Molecular and Cellular Endocrinology 339 (2011) 180–189

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

Betaglycan: A multifunctional accessory

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ARTICLE INFO

Article history:
Received 23 December 2010
Received in revised form 18 April 2011
Accepted 18 April 2011

Keywords:
Betaglycan
TGFβ receptor III
Inhibin

ABSTRACT

Betaglycan is a co-receptor for the TGFβ superfamily, particularly important in establishing the potency of its ligands on their target cells. In recent years, new insights have been gained into the structure and function of betaglycan, expanding its role from that of a simple co-receptor to include additional ligand-dependent and ligand-independent roles. This review focuses on recent advances in the betaglycan field, with a particular emphasis on its newly discovered actions in mediating the trafficking of TGFβ superfamily receptors and as a determinant of the functional output of TGFβ superfamily signalling. In addition, this review encompasses a discussion of the emerging roles of the betaglycan/inhibin pathway in reproductive cancers and disease.

Betaglycan was originally identified as a non-signalling co-receptor for Transforming Growth Factor-β (TGFβ), and its main function was defined as presenting ligand to the TGFβ signalling receptors (López-Casillas et al., 1991; Wang et al., 1991). Subsequently, betaglycan was also shown to bind a distantly related member of the TGFβ superfamily, inhibin A, regulating its binding to activin type II receptors (Lewis et al., 2000). In the last decade, additional ligand-dependent and -independent functions for betaglycan have been described which extend far beyond its role as a simple inhibin or TGFβ accessory receptor (Wiater and Vale, 2003; Kirkbride et al., 2008; Lee et al., 2009; Mythreye and Blobe, 2009; Looyenga et al., 2010; Webber et al., 2010). Notably, betaglycan is an important regulator of reproduction (Sarraj et al., 2007; Escalona et al., 2009; Wiater et al., 2009; Glister et al., 2010) and fetal development (Stenvers et al., 2003; Compton et al., 2007; Sarraj et al., 2007, 2010; Walker et al., 2011) and is a tumor suppressor in many tissue types (Dong et al., 2007; Hempel et al., 2007; Sharifi et al., 2007; Turley et al., 2007; Finger et al., 2008a; Gordon et al., 2008; Bilandzic et al., 2009; Mythreye and Blobe, 2009; Stenvers and Findlay, 2010). The current literature indicates that betaglycan has complex roles *in vivo*, broadly influencing the activities and interactions of a number of TGFβ superfamily members, thereby impacting diverse cellular processes. This review focuses on recent advances in our understanding of betaglycan structure and function, with a particular emphasis on its impact on inhibin and TGFβ action.

1. Betaglycan as a TGFβ superfamily co-receptor

The TGFβ superfamily is a large group of structurally related growth factors, which includes the TGFβs, activins, inhibins, Bone Morphogenetic Proteins (BMPs), and Growth and Differentiation Factors (GDFs). These factors take part in the regulation of multiple cellular processes, including cell survival, proliferation, migration, and differentiation. As such, the superfamily is important for normal cellular function and turnover both during fetal development and in adult tissues. The actions of nearly all members of the superfamily are mediated by pairs of serine/threonine kinase receptors, the type I and II receptors, which form heteromeric complexes on the cell surface (Fig. 1). Ligands bind to their respective type I and II receptors causing a cascade of phosphorylation events and the activation of specific downstream signalling molecules. In the canonical pathway, TGFβ superfamily members activate members of the SMAD transcription factor family (Fig. 1). Activins and TGFβs signal via SMAD2 and SMAD3 whereas BMPs signal via SMAD1/5/8. Receptor-activated SMADs then associate with the common SMAD4 and translocate to the nucleus to modify gene transcription (for review, see Hill, 2009). TGFβs can also activate members of the Mitogen Activated Protein (MAP) kinase signalling molecules, including JNK, p38, and ERKs, and the PI3 K/Akt pathway (for review, Ikushima and Miyazono, 2010).

