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Osteogenesis Imperfecta due to Mutations in Non-Collagenous Genes-Lessons in the Biology of Bone Formation

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Abstract

Purpose of Review—Osteogenesis imperfecta (OI), or "brittle bone disease", has mainly been considered a bone disorder caused by collagen mutations. Within the last decade, however, a surge of genetic discoveries has created a new paradigm for OI as a collagen-*related* disorder, where autosomal dominant type I collagen defects cause most cases, while rare, mostly recessive forms are due to defects in genes whose protein products interact with collagen protein. This review is both timely and relevant in outlining the genesis, development and future of this paradigm shift in the understanding of OI.

Recent Findings—BRIL and PEDF defects cause types V and VI OI via defective bone mineralization, while defects in CRTAP, P3H1 and CyPB cause types VII-IX via defective collagen post-translational modification. Hsp47 and FKBP65 defects cause types X and XI OI via aberrant collagen crosslinking, folding and chaperoning, while defects in SP7, WNT1, TRIC-B and OASIS disrupt osteoblast development. Finally, absence of the type I collagen C-propeptidase BMP1 causes type XII OI due to altered collagen maturation/processing.

Summary—Identification of these multiple causative defects has provided crucial information for accurate genetic counseling, inspired a recently proposed functional grouping of OI types by shared mechanism to simplify current nosology, and should prod investigations into common pathways in OI. Such investigations could yield critical information on cellular and bone tissue mechanisms and translate to new mechanistic insight into clinical therapies for patients.

Keywords

Osteogenesis Imperfecta; Bone Dysplasia; Recessive Osteogenesis Imperfecta; Collagen

Introduction

Osteogenesis imperfecta (OI), or "brittle bone disease", is a heritable bone dysplasia resulting in fragile, deformed bones, short stature, and, usually, low bone mass. The current OI paradigm is that of a collagen-related bone dysplasia, with most dominant cases caused by defects in type I collagen itself, while rare recessive forms are caused by defects in genes

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whose products interact with collagen (1, 2). The classical OI types I–IV contain the majority of cases (Table 1); they are dominantly inherited and caused by mutations in *COL1A1* or *COL1A2*, producing defects in type I collagen quantity or structure (3). Types V and VI OI (Table 1; Figure 1A) have defective bone mineralization. They were defined on clinical, histological and radiological features before their causative genes, *IFITM5* and *SERPINF1*, were identified (4). Types VII-XII, with autosomal recessive inheritance, were delineated as their causative genes were identified. Types VII-IX OI have defects in the collagen prolyl 3-hydroxylation complex (Table 1; Figure 1B), which alter the post-translational modification of collagen (5, 6). Types X and XI OI affect collagen folding and chaperone functions and are caused by mutations in *SERPINH1* and *FKBP10* (2). Finally, absence of the type I collagen C-propeptide processing enzyme, BMP1, results in type XII OI (7). A functional grouping of OI types by shared collagen-related mechanism was recently proposed (8).

Defects in collagen synthesis, structure or processing (*COLI* and *BMP1* Mutations)

Type I collagen is a heterotrimer synthesized as a procollagen precursor containing two proα1(I) and one proα2(I) polypeptide chains, encoded by the *COL1A1* and *COL1A2* genes, respectively. Procollagen undergoes post-translational modifications in the endoplasmic reticulum (ER) during chain synthesis and helix formation. Short N- and C-propeptide domains flank the central helical domain, which contains uninterrupted Gly-Xaa-Yaa tripeptides, where X is often proline, and Y hydroxyproline. Procollagen maturation entails cleavage of the propeptides by specific N- and C-terminal propeptidases (9).

Defects in either structure or synthesis of type I collagen can cause OI. Dominantly inherited OI types include mild, non-deforming type I, perinatal lethal type II, progressively deforming type III and moderately deforming type IV. Mutations in either the *COL1A1* or *COL1A2* gene can cause the structural defects in collagen that underlie types II-IV OI. In contrast, a null *COL1A1* allele causes type I OI, in which structurally normal type I collagen is synthesized at about half the normal amount. The collagen insufficiency of type I OI generally results from mutations causing premature termination, with nonsense mediated mRNA decay (NMD) of defective transcripts from the mutant allele, leaving only the structurally normal collagen from the normal allele (2, 3).

