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Fibrodysplasia ossificans progressiva: a blueprint for the metamorphosis

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Abstract

The most important milestone in understanding a genetic disease is the identification of the causative mutation. However, such knowledge is often insufficient to decipher the pathophysiology of the disorder or to effectively treat those affected. Fibrodysplasia ossificans progressiva (FOP) is a rare, disabling, genetic disease of progressive heterotopic endochondral ossification (HEO) enabled by missense mutations that promiscuously and provisionally activate ACVR1/ALK2, a bone morphogenetic protein (BMP) type I receptor, in all affected individuals. While activating mutations of the ACVR1/ALK2 receptor are necessary, disease activity and progression also depend on altered cell and tissue physiology. Recent findings identify inflammatory and immunological factors, vascular-derived mesenchymal stem cells, and a hypoxic lesional microenvironment that trigger, promote, and enable episodic progression of FOP in the setting of the genetic mutation. Effective therapies for FOP will need to consider these seminal pathophysiologic interactions.

Keywords

fibrodysplasia; ossificans progressiva; heterotopic ossification; BMP; ACVR1; ALK2

Between the acting of a dreadful thing and the first motion, All the interim is like a phantasma, or a hideous dream. The genius and the mortal instruments are then in council; And the state of man, like to a little kingdom, Suffers then the nature of an insurrection

Julius Caesar, II, I, Shakespeare

Introduction

Fibrodysplasia ossificans progressiva (FOP), a severely disabling genetic disorder of episodic and progressive heterotopic endochondral ossification (HEO), is caused by activating mutations in the gene encoding Activin A receptor type I/Activin-like kinase 2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type I receptor. ^(1,2) These activating mutations cause aberrant ACVR1/ALK2 receptor–FKBP1A interaction and consequent amplification of downstream bone morphogenetic protein (BMP) signaling. ^(3–6)

While the discovery of the FOP mutation is rapidly leading to an understanding of the genetic and molecular cause of FOP, less is known about the inflammatory triggers of FOP flare-ups, the cellular origins of FOP lesions, or the tissue microenvironment that supports episodic progression of the disease. Our central hypothesis is that soft tissue injury causes inflammation and tissue hypoxia that enhances and prolongs dysregulated BMP signaling, triggers the de-differentiation of vascular progenitor cells into mesenchymal stem cells (MSCs) through an endothelial-to-mesenchymal transition, and then differentiates the newly formed MSCs through an endochondral pathway in a BMP-conducive environment to form a second skeleton of heterotopic bone. A thorough understanding of the pathophysiology of FOP lesions will enable more informed approaches to effective therapies for this devastating disorder of skeletal metamorphosis.

There have been numerous, comprehensive reviews of FOP^(7–12) and the BMP signaling pathway. ^(13–16) Here, we focus on recent findings that foster a broad overview of the formation of FOP lesions.

The pathology of skeletal metamorphosis in FOP

Skeletal metamorphosis in FOP is a pathological process in which the normal structure and function of one tissue (skeletal muscle, for example) is destroyed and replaced by that of another tissue (bone) through an endochondral mechanism. ⁽¹⁷⁾ This process of skeletal metamorphosis in FOP has been well described, and begins with an intense catabolic stage in which a soft tissue injury triggers an inflammatory mononuclear cell infiltrate involving lymphocytes, macrophages, and mast cells that is associated with muscle cell injury and death. ^(17–22) Immediately following the catabolic phase, an anabolic phase supervenes and is characterized by a fibroproliferative lesion that matures through an endochondral process and culminates in the formation of a new ossicle of heterotopic bone containing mature marrow elements. ⁽¹⁷⁾ As the process of metamorphosis spreads through contiguous and adjacent sites with subsequent flare-ups, skeletal elements ramify to form a disabling second skeleton of heterotopic bone.

