Chapter 3
Emerging Roles of TGF-β Co-receptors in Human Disease

Alison E. Meyer, Karthikeyan Mythreye, and Gerard C. Blobe

Abstract TGF-β signaling is both regulated and mediated by signaling co-receptors. Several TGF-β co-receptors have been identified including endoglin (CD105), the type III TGF-β receptor (TβRIII, betaglycan), neuropilin-1/2, syndecan-2, CD109, and LRP1. These co-receptors serve diverse functions including the regulation of ligand access to other TGF-β receptors and receptor trafficking. The TGF-β co-receptors can also signal directly. The TGF-β co-receptors are broadly expressed, have essential roles in embryonic development, and are frequently altered during disease progression. TGF-β co-receptors regulate cancer initiation and progression through effects on cell growth, migration, invasion, proliferation, and angiogenesis. In addition to their roles in cancer, these co-receptors are dysregulated during development, in vascular disease and fibrotic disorders. Collectively, the TGF-β co-receptors influence disease biology through complex mechanisms involving the regulation of growth factor-dependent and independent signaling events as well as through interactions with diverse scaffolding protein partners.

Keywords Angiogenesis • Betaglycan • Cancer • Co-receptors • Development • Disease • Endoglin • Fibrosis • Neuropilin • Syndecan • TGF-β • TβRIII

3.1 Introduction

TGF-β signaling pathways have essential roles in multiple cellular processes including proliferation, differentiation, and apoptosis (Massague 1998). While canonical TGF-β signaling is mediated by the type I and type II TGF-β receptors, TGF-β

A.E. Meyer • K. Mythreye • G.C. Blobe (✉)
Division of Medical Oncology, Departments of Medicine, Pharmacology and Cancer Biology, Duke University Medical Center, 450 Research Dr. LSRC B354, Durham, NC 27708, USA
e-mail: gerard.blobe@duke.edu

A. Moustakas and K. Miyazawa (eds.), *TGF-β in Human Disease*,
DOI 10.1007/978-4-431-54409-8_3,

signaling is both regulated and mediated by signaling co-receptors. Multiple TGF-β co-receptors have been identified including endoglin (CD105) (Cheifetz et al. 1992), the type III TGF-β receptor (TβRIII, betaglycan) (Andres et al. 1991; Lopez-Casillas et al. 1991; Wang et al. 1991), neuropilin-1/2 (Glinka and Prud'homme 2008), syndecan-2 (Chen et al. 2004b), CD109 (Finnson et al. 2006), and LRP1 (Cabello-Verrugio and Brandan 2007). These co-receptors serve diverse functions including the regulation of ligand access to other TGF-β receptors and receptor trafficking. The co-receptors can also signal directly. The TGF-β co-receptors are broadly expressed, have essential roles in embryonic development, and are frequently altered during disease progression (Maring et al. 2012; Bernabeu et al. 2009; Staton et al. 2007; Li et al. 1999; Wild et al. 2012; Stenvers et al. 2003; Theocharis et al. 2010; Gatza et al. 2010). Here we summarize the emerging roles of TGF-β co-receptors in human disease with a focus on endoglin, TβRIII, neuropilin-1/2, and syndecan-2.

3.1.1 Structural Features and Ligand Binding Properties of TGF-β Co-receptors

Structurally, endoglin, TβRIII, neuropilin-1/2, and syndecan-2 all have a large extracellular domain, a short, single-pass transmembrane region, and a short cytoplasmic domain (Essner et al. 2006; Gougos et al. 1992; Mythreye and Blobe 2009a; Lopez-Casillas et al. 1991; Wild et al. 2012). The extracellular domains of TβRIII and syndecan-2 are modified with glycosaminoglycan chains. The extracellular domains of all co-receptors interact with multiple ligand classes (see Table 3.1). Furthermore, these co-receptors all undergo ectodomain shedding, with proteolytic cleavage releasing their soluble extracellular domains from the cell surface. The soluble ectodomains have diverse functions including sequestering ligand to inhibit signaling, binding ligand to facilitate signaling in *trans*, and potentially functioning as ligands themselves (Essner et al. 2006; Gatza et al. 2010; Bernabeu et al. 2009; Wild et al. 2012).

3.1.2 TGF-β Co-receptor Function

Endoglin, which is expressed predominantly in proliferating vascular endothelial cells and smooth muscle cells, has a critical role in angiogenesis (Bourdeau et al. 1999; Fonsatti et al. 2003). Endoglin null mice are embryonic lethal due to defects in vascular development (Li et al. 1999), while mutations of the endoglin gene, ENG, cause the autosomal dominant vascular disease, hereditary hemorrhagic telangiectasia (HHT; discussed in detail below) (McAllister et al. 1994). In endothelial cells, endoglin promotes proliferation through the endothelial-specific type I TGF-β receptor ALK1 and the Smad 1/5/8 pathway, while inhibiting proliferation through

Table 3.1 Ligand specificity of TGF-β co-receptors

Co-receptor	Ligand specificity	References
Endoglin	TGF-β1,3 ActivinA BMP 2,7,9 and 10	Bernabeu et al. (2009), Castonguay et al. (2011)
TβRIII (betaglycan)	TGF-β1, 2 and 3 Inhibin BMP 2, 4, 7 GDF-5 FGF2	Gatza et al. (2010)
Neuropilins 1/2	TGF-β1 Sema3A, 3F VEGF HGF FGF PDGF Shh	Wild et al. (2012)
Syndecan-2	TGF-β1 FGF VEGF PDGF	Essner et al. (2006), Chen et al. (2004b)

BMP bone morphogenetic protein, *FGF* fibroblast growth factor, *GDF* growth/differentiation factor, *HGF* hepatocyte growth factor, *PDGF* platelet-derived growth factor, *Shh* sonic hedgehog, *TGF-β* transforming growth factor-β, *VEGF* vascular endothelial growth factor

the canonical type I TGF-β receptor ALK5 and the Smad2/3 pathway (Goumans et al. 2002). Endoglin has also been shown to participate in Erk (Lee and Blobe 2007), H-Ras (Santibanez et al. 2010), and PI3K/Akt signaling (Lee et al. 2012). Despite its predominant role in angiogenesis, Endoglin is also expressed in some non-endothelial cell types (see Cancer section below). However, the signaling pathways that endoglin utilizes in these cell types have not been well characterized.

TβRIII is an important regulator of cell migration, invasion, growth, and angiogenesis (Gatza et al. 2010). TβRIII null mice are embryonic lethal and exhibit liver and heart defects (Stenvers et al. 2003). TβRIII mediates ligand presentation, whereby ligand is transferred from TβRIII to TβRII to potentiate signaling (Lopez-Casillas et al. 1991; Lopez-Casillas et al. 1993; Wang et al. 1991). In addition to facilitating signaling through the canonical Smad pathways, TβRIII regulates NFκB (Criswell and Arteaga 2007; You et al. 2009) , p38 (Santander and Brandan 2006), and Cdc42 signaling (Mythreye and Blobe 2009b).

Neuropilin-1/2 are vertebrate-specific proteins that are essential for the normal embryological development of the nervous and cardiovascular systems (Staton et al. 2007). Neuropilin-1/2 also regulate angiogenesis, with neuropilin-1 predominating in arterial endothelial cells and neuropilin-2 predominating in vein and lymphatic endothelial cells (Staton et al. 2007). Upon ligand binding, neuropilin-1/2 signal through the p38, Akt, focal adhesion kinase (FAK), and MAPK pathways to regulate numerous diverse processes including proliferation, survival, migration, adhesion, and vascular permeability (Wild et al. 2012).

Syndecan-2 has roles in numerous processes including adhesion, cytoskeletal organization, vesicle transport, synaptic transmission, and axonal migration (Essner et al. 2006). This co-receptor regulates binding to the extracellular matrix (ECM) components laminin, collagen, and fibronectin and can also regulate actin dynamics and FAK (Essner et al. 2006).

3.1.3 Co-receptor Interacting Proteins

While their extracellular domains largely mediate ligand binding, the cytoplasmic domains of the TGF-β co-receptors interact with numerous scaffold proteins to regulate receptor trafficking and signaling. Interestingly, endoglin, TβRIII, neuropilin-1/2, and syndecan-2 all interact with the PDZ domain-containing protein GIPC (GAIP-interacting protein C-terminus; also known as synectin or NIP) (Essner et al. 2006; Wang et al. 2006; Blobe et al. 2001; Lee et al. 2008; Cai and Reed 1999). In the case of neuropilin-1/2, this interaction is important for proper arterial branching morphogenesis and can promote the internalization of integrin to regulate cell adhesion to fibronectin (Chittenden et al. 2006; Valdembri et al. 2009). In contrast to integrin, both endoglin and TβRIII are stabilized on the cell surface through their interaction with GIPC (Blobe et al. 2001; Lee et al. 2008). In addition to GIPC, endoglin and TβRIII can associate with β-arrestin2, resulting in their internalization (Chen et al. 2003; Lee and Blobe 2007). Endoglin can also interact with zyxin (Conley et al. 2004) and zyxin-related protein 1 (Sanz-Rodriguez et al. 2004) to regulate cell adhesion, as well as with the cytosolic dynein light chain family member Tctex2β (Meng et al. 2006), which links endoglin with the microtubule-based transport machinery. Interestingly, the cytoplasmic domain of syndecan-2 has been shown to specifically associate with TβRIII, although the consequences of this interaction are unknown (Chen et al. 2004b). Syndecan-2 can also interact with the cell adhesion molecule fibronectin, α5β1 integrin, the PDZ domain proteins GIPC, CASK/LIN-2, synbindin, and syntenin, and the ERM family proteins ezrin, radixin, and moesin, with most of these interactions facilitating actin reorganization and cell-substrate adhesion (Essner et al. 2006).

3.2 TGF-β Co-receptors in Cancer

In normal epithelial cells and in the early stages of tumorigenesis, TGF-β acts as a tumor suppressor by inhibiting growth and inducing apoptosis or differentiation, when appropriate (Elliott and Blobe 2005). However, during cancer progression, cancer cells lose this inhibitory growth response and respond instead with increased migration and invasion (Elliott and Blobe 2005). TGF-β also functions to promote cancer progression by inhibiting the immune system and promoting angiogenesis (Elliott and Blobe 2005). Much like TGF-β ligands, the co-receptors regulate both

cancer initiation and progression. Below, we discuss the roles of the endoglin, TβRIII, neuropilin-1/2, and syndecan-2 in tumor initiation, progression and angiogenesis, as well as their influence on the tumor stroma.

3.2.1 Cancer Initiation and Progression

3.2.1.1 Endoglin

Germline mutations in the ENG gene have been reported in patients with early onset Juvenile polyposis (JP), a disease that is associated with the development of gastrointestinal malignancies (Sweet et al. 2005). However, a larger follow-up study failed to confirm this finding (Howe et al. 2007). While endoglin is primarily expressed on cells derived from the hemangioblast (i.e., endothelial and hematopoietic cells), there have been numerous reports of altered endoglin expression in cancer cells (see Table 3.2). While some studies suggest endoglin expression is increased in a variety of cancers, others have observed a decrease in endoglin expression. Collectively, these studies suggest that the role of endoglin in cancer initiation and progression may be context specific.

Endoglin has been reported to have complex roles in TGF-β-mediated processes, including cancer cell adhesion, proliferation, and migration (Conley et al. 2004; Sanz-Rodriguez et al. 2004; Lakshman et al. 2011; Romero et al. 2010). In many cancers, endoglin appears to act as a suppressor of cancer progression. Overexpression of endoglin in prostate cancer cells decreases proliferation, invasion, and metastasis in vivo by influencing TGF-β signaling (Lakshman et al. 2011). Similarly, overexpression of endoglin was reported to reduce the invasiveness and tumorigenicity of esophageal squamous cell carcinoma cells, although the effect of endoglin expression on TGF-β signaling was not examined (Wong et al. 2008). In a breast cancer metastasis model, endoglin overexpression was reported to block TGF-β-enhanced cell motility/invasion, resulting in reduced lung colonization (Henry et al. 2011). In contrast to these studies, endoglin expression has been reported to promote the anchorage-independent growth of Ewing sarcoma cells (Pardali et al. 2011).