Over 80% of the mutations altering type I collagen structure are single base pair changes resulting in substitutions of glycine residues in either the α1(I) or α2(I) chain. The larger side chain of the substituting residue causes a delay in helix folding and subsequent post-translational overmodification of lysine and proline residues along the length of the helical region. Phenotypic severity varies with amino acid substitution, chain and position (1, 3). A set of fascinating mutations, causing an autosomal dominant high bone mass phenotype, alters the C-propeptide cleavage site (10). Interestingly, mutations in *BMP1*, encoding the C-propeptidase of type I procollagen, cause a recessive counterpart to High Bone Mass OI (type XII OI; Figure 1A) (7). Conversely, mutations in the N-propeptide cleavage site, the N-anchor domain of the helical region, or the N-propeptidase ADAMTS-2 cause EDS or OI/EDS phenotypes (11).

Defects in Collagen Modification- 3-Hydroxylation Complex Components (*CRTAP*, *LEPRE1*, *PPIB*) Mutations

Cartilage-associated protein (CRTAP), prolyl 3-hydroxylase 1 (P3H1), and cyclophilin B (CyPB) were the first proteins linked to recessive OI, specifically causing types VII, VIII and IX, respectively (12-16). These 3 proteins associate in 1:1:1 proportion to form the ER-localized collagen prolyl 3-hydroxlyation complex (Figure 1B). This complex modifies discrete collagen proline residues, specifically, α1(I)/α1(II) Proline-986 and α2(I) Proline-707, while the collagen chains are unfolded (1). It also has peptidyl prolyl *cis-trans* isomerase (PPIase) activity and is a collagen chaperone (17). It is not yet clear whether it is the absence of the complex or the collagen 3-hydroxylation modification that causes the bone dysplasia.

CRTAP, the ‘helper’ in the complex, is mutually protective with P3H1 in the ER, so that absence of either protein results in absence of both proteins (18). CRTAP was first identified in cartilage and is expressed in multiple tissues (16). Normally, up to 12% of the CRTAP produced by dermal fibroblasts is secreted, so it may have an additional role in extracellular matrix (ECM) (18). Loss of the matrix function of CRTAP, speculated to affect supramolecular assembly, may exacerbate the bone dysplasia in OI type VII, and cause renal and lung defects. Patients with *CRTAP* deficiency have no prolyl 3-hydroxylation complex and, consequently, absent α1(I) Proline-986 hydroxylation (14). Conversely, overmodification of the collagen helix in type VII proband cells by lysyl hydroxylase and prolyl 4-hydroxylase suggests delayed helix folding. Clinical presentations include severe to lethal osteochondrodysplasia with rhizomelia, neonatal fractures, broad undertubulated long bones, fragile ribs, severe growth defects, and “popcorn” epiphyseal calcifications in the occasional survivors (5, 19).

P3H1 (the enzyme in the complex), was first described as the matrix proteoglycan leprecan, and is encoded by the *LEPRE1* (leucine and proline-enriched proteoglycan 1) gene. P3H1 may function in both the ECM and ER/Golgi compartments via its RGD cell adhesion domain and a KDEL ER-retention sequence, respectively, but the relative contribution of these roles to bone development is unknown (5). Type VIII OI, caused primarily by null *LEPRE1* alleles, is clinically similar to type VII OI. The most common *LEPRE1* allele is a founder mutation originating in West Africa that has also been reported in patients of African-American ancestry (20). Type I collagen from *LEPRE1*-null cells is overmodified, as in Types II-IV and VII OI, with an unanticipated 50% increase in collagen production versus controls (15).

CyPB, encoded by the *PPIB (*peptidyl- prolyl *cis-trans* isomerase B) gene, is the third protein in the 3-hydroxylation complex. Peptidyl-prolyl *cis-trans* isomerization is the rate limiting step in folding of the collagen helix, and CyPB was long considered the unique PPIase for this function. CyPB is ubiquitously expressed and its stability is independent of CRTAP/P3H1. *PPIB*-null cells, however, have moderately reduced CRTAP and P3H1 protein levels, suggesting CyPB provides some support to the complex (13, 18). Only 8 cases with *PPIB* defects have been reported, of which 4 have biochemical studies. Two lethal cases have 30% α1(I)Pro986 3-hydroxylation and overmodification of the collagen

helix (1). Collagen overmodification in these cases may result from absence of the PPIase role of CyPB. Two moderately severe cases have normal α1(I) Pro986 3-hydroxylation, suggesting that the CRTAP/P3H1 complex can function in the total absence of CyPB. In addition, the case with a *PPIB* start codon mutation has normal levels of collagen helical modification, suggesting another PPIase can contribute to collagen folding (13). Collectively, the features of OI types VII, VIII and IX patients can be considered manifestations of defects in collagen modification.

