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Review

Recent topics in fibrodysplasia ossificans progressiva

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ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder characterized by progressive heterotopic bone formation in skeletal muscle tissue. Patients with FOP show malformed digits, osteochondroma, and other skeletal abnormalities due to abnormal patterning during development. Heterozygous mutations in the Activin A receptor type I (*ACVR1*) gene, which encodes the bone morphogenetic protein (BMP) type I receptor ALK2, have been identified in not only typical FOP patients but also patients with unusually mild or severe clinical features. The serine/threonine kinase activity of ALK2 may be constitutively activated by mutations in the GS domain or the kinase domain. Based on these findings, selective small chemical inhibitors and allele-specific RNAi approaches for mutant ALK2 have been developed for preventing heterotopic bone formation in FOP. Other novel treatments have also been reported to block heterotopic bone formation in patients with FOP. These findings open the door to the next step in FOP treatment and related research.

Contents

1. Introduction

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder that causes progressive heterotopic bone formation in skeletal muscle tissue [1–3]. A heterozygous substitution of "G" with "A" in the Activin A receptor type I (*ACVR1*) gene at position 617 (c.617 G > A) has been identified in both familial and sporadic cases of FOP [4]. The *ACVR1* gene encodes ALK2, a type I receptor for bone morphogenetic proteins (BMPs), which are potent bone growth-inducing factors in mammals [3]. BMPs, but not the related transforming growth factor-β (TGF-β) or activin, are able to induce heterotopic bone formation in skeletal muscle tissue [3,5]. The differences in the biological activities of BMPs and other members of the TGF-β family are explained by the specific intracellular signaling pathways that are activated through cell surface BMP receptors.

The members of the TGF-β family bind to type I and type II receptors on their target cells [5] (Fig. 1). Both types of receptors are transmembrane serine/threonine kinases. Type I and type II receptors recognize different types of substrates and are classified on the basis of their structures. Type I receptors have a conserved "GS" domain, which is a glycine- and serine-rich domain in the intracellular region. These receptors are inactive kinases until bound to a ligand. Type II receptors lack the GS domain and are constitutive active kinases that phosphorylate the GS domain of

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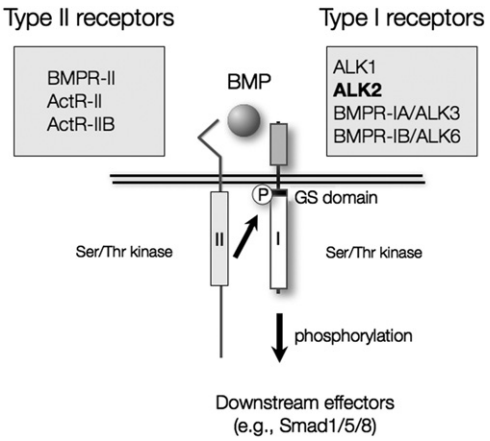

Fig. 1. BMP and its receptors. BMPs bind to type I and type II receptors, which are transmembrane serine/threonine kinases that are expressed on the cell membrane. The type II receptors (BMPR-II, ActR-II, and ActR-IIB) phosphorylate the GS domain of the type I receptors (ALK1, ALK2, BMPR-IA/ALK3, and BMPR-IB/ALK6). The activated type I receptors subsequently phosphorylate downstream effectors, such as Smad1/5/8, in the cytoplasm.

the type I receptors in the ternary complex that is formed on ligand binding. BMP signaling is transduced by 4 types of type I receptors (ALK1, ALK2, BMPR-IA/ALK3, and BMPR-IB/ALK6) and 3 types of type II receptors (BMPR-II, ActR-II, and ActR-IIB) (Fig. 1). The phosphorylation of the GS domain activates the kinase activity of type I receptors by changing their three-dimensional structures. Thus, the GS domain is considered the molecular switch of the type I receptor.

The c.617 G > A mutation in the *ACVR1* gene, which was first identified in patients with FOP, causes an arginine-to-histidine substitution at position 206 (p.R206H) in ALK2 [4]. The p.R206H mutation is located in the GS domain and is expected to change the kinase activity of ALK2 in patients with FOP [4]. The overexpression of the mutant ALK2 p.R206H induces a set of BMP signaling cascades in cultured cells [6,7]. Therefore, FOP is considered the first example of a genetic condition caused by the gain of function of BMP receptors in mammals. Recently, genetic diagnoses have identified variants of FOP that have different clinical features and are caused by novel mutations at different positions in ALK2. In addition, some novel potential treatments have been found to block or reduce the heterotopic bone formation induced by the mutant ALK2 in a mouse model of FOP and in patients with FOP.

