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Martina Rauner¹ · Lothar Seefried² · Eileen Shore³¹ Department of Medicine III & Center for Healthy Aging, Technische Universität Dresden, Dresden, Germany² Department of Orthopedics, University of Würzburg, Würzburg, Germany³ Departments of Orthopedics and Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA

Genetics and future therapy prospects of fibrodysplasia ossificans progressiva

Introduction

Fibrodysplasia ossificans progressiva (FOP, OMIM #135100) is an autosomal dominant genetic disease that has an estimated prevalence of 1 in 1–2 million and affects individuals regardless of gender, race, ethnicity or geographical location. In France, which has well-maintained national registries for rare diseases, the prevalence was determined to be 1 in 1.36 million [1]. Most cases of FOP are due to *de novo* mutations in the activin receptor 1 (ACVR1) gene, which is a type I bone morphogenetic protein (BMP) receptor [2].

Affected patients suffer from excessive heterotopic ossification in skeletal muscle, tendons, ligaments, and fascia that episodically occur in a non-predictable manner and is often preceded by flare-ups, which are soft-tissue swellings that are associated with pain and inflammation. In addition, all patients with the classical clinical presentation of FOP display characteristic malformations of the great toes, which are often short, deviated, and monophalangeal, but otherwise patients appear normal at birth.

The sporadically occurring flare-ups usually start within the first decade of life. Flare-ups may also occur as a result of minor trauma such as intramuscular immunisations, falls, bruises, and mandibular blocks for dental work. In particular, surgeries to remove or sample heterotopic bone must be avoided, as this tissue trauma provokes further

extensive and painful ossifications [3]. Interestingly, heterotopic ossification in FOP patients appears to follow a specific pattern, starting from cranial to caudal, from proximal to distal, from dorsal to ventral, and from axial to appendicular [4]. Some other muscles, including the diaphragm, tongue, and extra-ocular muscles, as well as the cardiac muscle and smooth muscles, are spared from heterotopic ossifications. During a patient's lifetime, heterotopic ossification continues to irreversibly accumulate, first leading to limitations of the daily activities of life, such as brushing teeth or combing hair, and later leading to progressive loss of mobility and autonomy. Patients are often bound to a wheel-chair and dependent on lifelong assistance by their second to third decade of life. Based on a cross-sectional study of 371 patients, the median age of survival was estimated to be about 56 years [5]. Death often results from complications of thoracic insufficiency syndrome, such as pneumonia or right-sided heart failure. To date, there have been no specific therapies for FOP.

Clinical presentation

Besides the defining hallmarks of classic FOP, which are the formation of postnatal heterotopic bone and malformation of the great toes, other skeletal anomalies have been reported, particularly in the thumbs and the cervical spine [6]. Stiffness of the neck due to congenital malformations, with tall narrow verte-

bral bodies, enlarged pedicles and large spinous processes, along with variable fusion of the posterior part, typically the facet joints of the segments C2–C7, is often an early finding in patients and precedes the development of heterotopic bone. Heterotopic ossifications occurring later may further impair mobility of the cervical spine [7]. Many patients develop severe scoliosis, which later in life can lead to thoracic insufficiency syndrome. In addition to the deformities in the vertebrae, further skeletal manifestations are short broad femoral necks, malformed thumbs and clinodactyly at the fifth digit, as well as osteochondromas, typically at the proximal medial tibia. Other reported anomalies include hearing loss, alopecia, mild mental retardation, cataracts, glaucoma, short stature, and some common facial characteristics such as reduced mandible and retrognathia, underdeveloped supra-orbital ridge, low-set ears and elongation of the lateral pterygoid plate [3, 8–10].