How might endoglin influence cancer progression? Endoglin is able to regulate the adhesion and migration of many cell types, in some cases by influencing TGF-β signaling (Sanz-Rodriguez et al. 2004; Conley et al. 2004; Lee et al. 2008; Lee and Blobe 2007; Ray et al. 2010; Guerrero-Esteo et al. 1999). While different cell types utilize different mechanisms to regulate adhesion and migration, insights into the function of endoglin in cancer may be derived from studies on non-tumorigenic cells. The cytosolic domain of endoglin likely plays a crucial role in endoglin's functions, as it mediates interactions with several proteins. Endoglin binds zyxin and zyxin-related protein 1, which are cytoskeleton-interacting proteins that localize to focal adhesions (Conley et al. 2004; Sanz-Rodriguez et al. 2004). Therefore, endoglin may regulate the organization of the actin cytoskeleton and the adhesive properties of cancer cells by interacting with these two proteins. Like TβRIII, the

Table 3.2 Expression of TGF-β co-receptors in human cancers

Cancer type	Increased expression	Decreased expression	References
Bladder	Syndecan-2		Marzioni et al. (2009)
Breast	Neuropilin-1, Neuropilin-2, soluble Endoglin	TβRIII, Endoglin	Ghosh et al. (2008), Yasuoka et al. (2009), Staton et al. (2007), Dong et al. (2007), Hempel et al. (2007), Henry et al. (2011), Calabro et al. (2003), Davidson et al. (2010), Li et al. (2000), Takahashi et al. (2001)
Colon	Neuropilin-1, Neuropilin-2, TβRIII, soluble Endoglin, Syndecan-2	Neuropilin-1	Parikh et al. (2004), Grandclement et al. (2011), Gray et al. (2008), Gatza et al. (2012), Takahashi et al. (2001), Park et al. (2002), Ryu et al. (2009)
Endometrial	Endoglin	TβRIII	Florio et al. (2005)
Esophageal		Endoglin, Syndecan-2	Wong et al. (2008), Huang et al. (2009)
Ewing sarcoma	Endoglin		Pardali et al. (2011)
GI Tract	Neuropilin-1	Neuropilin-2	Hansel et al. (2004), Cohen et al. (2001)
Granulosa tumor		TβRIII	Bilandzic et al. (2009)
Kidney		TβRIII	Copland et al. (2003), Cooper et al. (2010)
Leukemia	Neuropilin-1, TβRIII, soluble Endoglin		Younan et al. (2012), Klein et al. (2001), Jelinek et al. (2003), Calabro et al. (2003)
Liver	Neuropilin-1	TβRIII	Berge et al. (2011), Bae et al. (2009)
Melanoma	Neuropilin-1, Neuropilin-2, Endoglin, Syndecan-2		Lacal et al. (2000), Rushing et al. (2012), Pardali et al. (2011), Lee et al. (2009)
Mesothelioma	Syndecan-2		Gulyas and Hjerpe (2003)
Multiple myeloma		TβRIII	Lambert et al. (2011)
Neuroblastoma		TβRIII	Iolascon et al. (2000)
Non-Hodgkin's lymphoma	TβRIII		Woszczyk et al. (2004)
Non-small cell lung	Neuropilin-1, Neuropilin-2, soluble Endoglin	TβRIII	Kawakami et al. (2002), Finger et al. (2008), Kopczynska et al. (2012)
Osteosarcoma	Neuropilin-2	Syndecan-2	Handa et al. (2000), Orosco et al. (2007)
Ovarian	Neuropilin-1, Neuropilin-2, soluble Endoglin	TβRIII	Drenberg et al. (2009), Baba et al. (2007), Bock et al. (2011), Hempel et al. (2008)

(continued)

Table 3.2 (continued)

Cancer type	Increased expression	Decreased expression	References
Pancreatic	Neuropilin-1, Neuropilin-2, Syndecan-2	TβRIII	Parikh et al. (2004), Cohen et al. (2002), Li et al. (2004), Gordon et al. (2008)
Prostate	Neuropilin-1, Neuropilin-2, Endoglin, soluble Endoglin, Syndecan-2	TβRIII, Endoglin	Latil et al. (2000), Yacoub et al. (2009), Turley et al. (2007), Lakshman et al. (2011), Kassouf et al. (2004), Shariat et al. (2008), Popovic et al. (2010)
Salivary adenoid cystic carcinoma	Neuropilin-2		Cai et al. (2010)
Squamous cell carcinoma		TβRIII, Endoglin	Wong et al. (2008), Meng et al. (2011)
Thyroid	Neuropilin-2		Finley et al. (2004)

cytosolic domain of endoglin can associate with GIPC and β-arrestin 2 (Lee et al. 2008; Lee and Blobe 2007; Chen et al. 2003). The interaction between endoglin and GIPC was recently shown to regulate TGF-β pathway signaling events, endothelial cell migration, and capillary tube formation via the recruitment of PI3K and Akt (Lee et al. 2012). β-arrestin 2, in contrast, mediates the internalization of endoglin, resulting in changes in Erk activation and localization as well as endothelial cell migration in a TGF-β-dependent manner (Lee and Blobe 2007). Whether similar pathways mediate endoglin function in cancer cells remains to be defined. In addition, the role of endoglin in mediating the effects of BMPs and Activin in the context of cancer progression has not been explored.

3.2.1.2 TβRIII

While TβRIII mutations have not been reported in human cancers, a recent study demonstrated that myxoinflammatory fibroblastic sarcomas and hemosiderotic fibrolipomatous tumors contained a recurrent chromosome t(1:10) rearrangement, which involves the TGFBR3 gene (Antonescu et al. 2011), suggesting a potential role for TβRIII in the pathogenesis of these diseases. Additionally, the progressive loss of TβRIII has been documented in multiple cancers (see Table 3.2).

Importantly, loss of TβRIII expression during cancer progression is associated with increasing cancer grade and stage and a poorer patient prognosis, supporting an important functional role for loss of TβRIII expression (Lambert et al. 2011; Dong et al. 2007; Meng et al. 2011; Turley et al. 2007). In many of these cases, the loss of TβRIII leads to disrupted TGF-β signaling. Loss of TβRIII expression in human cancers can occur by multiple mechanisms including loss of heterozygosity (Dong et al. 2007; Turley et al. 2007; Finger et al. 2008), gene silencing by promoter methylation (Turley et al. 2007; Cooper et al. 2010; Hempel et al. 2007), and the

negative regulation of TGFBR3 promoter by TGF-β or BMP ligands (Hempel et al. 2008; Gordon et al. 2009). As many cancers are associated with increased TGF-ligand production (Massague 2008), the downregulation of TβRIII expression by ligand is likely a common event. Indeed, the ability of TGF-β ligand to downregulate TβRIII expression has been documented in breast (Dong et al. 2007; Hempel et al. 2007), ovarian (Hempel et al. 2007), and non-small cell lung cancer cell lines (Finger et al. 2008).

Consistent with its frequent loss of expression in a broad spectrum of human cancers, TβRIII has been demonstrated to inhibit both ligand-dependent and independent cancer initiation and cancer progression in preclinical models of these cancers. siRNA-mediated silencing of TβRIII expression in normal murine mammary gland cells (NMuMG) was sufficient to induce tumorigenicity in mice (Criswell and Arteaga 2007). In a reciprocal manner, restoring TβRIII expression decreased tumorigenicity in breast (Sun and Chen 1997; Bandyopadhyay et al. 2002a; Bandyopadhyay et al. 1999a), prostate (Turley et al. 2007), non-small cell lung cancer (Finger et al. 2008), and renal cell carcinoma models (Copland et al. 2003).

Mechanistically, TβRIII has been reported to influence different aspects of tumor biology in a context-dependent manner. Thus, in the context of breast cancer (Sun and Chen 1997), renal cell carcinoma (Copland et al. 2003; Margulis et al. 2008), and multiple myeloma (Lambert et al. 2011), TβRIII inhibited proliferation by mediating TGF-β signaling, while in the context of renal cell carcinoma (Copland et al. 2003; Margulis et al. 2008), TβRIII stimulated apoptosis. Most consistently, in the context of multiple myeloma (Lambert et al. 2011) and cancers of the breast (Dong et al. 2007; Lee et al. 2010), pancreatic (Gordon et al. 2008), ovary (Hempel et al. 2008; Bilandzic et al. 2009) prostate (Turley et al. 2007), and lung (Finger et al. 2008), TβRIII inhibited cancer cell migration and invasion by attenuating TGF-β signaling.

TβRIII inhibits migration and invasion through multiple mechanisms. In some contexts, TβRIII inhibits migration/invasion through the generation of soluble TβRIII, which is thought to bind and sequester free TGF-β ligand in the extracellular space, thereby inhibiting its pro-migratory effects (Bandyopadhyay et al. 2002a; Bandyopadhyay et al. 2002b; Bandyopadhyay et al. 2005; Bandyopadhyay et al. 1999b; Dong et al. 2007; Gordon et al. 2008; Sun and Chen 1997; Finger et al. 2008). TβRIII also inhibits migration and invasion through soluble TβRIII-independent mechanisms, with the interaction between TβRIII and GIPC mediating the anti-migratory and anti-invasive effects of TβRIII in the context of breast cancer (Lee et al. 2010). Through its interaction with β-arrestin2, TβRIII can also negatively regulate the pro-migratory and pro-invasive transcription factor NFκB (Criswell and Arteaga 2007; You et al. 2009). Additionally, TβRIII inhibits the intrinsic ability of epithelial cells to migrate through its interaction with β-arrestin2 (Mythreye and Blobe 2009b), with TβRIII mediating β-arrestin2-dependent constitutive activation of Cdc42 and alterations in the actin cytoskeleton (Mythreye and Blobe 2009b). Interestingly, these effects are also independent of TβRIII's role in ligand presentation (Mythreye and Blobe 2009b). TβRIII also functions to inhibit TGF-β and BMP-mediated EMT and EMT-associated increases in migration and

invasion (Gordon et al. 2008; Gordon et al. 2009; Criswell and Arteaga 2007; Mythreye and Blobe 2009b; Hempel et al. 2007). Finally, TβRIII may influence cell migration and invasion by regulating cell adhesion. Indeed, TβRIII has been shown to influence the interaction between multiple myeloma cells and bone marrow stromal cells and to regulate the adhesive properties of ovarian cancer, breast cancer, and granulosa cell tumors (Lambert et al. 2011; Mythreye et al. 2012; Bilandzic et al. 2009). Mechanistically, TβRIII affects focal adhesion dynamics by regulating the localization of α5 integrin (Mythreye et al. 2012).

In contrast to most cancers, TβRIII expression is increased at the protein level in colon cancer, where TβRIII is associated with an inhibition of chemotherapy-induced apoptosis, increased TGF-β signaling, colony formation in soft agar, migration, and ligand-stimulated proliferation in vitro and tumorigenicity in vivo (Gatza et al. 2012). The reasons for the opposing effects of TβRIII on colon versus other cancers are currently unknown. However, as K-Ras is mutated in up to 50 % of colon cancer patients (Benhattar et al. 1993), crosstalk between K-Ras and the TGF-β pathway may be involved. Interestingly, increased TβRIII expression has also been observed in non-Hodgkin's lymphoma and B-cell chronic lymphocytic leukemia (Woszczyk et al. 2004; Klein et al. 2001; Jelinek et al. 2003), although the effect of TβRIII on the biology of these cancers is unknown

3.2.1.3 Neuropilin-1/2

As co-receptors for VEGF and semaphorin ligands, the neuropilins have important roles in regulating angiogenesis. However, the neuropilins are also expressed on cancer cells (see Table 3.2) and function as TGF-β co-receptors in regulating the TGF-β responsiveness of cancer cells (Staton et al. 2007; Mak et al. 2010; Grandclement et al. 2011). Like endoglin, neuropilin-1/2 has context-dependent effects in regulating cancer progression.

Mechanistically, neuropilin-1/2 may promote cancer progression by activating latent TGF-β and enhancing signaling. This has been shown to occur in regulatory T-cells as well as breast cancer cells (Glinka and Prud'homme 2008). Furthermore, VEGF and neuropilin-1 have been shown to directly promote epithelial-mesenchymal transition (EMT) in prostate cancer cells (Mak et al. 2010), and the knockdown of neuropilin-2 in colon cancer cells has also been associated with EMT (Grandclement et al. 2011). As EMT can also be triggered by TGF-β, the neuropilins may also aid in TGF-β-mediated EMT, although this has not yet been directly demonstrated

3.2.1.4 Syndecan-2

While syndecan-2 does bind to TGF-β, it is currently unknown what roles this binding may play in cancer development and progression. However, altered syndecan-2 expression has been observed in several cancers (see Table 3.2), and syndecan-2 has

been shown to positively regulate cancer cell migration and invasion in a variety of cancer types (Choi et al. 2010; Lee et al. 2009; Orosco et al. 2007; Ryu et al. 2009).

Syndecan-2's role in colon cancer has been most thoroughly investigated. Increased mRNA and protein expression of syndecan-2 have been observed in human colon adenocarcinoma tissue samples in comparison with neighboring normal epithelium (Ryu et al. 2009). Additionally, high expression of syndecan-2 has been observed in colon cancer cell lines. This increased expression is associated with increased proliferation, migration, and invasion (Ryu et al. 2009; Park et al. 2002; Choi et al. 2010). Syndecan-2 regulates colon and fibrosarcoma cancer cell migration and invasion through Tiam1-dependent Rac activation (Park et al. 2005; Choi et al. 2010). Additionally, MMP7 activity and integrin α2 are upregulated upon syndecan-2 expression in colon cancer cells, which may influence adhesion, migration, and invasion (Ryu et al. 2009; Choi et al. 2010).

3.2.2 Cancer Stem Cells

In some cancers, a small percentage of tumor cells have been isolated that possess the unique capability of sustained self-renewal and differentiation (Grotenhuis et al. 2012). As such features are common to stem cells, these cells are referred to as cancer stem cells (CSCs) or tumor-initiating cells. CSCs are unique in that, unlike the majority of tumor cells, they are typically more chemoresistant and are more effective in generating xenografts in mouse models (Grotenhuis et al. 2012). CSCs are also capable of giving rise to non-CSC populations and thus can recapitulate the heterogeneity of the tumor from which they were isolated. Therefore, it has been suggested that CSCs can drive tumor initiation or recurrence. For a recent review on CSCs, please see Grotenhuis et al. 2012.

While endoglin, TβRIII, and the neuropilins have been shown to have roles primarily in TGF-β-mediated angiogenesis and/or cancer cell migration and invasion, a few reports have identified these co-receptors as CSC markers. In a cohort of matched primary/recurrent ovarian cancer specimens, along with the expression of several known markers of ovarian CSCs, endoglin was found to be significantly increased in persistent tumors compared to matched primary tumors (Steg et al. 2012). Additionally, endoglin-positive cells isolated from a rhabdoid meningioma surgical sample exhibited increased proliferation and had an increased ability to form single-cell tumor spheres in vitro compared to cells lacking endoglin expression (Hu et al. 2012). Interestingly, the endoglin-positive cells were found to have several cell surface markers in common with mesenchymal progenitor cells, which are multipotent and are the precursor cell type for several tissues including bone, muscle, and fat (Hu et al. 2012; Houthuijzen et al. 2012).

