Signal Transduction Pathway through Activin Receptors as a Therapeutic Target of Musculoskeletal Diseases and Cancer

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Abstract. Activin, myostatin and other members of the TGF-β superfamily signal through a combination of type II and type I receptors, both of which are transmembrane serine/threonine kinases. Activin type II receptors, ActRIIA and ActRIIB, are primary ligand binding receptors for activins, nodal, myostatin and GDF11. ActRIIs also bind a subset of bone morphogenetic proteins (BMPs). Type I receptors that form complexes with ActRIIs are dependent on ligands. In the case of activins and nodal, activin receptor-like kinases 4 and 7 (ALK4 and ALK7) are the authentic type I receptors. Myostatin and GDF11 utilize ALK5, although ALK4 could also be activated by these growth factors. ALK4, 5 and 7 are structurally and functionally similar and activate receptor-regulated Smads for TGF-β. BMPs signal through a combination of three type II receptors, BMPRII, ActRIIA, and ActRIIB and four type I receptors, ALK1, 2, 3, and 6. BMPs activate BMP-specific Smads, Smad1, 5 and 8. Smad proteins undergo multimerization with co-mediator Smad, Smad4, and translocated into the nucleus to regulate the transcription of target genes in cooperation with nuclear cofactors. The signal transduction pathway through activin type II receptors, ActRIIA and ActRIIB, with type I receptors is involved in various human diseases. In this review, we discuss the role of signaling through activin receptors as therapeutic targets of intractable neuromuscular diseases, endocrine disorders and cancers.

Key words: Activin, Myostatin, Activin receptor, Muscular dystrophy, Bone formation, Cancer, Targeted therapy

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I. An overview of activins, myostatin and BMPs that signal through activin receptors

Activins were first discovered as regulators of secretion of follicle-stimulating hormone from the anterior pituitary [1–3]. Various reproductive and non-reproductive roles of activins have been characterized [3, 4]. Activins have potent mesoderm inducing activity in *Xenopus laevis* embryos [5], although nodal is an authentic mesoderm inducer in many species including mammals [6]. Since nodal shares activin receptors with activins, exogenous administration of activins mimics the actions of an endogenous role of nodal (Table 1). Myostatin, like activins, belongs to the transforming growth factor-β (TGF-β) superfamily and has a distinct role in myogenesis [7]. Myostatin is an endogenous negative regulator of muscle growth and plays a major role in determining skeletal muscle mass. Mice with a targeted deletion of the myostatin gene were shown to have hypermuscular phenotypes [8]. Interestingly, inactivating mutations in the myostatin gene have been identified in double-muscling cattle breeds, sheep, dogs and even humans [9–11]. These findings indicate that myostatin works as a negative regulator of skeletal muscle growth and development. Myostatin is also known as growth and differentiation factor 8 (GDF8) and is structurally closest to GDF11, which is involved in development of spinal cord and kidney organogenesis [12, 13].

The TGF-β superfamily is subdivided into several subfamilies; TGF-β subfamily, activin/inhibin subfamily, myostatin/GDF11 subfamily and BMP subfamily. TGF-β, activin, myostatin, nodal activate TGF-β pathway-restricted Smads, Smad2 and 3 in the cytoplasm,
whereas BMPs phosphorylate and activate BMP-specific Smad, Smad1, 5 and 8 [14, 15]. Although the intracellular signaling pathway of BMPs is different from that of activins, activin type II receptors (ActRIIA and ActRIIB) are shared and can be activated by BMP6 and BMP7 [16, 17]. This difference is attributed to different type I receptors, which form complexes with ActRIIs by ligand stimulation (Table 1). ALK4/5/7 are structurally similar and activate Smad 2 and 3, receptor-regulated Smads specific for the TGF-β pathway [3, 4, 18, 19], whereas ALK1/2/3/6 activate receptor-regulated Smad specific for the BMP pathway [15] (see next section).