2. Typical features of FOP

The p.R206H mutation in ALK2 was the first identified substitution in FOP. This typical mutation is found not only in sporadic cases but also in familial cases of FOP in several different populations, including African-American, European American, European (UK), Korean, native Brazilian, and Japanese patients [4,7,8]. FOP is transmitted in an autosomal dominant fashion. In early studies, mutations in a 36 cM region at chromosome 4q27–31 and in the *NOG* gene (encoding the BMP antagonist noggin) were reported as potentially responsible for FOP, but the *ACVR1* gene was mapped to chromosome 2q23–24 [4,9,10]. Causative mutations in the *NOG* gene have since been excluded by linkage and mutational analyses [11]. The overexpression of BMP-4 in lymphocytes has been reported in FOP patients, suggesting that BMP-4 is one of the downstream target genes of BMP signaling in a positive feedback loop [12].

Most patients with the p.R206H mutation exhibit a malformation of the big toes (hallux), i.e., hallux valgus, as one of the typical phenotypes that can be recognized at birth before heterotopic bone formation begins. In 16 Japanese patients, 29 out of 31 feet (93.5%) showed hallux deformities at various degrees [13]. Patients with the p.R206H mutation also showed osteochondroma of the proximal tibia and other skeletal malformations due to disorganized patterning during development [1].

Heterotopic bone formation in FOP patients can be induced by local skeletal muscle injury, including intramuscular immunization, biopsy, and surgical operation [1]. Influenza-like illnesses are also known to induce heterotopic bone formation in FOP patients. However, heterotopic bone formation is not observed in the diaphragm, tongue, extra-ocular muscles, cardiac muscle, or smooth muscles of patients with FOP [1–3]. The molecular-level differences between the bone-inducible and bone-uninducible muscles are still unknown.

FKBP12 binds to the immunosuppressive drug FK506 and has been suggested to be involved in the suppression of intracellular signaling via type I TGF-β and BMP family receptors [14,15]. It binds to the GS domain of unbound receptors and is released through the phosphorylation of the GS domain by type II receptors in response to ligand binding [15]. The p.R206H mutation has been shown to reduce the affinity of ALK2 for FKBP12, in the absence of ligand binding, in a pH-dependent manner [16].

3. Variations in FOP

After the identification of the p.R206H mutation in ALK2 in 2006, additional genetic mutations have been found in the coding region of *ACVR1* in patients who show heterotopic bone formation and other skeletal abnormalities (Fig. 2). In the GS domain of ALK2, 4 mutations have been found in addition to p.R206H: p.L196P, p.P198-F199del_insL, p.R202I, and p.Q207E [17–19]. Moreover, several mutations have been found in the serine/threonine kinase domain of ALK2, such as p.R258S, p.G325A, p.G328E/R/W, p.G356D, and p.R375P [18–23]. Some of the mutations in the kinase domain have been suggested to be exposed at the interface with the GS domain and to be involved in the interaction with FKBP12 [19,20].

The clinical features in patients with these mutations in ALK2, except p.R258S, are different from those in patients with the

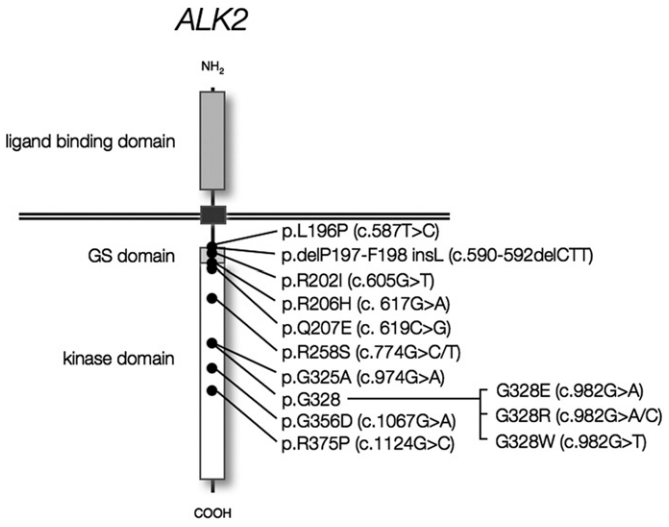

Fig. 2. Mutations in *ACVR1*/ALK2 identified in patients with FOP. Each number indicates the position of a mutation detected in the cDNA of the *ACVR1* gene (c) or in the ALK2 protein (p). Note that all of the mutations are localized to the intracellular domain of ALK2.

