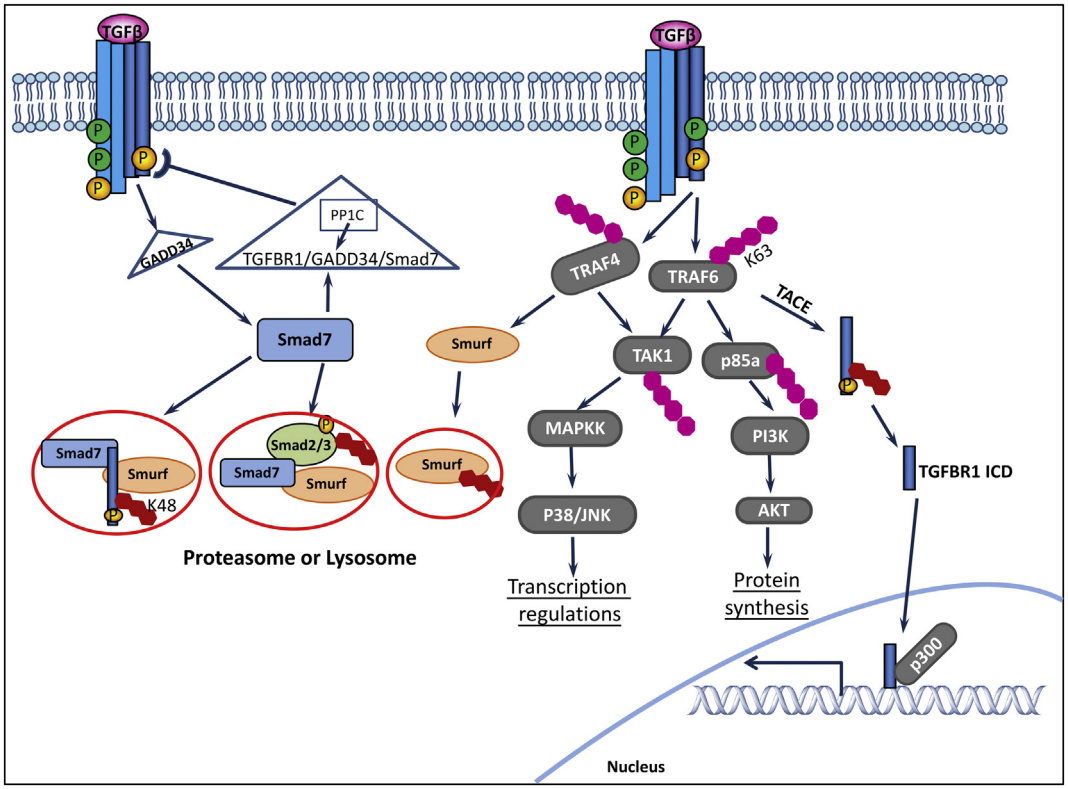

Fig. 3. Ubiquitination in signaling regulation. Ubiquitination plays roles not only in down-regulation of canonical TGF-β signaling (such as or SMAD7/SMURF1-mediated ubiquitination of TGFBR1 or p-SMAD2/3) but also in activation of noncanonical signaling such as TRAF4 or 6 self-ubiquitination, which further ubiquitinates the downstream TAK1 or p85a. TRAF4 could also ubiquitinate Smurf for degradation, thus promoting canonical signaling. SMAD7 could also be involved in dephosphorylating TGFBR1 and thus contribute to the down-regulation of canonical signaling.

manifold TGF-β signaling effects. Similar to the *Tgfbr1* knockout mice, *Tgfbr2* homozygous knockout mice suffer embryonic death at day 10.5 of gestation. These mice have defects in the yolk sac, in hematopoiesis, and in vasculogenesis, while heterozygous *Tgfbr2* knockout mice are developmentally normal [49]. Homozygous deletion of the TGF-β1 gene (*Tgfb1*) also results in embryonic death, and these mice have a phenotype undistinguishable from that of homozygous *Tgfbr2* knockouts. Chimeric mice generated using a *Tgfbr2*$^{-/-}$ embryonic stem cell line showed several congenital abnormalities. The embryonic death and congenital defects in these mice suggests that TGFBR2 is very important for normal development of a variety of organs. TGFBR2 has both Ser/Thr kinase activity and Tyr kinase activity.