Defects in Mineralization- Mutations in *SERPINF1* and *IFITM5*

OI types V and VI (Figure 1A) have unique clinical phenotypes, characterized by distinct defects in bone mineralization (21, 22). Patients with type V OI have dominant inheritance of moderately severe bone dysplasia and fracture incidence, including vertebral compressions and, often, scoliosis. Features of type V OI include radial head dislocation, ossification of the forearm interosseous membrane, and hyperplastic callus. There is also a radiographically dense band prominent in the forearm metaphyses. The combination of features present in any given patient is variable, as is the timing of appearance. All patients with type V OI have a distinctive mesh-like lamellation pattern on bone histology (21, 23).

Patients with type VI OI have recessive inheritance of bone dysplasia, with clinical characteristics and bone histology distinct from type V OI. They do not have fractures at birth, but later have frequent fractures, progressive bone deformity, vertebral compressions and scoliosis. Growth deficiency in type VI is moderately severe, sclerae are white and teeth are normal. Children with type VI OI have elevated serum alkaline phosphatase levels; with a mean of 409 U/L (range 200-650 U/L). Bone histology is remarkable for broad bands of unmineralized osteoid and a fish-scale pattern under polarized light (22, 24).

Recently, the genes responsible for types V and VI OI have been delineated. All cases of type V OI are caused by a recurrent heterozygous mutation (c.-14C>T) in the 5'-UTR of *IFITM5*, which encodes BRIL (Bone Restricted Ifitm-Like protein, previously known as "Ifitm5"), a transmembrane protein enriched in osteoblasts during mineralization (25). The type V OI mutation putatively adds 5 amino acids to the N-terminus of BRIL and may have a gain-of-function mechanism (26, 27). The causative gene for type VI OI is *SERPINF1*, which encodes Pigment Epithelium-Derived Factor (PEDF) (28, 29). PEDF is a ubiquitously expressed secreted protein best known as a potent anti-angiogenic factor that inhibits tumor growth and metastasis (30). PEDF binds to two distinct sites on type I collagen, and this binding is critical to its anti-angiogenic function (31). A variety of recessive null mutations in *SERPINF1* have been reported (28, 29, 32, 33). Serum PEDF is virtually absent in type VI OI patients, while normal PEDF values are reported in type V OI, as well as in OI caused by collagen defects (types I, III, and IV) (32).

The connection between BRIL and PEDF, and hence types V and VI OI, was revealed by a novel heterozygous *IFITM5* mutation (p.S40L) in the intracellular domain of BRIL (34**-36). Interestingly, the patient with the BRIL S40L substitution had no features of type V OI, but instead had severe OI with bone histology typical of type VI OI. Her dermal fibroblasts and cultured osteoblasts displayed minimal secretion of PEDF, implying a connection between BRIL and PEDF functions in bone mineralization. Osteoblasts from a

typical case of type V OI, with extended BRIL N-terminus, have increased *SERPINF1* expression and PEDF secretion during osteoblast differentiation. Together, these data suggest that the type V OI mutation causes gain-of-function while p.S40L causes loss of BRIL function in bone development (34**).

Defects in Collagen Folding- Mutations in Collagen chaperones (*SERPINH1*, *FKBP10*)

Types X and XI OI (Figure 1A) are caused by mutations in the *SERPINH1* and *FKBP10* genes, respectively. The protein products of these genes, HSP47 and FKBP65, respectively, play crucial roles in the proper folding of triple helical procollagen molecules. FKBP65 is also a PPIase (37).

HSP47 (encoded by *SERPINH1* gene) binds preferentially toward the N-terminus of triple helical procollagen, stabilizes the folded collagen in the ER, and assists shuttling of correctly folded collagen into the cis-Golgi. Only two *SERPINH1* mutations causing bone dysplasia have been reported: one is a recessive *SERPINH1* missense mutation (c.977T_C) in dachshunds (38); the second is a homozygous missense mutation (c.233T_C, p.Leu78Pro) in the only case of type X OI, whose clinical course was progressive and severe, with features both typical and atypical of OI (39). Mutant transcripts were stable, but HSP47 protein was substantially degraded. Residual HSP47 function likely enabled the survival of the child for 3 years, since *Serpinh1*-null mice are embryonic lethal (40). Knock-out mice have aggregation of collagen in the cell, delayed secretion and abnormal fibrillogenesis (41), while the collagen of the patient had near-normal collagen modification and secretion, despite increased site-specific susceptibility to proteolysis, again supporting residual function of the missense-containing HSP47.