With regard to TβRIII, a lack of TβRIII expression has been associated with prostate CSCs. Sharifi et al. showed that prostate cancer cells lacking TβRIII expression had higher levels of the prostate CSC marker CD133 than tumor cells that were positive for TβRIII expression, suggesting that the loss of TβRIII may increase the population of stem-like cells (Sharifi et al. 2007).

Notably, skin squamous cell carcinoma CSCs were found to lack endoglin expression; however, these cells did express high levels of neuropilin-1 (Beck et al. 2011). The expression of neuropilin-1 was shown to be critical for the ability of these CSCs to promote VEGF-stimulated tumor growth in a mouse model (Beck et al. 2011). Hamerlik et al. also detected neuropilin-1 expression on CSCs isolated from glioblastoma multiforme tumors (Hamerlik et al. 2012). Here, neuropilin-1 was found to stabilize VEGFR2 expression, thereby enhancing the self-renewal capacity and viability of the CSCs (Hamerlik et al. 2012). While it is unknown what role TGF-β family ligands play in CSCs, the expression of these TGF-β co-receptors on CSCs provides one more mechanism by which co-receptors can regulate the pathogenesis of human cancers.

3.2.3 Cancer-Associated Angiogenesis

3.2.3.1 Endoglin

Endoglin is intricately involved in the process of angiogenesis, which is required to sustain primary tumor growth and metastasis (Folkman et al. 1989; Neri and Bicknell 2005; Molema and Griffioen 1998). Endoglin expression is higher in nascent blood vessels, where it controls cell proliferation, migration, and capillary tube formation (Li et al. 1999; Fansatti et al. 2001; Lebrin et al. 2004; Goumans et al. 2002; Ma et al. 2000; Cheifetz et al. 1992; Li et al. 2000; Bourdeau et al. 1999; McAllister et al. 1994). While endoglin is highly expressed during angiogenesis in multiple cancer types, its expression is typically absent on vessels in normal tissues (Fansatti et al. 2001). Because of its lack of expression in normal vasculature, endoglin has been extensively used as a marker for measuring microvessel density (MVD), which is inversely correlated with prognosis (Fansatti et al. 2001; Brewer et al. 2000; Saad et al. 2004; Wikstrom et al. 2002; Kumar et al. 1999; Shariat et al. 2008; Schimming and Marme 2001; Tanaka et al. 2001). Endoglin has emerged as a powerful marker of tumor-associated neovascularization, with anti-endoglin antibodies being investigated to visualize tumors and their metastases (Fonsatti et al. 2010).

The dependence of tumors on the pro-angiogenic functions of endoglin has also made it an attractive target for anti-tumor therapies (Dallas et al. 2008). Several in vivo studies have revealed endoglin to be an important therapeutic target. First, endoglin haploinsufficient mice were shown to have decreased lung tumor vascularization and growth compared to their endoglin +/+ littermates (Duwel et al. 2007). This may be due to increased endothelial cell apoptosis, as endoglin was also shown to regulate eNOS levels and to prevent apoptosis in hypoxic endothelial cells (Duwel et al. 2007). Additionally, the suppression of tumor growth and metastasis and an increased survival rate have been observed using anti-endoglin antibodies alone or antibodies conjugated to immunotoxins or radiolabels in mice (Seon et al. 1997; Matsuno et al. 1999; Tabata et al. 1999; Tsujie et al. 2008; Takahashi et al. 2001;

Uneda et al. 2009). A phase I clinical trial using an anti-endoglin antibody (TRC105) in patients with advanced refractory cancers was recently reported, with the treatment is well tolerated, and resulting in disease control in nearly half of the patients (Rosen et al. 2008; Rosen et al. 2012) (NCT00582985).

3.2.3.2 TβRIII

Like endoglin, a few studies have implicated TβRIII in tumor-associated angiogenesis. In a xenograft mouse model of breast cancer, decreased tumor-associated angiogenesis was observed in mice injected with TβRIII-expressing cells vs. control cells (Dong et al. 2007). The administration of recombinant soluble TβRIII also decreased tumor vascularization in xenograft models of breast and prostate cancer (Bandyopadhyay et al. 2005; Bandyopadhyay et al. 2002a), and soluble TβRIII has been shown to inhibit the ability of human endothelial cells to form tubes in an in vitro Matrigel assay (Bandyopadhyay et al. 2002b). In contrast to these reports, SERPINE1, which is a known inhibitor of angiogenesis, was found to be downregulated in a gene array performed on prostate cancer cells lacking TβRIII expression (Sharifi et al. 2007). Taken together, these studies suggest an anti-angiogenic function for TβRIII.

3.2.3.3 The Neuropilins

Most of the work regarding neuropilin-1/2 and tumor angiogenesis has focused on their role as VEGF co-receptors, and little attention has been given to their potential role in angiogenesis as TGF-β co-receptors. The neuropilins are, however, clearly involved in tumor-associated angiogenesis. In breast cancer specimens, increased neuropilin-1 expression was observed in both smooth muscle and endothelial cells within the areas of invasion (Stephenson et al. 2002). Additionally, non-small cell lung cancer patients whose tumors expressed both neuropilins had increased vessel counts compared to those patients that lacked co-expression (Kawakami et al. 2002). The neuropilin ligands Sema3A and Sema3F (class 3 semaphorins) may also regulate tumor angiogenesis as they have been shown to inhibit the pro-angiogenic effects of VEGF in endothelial cells (Staton et al. 2007; Wild et al. 2012). Both of these ligands were found to inhibit endothelial cell migration, proliferation, and tube formation (Narazaki and Tosato 2006; Serini et al. 2003). As the interaction between neuropilin-1 and VEGF is important for tumor angiogenesis, several current strategies for anti-tumor therapy revolve around the inhibition of neuropilin-1, VEGF, both, or their interaction (Geretti and Klagsbrun 2007; Pan et al. 2007; Jia et al. 2010; Jia et al. 2006; Soker et al. 1997; von Wronski et al. 2006). The role of the neuropilins in angiogenesis as it relates to their role as TGF-β co-receptors requires additional investigation.

3.2.3.4 Syndecan-2

Very little is known regarding syndecan-2's role in tumor-associated angiogenesis. However, high syndecan-2 expression has been reported in the microvasculature of mouse gliomas (Fears et al. 2006), while downregulation of syndecan-2 resulted in decreased endothelial cell motility and a reduced formation of capillary tube-like structures (Fears et al. 2006). The ability of syndecan-2 to promote angiogenesis was found to be due to increased levels of soluble syndecan-2, which were increased during glioma progression (Fears et al. 2006).

3.2.4 TGF-β Co-receptors and Stromal Components

3.2.4.1 Endoglin

Endoglin is weakly expressed in some stromal cell types (Rokhlin et al. 1995; Gougos et al. 1992). In a mouse model of prostate cancer progression, endoglin (+/−)-derived tumors lacked the typically observed infiltration of cancer-associated fibroblasts (Romero et al. 2011). Therefore, endoglin may act to support the viability of CAFs in the tumor microenvironment by promoting neovascularization and growth. In a co-culture model of the prostate cancer cell line C4-2B and the bone marrow stromal cell line HS-27a, endoglin was significantly downregulated in the stromal cells only upon co-culture (O'Connor et al. 2007). This loss of endoglin resulted in attenuated TGF-β signaling and decreased stromal cell proliferation (O'Connor et al. 2007). Thus the prostate cancer cells, upon interaction with bone marrow stromal cells, may alter stromal cell TGF-β signaling to promote the formation of bone metastases (O'Connor et al. 2007).

3.2.4.2 TβRIII

Similar to cancer cells, the expression of TβRIII mRNA is significantly reduced in CAFs in oral squamous cell carcinoma (Meng et al. 2011). As increased amounts of TGF-β ligand are present within the oral cancer microenvironment, ligand-induced downregulation of TβRIII expression was thought to be a potential mechanism for downregulation (Meng et al. 2011). TβRIII also has a potential role in exosomes, which are secreted vesicles that participate in intercellular communication (Webber et al. 2010). Exosomes can deliver protein, mRNA, or microRNAs to recipient cells. Interestingly, TGF-β was recently shown to be expressed by prostate and breast cancer-derived exosomes (Webber et al. 2010). This exosomal TGF-β was capable of promoting fibroblast–myofibroblast differentiation (Webber et al. 2010). The association of TGF-β with the exosomal membrane was linked with TβRIII expression, suggesting that TβRIII acts as a TGF-β anchor on cancer-associated exosomes (Webber et al. 2010).

3.2.4.3 The Neuropilins

Neuropilin-1 has been shown to promote the activation of fibroblasts to myofibroblasts, which are important regulators of cancer progression (De Wever and Mareel 2003). Decreasing neuropilin-1 expression in fibroblasts enhanced Smad1/5 signaling but reduced Smad2/3 signaling (Cao et al. 2010b). Mechanistically, an interaction between neuropilin-1 and endogenous TβRII was associated with decreased fibroblast proliferation and a reversion to a quiescent state (Cao et al. 2010b). In the immune system, neuropilin-1 is expressed by regulatory T cells and has been shown to activate latent TGF-β in this cell type (Glinka and Prud'homme 2008). Indeed, T cells expressing neuropilin-1 could efficiently bind latent TGF-β1. However, this was not observed in cells lacking neuropilin-1 (Glinka and Prud'homme 2008). Similar results were observed in a breast cancer cell line, suggesting that this role of neuropilin-1 is common and may be important in cancer progression (Glinka and Prud'homme 2008).

3.3 TGF-β Co-receptors in Vascular Disease

As TGF-β plays a key role in physiological angiogenesis, it is not surprising that animal models and human studies have implicated TGF-β superfamily signaling in the initiation and progression of many vascular disorders. Due to the role of the co-receptors in regulating the TGF-β pathway, direct mutations or disruptions in their function have been tied to these disorders as well.

3.3.1 Endoglin

A critical role for endoglin in angiogenesis has come from studies of mice lacking this co-receptor. Endoglin-deficient mice die at midgestation (day 10.5) of angiogenic and cardiovascular defects (Sorensen et al. 2003). During development, endoglin-deficient mice lose structural, molecular, and functional distinctions between arteries and veins (Li et al. 1999). Additionally, these mice fail to form mature blood vessels in the yolk sac (Li et al. 1999). Such studies indicate that altered TGF-β signaling is the cause of the phenotypes observed in endoglin null mice and also establish a functional link between endoglin and the TGF-β pathway. Vasculogenesis in the endoglin null mice is normal, but angiogenesis and remodeling of the primary vascular plexus are impaired. The mice exhibit poor vascular smooth muscle cell (VSMC) development that results in dilation and rupture of the vascular channels. In the heterozygous mice, disease severity increases with age and can include the rupture of major vessels.

Mutations in endoglin can also lead to the vascular disease hereditary hemorrhagic telangiectasia (HHT), or Rendu–Osler–Weber syndrome. HHT is a rare autosomal dominant disorder that is characterized by arteriovenous malformations or localized abnormal arteriovenous connections that affect both the microvasculature and large vessels. HHT patients typically manifest spontaneous epistaxis (nose bleeds), cutaneous telangiectases (small dilated blood vessels), and arteriovenous malformations in internal organs. Additional features include highly variable expression and variable, age-dependent penetrance. More than 150 mutations have been reported in endoglin including deletions, insertions, missense mutations, and splice site changes, all of which result in reduced levels of endoglin on the surface of endothelial cells (McAllister et al. 1994). Patients with HHT also have significantly lower amounts of endoglin in peripheral monocytes compared to normal individuals (Abdalla and Letarte 2006). Interestingly, most of the known mutations in endoglin are within exons 1–12, which encode the extracellular domain, and very few mutations have been observed in exons 13 and 14, which encode the transmembrane and cytoplasmic domains. Many of these alterations result in deficient angiogenesis, i.e. the sprouting of new vessels from preexisting ones. One proposed explanation for the development of HHT is that mutations in endoglin result in misfolded proteins that are either incapable of heretodimerizing or are unable to reach the cell surface, both of which would account for the halpoinsufficiency that is observed in HHT1.

Preeclampsia, a systemic, pregnancy-associated hypertensive disorder, has also been linked with endoglin. Preeclampsia appears to originate in the placenta and is characterized by endothelial cell dysfunction. As such, several authors have reported changes in the expression of placental anti-angiogenic factors in preeclamptic patients [reviewed in (Maynard and Karumanchi 2011)]. Soluble endoglin has been found to be elevated in preeclampsia and has been proposed as a viable marker for this disorder as well. However, the molecular basis for preeclampsia and the exact role of soluble endoglin in this disorder remain unknown.

3.3.2 The Neuropilins

Neuropilin-1 mediates normal developmental angiogenesis, which has been observed in mouse and zebrafish models. Neuropilin-1 has also been shown to mediate pathological angiogenesis in tumors and retinal disease, particularly in the context of VEGF signaling, wherein neuropilin 1, which is highly expressed in the retinal endothelial cells, is upregulated by both VEGF and hypoxia to regulate a positive feedback mechanism in retinal neovascularization. As such, most of neuropilin-1/2 functions in angiogenesis and vascular biology are related to its roles as a receptor for VEGF and as a co-receptor for VEGFR2 (Soker et al. 1997). Currently, much less is known about the ability of neuropilin-1 to regulate TGF-β's function in angiogenesis.