In 2009, a large study with 112 FOP patients was conducted and a classification of FOP was attempted [8]. A small proportion of FOP patients (3%) have been described with phenotypic manifestations that are unusual for classic FOP. These either occur in addition to classic FOP (termed FOP plus) or present variations in one or both of the defining features (termed FOP variants). Manifestations described in that context include persistence of primary teeth, absence of finger and toenails, sparse hair, retinal

detachment, as well as mild cognitive impairment and cerebellar abnormalities [8, 11]. Building on that, a recent MRI study of 13 patients (11 with the R206H variant, 2 with non-R206H mutations) indicated various changes in the brain of FOP patients, including small lesions in the dorsal medulla and ventral pons, minor dysmorphism of the brainstem, and an enlarged origin of the vestibulocochlear nerves. However, all of these alterations were asymptomatic [12].

Diagnosis

In 2005, a survey was performed with 269 patient-members of the International FOP Association, with about half of them completing the questionnaire [13]. These patients were from 25 different countries and accounted for about half of all known FOP patients worldwide at that time. This study revealed that 87% of FOP patients were misdiagnosed at first, most frequently with cancer. It took a median of 4 years from the onset of the first symptoms until a correct diagnosis. Unnecessary invasive procedures, including biopsies, were performed in 67% of the patients and 68% received inappropriate therapies. In a more recent survey launched by the International FOP Association, with 196 enrolled patients, a mean age of 5.4 years was reported when patients noticed the first symptoms and 7.5 years when they were first diagnosed with FOP [14]. Provided that clinicians are aware of the cardinal symptoms of classic FOP, which is too often inadequately described in medical text books [13], the vast majority of cases can be correctly diagnosed if soft-tissue lesions are associated with the malformations of the great toe, even without radiography or genetic testing [15].

Genetics

All mutations associated with FOP have so far been mapped to the *ACVR1* gene and can be transmitted by autosomal dominant inheritance. Most cases of FOP occur because of spontaneous new mutations, although some familial cases have been reported [16–18]. Even though over 90% of all patients have the recurring

missense mutation c.617G>A; R206H, there is considerable phenotypic heterogeneity, likely through contributions by the varied genetic backgrounds of individual persons. In addition to genetic influences, the environment and lifestyle of the patient have significant influence, as demonstrated by the differences in disease progression among pairs of identical twins with FOP [19].

The R206H missense mutation is located in the glycine serine (GS)-rich domain of *ACVR1*, which is a critical site for binding and activation by ligand-activated BMP type II receptors and for FKBP12, which is an inhibitory protein that prevents the leakiness of BMP type I receptor signalling in the absence of ligand. In silico modelling supports the notion that the R206H mutation leads to a conformational change of the receptor [16]; such a structural change could weaken FKBP12 binding, bypass a requirement for ligand binding, and/or increase responsiveness to atypical ligands, thereby modulating downstream signalling events [2, 20–22].

In addition to the R206H mutation, which has been reported in over 200 patients, about 15 other mutations in the GS domain and the protein kinase domain of *ACVR1* have been identified in FOP patients. These have been summarised in Huning et al. [23] and were also predicted by protein structure homology modelling to activate the *ACVR1* protein and enhance receptor signalling [8]. With regard to the genotype–phenotype correlation, the p.G328W and p.G328E mutations show early disease onset and severe progression of heterotopic ossification without being influenced by trauma, whereas patients with the p.G356D mutation seem to have a later disease onset, but with a quick progression. Patients with p.G328R mutations seem to have a milder disease course, with the ossifications being closely associated with surgical intervention/trauma. The amino acid changes p.R258S, p.R375P, and p.L196P also seem to be associated with a milder disease course that is not related to trauma or great toe malformation [8, 24, 25]. In many cases, the number of patients with specific mutations is low; thus, these associations must be interpreted with caution.

More recently, studies examining the activation of the BMP signalling pathway by FOP variant *ACVR1* mutations, have supported the notion that, in general, kinase domain mutations and GS domain mutations might activate signalling through different molecular mechanisms and responsiveness to ligands [26, 27].