### II. Activin Receptors and their Unique Signal Transduction Pathway

Mathews and Vale performed expression cloning studies to identify activin receptors, and successfully isolated a transmembrane serine/threonine kinase receptor in 1991 [20] (Fig. 1). The cloned receptor from AtT20 cells was named as an activin type II receptor, ActRII [20]. ActRII is also known as ActRIIA or ACVR2 [20]. A second type of activin receptor, ActRIIB, also known as ACVR2B, was also identified [21]. ActRIIs are activin receptors; however, they also work as receptors for a subset of BMPs, notably BMP6 and BMP7 [16, 17]. The distinct TGF-β type II receptor (TGF-βRII) and BMP type II receptor (BMPRII) bind and transmit TGF-β and BMP signaling, respectively [14, 15]. Using degenerate DNA primers based on the conserved sequences of ActRII, TGF-βRII and C. elegans Daf-1 gene, a number of receptor serine/threonine kinases have been identified [15, 22, 23] and termed activin receptor-like kinases 1 to 7 (ALK1~7). Subsequent characterization of ALKs revealed that ALK4 (ACVR1B) and ALK7 (ACVR1C) act as type I receptors for activins and nodal [3, 14, 18, 19] (Fig. 1). ALK2 (ACVR1) was termed an activin type I receptor since it could bind activins; however, it is highly likely that ALK2 acts as a type I receptor for BMPs [15]. Myostatin and GDF11 bind ActRIIB and ActRIIA and utilize ALK5 and ALK4 as type I receptors [24–26] (Table 1).

The activin type II receptor has an extracellular ligand binding domain, a single transmembrane domain and an intracellular serine/threonine kinase domain. COOH-terminal sequences SSL/I are binding sites for PDZ proteins and are unique to activin type II receptors. In gastrointestinal cancers, polyadenine tracts in ACVR2 were identified as targets for frameshift mutations. Type I receptors have also a similar domain organization. In contrast with the type II receptor, the type I receptor has a GS domain that is located between transmembrane domain and kinase domain. The amino acid sequences of the GS domains of type I receptors for activins and BMPs show differences, reflecting the preference of Smad proteins.

### Table 1. Type II and type I receptors for activins, myostatin and the related TGF-β family

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Type II Receptors</th>
<th>Type I Receptors</th>
</tr>
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<tbody>
<tr>
<td>Activins</td>
<td>ActRIIA (ACVR2) &amp; ActRIIB (ACVR2B)</td>
<td>ALK4 (ACVR1B) &amp; ALK7 (ACVR1C)</td>
</tr>
<tr>
<td>nodal</td>
<td>ActRIIB (ACVR2B) &amp; ActRIIA (ACVR2)</td>
<td>ALK5 (TGFBRI1) &amp; ALK4 (ACVR1B)</td>
</tr>
<tr>
<td>Myostatin</td>
<td>ActRIIB (ACVR2B) &amp; ActRIIA (ACVR2)</td>
<td>ALK2 (ACVR1) &amp; ALK1, ALK3, ALK6</td>
</tr>
<tr>
<td>GDF11</td>
<td>ActRIIA (ACVR2) &amp; ActRIIB (ACVR2B)</td>
<td>ALK5 (TGFBRI1)</td>
</tr>
<tr>
<td>BMPs</td>
<td>BMPRII, ActRIIA, ActRIIB</td>
<td>ALK1, ALK3, ALK6</td>
</tr>
<tr>
<td>TGF-βs</td>
<td>TGF-βRII (TGFBRI2)</td>
<td>ALK5 (TGFBRI1)</td>
</tr>
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</table>

Various combinations of type II and type I receptors elicit signaling of activins and related ligands. Activins and nodal signal through a combination of type II receptors, ActRIIA/ActRIIB and type I receptors, ALK4/7. Myostatin and GDF11 signal through combination of type II receptors, ActRIIA/ActRIIB and type I receptors, ALK5/4. BMPs signal through a combination of type II receptors, BMPRII, ActRIIA and ActRIIB and type I receptors, ALK1/2/3/6.
located between transmembrane domain and kinase domain (Fig. 1). The amino acid sequences of GS domains of type I receptors for activins and BMP show distinct differences, reflecting the preference of Smad proteins (Fig. 1). Once ligands bind to activin type II receptors, type I receptors are recruited to the complex and GS domains of type I receptors are phosphorylated by ActRIIs. Then, receptor-specific Smads are phosphorylated by activated type I receptors. When ALK4/5/7 are activated by ligand/ActRIIs, TGF-β specific Smads, Smad2/3, are phosphorylated. Whereas, when ALK1/2/3/6 are activated by BMP/ActRIIs, BMP specific Smads, Smad1/5/8 are activated. Activated Smads form a complex with common-Smad4, and are transported to the nucleus to regulate expression of specific genes. Transcription factors and cofactors form complex with Smad and are responsible for the gene expression (Fig. 2).