Defects in *FKBP10* (encoding FKBP65) have been particularly interesting, in that they encompass a spectrum of disorders formerly thought to be unrelated, i.e., OI, Bruck and Kuskokwim syndromes. *FKBP10* mutations were first delineated in moderately severe OI (42). Shortly thereafter, Bruck syndrome I (BRKS1), a recessive disorder of severe OI with congenital contractures, was also shown to result from *FKBP10* mutations (43). Since contractures are not always present in patients with the same *FKBP10* mutation, even in siblings, it became clear that OI and BRKS1 were allelic conditions with variable contracture manifestation. Bruck syndrome can also be caused by mutations in *PLOD2* (44**), which encodes LH2, the enzyme responsible for hydroxylation of collagen telopeptide lysine. Finally, Kuskokwim syndrome, a congenital contracture syndrome with minimal skeletal manifestations that occurs among the Yup'ik Eskimos of Alaska, was traced to an in-frame deletion of a conserved tyrosine in the third PPIase domain of FKBP65 (45**).

Collagen secreted from *FKBP10*-defective cells exhibited normal helical modification and α1(I) Pro986 3-hydroxylation. However, collagen C-telopeptide lysines from fibroblasts with null *FKBP10* mutations showed less than 1% hydroxylation, versus 60% in normal cells (45**), a finding corroborated by data from bone tissue (46), while cells with the Kuskokwim mutation have 5-10% telopeptide hydroxylation (45**). The telopeptide lysine is critical to collagen crosslinking into matrix, likely underlying the reduced deposition of matrix collagen by mutant cells. It is not yet clear whether FKBP65 activates/stabilizes LH2,

or whether deficiency of FKBP65 PPIase function limits LH2 access to the collagen telopeptide. (45**).

Unclassified/New genes

In the past few years, several genes found to cause OI appear to primarily affect osteoblast differentiation (Figure 1B). First, a homozygous deletion (c.1052delA) was identified in *SP7/OSTERIX* (*OSX*) in an Egyptian child with recessive OI (47). In mice, *Osx* is essential for bone formation. *Osx*-null mice show deficient osteoblast differentiation, reduced expression of osteoblast markers, including *Col1a1*, and bone bending deformities similar to those of OI patients (48).

Next, mutations in *WNT1* were identified in multiple cases of OI (49, 50*, 51, 52). Heterozygous mutations lead to osteoporosis while several homozygous mutations cause severe OI (51). A number of WNT family members are key regulators of bone mass through β-catenin. WNT interacts with the cell surface low-density lipoprotein receptor–related protein 5 (LRP5) to activate bone formation. Homozygous mutations in *LRP5* cause juvenile osteoporosis, resembling OI type IV in its skeletal features (53). The *Wnt1* knockout mouse has severe abnormalities in brain development, but no reported skeletal phenotype. Conversely, only one of the OI patients reported with *WNT1* mutations had a neurodevelopmental defect (54).

Third, a founder mutation (p.Gly152Alafs*5) in *TMEM38B* that deleted exon 4, causing premature termination, was identified in autosomal recessive OI among Bedouins from Saudi Arabia and Israel (55, 56). *TMEM38B* encodes TRIC-B, a monovalent cation-specific channel involved in intracellular Ca^{2+} release and active in cell differentiation. *Tmem38b*-knockout mice show neonatal lethality, thus, the skeletal phenotype was not determined (57). Alteration in TRIC-B might lead to autosomal recessive OI through defective intracellular Ca^{2+} signaling in bone cells.

Most recently, a homozygous genomic deletion of *CREB3L1* gene, encoding OASIS (Old Astrocyte Specifically Induced Substance) was reported in a family with severe OI (58*). OASIS is an ER-stress transducer that regulates genes involved in developmental processes, differentiation, and maturation. *Creb3l1*- knockout mice have severe osteopenia and spontaneous fractures, and OASIS was shown to activate the transcription of *Col1a1* (59).