Current therapy

Current therapy for FOP patients includes avoiding injuries or trauma to prevent flare-ups and subsequent ossification. Once trauma-induced or spontaneous flare-ups and ossifications occur, glucocorticoids are used to alleviate pain and swelling, and may also be used preventatively before inevitable invasive procedures, especially in the jaw [6, 28, 29]. The successful use of non-steroidal anti-inflammatory drugs has also been reported in single cases, but there is no evidence showing efficacy of these drugs to modulate disease activity. Surgical interventions to remove heterotopic bone should be avoided, as it usually counterproductive and provokes further ossifications. Overall, the options for the treatment of FOP are limited at present. Guidelines for FOP treatment were established by an international clinical consortium on FOP in 2011 and updated recently to help physicians to treat their patients effectively [30, 31]. This is particularly important, as many aspects are unique when it comes to caring for patients with FOP (e.g. prophylaxis against pneumonia and influenza, dental visits, anaesthesia etc.). Specific recommendations are also provided in Pignolo et al. [6, 31].

Future therapeutic strategies based on the underlying mechanisms of FOP

After the identification of *ACVR1* as the causative gene for FOP, the door opened to investigations into the mechanisms of action of the disease. *ACVR1* is a BMP type I receptor that is usually activated upon binding of BMP ligands. Together with BMP type II receptors, *ACVR1* activates canonical Smad1/5/8 signalling, but also non-canonical BMP signalling,

such as through MAPK, has been identified. The gain-of-function mutations in the GS domain of the *ACVR1* lead to two distinct features of the protein: first, they result in the constitutive activation of the receptor, meaning that it can activate downstream Smad signalling, even in the absence of ligand [32–34], and second, it may alter the binding properties of ligands. As such, activin A, which normally transduces its signal via Smad2/3 through the ACVR2/ACVR1B complex, gains enhanced ability to activate the mutated ACVR1, induce Smad1/5/8 signalling, and promote heterotopic ossification similar to typical osteogenic TGF- β family members (i.e. BMP2, BMP4, BMP6, BMP7, BMP9) [22, 27, 35, 36]. Besides Smad1/5/8 signalling, mutated ACVR1 has also been shown to induce mTOR and phosphatidylinositol 3-kinase α (PI3K α) signalling [37, 38]. Based on these findings, various treatment strategies have been explored, either blocking excessive BMP/Smad signalling or inhibiting activin A or activin A-induced downstream signalling. These are discussed in more detail in the following sections.

Blocking hyperactive BMP signalling

Various approaches to blocking excessive BMP signalling have been examined. These include RNA interference approaches, blocking the activity of the mutant R206H ACVR1 receptor [39, 40]. These approaches decreased the increased Smad1/5/8 signalling in mesenchymal cells derived from FOP patients or in muscle and bone cells overexpressing mutant ACVR1. Other approaches were directed at blocking ACVR1, which belongs to the family of BMP type I receptors using dorso-morphin or other synthetic molecules (LDN-193189) [41, 42]. All of these approaches significantly reduced heterotopic ossification in mouse models of activated ACVR1 activity. However, these approaches block all three BMP type I receptors (BMPRI1/ALK3, BMPRI1B/ALK6, ACVR1/ALK2), and thus do not confer specificity to the FOP

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M. Rauner · L. Seefried · E. Shore

Genetics and future therapy prospects of fibrodysplasia ossificans progressiva

Abstract

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant genetic condition characterised by progressive extra-skeletal bone formation in connective tissues. Over time, heterotopic ossification entombs patients within a second skeleton, drastically impairing their mobility and autonomy. Mutations in the *ACVR1* gene have been identified as the cause of FOP. The single nucleotide missense mutation in *ACVR1*, c.617G > A, causes a single amino acid substitution, p.R206H, and is found in >90% of all patients. Heterotopic bone formation in FOP mimics embryonic skeletal endochondral ossification, with cartilage forming after fibroproliferative tissue condensation as an intermediate stage prior to osteogenesis and tissue ossification. In contrast to normal embryonic endochondral ossification,

heterotopic ossification in FOP involves an inflammatory phase that precedes cartilage and bone formation. New insights into the mechanisms of action of heterotopic bone formation in FOP have led to the discovery of new potential treatment targets including inhibitors of BMP signalling, activin A inhibitors, and mTOR inhibitors. This review summarises the current knowledge on mutations causing FOP, as well as the molecular basis of heterotopic ossification and the therapeutic options that result from these discoveries.