III. Crystal Structures of Activin Receptors

The crystal structure of the extracellular domain (ECD) of activin type II receptor (ActRII) in complex with ligand, BMP7, has been reported [27]. The ECD of ActRII has a fold similar to that of three finger toxins. Intriguingly, the ligand mediates cooperative receptor assembly without receptor contact [27]. The structure of the activin complex with ActRIIB was also revealed [28, 29]. The activin dimer exhibits an unexpected flexibility dependent on whether or not it contacts with receptors, and the affinity of activin to the two ActRIIBs is greatly affected by spatial localization of ActRIIB in the membrane [28, 29]. The dimeric nature of activin and TGF-β ligands suggests that the ligand/type II receptor/type I receptor form complexes with 1:2:2 stoichiometry. The knuckle region of activin or BMP-7 dimer has a type II receptor binding site, and the concave-shaped region of the ligands serves as type I receptor binding site [27, 28].

Fig. 2. An overview of signal transduction through activin receptors. Activin (Act), myostatin (MSTN) and BMP are dimeric ligands. Follistatin binds and neutralizes Act and MSTN, whereas BMP inhibitors, like noggin, bind to and inhibit BMPs. Once Act, MSTN and BMP bind to activin type II receptors, type I receptors are recruited to the complex and GS domains of type I receptors are phosphorylated by ActRIIs. Then, receptor-specific Smads are phosphorylated by activated type I receptors. When ALK4/5/7 is activated by ligand/ActRIIs, TGF-β specific Smads, Smad2/3, are phosphorylated. Whereas, when ALK1/2/3/6 is activated by BMP/ActRIIs, BMP specific Smads, Smad1/5/8 are activated. Activated Smads form a complex with common-Smad4, and are transported to the nucleus to regulate expression of specific genes. Transcription factors and cofactors form complex with Smad and are responsible for the gene expression.
IV. Activin Receptors as Therapeutic Targets of Neuromuscular Diseases, Endocrine Disorders and Cancers

A. Muscular dystrophy and related diseases

Muscular dystrophy is a severe muscle-wasting disorder. Although the genes responsible for various types of muscular dystrophies have been identified, no effective therapies are not available yet. The most common type is Duchenne muscular dystrophy (DMD) in which the dystrophin gene is mutated and defective. The milder Becker muscular dystrophy (BMD), Fukuyama congenital muscular dystrophy [30], myotonic dystrophy, and multiple types of limb girdle muscular dystrophy (LGMD) are other important muscular dystrophies [31]. Skeletal muscle in dystrophy patients becomes susceptible to tissue inflammation and atrophy. Progressive muscle weakness is also a characteristic feature of the disease. Most of the deficient molecules in muscular dystrophies are components of dystrophin-glycoprotein complexes [32]. Although gene therapy and cell transplantation therapy have greatly advanced, drug therapies to increase muscle size and strength and to reduce inflammation are also needed for patients. Insulin-like growth factor-1 (IGF-1) is a potent growth factor for myoblast growth and proliferation, whereas myostatin negatively controls myoblast growth. Myostatin inhibition is considered to be one of the most hopeful and realistic molecular therapies for muscular dystrophy. Monoclonal antibody-mediated myostatin blockade improved function of dystrophic muscle of \textit{mdx} mice, an animal model of DMD [33]. Studies where myostatin null mice were crossed with \textit{mdx} mice indicated that \textit{mdx} mice lacking myostatin were stronger and more muscular. Furthermore, muscles in \textit{mdx} mice without myostatin showed less fibrosis and fatty remodeling, suggesting improved regeneration process [34]. A number of endogenous peptides including myostatin propeptide and follistatin bind and inhibit myostatin [32, 35]. Myostatin propeptide, stabilized by fusion to IgG-Fc, was injected into \textit{mdx} mice to pharmacologically block myostatin [36]. This strategy is also effective to ameliorate dystrophic pathophysiology [36]. A mouse model of LGMD1C caused by a mutation of caveolin-3 was established and crossed with myostatin propeptide transgenic mice [37, 38]. Muscle atrophy caused by mutant caveolin-3 transgenic mice was dramatically recovered [37]. Myostatin propeptide was used for gene therapy using adeno-associated virus (AAV) vector in LGMD2A caused by mutation in the calpain 3 and LGMD2D caused by mutation in the \(\alpha\)-sarcoglycan gene (SGCA) [39]. Interestingly, in calpain 3-deficient mice, muscle mass and force were recovered by myostatin inhibition, whereas in the highly regenerative Sgca-null mice, survival was not improved [39]. In addition, myostatin blockage in early stage in a murine model of \(\delta\)-sarcoglycan-deficient muscular dystrophy was effective to improve muscle loss, regeneration and reduce fibrosis [40]. Importantly, elimination of myostatin did not combat a laminin-\(\alpha\)-2-deficient \textit{dyw} mouse model but did increase postnatal lethality due to fat loss [41]. Taken together, these studies suggest that although myostatin inhibition can ameliorate several different types of muscular dystrophy, it is important to choose the proper type of dystrophy and disease stages. One report showed that neurogenic muscle atrophy by amyotrophic lateral sclerosis could be slowed by myostatin inhibition [42].