p.R206H mutation. Four independent patients with the p.G356D mutation exhibited shortening/truncation malformations of the thumbs and halluces [18,23]. Severe malformations in the thumbs and halluces were observed in other patients who had the p.G328W and p.G328E mutations [18,22]. The tight link between heterotopic bone formation, the mutations in ALK2, and the malformations of the digits suggests that the fine-tuning of BMP signaling is required for the normal development of the skeletal muscle, thumbs, and halluces. Indeed, it was reported that the transient activation of BMP signaling is essential for normal muscle regeneration in adult mice [24]. Moreover, deletion of the *Bmp-4* and/or *Bmp-7* gene causes skeletal abnormalities, including polydactyly, in newborn mice [25].

In contrast to the severe digital phenotypes seen in FOP patients, some patients who have other mutations in ALK2 have milder phenotypes, especially with respect to heterotopic bone formation in the muscle. One patient did not have hallux malformations at birth but developed trismus and heterotopic bone formation in the thigh muscle after a motorbike accident at the age of 21 years [17]. The p.L196P mutation was identified in this patient by sequencing [17]. Modeling of p.L196P *in silico* revealed a steric clash with the kinase domain that is predicted to weaken its interactions with FKBP12 [17]. The overexpression of the p.L196P mutant in C2C12 myoblasts induced BMP signaling equivalent to that of the p.R206H mutant, at least *in vitro*, suggesting that the p.L196P mutation activates ALK2. However, ALK2 activity may have been suppressed *in vivo* (*i.e.*, in the patient) by some unknown molecular mechanism prior to the motorbike accident [26].

Recently, another novel mutation in ALK2 was identified in a patient with congenital hallux valgus. In this patient, heterotopic bone formation was induced by a viral illness at age of 47 years [27]. Analysis of the *ACVR1* gene revealed heterozygosity of a c974G > C mutation that causes a p.G325A substitution in ALK2 [27]. Another FOP patient, who had normal toes and showed slow progression of heterotopic bone formation, had a c.1124 G > C mutation that caused a p.R375P substitution [18]. Together with the p.L196P case, these FOP cases with late-onset heterotopic bone formation suggest the importance of the genetic diagnosis of FOP even in patients who do not show typical clinical features.

4. Development of treatments for preventing heterotopic bone formation

Although there is no effective treatment for preventing heterotopic bone formation in FOP, several trials of new treatments have been initiated based on the ALK2 findings (Fig. 3).

Because most of the ALK2 mutations found in FOP patients represent activated forms of the BMP receptor, a specific inhibitor of this receptor would prevent the intracellular signaling induced by the mutant ALK2. LDN-193189 was developed on the basis of structure of dorsomorphin, which inhibits the phosphorylation of Smad1/5/8 but not p38 by BMP type I receptors. Treatment with LDN-193189 reduced heterotopic bone formation in mice carrying a p.Q207D mutation in ALK2 [28]; it should be noted that this mutation has not been identified in FOP patients. Recently, two small compounds produced by fungi, NG-391 and NG-393, were shown to inhibit BMP signaling by mutant ALK2 (p.R206H) *in vitro* [29].

Recently, retinoic acid and related chemical compounds were found to be potent inhibitors of BMP signaling induced heterotopic bone formation in the skeletal muscle [30]. Because BMPs induce heterotopic bone formation via endochondral ossification, retinoic acid was examined as an inhibitor of chondrogenesis *in vitro* and *in vivo*. The inhibitory activity of retinoic acid is

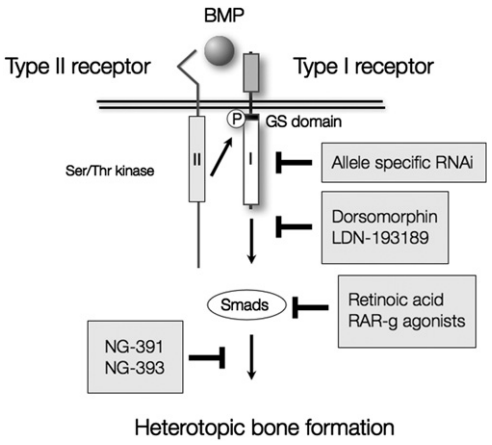

Fig. 3. Treatments for preventing heterotopic bone formation in FOP. Treatments developed for preventing heterotopic bone formation are indicated in this schematic of BMP signal transduction. The details are explained in the text.