3.3.3 Syndecan-2

Syndecan-2 has been shown to regulate endothelial cell functions in vitro, including migration and cytoskeletal organization (Noguer et al. 2009). These functions may in turn contribute to its roles in capillary tube formation. Studies in zebrafish have demonstrated specific roles for syndecan-2 in regulating sprouting during angiogenesis (Chen et al. 2004a). Notably, the role of syndecan-2 in regulating TGF-β signaling in the context of endothelial biology has not been established and requires further exploration.

3.4 TGF-β Co-receptors and Developmental Defects

3.4.1 Endoglin

Genes that are required for proper vascular development also often affect blood flow. In addition, genes that are expressed in the endocardial lining of the heart can affect cardiac development, as in the case for the TGF-β co-receptors including endoglin, TβRIII, neuropilin-1, and syndecan-2. In addition to endoglin's well-studied role in vascular development, endoglin knockout mice have revealed a role for endoglin in cardiovascular development. In endoglin null mice, the atrioventricular canal endocardium fails to undergo mesenchymal transformation and does not form cushions (Li et al. 1999). These heart valve formation defects may be due to a perturbation in TGF-β signaling. Interestingly, endoglin has also been detected in hematopoietic stem cells in adult bone marrow and in the AGM (aorta–gonal mesonephros) at E11.5 (Chen et al. 2002) as well as in fetal liver cells (Pimanda et al. 2008). In addition to cardiovascular defects, endoglin null mouse embryos also display anemia of the yolk sac, which was, until recently, assumed to be an indirect result of insufficient blood flow. However, recent evidence demonstrates that endoglin plays a direct role in hematopoiesis. Endoglin is expressed in the first hematopoietic progenitor cells during embryonic development where it has been shown to regulate TGF-β/BMP signaling during the initiation of hematopoiesis (Borges et al. 2012).

3.4.2 TβRIII

Similar to endoglin, the deletion of TβRIII in mice results in embryonic lethality due to failed coronary vessel development and palate fusion (Compton et al. 2007). TβRIII null mice exhibit significantly impaired coronary vasculogenesis, defects in the epicardium, and dysmorphic and distended vessels. Collectively, these phenotypes demonstrate a requirement for TβRIII during coronary vessel development,

which is essential for embryonic viability (Compton et al. 2007). More recently, an analysis of E13.5 TβRIII null embryos revealed a lower rate of epicardial cell proliferation and decreased epicardial-derived cell invasion. This effect is mediated by the interaction of TβRIII's cytoplasmic domain with GIPC (Sanchez et al. 2011), with loss of responsiveness to TGF-β and FGF2, two important regulators of epicardial cell behavior (Sanchez et al. 2011). In addition to its role in proper heart development, TβRIII has also been shown to participate in cord formation, fetal Leydig cell development, and the establishment of fetal endocrine testis function. Collectively, the observations implicate TGF-β superfamily members as regulators of early fetal testis structure and function (Sarraj et al. 2010). TβRIII mRNA has a distinct expression pattern during gonadogenesis, where it is expressed at higher levels in developing testes compared to developing ovaries. TβRIII is predominantly expressed by Leydig cells within the fetal testis interstitium; however, at birth, expression is shifted to the seminiferous cords, suggesting possible roles for TβRIII in the gonadogenesis (Sarraj et al. 2007). Interestingly, TβRIII can bind inhibin and can regulate ovarian and granulosa carcinogenesis through this interaction.

3.4.3 Neuropilin-1

Neuropilin-1 plays key roles in vascular biology. Neuropilin-1 mutant mouse embryos have impaired arterial differentiation, which appears to be independent of blood flow patterns (Jones et al. 2008). Neuropilin-1's role in arterial specification during vascular development is primarily due to its ability to regulate VEGF/VEGFR2 function. The function of neuropilin-1 in development can be additionally regulated at the transcriptional level. As such, the Notch signaling pathway, which directs cell fate decisions during embryonic development, has been shown to regulate the neuropilin-1 promoter to alter cell responsiveness to several ligands including VEGF (Sorensen et al. 2009) and, potentially, TGF-β.

In addition to its roles in vascular development (see angiogenesis), neuropilin-1 plays pivotal roles in the development of the neuronal system as a receptor for members of the class-3 semaphorin family of axonal guidance factors [reviewed in (Geretti and Klagsbrun 2007)]. Much less is known about its role in regulating TGF-β's role in developmental processes.

3.4.4 Syndecan-2

The role of syndecan-2 in development has been best studied in Xenopus embryos. Here, syndecan-2 has been shown to be a regulator of left–right development in the embryonic mesoderm (Kramer and Yost 2002). This function of syndecan-2 appears to be mediated via the functional interactions of its heparan sulfate glycosaminoglycan chains with the TGF-β superfamily cell–cell signaling molecule Vg1, which is

known to regulate early left–right development. Syndecan-2 is expressed in the ectoderm and likely presents Vg1 to the migrating mesoderm in a unilateral manner, demonstrating that syndecan-2 can function in cell signaling by directly affecting neighboring cells or in a cell-autonomous manner. Additional mechanistic studies indicate that PKCγ can phosphorylate syndecan-2 and that this phosphorylation event is required in the right-side ectodermal cells (Kramer et al. 2002). While studies in zebrafish have revealed a similar role for syndecan-2 in left–right development, knockdown experiments have also demonstrated a requirement for syndecan-2 in embryonic angiogenesis. During both zebrafish and mouse development, syndecan-2 is expressed in the mesenchymal cell layer surrounding the axial blood vessels, suggesting a potential role for this molecule in coordinating and organizing vascular development (Chen et al. 2004a). Syndecan 2 and VEGF are thought to act synergistically to facilitate angiogenesis.

3.5 TGF-β Co-receptors in Fibrosis

Fibrosis, which is characterized by the fibroblast-mediated deposition of the ECM proteins collagen and fibronectin, can play roles in diverse pathological conditions including the autoimmune disease systemic sclerosis (SSc), wound healing (particularly after myocardial infarction), Crohn's disease, pulmonary hypertension, and diabetic nephropathy. Hepatic fibrosis can also set the stage for the development of cirrhosis and, in some cases, hepatocellular carcinoma (HCC). TGF-β is a key regulator of the fibrotic processes [reviewed in (Hawinkels and Ten Dijke 2011)]. Not all of the TGF-β co-receptors have established roles in each of the pathological conditions associated with fibrosis; however, some common themes exist regarding the ability of the co-receptors to modulate TGF-β signaling during the fibrotic process.

3.5.1 Endoglin

Endoglin has been shown to be a negative regulator of TGF-β1 signaling in the intestinal fibroblast, where it modulates Smad3 phosphorylation, Smad binding element (SBE) promoter activity, connective tissue growth factor (CTGF) production, and collagen contraction (Burke et al. 2009). Endoglin is also upregulated in patients suffering from fibrosis or scleroderma, where increased soluble endoglin levels are present as well (Wipff et al. 2008; Coral-Alvarado et al. 2010; Dharmapatni et al. 2001). Endoglin can both stimulate and inhibit TGF-β-induced fibrosis, depending on the context. For instance, in human and rat cell line models using myoblasts and myofibroblasts, endoglin was shown to reduce cell responsiveness to TGF-β, thereby reducing collagen production via an ERK-dependent mechanism (Rodriguez-Barbero et al. 2006). In addition, fibroblasts derived from patients with fibrosis or SSc have higher basal levels of CTGF and collagen relative to healthy individuals, and the overexpression of endoglin in control fibroblasts (from healthy

donors) was shown to block TGF-β-induced CTGF expression. Collectively, these studies suggest an inhibitory role for endoglin in fibrosis (Holmes et al. 2011). In constrast, endoglin has also been shown to positively regulate fibrosis, especially in the context of cardiac fibroblasts. Here, endoglin expression is upregulated by TGF-β and angiotensin II, and blocking this upregulation resulted in reduced collagen II expression (Shyu et al. 2010), reviewed in (Maring et al. 2012). Fibroblasts from patients suffering from Crohn's disease have also been shown to express high levels of endoglin. Future studies on how endoglin expression is regulated should shed more light on the dichotomous roles of this co-receptor in fibrosis.

3.5.2 TβRIII

Given the structural and functional similarities between endoglin and TβRIII, similar roles for these two co-receptors in fibrosis could be predicted. Consistent with this idea, soluble TβRIII has been shown to inhibit fibrous airway obliteration (Liu et al. 2002) and can prevent myocardial fibrosis in spontaneously hypertensive rats (Hermida et al. 2009) via the sequestration of TGF-β. Like endoglin, TβRIII levels are elevated in patients with SSc, where TGF-β activity is enhanced (Holmes et al. 2011). Some evidence indicates that TβRIII expression is lost during fibroblast differentiation, suggesting that TβRIII may be required for suppressing lung fibrosis; however, the precise mechanism behind TβRIII's effects on fibroblastic differentiation remains to be elucidated (Ahn et al. 2010).

3.5.3 Neuropilin-1/2

Neuropilin-1 has been implicated as a regulator of the fibrotic response, as it has been suggested to amplify TGF-β and PDGF signaling in hepatic stellate cells (HSC) and in HCC. In two rat models of liver fibrosis, neuropilin-1 was found to be upregulated in activated HSCs, which exhibit the highly motile myofibroblast phenotype (Cao et al. 2010a). Neuropilin-1 overexpression has also been shown to increase cell motility and TGF-β-dependent collagen production (Cao et al. 2010a). While these studies reveal a role for neuropilin-1 in liver fibrosis as a modulator of multiple growth factor targets, additional in vivo fibrosis studies must be performed to clarify the exact effects of neuropilin-1 on TGF-β, PDGF, and VEGF signaling during this process.

3.5.4 Syndecan-2

Syndecan-2 levels are elevated in renal interstitial cells under diabetic conditions. In addition, syndecan-2 has been shown to modulate TGF-β's ability to increase matrix deposition in several cell lines, possibly via effecting TβRIII expression levels (Chen et al. 2004b). Whether syndecan-2's role in fibrosis is mediated via TβRIII or via a direct modulation of TGF-β signaling remains to be determined.

3.6 Conclusions and Perspectives

The TGF-β signaling pathway has essential roles in many physiological processes including development, growth, differentiation, cell cycle regulation, cytokine and ECM production. Deregulation of these events results in a broad spectrum of human disease. The TGF-β co-receptors have diverse roles in regulating and mediating the TGF-β response. They may perform their actions through the regulation of signaling either in a cell autonomous or a non-cell autonomous manner through regulated ectodomain shedding, by localizing signaling in a spatio-temporal manner, or by orchestrating signaling with other growth factor receptors. Through a combination of these functions, the TGF-β co-receptors play essential roles in regulating physiological and pathophysiological processes in a tissue- and context-dependent manner. While the current body of literature supports complex roles for the co-receptors in mediating TGF-β's effects, many questions remain in terms of how these receptors function under physiological circumstances and during disease progression. Additional complexity exists due to the ability of the TGF-β co-receptors to bind multiple ligands through their extracellular domains as well as other proteins through their cytoplasmic domains. Defining the precise nature and relationship of these interactions and their functional consequences remains a challenge, particularly in determining which interactions mediate the biological functions of individual co-receptors. Further refining the structural domains mediating these interactions and assessing the role of loss of function mutants in vitro and in vivo should provide further insight into TGF-β co-receptor function. Despite these challenges, additional studies regarding the roles and mechanisms of action of the TGF-β co-receptors in signaling, biology, and human disease should advance our ability to target the TGF-β signaling pathway and these co-receptors in human disease.