In addition to myostatin antibody and myostatin propeptide, soluble forms of ActRIIB and follistatin-related peptide would effectively block myostatin \textit{in vivo} [24, 43]. The soluble form of ActRIIB has a strong muscle enhancing activity. Only 2 weeks are required for up to 60% increase of muscle mass by soluble form of ActRIIB in mice studies [24]. Since myostatin regulates skeletal muscle mass even in adults [44], myostatin inhibition would ameliorate muscle atrophy by aging (sarcopenia), disuse atrophy and even cachexia [32].

B. Bone formation

BMPs are identified by their ability to induce ectopic bone formation [15]. Activin is also involved in bone remodeling and tooth development. Activin is an essential cofactor for osteoclastogenesis and powerfully synergizes with receptor activator of NF-kappaB ligand (RANKL) for induction of osteoclast-like cells [45, 46]. Activins are also potent inhibitors for mineralization in osteoblast, whereas follistatin, the activin antagonist, increased mineralization [47]. The osteogenic signal by BMPs is transmitted through a combination of BMP type II receptors (BMPRII, ActRIIA and ActRIIB) and BMP type I receptors (ALK1, 2, 3, 6). Fibrodysplasia ossificans progressiva (FOP) is a
disabling genetic disorder that leads to the formation of a second (heterotopic) skeleton. It is the most catastrophic disorder of heterotopic ossification in humans. Recently, a recurrent mutation in the juxtamembrane glycine-serine domain of the ALK2 (ACVR1, ActRIA) was reported in all sporadic and familial cases of classic FOP [48]. The ACVR1 617G>A mutation is recurrent in all the affected FOP patients including Japanese and Taiwanese [49] (Fig. 1). Since the mutated molecule for FOP was identified, gene diagnosis will become possible and a therapeutic strategy could be developed in near future.

C. Cancers

The involvement of TGF-β in the regulation of growth of cancer cells is well characterized [14]. TGF-β has a dual role in tumorigenesis. TGF-β inhibits growth of cancer cells in early phase of tumor formation, and TGF-β regulates metastasis in the later phase of cancer progression. Mutation of TGF-β signaling pathway including TGF-βRII, Smad4 (Dpc4) and Smad2 have been reported in various cancers including colorectal and pancreatic cancers [50–52].

The importance of activins and their receptors in cancer biology is also well recognized. Expression of activin receptors is dramatically altered in cancers [53]. Furthermore, somatic mutations of signal transduction pathways through activin receptors have been characterized in colon and pancreatic cancers [54, 55] (Table 2). In the case of ACVR2, 8-bp polyadenine tracts were identified as targets for frameshift mutations in gastrointestinal cancers with microsatellite instability [54] (Fig. 1). Deletion and frame-shift mutations of ACVR1B were identified in pancreatic cancer xenograft [55]. In addition, several truncated ACVR1B receptor isoforms, that are not functionally active, are exclusively expressed in human pituitary tumors [56].

Inhibin is an antagonist hormone for activins. In mice deficient of the inhibin βα gene, sex cord-stromal tumors developed as early as 4 weeks of age both in males and females [57]. The tumors cause an activin-dependent cachexia and wasting syndrome and affects mortality due to the absence of inhibin [58]. Activins secreted from tumors activate ACVR2 in excess and cause apoptosis of hepatocytes [57].

V. Inhibitors of Signaling through Activin Receptors

As discussed above, signaling through activin receptors is a target of multiple diseases (Table 2). Therefore, various strategies are possible to regulate signaling through activin receptors for therapies against various diseases.