4.1. Phosphorylation

In the 1990s, Weinberg and Lodish's group demonstrated for the first time that TGFBR2 was phosphorylated even in the absence of TGF-β and that phosphorylation occurred on multiple Ser residues [50]. Massague's group later showed that the phosphorylation patterns and the amount of TGFBR2 phosphorylation were both independent of TGF-β1 treatment. Mutation of lysine 277 in the putative ATP binding site destroys the kinase and signaling activities of TGFBR2 [51]. Studies have since reported that TGFBR2 can be autophosphorylated on Tyr259, Tyr336, and Tyr424. Mutation of these three residues inhibited its kinase activity, but not the canonical signaling activity, in reporter assays [52].

Although this result was puzzling then, it's clear now that the tyrosine kinase activity of TGFBR2 is responsible for noncanonical signaling but not for the canonical signaling that was tested. For example, SRC (a non-receptor tyrosine kinase) phosphorylates TGFBR2 on Tyr284 and recruits the Src homology 2–containing adaptors, Shc and GRB2 to the receptor. This phosphorylation may play an important role in TGF-β-mediated p38 activation, but it has no effect on canonical signaling [52]. TGFBR1 can also be tyrosine-phosphorylated after stimulation by TGF-β, but we don't know whether this is due to autophosphorylation or phosphorylation by TGFBR2. Tyrosine-phosphorylated TGFBR1 induces phosphorylation of both tyrosine and serine residues of Shc, leading to the recruitment of GRB2 and SOS, which is a guanine nucleotide exchange factor for Ras, and then to ERK activation (Fig. 1) [24]. Taken together, these studies showed that TGFBR2 is constitutively phosphorylated by cellular kinases and also has the ability to autophosphorylate.

4.2. Interaction with other receptors

Moses' group generated the first *Tgfbr2* exon 2–floxed mice 15 years ago, which allowed for cell-specific deletion of *Tgfbr2* by crossing these mice with promoter-driven *Cre* mice [53]. Almost all available *Cre* mice have been crossed with this *Tgfbr2* floxed mouse in order to study the cell-specific effects of TGF-β signaling [54–70]. There have, however, been discrepancies between TGFBR2 and downstream pSmad2C expression, suggesting that TGFBR2 plays a role beyond activating TGF-β signaling [71]. Advances have revealed interactions of TGFBRs with other proteins that contribute significantly to the stability of the receptors and to the diverse noncanonical TGF-β signaling [72–74]. We are interested in studies on the direct physical interactions of TGFBR2 with other receptors and how these direct interactions are involved in the cross talk between canonical TGF-β signaling and other signaling pathways. Thus, we here review the direct physical interactions of TGFBR2 with other cell surface receptors such as GPCRs (G protein–coupled receptors), RTKs (receptor tyrosine kinases), and the type I cytokine receptor.