Keywords

Fibrodysplasia ossificans progressiva · FOP · Heterotopic ossification · BMP signaling · ACVR1

Genetik der Fibrodysplasia ossificans progressiva und zukünftige Therapieansätze

Zusammenfassung

Fibrodysplasia ossificans progressiva (FOP) ist eine äußerst seltene Erkrankung, die autosomal-dominant vererbt wird und zu einer extraskelettalen Ossifikation von Bindegewebe führt. Die über die Zeit akkumulierenden Ossifikationen zwingen Patienten in ein zweites Skelett, welches ihre Mobilität und Autonomie drastisch einschränkt. Als Ursache dieser Erkrankung wurden Mutationen im *ACVR1*-Gen identifiziert. Die am häufigsten auftretende Mutation ist eine Punktmutation, c.617G > A, welche eine Substitution der Aminosäure p.R206H hervorruft. Dies führt zu einer veränderten Signalweitergabe durch den ACVR1-Rezeptor, welcher Teil des osteogenen *bone morphogenetic protein* (BMP)-Signalwegs ist und Ossifikationen

auch außerhalb des Knochens verursacht. Durch die kürzlich erworbenen Erkenntnisse über die der heterotopen Ossifikation bei FOP zugrunde liegenden Mechanismen konnten neue potenzielle Therapiestrategien entwickelt werden. Diese umfassen den Einsatz von Hemmern des BMP-Signalwegs sowie Activin A- und mTOR-Inhibitoren. Dieser Übersichtsartikel fasst die aktuellen Erkenntnisse zur Pathogenese der FOP zusammen und erläutert die sich daraus ergebenden neuen Therapieansätze.

Schlüsselwörter

Ektopen Ossifikation · Knochenerkrankungen · Osteoblast · Osteoklast · Versteinerung

mutations, possibly causing adverse effects.

Additional approaches include the inhibition of ligand binding to ACVR1. As such, ligand traps have been used, including ACVR2B-Fc and ACVR2A-Fc. These ligand traps are made of the extracellular domain of ACVR2B and ACVR2A and are fused to the constant region of IgG1 [43]. Both molecules blocked het-

erotic ossification in mice, indicating that one or more of the ligands that are blocked by these traps are required to induce heterotopic ossification in FOP [21]. In another study, the BMP binding properties of transferrin receptor 2 were used as a ligand trap and also showed efficacy in reducing BMP-2-induced heterotopic ossification [44]. However, this

latter approach requires further validation in mouse models of FOP.

Finally, one of the most promising approaches in blocking BMP signalling is palovarotene, a retinoic acid receptor agonist that has been identified to indirectly block Smad1/5/8 signalling by activating the retinoid signalling pathway through RAR γ receptors and inhibiting chondrogenesis and subsequent heterotopic endochondral ossification [45, 46]. This agent showed great success in reducing the volume of new heterotopic ossifications in patients with FOP (>70%) in a phase II trial and is currently being tested in the MOVE trial (NCT03312634), a phase III clinical study. Even though palovarotene is generally well tolerated and showed the expected side effect profile of retinoids (e.g. mucocutaneous side effects, liver toxicity and abnormalities of serum lipid profiles), high levels of daily intraperitoneal treatment with palovarotene in juvenile animals carrying the R206H mutation suggested synovial joint overgrowth and long bone growth plate ablation [47]. However, lower doses of an orally administered RAR γ agonist inhibited HO formation in juvenile *Acvr1*^{R206H/+} mice without these negative effects and additionally partially rescued growth plate defects induced by the FOP mutation [46]. Long-term follow-ups and monitoring of patients will be necessary to fully evaluate the spectrum of effects of palovarotene on children and adults with FOP.