A. Dominant negative forms of activin receptors

ActRIIs (ActRIIA and ActRIIB) are primary ligand-binding receptors for activins, myostatin and GDF11. Soluble forms of ActRIIs containing the extracellular domain lacking transmembrane and cytoplasmic ki-

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Other names</th>
<th>Gene locus in human</th>
<th>Ligands</th>
<th>Relationship to diseases</th>
<th>OMIM</th>
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</thead>
<tbody>
<tr>
<td>ACVR2</td>
<td>ActRII ActRIIA</td>
<td>2q22.2-23.3</td>
<td>Activins, BMPs</td>
<td>Gastrointestinal cancers</td>
<td>102581</td>
</tr>
<tr>
<td>ACVR2B</td>
<td>ActRIIB</td>
<td>3p22-21.3</td>
<td>Activins, nodal GDF11, myostatin</td>
<td>Left-right axis malformation</td>
<td>+602730</td>
</tr>
<tr>
<td>ACVR1</td>
<td>ALK2 ACVRLK2</td>
<td>2q23-24</td>
<td>BMPs</td>
<td>Fibrodysplasia ossificans progressiva (FOP, OMIM135100)</td>
<td>102576</td>
</tr>
<tr>
<td>ACVR1B</td>
<td>ALK4 ACVRLK4</td>
<td>12q13</td>
<td>Activins, nodal GDF11, myostatin</td>
<td>Pancreatic carcinoma, Pituitary tumor</td>
<td>601300</td>
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<tr>
<td>ACVR1C</td>
<td>ALK7</td>
<td>2q24.1-3</td>
<td>Activin AB, activin B, nodal</td>
<td></td>
<td>608981</td>
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<tr>
<td>TGFBR1</td>
<td>ALK5</td>
<td>9q33-34</td>
<td>TGF-βs, GDF11, myostatin</td>
<td>Aortic aneurysm, Loeys-Dietz syndrome</td>
<td>190181</td>
</tr>
</tbody>
</table>

Gene locus and relationship to human diseases of the listed activin receptors are available from OMIM database.
nase domains retain ligand-binding activity similar to wildtype receptors. Soluble ActRIIs are useful to block actions of ligands that bind to ActRIIs. To enhance stability in vivo, the Fc domain of IgG was fused at the COOH-termini of ActRIIs. As mentioned above, soluble ActRIIB has a strong muscle enhancing activity [24]. When 6 week-old female mice were injected with ActRIIB/Fc, a 39–61% increase of skeletal muscle mass was achieved [24]. It is likely that soluble ActRIIB/Fc may inhibit the activities of various ligands including myostatin, activins, GDF11 and other unidentified ligands. Whether soluble ActRII has a similar activity to soluble ActRIIB remains to be determined. Since activin signaling through ActRII is involved in the development of pancreatic islets, apoptosis of hepatocytes, tubulogenic morphogenesis of vessels and osteogenesis, soluble ActRII would affect digestive organs, endocrine pancreas, vasculogenesis and osteogenesis [45, 46, 59–61].

Interestingly, the pseudo-receptor BMP and activin membrane-bound inhibitor, called BAMBI, was identified [62]. BAMBI shares 53% similarity with BMP type I receptor, ALK3, and lacks an intracellular serine/threonine kinase domain. BAMBI interacts with the intracellular domain of several type I receptors for TGF-β, activin and BMPs, and inhibits the formation of active receptor signaling complex. In this sense, BAMBI serves as an endogenous dominant negative receptor. Interestingly, the expression level of BAMBI was aberrantly elevated in most colorectal and hepatocellular carcinomas by activation of β-catenin signaling [63]. This suggests that β-catenin interferes with TGF-β and activin-mediated growth arrest by inducing the expression of BAMBI, and this may contribute to colorectal and hepatocellular tumorigenesis [63].

B. Ligand binding proteins

Many of the TGF-β superfamily member have distinct ligand-binding proteins. They are important regulators of signaling for the TGF-β superfamily. Follistatin is the prototype of activin-binding protein [64, 65] and is a cysteine-rich single chain protein that exhibits a high affinity activin binding activities. Mice lacking the follistatin gene showed musculoskeletal and cutaneous abnormalities due to excess signaling of activins and other related ligands [66]. In fact, follistatin not only inhibits activins but also myostatin and GDF11 [32, 43].

The crystallographic structures of the follistatin-activin complex were reported [67, 68]. The activin-inhibiting fragment of follistatin comprises two consecutive follistatin domains. They encircle activin, neutralizing the ligand by burying one-third of its residues and receptor binding sites. Both type I and type II receptor binding sites of activin are blocked by follistatin binding to activin, explaining the strong activin inhibiting actions of follistatin [67, 68]. The follistatin-related gene, called FLRG, is a recently characterized follistatin-domain containing protein. Like follistatin, FLRG binds and neutralizes activin, myostatin and a subset of BMPs [69, 70]. Both in human and mouse sera, FLRG proteins were shown to be associated with myostatin [71]. FLRG gene deletion indicates that FLRG is involved in glucose metabolism and fat homeostasis by regulating the action of activin, myostatin and related ligands [72]. Noggin, chordin, and DAN/Cer family are BMP inhibitors that regulate BMP activities [73]. Each BMP inhibitor shows a preferential binding to BMP family members.