References

Abdalla SA, Letarte M (2006) Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease. J Med Genet 43(2):97–110. doi:10.1136/jmg.2005.030833

Ahn JY, Park S, Yun YS, Song JY (2010) Inhibition of type III TGF-β receptor aggravates lung fibrotic process. Biomed Pharmacother 64(7):472–476. doi:10.1016/j.biopha.2010.01.006

Andres JL, Ronnstrand L, Cheifetz S, Massague J (1991) Purification of the transforming growth factor-β (TGF-β) binding proteoglycan betaglycan. J Biol Chem 266(34):23282–23287

Antonescu CR, Zhang L, Nielsen GP, Rosenberg AE, Dal Cin P, Fletcher CD (2011) Consistent t(1;10) with rearrangements of TGFBR3 and MGEA5 in both myxoinflammatory fibroblastic sarcoma and hemosiderotic fibrolipomatous tumor. Genes Chromosomes Cancer 50(10):757–764. doi:10.1002/gcc.20897

Baba T, Kariya M, Higuchi T, Mandai M, Matsumura N, Kondoh E, Miyanishi M, Fukuhara K, Takakura K, Fujii S (2007) Neuropilin-1 promotes unlimited growth of ovarian cancer by evading contact inhibition. Gynecol Oncol 105(3):703–711

Bae HJ, Eun JW, Noh JH, Kim JK, Jung KH, Xie HJ, Park WS, Lee JY, Nam SW (2009) Down-regulation of transforming growth factor β receptor type III in hepatocellular carcinoma is not directly associated with genetic alterations or loss of heterozygosity. Oncol Rep 22(3): 475–480

Bandyopadhyay A, Lopez-Casillas F, Malik SN (2002a) Antitumor activity of a recombinant soluble betaglycan in human breast cancer xenograft. Cancer Res 63:4690–4695

Bandyopadhyay A, Wang L, Lopez-Casillas F, Mendoza V, Yeh IT, Sun L (2005) Systemic administration of a soluble betaglycan suppresses tumor growth, angiogenesis, and matrix metalloproteinase-9 expression in a human xenograft model of prostate cancer. Prostate 63(1):81–90

Bandyopadhyay A, Zhu Y, Cibull LB (1999a) A soluble transforming growth factor β type III receptor suppresses tumorigenicity and metastasis of human breast MDA-MB-231 cells. Cancer Res 59:5041–5046

Bandyopadhyay A, Zhu Y, Cibull LB, Chen C, Sun L-Z (1999b) A soluble transforming growth factor β type III receptor suppresses tumorigenicity and metastasis of human breast cancer. Cancer Res 59:5041–5046

Bandyopadhyay A, Zhu Y, Malik SN, Kreisberg J, Brattain MG, Sprague E, Luo J, Lopez-Casillas F, Sun L-Z (2002b) Extracellular domain of TGFβ type III receptor inhibits angiogenesis and tumor growth in human cancer cells. Oncogene 21:3541–3551

Beck B, Driessens G, Goossens S, Youssef KK, Kuchnio A, Caauwe A, Sotiropoulou PA, Loges S, Lapouge G, Candi A, Mascre G, Drogat B, Dekoninck S, Haigh JJ, Carmeliet P, Blanpain C (2011) A vascular niche and a VEGF-Nrp1 loop regulate the initiation and stemness of skin tumours. Nature 478(7369):399–403. doi:10.1038/nature10525

Benhattar J, Losi L, Chaubert P, Givel JC, Costa J (1993) Prognostic significance of K-ras mutations in colorectal carcinoma. Gastroenterology 104(4):1044–1048

Berge M, Allanic D, Bonnin P, de Montrion C, Richard J, Suc M, Boivin JF, Contreres JO, Lockhart BP, Pocard M, Levy BI, Tucker GC, Tobelem G, Merkulova-Rainon T (2011) Neuropilin-1 is upregulated in hepatocellular carcinoma and contributes to tumour growth and vascular remodeling. J Hepatol 55(4):866–875

Bernabeu C, Lopez-Novoa JM, Quintanilla M (2009) The emerging role of TGF-β superfamily coreceptors in cancer. Biochim Biophys Acta 1792(10):954–973. doi:10.1016/j.bbadis.2009.07.003

Bilandzic M, Chu S, Farnworth PG, Harrison C, Nicholls P, Wang Y, Escalona RM, Fuller PJ, Findlay JK, Stenvers KL (2009) Loss of betaglycan contributes to the malignant properties of human granulosa tumor cells. Mol Endocrinol 23(4):539–548. doi:me.2008-0300 [pii] 10.1210/me.2008-0300

Blobe GC, Liu X, Fang SJ, How T, Lodish HF (2001) A novel mechanism for regulating transforming growth factor β (TGF-β) signaling. Functional modulation of type III TGF-β receptor expression through interaction with the PDZ domain protein, GIPC. J Biol Chem 276(43):39608–39617

Bock AJ, Tuft Stavnes H, Kaern J, Berner A, Staff AC, Davidson B (2011) Endoglin (CD105) expression in ovarian serous carcinoma effusions is related to chemotherapy status. Tumour Biol 32(3):589–596

Borges L, Iacovino M, Mayerhofer T, Koyano-Nakagawa N, Baik J, Garry D, Kyba M, Letarte M, Perlingeiro RCR (2012) A critical role for endoglin in the emergence of blood during embryonic development. Blood 119:5417–5428

Bourdeau A, Dumont DJ, Letarte M (1999) A murine model of hereditary hemorrhagic telangiectasia. J Clin Invest 104:1343–1351

Brewer CA, Setterdahl JJ, Li MJ, Johnston JM, Mann JL, McAsey ME (2000) Endoglin expression as a measure of microvessel density in cervical cancer. Obstet Gynecol 96(2):224–228

Burke JP, Watson RW, Murphy M, Docherty NG, Coffey JC, O'Connell PR (2009) Simvastatin impairs smad-3 phosphorylation and modulates transforming growth factor β1-mediated activation of intestinal fibroblasts. Br J Surg 96(5):541–551. doi:10.1002/bjs.6577

Cabello-Verrugio C, Brandan E (2007) A novel modulatory mechanism of transforming growth factor-β signaling through decorin and LRP-1. J Biol Chem 282(26):18842–18850. doi:10.1074/jbc.M700243200

Cai Y, Wang R, Zhao YF, Jia J, Sun ZJ, Chen XM (2010) Expression of Neuropilin-2 in salivary adenoid cystic carcinoma: its implication in tumor progression and angiogenesis. Pathol Res Pract 206(12):793–799

Cai H, Reed RR (1999) Cloning and characterization of neuropilin-1-interacting protein: a PSD-95/Dlg/ZO-1 domain-containing protein that interacts with the cytoplasmic domain of neuropilin-1. J Neurosci 19(15):6519–6527

Calabro L, Fonsatti E, Bellomo G, Alonci A, Colizzi F, Sigalotti L, Altomonte M, Musolino C, Maio M (2003) Differential levels of soluble endoglin (CD105) in myeloid malignancies. J Cell Physiol 194(2):171–175

Cao S, Yaqoob U, Das A, Shergill U, Jagavelu K, Huebert RC, Routray C, Abdelmoneim S, Vasdev M, Leof E, Charlton M, Watts RJ, Mukhopadhyay D, Shah VH (2010a) Neuropilin-1 promotes cirrhosis of the rodent and human liver by enhancing PDGF/TGF-β signaling in hepatic stellate cells. J Clin Invest 120(7):2379–2394. doi:10.1172/JCI41203

Cao Y, Szabolcs A, Dutta SK, Yaqoob U, Jagavelu K, Wang L, Leof EB, Urrutia RA, Shah VH, Mukhopadhyay D (2010b) Neuropilin-1 mediates divergent R-Smad signaling and the myofibroblast phenotype. J Biol Chem 285(41):31840–31848. doi:10.1074/jbc.M110.151696

Castonguay R, Werner ED, Matthews RG, Presman E, Mulivor AW, Solban N, Sako D, Pearsall RS, Underwood KW, Seehra J, Kumar R, Grinberg AV (2011) Soluble endoglin specifically binds bone morphogenetic proteins 9 and 10 via its orphan domain, inhibits blood vessel formation, and suppresses tumor growth. J Biol Chem 286(34):30034–30046. doi:10.1074/jbc.M111.260133

Cheifetz S, Bellon T, Cales C, Vera S, Bernabeu C, Massague J, Letarte M (1992) Endoglin is a component of the transforming growth factor-β receptor system in human endothelial cells. J Biol Chem 267(27):19027–19030

Chen CZ, Li M, de Graaf D, Monti S, Gottgens B, Sanchez MJ, Lander ES, Golub TR, Green AR, Lodish HF (2002) Identification of endoglin as a functional marker that defines long-term repopulating hematopoietic stem cells. Proc Natl Acad Sci USA 99(24):15468–15473. doi:10.1073/pnas.202614899

Chen E, Hermanson S, Ekker SC (2004a) Syndecan-2 is essential for angiogenic sprouting during zebrafish development. Blood 103(5):1710–1719. doi:10.1182/blood-2003-06-1783

Chen L, Klass C, Woods A (2004b) Syndecan-2 regulates transforming growth factor-β signaling. J Biol Chem 279(16):15715–15718. doi:10.1074/jbc.C300430200 C300430200 [pii]

Chen W, Kirkbride KC, How T, Nelson CD, Mo J, Frederick JP, Wang XF, Lefkowitz RJ, Blobe GC (2003) Beta-arrestin 2 mediates endocytosis of type III TGF-β receptor and down-regulation of its signaling. Science 301(5638):1394–1397

Chittenden TW, Claes F, Lanahan AA, Autiero M, Palac RT, Tkachenko EV, Elfenbein A, Ruiz de Almodovar C, Dedkov E, Tomanek R, Li W, Westmore M, Singh JP, Horowitz A, Mulligan-Kehoe MJ, Moodie KL, Zhuang ZW, Carmeliet P, Simons M (2006) Selective regulation of arterial branching morphogenesis by synectin. Dev Cell 10(6):783–795

Choi Y, Kim H, Chung H, Hwang JS, Shin JA, Han IO, Oh ES (2010) Syndecan-2 regulates cell migration in colon cancer cells through Tiam1-mediated Rac activation. Biochem Biophys Res Commun 391(1):921–925. doi:10.1016/j.bbrc.2009.11.165

Cohen T, Gluzman-Poltorak Z, Brodzky A, Meytal V, Sabo E, Misselevich I, Hassoun M, Boss JH, Resnick M, Shneyvas D, Eldar S, Neufeld G (2001) Neuroendocrine cells along the digestive tract express neuropilin-2. Biochem Biophys Res Commun 284(2):395–403

Cohen T, Herzog Y, Brodzky A, Greenson JK, Eldar S, Gluzman-Poltorak Z, Neufeld G, Resnick MB (2002) Neuropilin-2 is a novel marker expressed in pancreatic islet cells and endocrine pancreatic tumours. J Pathol 198(1):77–82

Compton LA, Potash DA, Brown CB, Barnett JV (2007) Coronary vessel development is dependent on the type III transforming growth factor β receptor. Circ Res 101(8):784–791. doi:CIRCRESAHA.107.152082 [pii] 10.1161/CIRCRESAHA.107.152082

Conley BA, Koleva R, Smith JD, Kacer D, Zhang D, Bernabeu C, Vary CP (2004) Endoglin controls cell migration and composition of focal adhesions: function of the cytosolic domain. J Biol Chem 279(26):27440–27449. doi:10.1074/jbc.M312561200

Cooper SJ, Zou H, Legrand SN, Marlow LA, von Roemeling CA, Radisky DC, Wu KJ, Hempel N, Margulis V, Tun HW, Blobe GC, Wood CG, Copland JA (2010) Loss of type III transforming growth factor-β receptor expression is due to methylation silencing of the transcription factor

GATA3 in renal cell carcinoma. Oncogene 29(20):2905–2915. doi:onc201064 [pii] 10.1038/onc.2010.64

Copland JA, Luxon BA, Ajani L, Maity T, Campagnaro E, Guo H, LeGrand SN, Tamboli P, Wood CG (2003) Genomic profiling identifies alterations in TGFβ signaling through loss of TGFβ receptor expression in human renal cell carcinogenesis and progression. Oncogene 22(39): 8053–8062. doi:10.1038/sj.onc.1206835 1206835 [pii]

Coral-Alvarado PX, Garces MF, Caminos JE, Iglesias-Gamarra A, Restrepo JF, Quintana G (2010) Serum endoglin levels in patients suffering from systemic sclerosis and elevated systolic pulmonary arterial pressure. Int J Rheumatol. doi:10.1155/2010/969383

Criswell TL, Arteaga CL (2007) Modulation of NFκB activity and E-cadherin by the type III transforming growth factor β receptor regulates cell growth and motility. J Biol Chem 282(44): 32491–32500. doi:10.1074/jbc.M704434200

Dallas NA, Samuel S, Xia L, Fan F, Gray MJ, Lim SJ, Ellis LM (2008) Endoglin (CD105): a marker of tumor vasculature and potential target for therapy. Clin Cancer Res 14(7):1931–1937. doi:10.1158/1078-0432.CCR-07-4478

Davidson B, Stavnes HT, Forsund M, Berner A, Staff AC (2010) CD105 (endoglin) expression in breast carcinoma effusions is a marker of poor survival. Breast 19(6):493–498

De Wever O, Mareel M (2003) Role of tissue stroma in cancer cell invasion. J Pathol 200(4): 429–447

Dharmapatni AA, Smith MD, Ahern MJ, Simpson A, Li C, Kumar S, Roberts-Thomson PJ (2001) The TGF β receptor endoglin in systemic sclerosis. Asian Pac J Allergy Immunol 19(4):275–282

Dong M, How T, Kirkbride KC, Gordon KJ, Lee JD, Hempel N, Kelly P, Moeller BJ, Marks JR, Blobe GC (2007) The type III TGF-β receptor suppresses breast cancer progression. J Clin Invest 117(1):206–217

Drenberg CD, Livingston S, Chen R, Kruk PA, Nicosia SV (2009) Expression of Semaphorin 3F and its receptors in epithelial ovarian cancer, fallopian tubes, and secondary mullerian tissues. Obstet Gynecol Int (epub). doi:10.1155/2009/730739

Duwel A, Eleno N, Jerkick M, Arevalo M, Blolanos JP, Bernabeu C, Lopez-Novoa JM (2007) Reduced tumor growth and angiogenesis in endoglin-haploinsufficient mice. Tumour Biol 28(1):1–8

Elliott RL, Blobe GC (2005) Role of transforming growth factor β in human cancer. J Clin Oncol 23(9):2078–2093

Essner JJ, Chen E, Ekker SC (2006) Syndecan-2. Int J Biochem Cell Biol 38(2):152–156. doi:10.1016/j.biocel.2005.08.012

Fansatti E, Vecchio LD, Altomonte M, Sigalotti L, Nicotra MR, Coral S, Natali PG, Maio M (2001) Endoglin: an accessory component of the TGF-β-binding receptor-complex with diagnostic, prognostic, and bioimmunotherapeutic potential in human malignancies. J Cell Physiol 188:1–7

Fears CY, Gladson CL, Woods A (2006) Syndecan-2 is expressed in the microvasculature of gliomas and regulates angiogenic processes in microvascular endothelial cells. J Biol Chem 281(21):14533–14536. doi:C600075200 [pii] 10.1074/jbc.C600075200