Inflammation and FOP

The heterozygous missense mutations in ACVR1/ALK2 that cause FOP are necessary but probably not sufficient to trigger the disabling, episodic, postnatal flare-ups of heterotopic ossification. Importantly, signals generated by the innate immune system act as triggers for many regenerative and pathological processes. ⁽²³⁾ Activation of inflammatory pathways through the innate immune system appears to be an important trigger for postnatal flare-ups of FOP. ^(20,24)

Presently, several animal models reproduce various clinical and pathological features of FOP-like heterotopic ossification, and in all, inflammatory triggers play a key role in lesion initiation and disease progression. ^(21, 24–28) In a unique FOP case study and associated murine bone marrow transplantation experiments, the innate immune system was required for disease flare-ups, but the presence of the FOP mutation in cells of the innate immune

system was not required to induce a flare-up of disease activity. ⁽²⁴⁾ Rather, normal innate immune cells were sufficient to trigger disease flare-ups in the connective tissues of a genetically susceptible chimeric host.

Several mouse models of heterotopic ossification strongly support roles for inflammation and immune cells. In a transgenic mouse model of BMP-induced heterotopic ossification, the activity of circulating monocytes and tissue macrophages was inhibited pharmacologically and genetically and found to substantially abrogate heterotopic ossification. ⁽²⁶⁾ In a related study, local muscle inflammation was sufficient to induce heterotopic ossification in a transgenic mouse model in which BMP4 was overexpressed at the neuromuscular junction. ⁽²⁵⁾ In another *in vivo* study, the conditional activation of inflammatory pathways in a constitutively active ACVR1/ALK2 mouse model led to heterotopic ossification at sites of inflammation, whereas activation of the mutant ACVR1/ALK2 gene alone did not. ⁽²⁷⁾ Together, these findings strongly support that an inflammatory microenvironment established and sustained by the innate immune system triggers heterotopic ossification in the setting of dysregulated BMP signaling.

Hypoxia and FOP

Inflammation induces tissue hypoxia and tissue hypoxia induces inflammation. ⁽²⁹⁾ We predicted that cellular and tissue hypoxia alone would amplify BMP signaling from the mutant ACVR1/ALK2 receptor. Generation of a hypoxic microenvironment triggered by BMP2 in skeletal muscle has recently been shown to be a critical step in the formation of heterotopic bone in a mouse model. ⁽³⁰⁾ To better understand the physiological implications of a hypoxic microenvironment in the context of the FOP mutation, we tested the hypothesis that a hypoxic microenvironment enhances signaling through the mutant ACVR1/ALK2 receptor and demonstrated that BMP signaling was both enhanced and prolonged in the presence of the canonical ACVR1/ALK2 (R206H) mutation under hypoxic conditions compared to normoxic conditions. ⁽³¹⁾ Ongoing work supports an even more encompassing role for hypoxia in BMP-induced heterotopic ossification.

Stem cells and FOP

The process of bone formation in FOP appears normal, but the temporal and spatial patterns of ectopic skeletogenesis are misregulated. BMP signaling is a well-established regulator of stem cell fate. ⁽¹⁴⁾ Importantly, the FOP gene mutation leads to dysregulated BMP signaling and increases osteogenesis in targeted progenitor cells. ^(32,33) These observations suggest that BMP signaling pathways regulate stem cell fate commitment, findings recently established in FOP-like animal models. ^(28,33)

Observations from a unique FOP patient who had bone marrow transplantation for an unrelated intercurrent illness established that cells of hematopoietic origin contribute to the formation of an ectopic skeleton, although they are not sufficient to form FOP lesions. ⁽²⁴⁾ In FOP-like mouse models, Tie2-expressing connective tissue progenitor cells of endothelial origin respond to an inflammatory trigger, differentiate through an endochondral process, and contribute to every stage of the heterotopic anlagen. ⁽²⁸⁾

Recent studies have shown that Tie2-expressing endothelial progenitor cells can transform into multipotent stem-like cells by an ACVR1/ALK2-dependent mechanism. ⁽³³⁾ In lesions from individuals with FOP, or from transgenic mice expressing constitutively active ACVR1/ALK2, chondrocytes and osteoblasts expressed endothelial markers. Expression of constitutively active ACVR1/ALK2 in endothelial cells caused an endothelial-to-mesenchymal transition and the acquisition of a stem cell-like phenotype. ⁽³³⁾ Taken together, these studies suggest that conversion of endothelial progenitor cells to

mesenchymal stem-like cells may be among the early anabolic events in the formation of FOP-like lesions.