In addition to the kinase receptors, a number of other membrane-bound proteins participate in TGFβ superfamily ligand binding and signalling. Of these, betaglycan is the most abundant TGFβ receptor in many cell types (Segarini et al., 1989; Cheifetz et al., 1990). Betaglycan was originally identified as an accessory receptor for the TGFβs and is formally known as the type III TGFβ receptor (TGFBR3) (López-Casillas et al., 1991; Wang et al., 1991). As betaglycan lacks a signalling domain and exhibits a slightly lower

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doi:10.1016/j.mce.2011.04.014

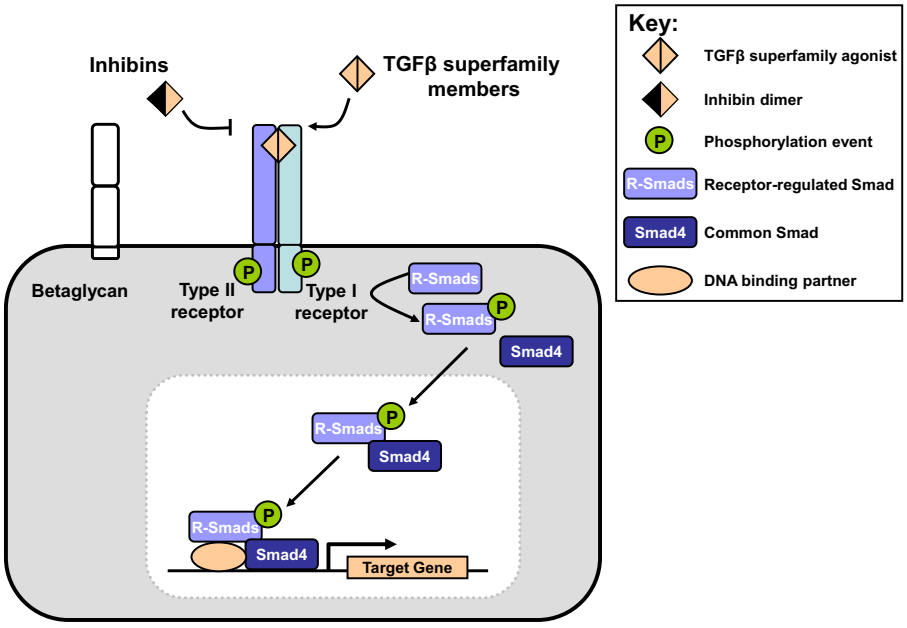

Fig. 1. TGFβ superfamily signalling pathway. The diverse actions of the TGFβ superfamily of growth and differentiation factors are mediated by pairs of serine-threonine kinase type I and type II receptors. In the canonical signalling pathway, agonists bind to specific sets of type I and type II receptors on the cell surface, which results in the phosphorylation and activation of downstream signalling molecules, the receptor regulated (R-)SMADs. Activated R-SMADs then associate with the common co-SMAD, SMAD4, and translocate to the nucleus where, in combination with cell-type specific binding partners, they regulate gene transcription and cellular function. The membrane-bound form of the accessory receptor, betaglycan, increases the binding of its ligands, the TGFβs, inhibins, and BMPs, to their signalling receptors. This generally enhances the signalling of TGFβs and BMPs and enhances the ability of inhibins to block the functions of other TGFβ superfamily members. See text for details.

affinity for TGFβs than the type I/II receptor complex, the main function of this receptor was thought to be to bind TGFβs and present them to the type II receptor (López-Casillas et al., 1991; Wang et al., 1991). In accordance with this role, the presence of betaglycan on the cell surface increases the binding of the TGFβs to their type II receptors and increases ligand efficacy in biological assays (López-Casillas et al., 1993, 1994; Stenvers et al., 2003; Bilandzic et al., 2009). This effect is most pronounced for TGFβ2, which binds poorly to the TGFβ type II receptor in the absence of betaglycan (López-Casillas et al., 1993, 1994).