Finley DJ, Arora N, Zhu B, Gallagher L, Fahey TJ 3rd (2004) Molecular profiling distinguishes papillary carcinoma from benign thyroid nodules. J Clin Endcrinol Metab 89(7):3214–3223

Finger EC, Turley RS, Dong M, How T, Fields TA, Blobe GC (2008) TβRIII suppresses non-small cell lung cancer invasiveness and tumorigenicity. Carcinogenesis 29(3):528–535. doi:bgm289 [pii] 10.1093/carcin/bgm289

Finnson KW, Tam BY, Liu K, Marcoux A, Lepage P, Roy S, Bizet AA, Philip A (2006) Identification of CD109 as part of the TGF-β receptor system in human keratinocytes. FASEB J 20(9):1525–1527. doi:10.1096/fj.05-5229fje

Florio P, Ciarmela P, Reis FM, Toti P, Galleri L, Santopietro R, Tiso E, Tosi P, Petraglia F (2005) Inhibin alpha-subunit and the inhibin coreceptor betaglycan are downregulated in endometrial carcinoma. Eur J Endocrinol 152(2):277–284

Folkman J, Watson K, Ingber D, Hanahan D (1989) Induction of angiogenesis during the transition from hyperplasia to neoplasia. Nature 339(6219):58–61

Fonsatti E, Altomonte M, Nicotra MR, Natali PG, Maio M (2003) Endoglin (CD105): a powerful therapeutic target on tumor-associated angiogenetic blood vessels. Oncogene 22(42):6557–6563. doi:10.1038/sj.onc.1206813

Fonsatti E, Nicolay HJ, Altomonte M, Covre A, Maio M (2010) Targeting cancer vasculature via endoglin/CD105: a novel antibody-based diagnostic and therapeutic strategy in solid tumours. Cardiovasc Res 86(1):12–19. doi:10.1093/cvr/cvp332

Gatza CE, Holtzhausen A, Kirkbride KC, Morton A, Gatza ML, Datto MB, Blobe GC (2012) Type III TGF-β receptor enhances colon cancer cell migration and anchorage-independent growth. Neoplasia 13(8):758–770

Gatza CE, Oh SY, Blobe GC (2010) Roles for the type III TGF-β receptor in human cancer. Cell Signal 22(8):1163–1174. doi:S0898-6568(10)00033-1 [pii] 10.1016/j.cellsig.2010.01.016

Geretti E, Klagsbrun M (2007) Neuropilins: novel targets for anti-angiogenesis therapies. Cell Adh Migr 1(2):56–61

Glinka Y, Prud'homme GJ (2008) Neuropilin-1 is a receptor for transforming growth factor β-1, activates its latent form, and promotes regulatory T cell activity. J Leukoc Biol 84(1):302–310. doi:10.1189/jlb.0208090

Gordon KJ, Dong M, Chislock EM, Fields TA, Blobe GC (2008) Loss of type III transforming growth factor β receptor expression increases motility and invasiveness associated with epithelial to mesenchymal transition during pancreatic cancer progression. Carcinogenesis 29(2):252–262. doi:bgm249 [pii] 10.1093/carcin/bgm249

Gordon KJ, Kirkbride KC, How T, Blobe GC (2009) Bone morphogenetic proteins induce pancreatic cancer cell invasiveness through a Smad1-dependent mechanism that involves matrix metalloproteinase-2. Carcinogenesis 30(2):238–248. doi:10.1093/carcin/bgn274

Ghosh S, Sullivan CA, Zerkowski MP, Molinaro AM, Rimm DL, Camp RL, Chung GG (2008) High levels of vascular endothelial growth factor and its receptors (VEGFR-1, VEGFR-2, neuropilin-1) are associated with worse outcome in breast cancer. Hum Pathol 39(12): 1835–1843

Gougos A, St Jacques S, Greaves A, O'Connell PJ, d'Apice AJ, Burhring HJ, Bernabeu C, van Mourik JA, Letarte M (1992) Identification of distinct epitopes of endoglin, an RGD-containing glycoprotein of endothelial cells, leukemic cells, and syncytiotrophoblasts. Int Immunol 4(1):83–92

Goumans M-J, Valdimarsdottir G, Itoh S, Rosendahl A, Sideras P, ten Dijke P (2002) Balancing the activation state of the endothelium via two distinct TGF-β type I receptors. EMBO J 21(7):1743–1752

Grandclement C, Pallandre JR, Degano SV, Viel E, Bouard A, Balland J, Remy-Martin J-P, Simon B, Rouleau A, Boireau W, Klagsbrun M, Ferrand C, Borg C (2011) Neuropilin-2 expression promotes TGF-β1-mediated epithelial to mesenchymal transition in colorectal cancer cells. PLoS One 6(7):e20444. doi:10.1371/journal.pone.0020444.t001

Gray MJ, Van Buren G, Dallas NA, Xia L, Wang X, Yang AD, Somcio RJ, Lin YG, Lim S, Fan F, Mangala LS, Arumugam T, Logsdon CD, Lopez-Berestein G, Sood AK, Ellis LM (2008) Therapeutic targeting of neuropilin-2 on colorectal carcinoma cells implanted in the murine liver. J Natl Cancer Inst 100(2):109–120

Grotenhuis BA, Wijnhoven BP, van Lanschot JJ (2012) Cancer stem cells and their potential implications for the treatment of solid tumors. J Surg Oncol. doi:10.1002/jso.23069

Guerrero-Esteo M, Lastres P, Letamendía A, Pérez-Alvarez MJ, Langa C, López LA, Fabra A, García-Pardo A, Vera S, Letarte M, Bernabéu C (1999) Endoglin overexpression modulates cellular morphology, migration, and adhesion of mouse fibroblasts. Eur J Cell Biol 78(9):614–623. doi:10.1016/s0171-9335(99)80046-6

Gulyas M, Hjerpe A (2003) Proteoglycans and WT1 as markers for distinguishing adenocarcinoma, epithelioid mesothelioma, and benign mesothelium. J Pathol 199(4):179–187

Hamerlik P, Lathia JD, Rasmussen R, Wu Q, Bartkova J, Lee M, Moudry P, Bartek J Jr, Fischer W, Lukas J, Rich JN, Bartek J (2012) Autocrine VEGF-VEGFR2-Neuropilin-1 signaling promotes glioma stem-like cell viability and tumor growth. J Exp Med 209(3):507–520. doi:10.1084/jem.20111424

Handa A, Tokunaga T, Tsuchida T, Lee YH, Kijima H, Yamazaki H, Ueyama Y, Fukuda H, Nakamura M (2000) Neuropilin-2 expression affects the increased vascularization and is a prognostic factor in osteosarcoma. Int J Oncol 17(2):291–296

Hansel DE, Wilentz RE, Yeo CJ, Schulick RD, Montgomery E, Maitra A (2004) Expression of neuropilin-1 in high-grade dysplasia, invasive cancer, and metastases of the human gastrointestinal tract. Am J Surg Pathol 28:347–356

Hawinkels LJ, Ten Dijke P (2011) Exploring anti-TGF-β therapies in cancer and fibrosis. Growth Factors 29(4):140–152. doi:10.3109/08977194.2011.595411

Hempel N, How T, Cooper SJ, Green TR, Dong M, Copland JA, Wood CG, Blobe GC (2008) Expression of the type III TGF-β receptor is negatively regulated by TGF-β. Carcinogenesis 29(5):905–912. doi:10.1093/carcin/bgn049

Hempel N, How T, Dong M, Murphy SK, Fields TA, Blobe GC (2007) Loss of betaglycan expression in ovarian cancer: role in motility and invasion. Cancer Res 67(11):5231–5238

Henry LA, Johnson DA, Sarrio D, Lee S, Quinlan PR, Crook T, Thompson AM, Reis-Filho JS, Isacke CM (2011) Endoglin expression in breast tumor cells suppresses invasion and metastasis and correlates with improved clinical outcome. Oncogene 30(9):1046–1058. doi:10.1038/onc.2010.488

Hermida N, Lopez B, Gonzalez A, Dotor J, Lasarte JJ, Sarobe P, Borras-Cuesta F, Diez J (2009) A synthetic peptide from transforming growth factor-β1 type III receptor prevents myocardial fibrosis in spontaneously hypertensive rats. Cardiovasc Res 81(3):601–609. doi:10.1093/cvr/cvn315

Holmes AM, Ponticos M, Shi-Wen X, Denton CP, Abraham DJ (2011) Elevated CCN2 expression in scleroderma: a putative role for the TGFβ accessory receptors TGFβRIII and endoglin. J Cell Commun Signal 5(3):173–177. doi:10.1007/s12079-011-0140-4

Houthuijzen JM, Daenen LG, Roodhart JM, Voest EE (2012) The role of mesenchymal stem cells in anti-cancer drug resistance and tumour progression. Br J Cancer 106(12):1901–1906. doi:10.1038/bjc.2012.201

Howe JR, Haidle JL, Lal G, Bair J, Song C, Pechman B, Chinnathambi S, Lynch HT (2007) ENG mutations in MADH4/BMPR1A mutation negative patients with juvenile polyposis. Clin Genet 71(1):91–92. doi:10.1111/j.1399-0004.2007.00734.x

Hu D, Wang X, Mao Y, Zhou L (2012) Identification of CD105 (endoglin)-positive stem-like cells in rhabdoid meningioma. J Neurooncol 106(3):505–517. doi:10.1007/s11060-011-0705-3

Huang X, Xiao D-W, Xu L-Y, Zhong H-J, Liao L-D, Xie Z-F, Li E-M (2009) Prognostic significance of altered expression of SDC2 and CYR61 in esophageal squamous cell carcinoma. Oncol Rep 21(4):1123–1129

Iolascon A, Giordani L, Borriello A, Carbone R, Izzo A, Tonini GP, Gambini C, Della Ragione F (2000) Reduced expression of transforming growth factor-β receptor type III in high stage neuroblastomas. Br J Cancer 82(6):1171–1176

Jelinek DF, R.C. T, Stolovitzky GA (2003) Identification of a global gene expression signature of B-chronic lymphocytic leukemia. Mol Cancer Res 1:346–361

Jia H, Bagherzadeh A, Hartzoulakis B, Jarvis A, Lohr M, Shaikh S, Aqil R, Cheng L, Tickner M, Esposito D, Harris R, Driscoll PC, Selwood DL, Zachary IC (2006) Characterization of a bicyclic peptide neuropilin-1 (NP-1) antagonist (EG3287) reveals importance of vascular endothelial growth factor exon 8 for NP-1 binding and role of NP-1 in KDR signaling. J Biol Chem 281(19):13493–13502. doi:10.1074/jbc.M512121200

Jia H, Cheng L, Tickner M, Bagherzadeh A, Selwood D, Zachary I (2010) Neuropilin-1 antagonism in human carcinoma cells inhibits migration and enhances chemosensitivity. Br J Cancer 102(3):541–552. doi:10.1038/sj.bjc.6605539

Jones EA, Yuan L, Breant C, Watts RJ, Eichmann A (2008) Separating genetic and hemodynamic defects in neuropilin 1 knockout embryos. Development 135(14):2479–2488. doi:10.1242/dev.014902

Kassouf W, Ismail HR, Aprikian AG, Chevalier S (2004) Whole-mount prostate sections reveal differential endoglin expression in stromal, epithelial, and endothelial cells with the development of prostate cancer. Prostate Cancer Prostatic Dis 7(2):105–110

Kawakami T, Tokunaga T, Hatanaka H, Kijima H, Yamazaki H, Abe Y, Osamura Y, Inoue H, Ueyama Y, Nakamura M (2002) Neuropilin 1 and neuropilin 2 co-expression is significantly correlated with increased vascularity and poor prognosis in nonsmall cell lung carcinoma. Cancer 95(10):2196–2201. doi:10.1002/cncr.10936

Klein U, Tu Y, Stolovitzky GA, Mattioli M, Cattoretti G, Husson H, Freedman A, Inghirami G, Cro L, Baldini L, Neri A, Califano A, Dalla-Favera R (2001) Gene expression profiling of B cell chronic lymphocytic leukemia reveals a homogeneous phenotype related to memory B cells. J Exp Med 194(11):1625–1638

Kopczynska E, Dancewicz M, Kowalewski J, Makarewicz R, Kardymowicz H, Kaczmarczyk A, Tyrakowski T (2012) Influence of surgical resection on plasma endoglin (CD105) level in non-small cell lung cancer patients. Exp Oncol 34(1):53–56

Kramer KL, Barnette JE, Yost HJ (2002) PKCγ regulates syndecan-2 inside-out signaling during xenopus left-right development. Cell 111(7):981–990

Kramer KL, Yost HJ (2002) Ectodermal syndecan-2 mediates left-right axis formation in migrating mesoderm as a cell-nonautonomous Vg1 cofactor. Dev Cell 2(1):115–124

Kumar S, Ghellal A, Li C, Byrne G, Haboubi N, Wang JM, Bundred N (1999) Breast carcinoma: vascular density determined using CD105 antibody correlates with tumor prognosis. Cancer Res 59:856–861

Lacal PM, Failla CM, Pagani E, Odorisio T, Schietroma C, Falcinelli S, Zambruno G, D'Atri S (2000) Human melanoma cells secrete and respond to placenta growth factor and vascular endothelial growth factor. J Invest Dermatol 115:1000–1007

Lakshman M, Huang X, Ananthanarayanan V, Jovanovic B, Liu Y, Craft CS, Romero D, Vary CP, Bergan RC (2011) Endoglin suppresses human prostate cancer metastasis. Clin Exp Metastasis 28(1):39–53. doi:10.1007/s10585-010-9356-6