Inhibiting activin A signalling

The discovery that the R206H mutation in the *ACVR1* gene leads to increased Smad1/5/8 responsiveness to activin A has led to the development of neutralising antibodies for activin A as a treatment for heterotopic ossification in FOP [21]. This approach been tested in cells carrying the R206H *ACVR1* mutation and in mouse models of FOP and showed great efficacy in reducing heterotopic ossification. Moreover, pSmad1/5/8 signalling by activin A has also been demonstrated in induced pluripotent stem cells (iPS) from FOP patients [22]. This antibody is now also under in-

vestigation in clinical trials (REGN2477, NCT03188666). Activin A is important in several cell and tissues, including immune cells and the reproductive system; therefore, as for palovarotene, careful monitoring and patient follow-up will provide information about the long-term effects of this treatment.

Additional treatment strategies

Another strategy to block aberrant *ACVR1* signalling is focused on mTOR signalling. This pathway was identified in a large chemical screen on FOP-iPSc, which shows increased chondrogenic and osteogenic potential in vitro [48]. Blocking mTOR signalling with rapamycin prevented activin A-induced chondrogenic and osteogenic differentiation and inhibited heterotopic bone formation in vivo [37]. In addition, BYL719, an inhibitor of PI3K α , inhibited Smad, Akt and mTOR signalling in cells or mice carrying *ACVR1* R206H or Q207D mutations [38]. Thus, these studies highlight the potential of blocking mTOR signalling for the treatment of FOP. However, mTOR signalling exerts direct functions on the skeleton that will need to be considered in the safety profile [49].

Finally, besides directly targeting aberrant pathways, the inflammatory phase of FOP is also a critical mechanism preceding heterotopic ossification and thus has been examined as a therapeutic intervention point. In particular, lesions are frequently heavily infiltrated with monocytes, macrophages and mast cells that may enhance the inflammatory immune response. Mast cells and macrophages from FOP patients have been shown to have an increased production of cytokines (IL-3, IL-7, IL-8 and IL-10) and chemokines (CCL5, CCR7 and CXCL10), as well as enhanced TGF- β , NF- κ B and MAPK signalling [50, 51]. Depletion of macrophages and mast cells decreased heterotopic ossification in a mouse model of FOP, suggesting that this might be an effective approach to halting ossification in FOP patients [51].

Considering that particularly the early, hypoxic inflammatory stages of

FOP flare-ups involve—amongst others—activation of HIF1- α , c-KIT, PDGFR- α and multiple MAP kinases, an off-label attempt has been made in a small series of seven children using the tyrosine kinase inhibitor imatinib, basically developed and approved for chronic myeloid leukaemia. Although not controlled study data, the results support the notion that treatment was well-tolerated and a decrease in the intensity of flare-ups was achieved in six of the patients [52]. Another approach that is being made concerns the development of a small molecule inhibitor with sufficient specificity for the ALK2 receptor to control undesired receptor activity [53].

Conclusions

Following the identification of mutations in *ACVR1* as the cause of FOP in 2006, we are now beginning to gain important insights into the molecular mechanism underlying this debilitating disease. In light of the rarity and severity of the disease, the robust interest in understanding its mechanisms of action and the great efforts that are being undertaken to develop new therapeutic approaches are highly promising. Many are working to translate these efforts into effective therapies that will benefit FOP patients, allowing them to conduct simple actions of daily life and to maintain mobility and autonomous living throughout their lives.

Corresponding address

Martina Rauner, PhD
Department of Medicine III & Center for Healthy Aging, Technische Universität Dresden
01307 Dresden, Germany
martina.rauner@ukdd.de

Compliance with ethical guidelines

Conflict of interest M. Rauner, L. Seefried and E. Shore declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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Hier steht eine Anzeige.