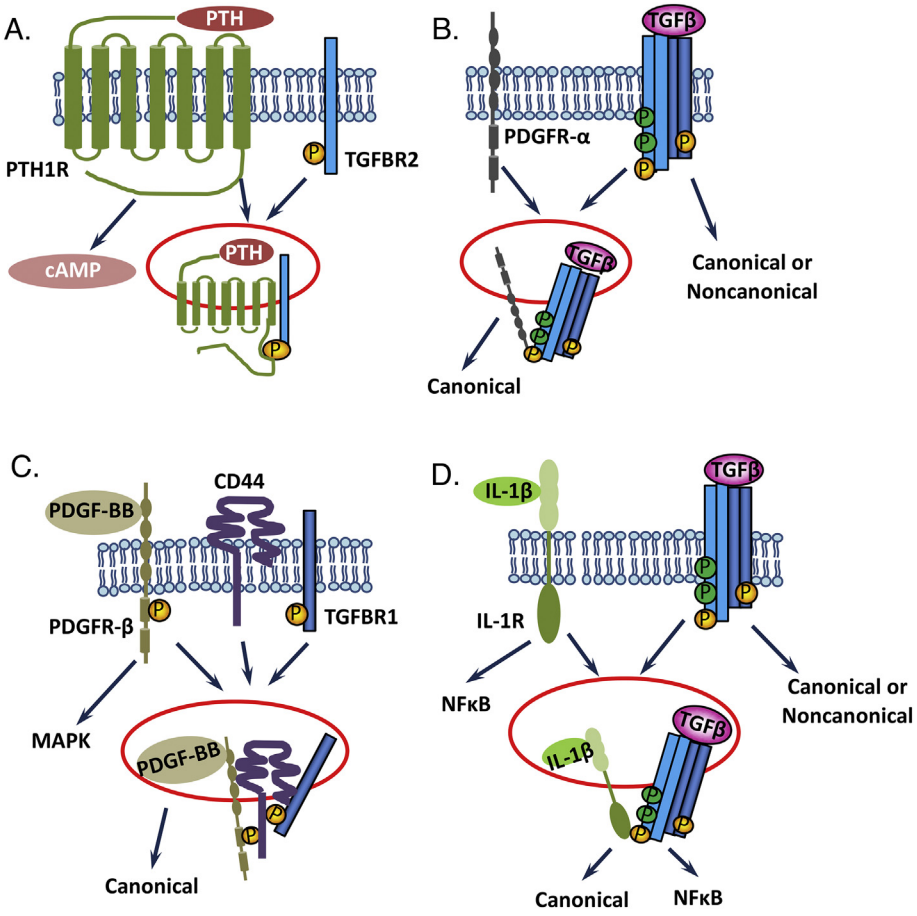

Fig. 4. Interactions with other receptors. A. PTH binding with PTH1R activates its downstream signaling. On the other hand, PTH/PTH1R could be phosphorylated by TGFBR2, which would result in the endocytosis of PTH/PTH1R/TGFBR2 for degradation, thus down-regulating TGF-β signaling. B. TGF-β binding with TGFBR2 causes recruitment of TGFBR1 and further of PDGFR-α for internalization. This process could promote canonical TGF-β signaling. C. PDGF-BB binding with PDGFR-β activates its downstream signaling and could induce canonical TGF-β signaling through CD44-mediated physical interactions of PDGF-BB/PDGFR-β, CD44, and TGFBR1. In addition, PDGFR-β can form a complex with TGFBR1 or TGFBR2 independent of ligand binding or of the receptor kinase activity of either receptor. D. Physical interaction of IL1R and TGFBR2 allows the cross talk between their signaling, such as TGF-β activating NFκB or IL-1β activating canonical TGF-β signaling. The red ovals are representative of endosomes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.2.1. G protein–coupled receptors (GPCRs)

GPCR agonists such as thrombin and endothelin-1, binding to the protease-activated receptor-1/2 (PAR-1/2) and endothelin receptor, respectively, are able to transactivate TGFBR1 and the canonical TGF-β pathway [75]. However, the mechanism such as whether these GPCRs direct interact with TGFBR1 is unknown. Ligand binding with GPCRs activates the direct downstream PKA, PKB, or PLC signaling, depending on the Gα subunit type. The activated GPCRs are then phosphorylated by G protein–coupled receptor kinases (GRKs), which are Ser/Thr kinases, and subsequently internalized for degradation or recycling back to the membrane. This process serves the purpose of desensitization and tight control of the downstream signaling [76–78].

One study showed that TGFBR2 can act as a GRK, which phosphorylates PTH1R (parathyroid hormone [PTH]/parathyroid hormone-related peptide [PTHrP] receptor) and induces endocytosis of both receptors upon stimulation by PTH, but not by TGF-β (Fig. 4A). Therefore, loss of TGFBR2 is expected to result in PTH1R being maintained on the cell membrane and available for continuing activation of downstream signaling upon simulation by ligand [54]. This mechanism explains at least in part the anabolic effect of PTH/PTHrP in osteoblasts, and it was confirmed in vivo using mice with a *Tgfbr2* knockout in osteoblasts. Those mice have increased bone formation, a phenotype similar to that of mice expressing constitutively active PTH1R. The process of PTH1R–TGFBR2 endocytosis was blocked using a Ser/Thr kinase-dead mutation of TGFBR2 [54]. This study demonstrated that TGFBR2 directly phosphorylates proteins other than itself or TGFBR1. This is different from TGFBR2 phosphorylation of Par6, a process that is dependent on TGF-β stimulation and TGFBR1 binding with Par6 [79]. The direct phosphorylation of PTH1R by TGFBR2 raises other questions, such as why TGFBR2, but not GRK, phosphorylates PTH1R. Whether TGFBR2 specifically phosphorylates PTH1R, other GPCRs, or other proteins? And whether TGFBR1 could also interact with GPCRs?