Lambert KE, Huang H, Mythreye K, Blobe GC (2011) The type III transforming growth factor-β receptor inhibits proliferation, migration, and adhesion in human myeloma cells. Mol Biol Cell 22(9):1463–1472. doi:10.1091/mbc.E10-11-0877

Latil A, Bieche I, Pesche S, Valeri A, Fournier G, Cussenot O, Lidereau R (2000) VEGF overexpression in clinically localized prostate tumors and neuropilin-1 overexpression in metastatic forms. Int J Cancer 89:167–171

Lebrin F, Goumans M-J, Jonker L, Carvalho RLC, Valdimarsdottir G, Thorikay M, Mummery C, Arthur HM, ten Dijke P (2004) Endoglin promotes endothelial cell proliferation and TGF-β/ALK1 signal transduction. EMBO J 23:4018–4028. doi:10.1038/

Lee JD, Hempel N, Lee NY, Blobe GC (2010) The type III TGF-β receptor suppresses breast cancer progression through GIPC-mediated inhibition of TGF-β signaling. Carcinogenesis 31(2):175–183. doi:bgp271 [pii] 10.1093/carcin/bgp271

Lee JH, Park H, Chung H, Choi S, Kim Y, Yoo H, Kim TY, Hann HJ, Seong I, Kim J, Kang KG, Han IO, Oh ES (2009) Syndecan-2 regulates the migratory potential of melanoma cells. J Biol Chem 284(40):27167–27175. doi:10.1074/jbc.M109.034678

Lee NY, Blobe GC (2007) The interaction of endoglin with β-arrestin2 regulates transforming growth factor-β-mediated ERK activation and migration in endothelial cells. J Biol Chem 282(29):21507–21517. doi:M700176200 [pii] 10.1074/jbc.M700176200

Lee NY, Golzio C, Gatza CE, Sharma A, Katsanis N, Blobe GC (2012) Endoglin regulates PI3-kinase/Akt trafficking and signaling to alter endothelial capillary stability during angiogenesis. Mol Biol Cell 23(13):2412–2423

Lee NY, Ray B, How T, Blobe GC (2008) Endoglin promotes transforming growth factor β-mediated Smad 1/5/8 signaling and inhibits endothelial cell migration through its association with GIPC. J Biol Chem 283(47):32527–32533. doi:M803059200 [pii] 10.1074/jbc.M803059200

Li C, Hampson IN, Hampson L, Kumar P, Bernabeu C, Kumar S (2000) CD105 antagonizes the inhibitory signaling of transforming growth factor β1 on human vascular endothelial cells. FASEB J 14:55–64

Li DY, Sorensen LK, Brooke BS, Urness LD, Davis EC, Taylor DG, Boak BB, Wendel DP (1999) Defective angiogenesis in mice lacking endoglin. Science 284(5419):1534–1537

Li Q, Shirabe K, Kuwada JY (2004) Chemokine signaling regulates sensory cell migration in zebrafish. Dev Biol 269(1):123–136

Liu M, Suga M, Maclean AA, St George JA, Souza DW, Keshavjee S (2002) Soluble transforming growth factor-β type III receptor gene transfection inhibits fibrous airway obliteration in a rat model of Bronchiolitis obliterans. Am J Respir Crit Care Med 165(3):419–423

Lopez-Casillas F, Cheifetz S, Doody J, Andres JL, Lane WS, Massague J (1991) Structure and expression of the membrane proteoglycan betaglycan, a component of the TGF-β receptor system. Cell 67(4):785–795

Lopez-Casillas F, Wrana JL, Massague J (1993) Betaglycan presents ligand to the TGF β signaling receptor. Cell 73(7):1435–1444. doi:0092-8674(93)90368-Z [pii]

Ma X, Labinaz M, Goldstein J, Miller H, Keon WJ, Letarte M, O'Brien E (2000) Endoglin is overexpressed after arterial injury and is required for transforming growth factor-β-induced inhibition of smooth muscle cell migration. Arterioscler Thromb Vasc Biol 20(12):2546–2552. doi:10.1161/01.atv.20.12.2546

Mak P, Leav I, Pursell B, Bae D, Yang X, Taglienti CA, Gouvin LM, Sharma VM, Mercurio AM (2010) ERβ impedes prostate cancer EMT by destabilizing HIF-1α and inhibiting VEGF-mediated snail nuclear localization: implications for Gleason grading. Cancer Cell 17(4): 319–332. doi:10.1016/j.ccr.2010.02.030

Margulis V, Maity T, Zhang XY, Cooper SJ, Copland JA, Wood CG (2008) Type III transforming growth factor-β (TGF-β) receptor mediates apoptosis in renal cell carcinoma independent of the canonical TGF-β signaling pathway. Clin Cancer Res 14(18):5722–5730. doi:14/18/5722 [pii] 10.1158/1078-0432.CCR-08-0546

Marzioni D, Lorenzi T, Mazzucchelli R, Capparuccia L, Morroni M, Fiorini R, Bracalenti C, Catalano A, David G, Castellucci M, Muzzonigro G, Montironi R (2009) Expression of basic fibroblast growth factor, its receptors and syndecans in bladder cancer. Int J Immunopathol Pharmacol 22(3):627–638

Maring JA, Trojanowska M, ten Dijke P (2012) Role of endoglin in fibrosis and scleroderma. Int Rev Cell Mol Biol 297:295–308

Massague J (1998) TGF-β signal transduction. Annu Rev Biochem 67:753–791

Massague J (2008) TGFβ in cancer. Cell 134:215–230. doi:10.1016/j.cell.2008.07.001

Matsuno F, Haruta Y, Kondo M, Tsai IY, Barcos M, Seon BK (1999) Induction of lasting complete regression of preformed distinct solid tumors by targeting the tumor vasculature using two new anti-endoglin monoclonal antibodies. Clin Cancer Res 5:371–382

Maynard SE, Karumanchi SA (2011) Angiogenic factors and preeclampsia. Semin Nephrol 31(1):33–46. doi:10.1016/j.semnephrol.2010.10.004

McAllister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbodl EA, Markel DS, McKinnon WC, Murrell J, McCormick MK, Pericak-Vance MA, Heutink P, Oostra BA, Haitjema T, Westerman CJJ, Porteous ME, Guttmacher AE, Letarte M, Marchuk DA (1994) Endoglin, a TGF-β binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat Genet 8:345–351

Meng Q, Lux A, Holloschi A, Li J, Hughes JM, Foerg T, McCarthy JE, Heagerty AM, Kioschis P, Hafner M, Garland JM (2006) Identification of Tctex2β, a novel dynein light chain family member that interacts with different transforming growth factor-β receptors. J Biol Chem 281(48):37069–37080. doi:10.1074/jbc.M608614200

Meng W, Xia Q, Wu L, Chen S, He X, Zhang L, Gao Q, Zhou H (2011) Downregulation of TGF-β receptor types II and III in oral squamous cell carcinoma and oral carcinoma-associated fibroblasts. BMC Cancer 11:88. doi:10.1186/1471-2407-11-88

Molema G, Griffioen AW (1998) Rocking the foundations of solid tumor growth by attacking the tumor's blood supply. Immunol Today 19(9):392–394

Mythreye K, Blobe GC (2009a) Proteoglycan signaling co-receptors: roles in cell adhesion, migration and invasion. Cell Signal 21:1548–1558. doi:S0898-6568(09)00154-5 [pii] 10.1016/j.cellsig.2009.05.001

Mythreye K, Blobe GC (2009b) The type III TGF-β receptor regulates epithelial and cancer cell migration through β-arrestin2-mediated activation of Cdc42. Proc Natl Acad Sci USA 106(20):8221–8226. doi:10.1073/pnas.0812879106

Mythreye K, Knelson EH, Gatza CE, Gatza ML, Blobe GC (2012) TβRIII/β-arrestin2 regulates integrin α5β1 trafficking, function, and localization in epithelial cells. Oncogene. doi:10.1038/onc.2012.157

Narazaki M, Tosato G (2006) Ligand-induced internalization selects use of common receptor neuropilin-1 by VEGF165 and semaphorin3A. Blood 107:3892–3901. doi:10.1182/blood-2005-10-4113 10.1182/blood-2005-104113

Neri D, Bicknell R (2005) Tumour vascular targeting. Nat Rev Cancer 5(6):436–446. doi:10.1038/nrc1627

Noguer O, Villena J, Lorita J, Vilaro S, Reina M (2009) Syndecan-2 downregulation impairs angiogenesis in human microvascular endothelial cells. Exp Cell Res 315(5):795–808. doi:10.1016/j.yexcr.2008.11.016

O'Connor JC, Farach-Carson MC, Schneider CJ, Carson DD (2007) Coculture with prostate cancer cells alters endoglin expression and attenuates transforming growth factor-β signaling in reactive bone marrow stromal cells. Mol Cancer Res 5(6):585–603. doi:10.1158/1541-7786.MCR-06-0408

Orosco A, Fromigue O, Bazille C, Entz-Werle N, Levillain P, Marie PJ, Modrowski D (2007) Syndecan-2 affects the basal and chemotherapy-induced apoptosis in osteosarcoma. Cancer Res 67(8):3708–3715. doi:10.1158/0008-5472.CAN-06-4164

Pan Q, Chanthery Y, Liang WC, Stawicki S, Mak J, Rathore N, Tong RK, Kowalski J, Yee SF, Pacheco G, Ross S, Cheng Z, Le Couter J, Plowman G, Peale F, Koch AW, Wu Y, Bagri A, Tessier-Lavigne M, Watts RJ (2007) Blocking neuropilin-1 function has an additive effect with anti-VEGF to inhibit tumor growth. Cancer Cell 11(1):53–67. doi:S1535-6108(06)00367-9 [pii] 10.1016/j.ccr.2006.10.018

Pardali E, van der Schaft DW, Wiercinska E, Gorter A, Hogendoorn PC, Griffioen AW, ten Dijke P (2011) Critical role of endoglin in tumor cell plasticity of Ewing sarcoma and melanoma. Oncogene 30(3):334–345. doi:10.1038/onc.2010.418

Parikh AA, Fan F, Liu WB, Ahmad SA, Stoeltzing O, Reinmuth N, Bielenberg D, Bucana CD, Klagsbrun M, Ellis LM (2004) Neuropilin-1 in human colon cancer: expression, regulation, and role in induction of angiogenesis. Am J Pathol 164(6):2139–2151

Park H, Han I, Kwon HJ, Oh ES (2005) Focal adhesion kinase regulates syndecan-2-mediated tumorigenic activity of HT1080 fibrosarcoma cells. Cancer Res 65(21):9899–9905. doi:10.1158/0008-5472.CAN-05-1386

Park H, Kim Y, Lim Y, Han I, Oh ES (2002) Syndecan-2 mediates adhesion and proliferation of colon carcinoma cells. J Biol Chem 277(33):29730–29736. doi:10.1074/jbc.M202435200

Pimanda JE, Chan WY, Wilson NK, Smith AM, Kinston S, Knezevic K, Janes ME, Landry JR, Kolb-Kokocinski A, Frampton J, Tannahill D, Ottersbach K, Follows GA, Lacaud G, Kouskoff V, Gottgens B (2008) Endoglin expression in blood and endothelium is differentially regulated by modular assembly of the Ets/Gata hemangioblast code. Blood 112(12):4512–4522. doi:10.1182/blood-2008-05-157560

Popovic A, Demirovic A, Spajic B, Stimac G, Kruslin B, Tomas D (2010) Expression and prognostic role of syndecan-2 in prostate cancer. Prostate Cancer Prostate Dis 13(1):78–82

Ray BN, Lee NY, How T, Blobe GC (2010) ALK5 phosphorylation of the endoglin cytoplasmic domain regulates Smad1/5/8 signaling and endothelial cell migration. Carcinogenesis 31(3):435–441. doi:bgp327 [pii] 10.1093/carcin/bgp327

Rodriguez-Barbero A, Obreo J, Alvarez-Munoz P, Pandiella A, Bernabeu C, Lopez-Novoa JM (2006) Endoglin modulation of TGF-β1-induced collagen synthesis is dependent on ERK1/2 MAPK activation. Cell Physiol Biochem 18(1–3):135–142. doi:10.1159/000095181

Rokhlin OW, Cohen MB, Kubagawa H, Letarte M, Cooper MD (1995) Differential expression of endoglin on fetal and adult hematopoietic cells in human bone marrow. J Immunol 154(9):4456–4465

Romero D, O'Neill C, Terzic A, Contois L, Young K, Conley BA, Bergan RC, Brooks PC, Vary CP (2011) Endoglin regulates cancer-stromal cell interactions in prostate tumors. Cancer Res 71(10):3482–3493. doi:10.1158/0008-5472.CAN-10-2665

Romero D, Terzic A, Conley BA, Craft CS, Jovanovic B, Bergan RC, Vary CP (2010) Endoglin phosphorylation by ALK2 contributes to the regulation of prostate cancer cell migration. Carcinogenesis 31(3):359–366. doi:10.1093/carcin/bgp217

Rosen LS, Gordon MS, Hurwitz HI, Mendelson DS, Kleinzweig D, Adams BJ, C.P. T (2008) Early evidence of toelrability and clinical activity from a phase 1 study of TRC105 (anti-CD105 antibody) in patients with advanced refractory cancer. Eur J Cancer Supplements 6(126)

Rosen LS, Hurwitz HI, Wong MK, Goldman J, Mendelson DS, Fig. WD, Spencer S, Adams BJ, Alvarez D, Seon BK, Theuer CP, Leigh B, Gordon MS (2012) A phase 1 first-in-human study of TRC105 (anti-endoglin antibody) in patients with advanced cancer. Clin Cancer Res 18(17):4820–4829. doi:10.1158/1078-0432.CCR-12-0098