In addition to binding TGFβs, betaglycan binds to inhibins with high affinity (Lewis et al., 2000) and is a major determinant of inhibin potency on pituitary gonadotrope cells (Escalona et al., 2009; Wiater et al., 2009). Within the TGFβ superfamily, inhibins are unique as dedicated signalling receptors have yet to be reported. However, inhibins can bind to the type II receptors of other superfamily members (Lewis et al., 2000; Wiater and Vale, 2003). Notably, inhibins are closely related to activins. Mature activins (activin A, activin B, and activin AB) are disulfide-linked homo- or heterodimers of two β subunits (βAβA, βBβB, and βAβB) while inhibins (inhibin A and inhibin B) are heterodimers of α- and β-subunits (αβA, αβB). Inhibins are capable of binding type II activin receptors through their β-subunits and functionally antagonizing activins by preventing the recruitment of activin type I receptors. However, inhibins can only bind with low affinity to the activin type II receptors, and are therefore not efficient competitors on their own (Lewis et al., 2000). For high potency inhibin action, the presence of betaglycan is required (Lewis et al., 2000; Escalona et al., 2009; Wiater et al., 2009). Betaglycan forms a stable complex with inhibin and type II activin receptors, thus sequestering activin type II receptors and reducing their availability to propagate activin signalling (Lewis et al., 2000). In a similar fashion, inhibin A also antagonizes the binding of BMPs to activin and BMP type II receptors in the presence of betaglycan, resulting in the inhibition of BMP function (Wiater and Vale, 2003; Farnworth et al., 2006a). In addition, BMP-2, -4, -7 and GDF-5 have recently been shown to bind directly to the core domain of betaglycan, which may impact on both BMP receptor signalling and trafficking (see below; Kirkbride et al., 2008; Lee et al., 2009).

As betaglycan can bind to several classes of TGFβ superfamily ligands, it is not surprising that the functional impact of this receptor appears to be both context- and cell-type dependent. Indeed, as TGFβs, inhibins, and BMPs can be produced simultaneously by the same tissues, these ligands may compete at betaglycan to functionally antagonize each other (Ethier et al., 2002; Wiater et al., 2006; Farnworth et al., 2007; Kirkbride et al., 2008; Bilandzic et al., 2009; Looyenga et al., 2010). For example, there is significant overlap in the binding sites for TGFβs and inhibins within the membrane-proximal domain of betaglycan (discussed below) (Wiater et al., 2006). The TGFβs have a higher affinity for betaglycan than inhibins, and neither inhibin A nor inhibin B are able to compete for betaglycan binding sites against [^{125}I]TGFβ1 or [^{125}I]TGFβ2 in gonadal or adrenal cell lines (Farnworth et al., 2007; Looyenga et al., 2010). The functional impact of this has been demonstrated in murine LβT2 gonadotrope cells, in which TGFβs can block the access of inhibin A to betaglycan, thereby relieving the inhibin-mediated antagonism of activin responses (Ethier et al., 2002). Other mechanisms may also come into play as TGFβ1 and TGFβ2 also down-regulate the expression of the betaglycan gene in gonadal or adrenal cell lines and therefore may also indirectly reduce cellular sensitivity to inhibins in this manner (Farnworth et al., 2007). Furthermore, in some contexts, inhibins or BMPs may also inhibit TGFβs via betaglycan (Kirkbride et al., 2008; Looyenga et al., 2010). To what degree competition occurs between betaglycan ligands *in vivo* is yet unclear, but the *in vitro* data suggest that betaglycan might integrate multiple TGFβ superfamily inputs into discrete functional outcomes. Emerging data indicate that this occurs not only via betaglycan's role in ligand presentation, but also through its distinct effects on the receptor trafficking and downstream signalling of each of its ligand subtypes, which are discussed further below.