Emerging cellular principles of skeletal metamorphosis in FOP

Recent studies are beginning to elucidate a set of principles that guide our understanding of the cellular process of tissue metamorphosis in FOP. Data from FOP patients and from *in vivo* animal models of FOP support that inflammatory signals (in response to soft tissue injury) enhance hypoxia, mobilize resident connective tissue progenitor cells of vascular origin, dedifferentiate those cells to form mesenchymal stem cells through an endothelial-to-mesenchymal transition, and redifferentiate them to every stage in the development of the heterotopic anlagen. ^(24,28,33) These principles are summarized below.

1. Mononuclear inflammatory cells of hematopoietic origin (including monocytes, macrophages, lymphocytes, and mast cells) produce inflammatory signals in response to soft tissue injury and are sufficient to induce the process of HEO in a BMP-conductive environment. ^(21,24,26–28)
2. The presence of the FOP mutation is not required to trigger inflammation-induced HEO because even normal inflammatory cells can induce FOP-like lesions in a genetically susceptible host. ⁽²⁴⁾
3. Immunoablation followed by immunosuppression has been correlated with decreased heterotopic ossification in FOP. ⁽²⁴⁾
4. Circulating osteoprogenitor cells of hematopoietic origin from an unaffected host may seed areas of evolving ossification in FOP, but do not contribute to the endochondral anlagen of FOP lesions. ⁽³⁴⁾
5. Inflammatory signals mobilize resident connective tissue progenitor cells of vascular origin and de-differentiate those cells to form mesenchymal stem-like cells by an endothelial-to-mesenchymal transition. ⁽³³⁾
6. Newly reprogrammed mesenchymal stem cells contribute to every stage in the development of the heterotopic anlagen of FOP lesions. ⁽³³⁾

Treatment strategies for inhibiting skeletal metamorphosis in FOP

Attempts to effectively prevent and treat FOP have been frustrating, if not elusive. Clinical management remains symptomatic. ⁽³⁵⁾ The discovery of the FOP metamorphogene along with emerging insights into the pathophysiology of ACVR1/ALK2-mediated heterotopic ossification reveals at least four plausible approaches to the treatment and/or prevention of FOP. ⁽³⁶⁾ These approaches include

1. blocking activity of the mutant FOP receptor;
2. inhibiting the inflammatory triggers of FOP flare-ups;
3. diverting the responding MSCs to a soft tissue fate; and
4. altering the inductive and/or conductive microenvironments that promote the formation of FOP lesions.

Here, we will briefly highlight two promising approaches: blocking activity of the mutant receptor, and diverting the responding MSCs and pre-osseous chondroprogenitor cells to a soft tissue fate.

Blocking activity of the mutant receptor in FOP

Signal transduction inhibitors (STIs) are important molecular tools for interrogating signal transduction pathways and have the potential for development into powerful therapeutic agents. Recently, the small molecule STI dorsomorphin was identified in a screen for compounds that perturb dorsoventral axis formation in zebrafish.⁽³⁷⁾ Dorsomorphin and its derivatives inhibit all type I BMP receptors (ALK2, ALK3, and ALK6), and block BMP-mediated SMAD phosphorylation, target gene transcription, and chondro-osseous differentiation.⁽²⁷⁾ Importantly, dorsomorphin blocks all BMP-specific SMAD signaling in FOP cells.⁽⁴⁾ Residues close to the ATP-binding site of ALK2 are being exploited to achieve selectivity, even among closely related receptor serine–threonine kinases such as BMPRIA/ALK3, BMPRII/ALK6, and ACVR1/ALK2. However, a safe and effective STI for FOP will inhibit ALK2 preferentially over ALK3 and ALK6.⁽³⁷⁾ STIs designed to specifically block ALK2 must have specificity, efficacy, tolerance to resistance, lack of rebound effect, and acceptable safety profiles before they can be tested in clinical trials for FOP. Additional studies in *in vivo* models of classic FOP are needed to determine potential efficacy of this class of molecules in preventing inflammation-induced flare-ups of the condition.