Rushing EC, Stine MJ, Hahn SJ, Shea S, Eller MS, Naif A, Khanna S, Westra WH, Jungbluth AA, Busam KJ, Mahalingam M, Alani RM (2012) Neuropilin-2: a novel biomarker for malignant melanoma? Hum Pathol 43(3):381–389

Ryu HY, Lee J, Yang S, Park H, Choi S, Jung KC, Lee ST, Seong JK, Han IO, Oh ES (2009) Syndecan-2 functions as a docking receptor for pro-matrix metalloproteinase-7 in human colon cancer cells. J Biol Chem 284(51):35692–35701. doi:10.1074/jbc.M109.054254

Saad RS, Liu YL, Nathan G, Celebrezze J, Medich D, Silverman JF (2004) Endoglin (CD105) and vascular endothelial growth factor as prognostic markers. Mod Pathol 17(2):197–203

Sanchez NS, Hill CR, Love JD, Soslow JH, Craig E, Austin AF, Brown CB, Czirok A, Camenisch TD, Barnett JV (2011) The cytoplasmic domain of TGFβR3 through its interaction with the scaffolding protein, GIPC, directs epicardial cell behavior. Dev Biol 358(2):331–343. doi:10.1016/j.ydbio.2011.08.008

Santander C, Brandan E (2006) Betaglycan induces TGF-β signaling in a ligand-independent manner, through activation of the p38 pathway. Cell Signal 18(9):1482–1491. doi:S0898-6568(05)00327-X [pii] 10.1016/j.cellsig.2005.11.011

Santibanez JF, Perez-Gomez E, Fernandez LA, Garrido-Martin EM, Carnero A, Malumbres M, Vary CP, Quintanilla M, Bernabeu C (2010) The TGF-β co-receptor endoglin modulates the expression and transforming potential of H-Ras. Carcinogenesis 31(12):2145–2154. doi:10.1093/carcin/bgq199

Sanz-Rodriguez F, Guerrero-Esteo M, Botella LM, Banville D, Vary CP, Bernabeu C (2004) Endoglin regulates cytoskeletal organization through binding to ZRP-1, a member of the Lim family of proteins. J Biol Chem 279(31):32858–32868. doi:10.1074/jbc.M400843200

Sarraj MA, Chua HK, Umbers A, Loveland KL, Findlay JK, Stenvers KL (2007) Differential expression of TGFBR3 (betaglycan) in mouse ovary and testis during gonadogenesis. Growth Factors 25(5):334–345. doi:789171518 [pii] 10.1080/08977190701833619

Sarraj MA, Escalona RM, Umbers A, Chua HK, Small C, Griswold M, Loveland K, Findlay JK, Stenvers KL (2010) Fetal testis dysgenesis and compromised Leydig cell function in Tgfbr3 (β glycan) knockout mice. Biol Reprod 82(1):153–162. doi:biolreprod.109.078766 [pii]10.1095/biolreprod.109.078766

Schimming R, Marme D (2001) Endoglin (CD105) expression in squamous cell carcinoma of the oral cavity. Head Neck 24(2):151–156

Seon BK, Matsuno F, Haruta Y, Kondo M, Barcos M (1997) Long-lasting complete inhibition of human solid tumors in SCID mice by targeting endothelial cells of tumor vasculature with antihuman endoglin immunotoxin. Clin Cancer Res 3:1031–1044

Serini G, Valdembri D, Zanivan S, Morterra G, Burkhardt C, Caccavari F, Zammataro L, Primo L, Tamagnone L, Logan M, Tessier-Lavigne M, Taniguchi M, Puschel AW, Bussolino F (2003) Class 3 semaphorins control vascular morphogenesis by inhibiting integrin function. Nature 424(6947):391–397. doi:10.1038/nature01784 nature01784 [pii]

Shariat SF, Karam JA, Walz J, Roehrborn CG, Montorsi F, Margulis V, Saad F, Slawin KM, Karakiewicz PI (2008) Improved prediction of disease relapse after radical prostatectomy through a panel of preoperative blood-based biomarkers. Clin Cancer Res 14(12):3785–3791. doi:10.1158/1078-0432.CCR-07-4969

Sharifi N, Hurt EM, Kawasaki BT, Farrar WL (2007) TGFBR3 loss and consequences in prostate cancer. Prostate 67(3):301–311. doi:10.1002/pros.20526

Shyu HY, Fong CS, Fu YP, Shieh JC, Yin JH, Chang CY, Wang HW, Cheng CW (2010) Genotype polymorphisms of GGCX, NQO1, and VKORC1 genes associated with risk susceptibility in patients with large-artery atherosclerotic stroke. Clin Chim Acta 411(11–12):840–845. doi:10.1016/j.cca.2010.02.071

Soker S, Gollamudi-Payne S, Fidder H, Charmahelli H, Klagsbrun M (1997) Inhibition of vascular endothelial growth factor (VEGF)-induced endothelial cell proliferation by a peptide corresponding to the exon 7-encoded domain of VEGF165. J Biol Chem 272(50):31582–31588

Sorensen I, Adams RH, Gossler A (2009) DLL1-mediated Notch activation regulates endothelial identity in mouse fetal arteries. Blood 113(22):5680–5688. doi:10.1182/blood-2008-08-174508

Sorensen LK, Brooke BS, Li DY, Urness LD (2003) Loss of distinct arterial and venous boundaries in mice lacking endoglin, a vascular-specific TGFβ coreceptor. Dev Biol 261(1): 235–250

Staton CA, Kumar I, Reed MW, Brown NJ (2007) Neuropilins in physiological and pathological angiogenesis. J Pathol 212(3):237–248. doi:10.1002/path.2182

Steg AD, Bevis KS, Katre AA, Ziebarth A, Dobbin ZC, Alvarez RD, Zhang K, Conner M, Landen CN (2012) Stem cell pathways contribute to clinical chemoresistance in ovarian cancer. Clin Cancer Res 18(3):869–881. doi:10.1158/1078-0432.CCR-11-2188

Stenvers KL, Tursky ML, Harder KW, Kountouri N, Amatayakul-Chantler S, Grail D, Small C, Weinberg RA, Sizeland AM, Zhu HJ (2003) Heart and liver defects and reduced transforming growth factor β2 sensitivity in transforming growth factor β type III receptor-deficient embryos. Mol Cell Biol 23(12):4371–4385

Stephenson JM, Banerjee S, Saxena NK, Cherian R, Banerjee SK (2002) Neuropilin-1 is differentially expressed in myoepithelial cells and vascular smooth muscle cells in preneoplastic and neoplastic human breast: a possible marker for the progression of breast cancer. Int J Cancer 101(5):409–414. doi:10.1002/ijc.10611

Sun L, Chen C (1997) Expression of transforming growth factor β type III receptor suppresses tumorigenicity of human breast cancer MDA-MB-231 cells. J Biol Chem 272(40): 25367–25372

Sweet K, Willis J, Zhou X, Gallione C, Sawada T, Alhopuro P, Khoo S, Patocs A, Martin C, Bridgeman S, Heinz J, Pilarski R, Lehtonen R, Prior T, Rebourg T, Teh B, Marchuk D, Aaltonen L, Eng C (2005) Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. JAMA 294(19):2465–2473

Tabata M, Kondo M, Haruta Y, Seon BK (1999) Antiangiogenic radioimmunotherapy of human solid tumors in SCID mice using 125I-labeled anti-endoglin monoclonal antibodies. Int J Cancer 82:737–742

Takahashi N, Haba A, Matsuno F, Seon BK (2001) Antiangiogenic therapy of established tumors in human skin/severe combined immunodeficiency mouse chimerias by anti-endoglin (CD105) monoclonal antibodies, and synergy between anti-endoglin antibody and cyclophosphamide. Cancer Res 61:7846–7854

Tanaka F, Otake Y, Yanagihara K, Kawano Y, Miyahara R, Li M, Yamada T, Hanaoka N, Inui K, Wada H (2001) Evaluation of angiogenesis in non-small cell lung cancer: comparison between anti-CD35 antibody and anti-CD105 antibody. Clin Cancer Res 7:3410–3415

Theocharis AD, Skandalis SS, Tzanakakis GN, Karamanos NK (2010) Proteoglycans in health and disease: novel roles for proteoglycans in malignancy and their pharmacological targeting. FEBS J 277(19):3904–3923. doi:10.1111/j.1742-4658.2010.07800.x

Tsujie M, Tsujie T, Toi H, Uneda S, Shiozaki K, Tsai H, Seon BK (2008) Anti-tumor activity of an anti-endoglin monoclonal antibody is enhanced in immunocompetent mice. Int J Cancer 122(10):2266–2273. doi:10.1002/ijc.23314

Turley RS, Finger EC, Hempel N, How T, Fields TA, Blobe GC (2007) The type III transforming growth factor-β receptor as a novel tumor suppressor gene in prostate cancer. Cancer Res 67(3):1090–1098. doi:10.1158/0008-5472.CAN-06-3117

Uneda S, Toi H, Tsujie T, Tsujie M, Harada N, Tsai H, Seon BK (2009) Anti-endoglin monoclonal antibodies are effective for suppressing metastasis and the primary tumors by targeting tumor vasculature. Int J Cancer 125(6):1446–1453. doi:10.1002/ijc.24482

Valdembri D, Caswell PT, Anderson KI, Schwarz JP, Konig I, Astanina E, Caccavari F, Norman JC, Humphries MJ, Bussolino F, Serini G (2009) Neuropilin-1/GIPC1 signaling regulates α5β1 integrin traffic and function in endothelial cells. PLoS Biol 7(1):e25. doi:08-PLBI-RA-0162 [pii] 10.1371/journal.pbio.1000025

von Wronski MA, Raju N, Pillai R, Bogdan NJ, Marinelli ER, Nanjappan P, Ramalingam K, Arunachalam T, Eaton S, Linder KE, Yan F, Pochon S, Tweedle MF, Nunn AD (2006) Tuftsin binds neuropilin-1 through a sequence similar to that encoded by exon 8 of vascular endothelial growth factor. J Biol Chem 281(9):5702–5710. doi:10.1074/jbc.M511941200

Wang L, Mukhopadhyay D, Xu X (2006) C terminus of RGS-GAIP-interacting protein conveys neuropilin-1-mediated signaling during angiogenesis. FASEB J 20(9):1513–1515. doi:fj.05-5504fje [pii] 10.1096/fj.05-5504fje

Wang XF, Lin HY, Ng-Eaton E, Downward J, Lodish HF, Weinberg RA (1991) Expression cloning and characterization of the TGF-β type III receptor. Cell 67(4):797–805. doi:0092-8674(91)90074-9 [pii]

Webber J, Steadman R, Mason MD, Tabi Z, Clayton A (2010) Cancer exosomes trigger fibroblast to myofibroblast differentiation. Cancer Res 70(23):9621–9630. doi:10.1158/0008-5472.CAN-10-1722

Wikstrom P, Lissbrant IF, Stattin P, Egevad L, Bergh A (2002) Endoglin (CD105) is expressed on immature blood vessels and is a marker for survival in prostate cancer. Prostate 51(4):268–275. doi:10.1002/pros.10083

Wild JR, Staton CA, Chapple K, Corfe BM (2012) Neuropilins: expression and roles in the epithelium. Int J Exp Pathol 93(2):81–103. doi:10.1111/j.1365-2613.2012.00810.x

Wipff J, Avouac J, Borderie D, Zerkak D, Lemarechal H, Kahan A, Boileau C, Allanore Y (2008) Disturbed angiogenesis in systemic sclerosis: high levels of soluble endoglin. Rheumatology (Oxford) 47(7):972–975. doi:10.1093/rheumatology/ken100

Wong VC, Chan PL, Bernabeu C, Law S, Wang LD, Li JL, Tsao SW, Srivastava G, Lung ML (2008) Identification of an invasion and tumor-suppressing gene, Endoglin (ENG), silenced by both epigenetic inactivation and allelic loss in esophageal squamous cell carcinoma. Int J Cancer 123(12):2816–2823. doi:10.1002/ijc.23882

Woszczyk D, Gola J, Jurzak M, Mazurek U, Mykala-Ciesla J, Wilczok T (2004) Expression of TGF β1 genes and their receptor types I, II, and III in low- and high-grade malignancy non-Hodgkin's lyphomas. Med Sci Monit 10(1):CR33–CR37

Yacoub M, Coulon A, Celhay O, Irani J, Cussenot O, Fromont G (2009) Differential expression of the semaphorin 3A pathway in prostatic cancer. Histopathology 55(4):392–398

Yasuoka H, Kodama R, Tsujimoto M, Yoshidome K, Akamatsu H, Nakahara M, Inagaki M, Sanke T, Nakamura Y (2009) Neuropilin-2 expression in breast cancer: correlation with lymph node metastasis, poor prognosis, and regulation of CXCR4 expression. BMC Cancer 9:220

You HJ, How T, Blobe GC (2009) The type III transforming growth factor-β receptor negatively regulates nuclear factor κ B signaling through its interaction with β-arrestin2. Carcinogenesis 30(8):1281–1287. doi:bgp071 [pii] 10.1093/carcin/bgp071

Younan S, Elhoseiny S, Hammam A, Gawdat R, El-Wakil M, Fawzy M (2012) Role of neuropilin-1 and its expression in Egyptian acute myeloid and acute lymphoid leukemia patients. Leuk Res 36(2):169–173