Indeed, one of the orphan GPCRs, GPR50, was shown to directly interact with TGFBR1 independent of TGF-β stimulation [80]. This binding activates the Ser/Thr kinase activity of TGFBR1 and downstream canonical signaling without TGFBR2. Functionally, GPR50 overexpression could mimic TGF-β-mediated cellular responses, such as inhibiting MDA-MB-231 cell proliferation and tumor growth, as well as promoting 4 T1 cell migration. Mechanistically, GPR50 competes with FKBP12 (the 12-kDa FK506-binding protein; FK506 is an mTOR inhibitor and an immunosuppressive drug), whose binding maintains the inactive conformation of TGFBR1 in the absence of ligand, thus preventing the activation of TGF-β signaling [81,82]. The unanswered question is, what factors induce the competition of GPR50 over FKBP12 binding with TGFBR1?

4.2.2. Receptor tyrosine kinases (RTKs)

Platelet-derived growth factor receptor-alpha (PDGFR-α), but not PDGFR-β, was shown to promote TGF-β signaling in cultured human hepatic stellate cells [83]. PDGFR-α KO inhibits canonical TGF-β signaling, but not non-canonical signaling such as AKT or ERK. Interestingly, this effect correlated with PDGFR-α KO repressing TGFBR1 but increasing TGFBR2 at the transcriptional level, as well as blocking the TGF-β-induced internalization of TGFBR2 at the protein level. Together, these effects suppressed SMAD phosphorylation. Further studies using confocal microscopy and immunoprecipitation showed that TGF-β induced the co-localization of TGFBR1, TGFBR2, and further recruitment of PDGFR-α (Fig. 4B) [83]. We suspect that the tyrosine kinase activity of TGFBR2 might play an essential role in forming the complex. Functionally, PDGFR-α KO in hepatic stellate cells reduced the paracrine effects that promote liver metastatic cancer cell colonization. Increases of smooth muscle actin (a TGF-β target gene) and

PDGFR-α were found together in hepatic stellate cells of liver metastatic tissues. However, the role of PDGF and its influence on PDGFR-α downstream signaling in this process were not addressed in this study [83].

On the other hand, another study [84] demonstrated that in dermal fibroblasts, PDGFR-β can form a complex with TGFBR1 or TGFBR2 independent of ligand binding or the receptor kinase activity of either receptor. Functionally, PDGF-BB treatment could induce SMAD2 phosphorylation and decrease TGFBR1 on the cell surface. The knockdown of PDGFR-β decreased TGF-β-induced canonical signaling. However, TGF-β treatment could not influence the amount of PDGFR-β on the cell surface. It was further shown that the physical interactions are mediated by the extracellular or transmembrane domain of PDGFR-β and are likely mediated by CD44 (Fig. 4C). Knockdown of CD44 resulted in increases of PDGF-BB-induced and TGF-β-induced p-Smad2C, as well as PDGFR-β activation, suggesting that CD44 is a negative regulator of both signaling pathways through physical interactions with PDGFR-β and TGFBRs. In addition, interactions between CD44 and TGFBR1 have also been reported in breast cancer cells [85] and renal proximal tubular cells [86]. A CD44 ligand, hyaluronan, was shown to increase p-SMAD2 in breast cancer and to decrease p-Smad2C in renal cells, but the mechanisms are not clear.

4.2.3. Type I cytokine receptor

Both TGFBR1 and TGFBR2 are able to immunoprecipitate with the interleukin receptor. This is the mechanism for IL-1β (at greater than 2 nM) activating SMAD signaling and TGF-β activating NFκB, the IL-1β downstream signal [87]. In chondrocytes, IL-1β causes TGFBR2 degradation, possibly due to IL-1β increasing caveolin-1 expression, leading to the internalization of TGFBR2 in lipid rafts and its subsequent degradation by the proteasome [88]. Additionally, internalization in lipid rafts could be promoted by a physical interaction between the IL-1 receptor (IL-1R) and TGFBR2 in a complex called a “receptosome”. Thus, association of the two types of receptors triggers the cross talk between their signaling pathways (Fig. 4D). The term “receptosome” first appeared in 2001 in a study from Taniguchi's group [89] to describe an assembly of cytokine receptor subunits, which represents a structure that allows unique signaling and cross talk to occur.