mediated via RAR-γ but not RAR-α or RAR-β [30]. A synthetic selective agonist of RAR-γ inhibited heterotopic bone formation induced by BMP-2 in skeletal muscle [30]. Other types of RAR-γ agonists also had similar effects on heterotopic bone formation. Among them, CD1530 blocked FOP-like heterotopic bone formation in mutant mice carrying the ALK2 p.Q207D mutation [30]. CD1530 has been suggested to inhibit BMP signaling by reducing SMAD protein levels [30].

Chemical inhibitors of BMP receptors may suppress the intracellular signaling induced by both wild-type and mutant ALK2. To develop a specific inhibitor of mutant ALK2, allele-specific RNAi has been tested. Double-stranded small RNAs with simple mutations targeting the p.R206H-coding transcript were not allele specific and inhibited both the mutant and wild-type *ACVR1* transcripts *in vitro* [31]. However, the introduction of a single additional nucleotide mutation in the RNA generated an allele-specific dsRNA that suppressed the expression of only the mutant ALK2 [31]. This allele-specific inhibition by RNAi was confirmed to suppress expression of both the p.R206H and p.G356D mutant proteins [31]. Thus, allele-specific RNAi may represent a novel type of treatment for FOP.

5. Treatments preventing heterotopic bone formation in FOP

There has been one case report of FOP that described the prevention of heterotopic bone formation for 14 years [32]. The patient, who had a c.617 G > A mutation, received bone marrow transplantation for the treatment of intercurrent aplastic anemia. No heterotopic bone formation occurred during the 14 years during which the patient received immunosuppressive drug treatment (prednisone, cyclosporine, and methotrexate) after the bone marrow transplantation [32]. However, heterotopic bone formation resumed when the patient discontinued these medications. This resumption of heterotopic bone formation indicates that bone marrow transplantation is not an effective treatment for FOP in spite of the fact that BMP-4 overexpression in lymphocytes has been reported previously to underlie heterotopic bone formation. This case also suggests that the immune system may be involved in the induction of bone formation in FOP patients.

Recently, it was reported that a combination of rosiglitazone and low doses of prednisone effectively prevented heterotopic bone formation in a patient with FOP [33]. The suggested molecular mechanism of this action is that rosiglitazone induces the activation of PPAR-γ, which promotes the differentiation of bone marrow mesenchymal stem cells into adipocytes rather

than into osteoblasts. These two case reports suggest that treatments that do not directly block BMP signaling may still effectively prevent heterotopic bone formation in FOP patients.

A recent finding describing a role for vascular cells suggests an alternative treatment strategy [34]. Endothelial cells express some cell surface-specific markers, such as Von Willebrand factor (vWF) and TIE-2. Immunohistochemical staining of the heterotopic bones formed in FOP patients showed that both chondrocytes and osteoblasts, which were identified by staining with anti-Sox9 and anti-osteocalcin respectively, were co-stained with vWF and Tie-2. In normal bone tissues, these endothelial markers were not detected in either chondrocytes or osteoblasts, suggesting that endothelial cells transdifferentiate into mesenchymal cells in FOP patients. Indeed, the over-expression of ALK2 p.R206H, but not wild-type ALK2, induced the mesenchymal transdifferentiation of cultured endothelial cells into osteoblasts, chondrocytes, and adipocytes [34]. Moreover, the treatment of endothelial cells with BMP-4 and TGF-β2 did not induce heterotopic bone formation *in vivo* but did induce the same changes *in vitro* [34]. These findings suggest that the conversion of endothelial cells into mesenchymal cells is a critical molecular mechanism underlying heterotopic bone formation in FOP patients.

6. Conclusions

All patients with FOP exhibit mutations in the GS domain or kinase domain of ALK2, a type I BMP receptor. Although most FOP patients share many common clinical features, several novel phenotypic variations that characterize FOP have also been found. The genetic diagnosis of FOP through the sequencing of the *ACVR1* gene is useful. The development of specific inhibitors of ALK2 and other types of treatment will be useful to prevent heterotopic bone formation in FOP patients.

Conflict of interest

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