Diverting MSCs and chondroprogenitor cells from an osseous to a soft tissue fate

In a recent landmark study, Shimono *et al.* demonstrated a novel approach that blocks FOP-like HEO, not prior to induction, but after the inflammation events leading to HEO have already begun.⁽³⁸⁾ The authors build on well-established findings that retinoic acid is a potent skeletal teratogen that inhibits chondrogenesis, a crucial function they exploit to inhibit heterotopic chondrogenesis using retinoic acid receptor gamma (RAR γ) agonists.⁽³⁹⁾

RAR γ agonists effectively inhibit HEO during a wide treatment window that includes the prechondrogenic fibroproliferative phase, up to, but not including, the ossification phase. Remarkably, when RAR γ agonists are discontinued, no significant rebound effect occurs, indicating that the RAR γ effect may be irreversible, perhaps through the mechanisms that redirect cell fate decisions in prechondrogenic mesenchymal stem cells to a non-osseous lineage. *In vitro* studies and mouse models show that both the prechondrogenic and chondrogenic stages of HEO are exquisitely sensitive to the inhibitory effects of RAR γ agonists, which block BMP signaling and the skeletogenic potential of progenitor cells by promoting the proteasome-regulated degradation of BMP pathway-specific phosphorylated Smads.^(38,39)

The study by Shimono *et al.* thus identifies RAR γ agonists as a class of compounds that profoundly inhibit BMP-induced chondrogenesis required for the cartilaginous scaffold of HEO. The beauty of this approach is that it does not just target the BMP signaling pathway, but also modifies a specific pathological process of tissue metamorphosis that requires the BMP signaling pathway to cause disabling disease.⁽³⁹⁾

Conclusions

The FOP metamorphogene and its encoded receptor are important therapeutic targets for FOP, but are only part of the story of the generation of disabling FOP lesions.^(8,10)

Additional understanding of inflammatory triggers, vascular-derived mesenchymal stem cells, and the hypoxic microenvironment are critical to understanding the interacting factors that create the pathologic novelty, progression, and disability of FOP lesions.

As David Brooks wrote, “We often try to understand problems by taking them apart and studying their constituent parts. But emergent problems cannot be totally understood this way. Emergent systems are ones in which many different elements interact. The pattern of interaction then produces a new element that is greater than the sum of the parts, which then exercises a top-down influence on the constituent elements.”⁽⁴⁰⁾ Such is the case with FOP, and is exemplified in a preliminary blueprint for lesion formation that integrates the mutated gene, the inflammatory triggers, the relevant progenitor cells, the responding MSCs, and the hypoxic microenvironment, but engenders a physiologic understanding that is greater than the component parts (Fig. 1).

The discovery of the FOP gene has provided one of the most important clues to the pathophysiology of FOP, but it is not the end of the story; it is the beginning of a new chapter. There are many outstanding questions:

- Why is there so much inflammation with most FOP flare-ups?
- Why do some flare-ups disappear spontaneously without forming bone?
- Why do flare-ups occur in specific patterns throughout the body?
- How does the BMP pathway drive the progression of the disease, and what other interacting pathways are involved?
- What are the most effective therapies to prevent or abort FOP flare-ups?

There are many more questions to answer before we can safely prevent the creation of a second skeleton, but an early blueprint for the disabling metamorphosis of FOP is beginning to emerge and guide our understanding.

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Figure 1.

An early blueprint for the metamorphosis. In FOP, connective tissue injury leads to inflammation and hypoxia, which amplifies and prolongs BMP signaling from the mutant ACVR1/ALK2 receptor and triggers endothelial progenitor cells (EPC) to dedifferentiate by endothelial-to-mesenchymal transition (EMT) into mesenchymal stem cells (MSC) and then to the chondro-osseous scaffold of HEO. Glucocorticoids (GC), dorsomorphin (DM) derivatives, and retinoic acid receptor gamma (RAR γ) agonists inhibit inflammation, BMP signaling, and pre-osseous chondroprogenitor cells, respectively, in the pathophysiologic pathways that orchestrate the formation of FOP lesions. Arrows indicate stimulatory pathways; blunt-ended lines indicate inhibitory pathways; red “X” indicates downregulated pathways in FOP.