C. Cripto

The nodal co-receptor Cripto plays a regulatory role in signaling through activin receptors [6, 74]. Cripto can bind both to nodal and activin receptors and is an essential component of nodal signaling. Interestingly, Cripto also binds and inhibits activin B, and functional blocking of Cripto by monoclonal antibody enhances activin B signaling and suppresses tumor cell growth [74]. Cripto also has TGF-β binding activity and can reduce association of TGF-β with its type I receptor and inhibits TGF-β signaling [75].

D. Chemical kinase inhibitors

SB431542 was the first chemical inhibitor of TGF-β type I receptor kinase to be developed [76]. SB431542 is selective for inhibition of ALK4/5/7. Chemical TGF-β type I receptor inhibitors may offer novel drug options for cancer therapy by preventing cell proliferation, angiogenesis, metastasis and fibrosis [76, 77]. Other chemical TGF-β inhibitors, SB505124, LY364947, A-83-01, Ki26894 have also been subsequently developed [78–81].

TGF-β type I receptor kinase inhibitors inhibit TGF-β, activins, nodal and myostatin that signal
through ALK4/5/7. Since intracellular kinase domains of ALK4/5/7 are structurally very similar, SB431542 and chemical TGF-β type I receptor inhibitors do not discriminate ALK4/5/7 and inhibit all three receptors. Thus, it must be kept in mind that undesirable side effects may occur by inhibiting multiple ligands.

VI. Perspectives

Signaling through activin receptors controls cell growth and differentiation, hormonal homeostasis, and development and regeneration of musculoskeletal system. Understanding the regulation of signaling through activin receptors should shed light on the mechanism of this diverse signal transduction network. Activin, myostatin, GDF11 and nodal signal through receptor combinations of ActRIIs and ALK4/5/7. TGF-β-specific Smads, Smad2/3, act downstream of activin, myostatin, GDF11 and nodal. ActRIIs are shared with BMP6 and BMP7. BMPs signal through a combination of type II receptors, ActRIIs and BMPRII, and type I receptors, ALK1/2/3/6. BMP-specific Smads, Smad1/5/8 are downstream effectors for BMPs. Extracellular ligand binding proteins are important regulators of the TGF-β superfamily. Follistatin and related proteins are potent inhibitors of activins and myostatin, whereas BMP inhibitors control BMP activities throughout development and in adulthood.

To inhibit signaling through activin receptors, various strategies are possible. In section V, dominant negative activin receptors, ligand-binding proteins, Cripto and chemical kinase inhibitors are listed as inhibitors of activin receptor signaling, since they are useful therapeutic tools for human diseases. Small interfering RNAs for components of activin receptors may also become promising therapeutic tools to inhibit activin receptor signaling. In addition, functions of signaling through activin receptors are regulated by intracellular receptor binding proteins. Adaptor protein Dok-1 associates both with activin receptors and Smads, and is indispensable for activin-induced apoptosis [82]. Activin type II receptors are unique among serine/threonine kinase receptors in that PDZ protein-binding motifs are found at their COOH-terminus (Fig. 1). Two PDZ proteins, activin receptor interacting proteins I and 2 (ARIP1 and 2), were identified by two-hybrid screening system to bind with ActRIIs [83, 84]. ARIP1 is likely to act as a scaffolding molecule for ActRIIs in the submembraneous regions [83]. ARIP2 is involved in endocytosis and trafficking of ActRIIs [84]. FKBP12 that associates with the GS domain for type I receptors might have inhibitory role of receptor activation [85].

Signaling through activin receptors are targets of multiple human diseases including muscular dystrophy, bone formation and cancers. Inhibition of myostatin is one of the plausible options of therapy against muscular dystrophies. Abnormalities of activin receptor signaling are common in cancers of digestive and endocrine organs. Disregulation of the activin signaling pathway has a role in pathogenesis of tumors and regulation of this pathway would have therapeutic potential in cancer.

In summary, the signaling pathway through activin receptors and its involvement in intractable muscular diseases and cancer are highlighted in this review. It is hoped that therapeutic interventions targeted to this signaling pathway through activin receptors would enter clinic trials in near future.

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