5. TGFBR3 is more than a TGF-β co-receptor

TGFBR3, also known as betaglycan, and is the most abundantly expressed TGFBR. This receptor is an 849-amino acid proteoglycan with a short (41-amino acid) cytoplasmic domain. TGFBR3 has no kinase activity, but it can bind all three TGF-β forms with high affinity and is known to facilitate ligand binding to TGFBR2, particularly the binding of TGF-β2. In addition, the extracellular domain of TGFBR3 can be cleaved to a soluble extracellular domain (*s*TGFBR3) that serves as an antagonist of TGF-β to prevent its binding to TGFBR2, while the short cytoplasmic domain can interact with other proteins. Due to its structural characteristics and lack of obvious signaling motifs, TGFBR3 was originally thought to function as a TGF-β co-receptor serving only to sequester and present ligand to TGFBR2 [90,91]. This assumption has been challenged by studies demonstrating the embryonic death of *Tgfbr3* KO mice [92–95]. These mice do not survive past day 14.5, when functional coronary vasculature is required for embryo viability. These mice indeed develop cardiac as well as hepatic defects that lead to embryonic death. *Tgfbr3* KO results in only a slight decrease in pSmad2C activity, suggesting that TGFBR3 works via a pathway that is noncanonical.

5.1. Tumor-suppressive role of TGFBR3

TGFBR3 has been identified as a tumor suppressor gene in prostate cancer [96]. Less TGFBR3 was found in prostate cancer cells than in benign tissues, in metastatic versus primary tumors, and in advanced clinical stage tumors or in tumors with higher PSA recurrence; a loss of heterozygosity in the *TGFBR3* genomic locus was found in prostate cancer cells [96]. A loss of TGFBR3 has been reported also in renal cell carcinoma and endometrial cancer, and exogenous administration of secreted TGFBR3 was shown to suppress breast cancer tumorigenicity in vivo [97–101]. Aguirre-Ghiso's group determined that TGF-β2 dictates disseminated tumor cell fate through TGFBR3 and p38α/β signaling. RNAi against TGFBR3 was shown to completely eliminate the growth-inhibition capacity of TGF-β2 [102,103]. However, the question of how only TGF-β2/TGFBR3 activates p38α/β signaling for growth inhibition was not answered in this study.

5.2. TGFBR3 interaction with scaffold proteins

Although the cytoplasmic domain of TGFBR3 is not required for the binding of TGF-β or of TGFBR2, nor for enhancing TGF-β binding to TGFBR2, it is required for enhancing TGF-β signaling and interactions with other proteins such as GIPC and β-arrestin 2, as well as with the autophosphorylated (active) form of TGFBR2 [91]. GIPC binding stabilizes TGFBR3 on the cell surface, increasing TGF-β responsiveness, while β-arrestin 2 binding results in the internalization of both TGFBR3 and TGFBR2, leading to down-regulation of TGF-β signaling [104]. β-Arrestin is a well-known scaffold protein that is recruited to GPCRs after ligand binding and phosphorylation by GRKs [105,106]. This leads to the degradation of the GPCR or initiation of alternative G protein–independent pathways including the β-arrestin signaling, such as ERK signaling [107,108]. Thus, TGFBR3 may initiate signaling through such alternatives to TGF-β signaling by binding with these scaffolding proteins.

6. Concluding remarks

TGFBRs play important roles in mediating the diverse effects of TGF-β and in fine tuning its signaling. The finding of TGFBRs by ligand-crosslinking experiments was reported in 1980s [109–114], but the structure and function of these receptors were not known until they were molecularly cloned in 1990s [50,115,116]. Ever since then, the Ser/Thr kinase activities and the dynamic presentations of the TGFBRs on the plasma membranes have been studied extensively in activation of the downstream canonical or noncanonical signaling pathways. Recent observations of cross talk among TGF-β and other signaling pathways have led to progress on understanding the physical interactions of TGFBRs with other receptors. Furthermore, there are novel discoveries of the independent roles of TGFBR3. In the future, studies on the nuclear function of TGFBR1, the interactions of TGFBR2 with other membrane proteins (such as cytokine receptors or GPCRs as kinases), and the independent TGFBR3 pathways will help us more fully understand the diverse roles of TGF-β and its signaling.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

This study was supported by DOD PCRP (W81XWH-12-1-0271 to X.L.) and Van Andel Research Institute internal funding (53010A to X.L.). We thank David Nadziejka for his technical editing of this manuscript. The content is solely the responsibility of the authors.

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