Conclusions

Within the last decade, a virtual flood of genetic discoveries has generated a new paradigm for OI as a collagen-related disorder, in which autosomal dominant defects in the structure or synthesis of type I collagen are responsible for the great majority of cases, while rare, mostly recessive forms of OI are caused by defects in genes whose protein products interact with collagen post-translationally. In addition to the identification of causative defects providing the information essential for accurate genetic counseling, each of these discoveries has revealed proteins whose critical role in normal bone development had not been previously appreciated. The collagen-associated proteins are involved in collagen modification (members of the collagen prolyl 3-hydroxylation complex: CRTAP, P3H1 and

CyPB), collagen mineralization (BRIL and PEDF), collagen folding, crosslinking and chaperoning (HSP47 and FKBP65), and osteoblast development (SP7, WNT1, TRIC-B and OASIS). Investigations of common pathways in dominant and recessive OI can be expected to yield critical insights into mechanism at cellular and bone tissue levels. The dynamism of OI research continues, with additional novel genes on the horizon and the potential to translate new understanding of mechanism into clinical therapies for affected individuals. Additionally, a novel approach to categorizing existing OI types based on connected metabolic mechanisms should prove effective in simplifying current nosology (8).

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Key Points

➢ The current OI paradigm is that of a collagen-related bone dysplasia, with most dominant cases caused by defects in type I collagen itself, and producing defects in type I collagen quantity or structure.

➢ Within the last decade, a flood of genetic discoveries has generated a new paradigm for OI as a collagen-related disorder, in which autosomal dominant defects in the structure or synthesis of type I collagen are responsible for the great majority of cases, while rare, mostly recessive, forms of OI are caused by defects in genes whose protein products interact with collagen post-translationally and whose critical role in normal bone development had not been previously appreciated.

➢ The collagen-related proteins are involved in collagen modification (members of the collagen prolyl 3-hydroxylation complex: CRTAP, P3H1 and CyPB), collagen mineralization (BRIL and PEDF), collagen folding, crosslinking and chaperoning (HSP47 and FKBP10), and osteoblast development (OSX, WNT1, TRICB and OASIS).

➢ Investigations of common pathways in dominant and recessive OI can be expected to yield critical insights into mechanism at cellular and bone tissue levels.

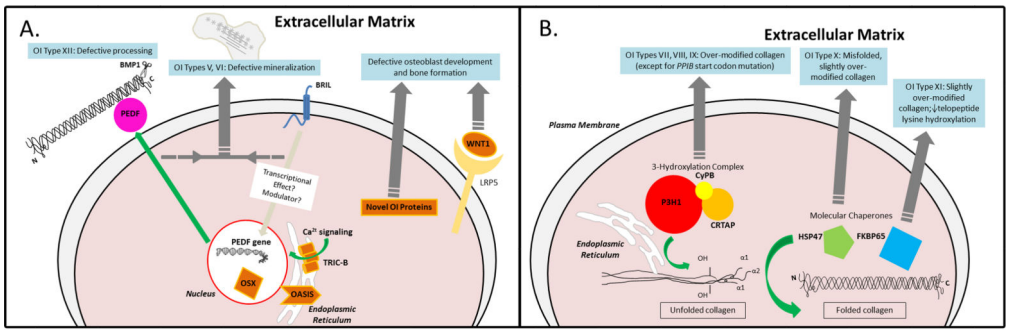

Figure 1.

Abnormal molecular mechanisms in OI types caused by defects in collagen-related molecules. Dark grey arrows and the text in blue boxes show the aberrant mechanism in most OI cases linked to defects in the specific protein. A) Green arrow shows the normal secretion of PEDF (and subsequent collagen binding) after transcription in response to effects of BRIL protein and a possible modulator. The novel OI proteins all affect osteoblast development: specifically, nuclear OSTERIX affects osteoblast differentiation genes, the trimeric TRIC-B channel affects intracellular Ca^{2+} signaling, the ER-stress transducer OASIS modulates *Col1* transcription when nuclear, and WNT1 binds LRP5 to affect bone formation. B) Green arrows show the normal effect of the proteins on collagen. The ER resident complex of CRTAP/P3H1/CyPB 3-hydroxylates specific prolines on the α1(I) and α2(I) chains, while chaperones contribute to normal folding of the collagen trimer.

Table 1

OI types caused by defects in genes and the collagen-related proteins which they encode. The mode of inheritance for the OI types is shown on the left, with the proportion of known OI cases on the right. The current nosology is shown only up to type XII, after which the OI types remain largely unclassified. The majority (85-90%) of OI cases, resulting from defects in collagen genes and subsequent defective quantitative and qualitative (structural) mechanisms, are listed as types I-IV. Defects in *IFITM5* and *SERPINH1* result in the mineralization defects seen in most OI types V and VI, respectively. Defects in *CRTAP, LEPRE1*, and *PPIB* result in the collagen 3-hydroxylation defects of most cases of OI types VII, VIII and IX, respectively. Defects in *SERPINH1* and *FKBP10* result in the collagen chaperoning and hydroxylation defects of OI types X and XI, respectively. Defects in *BMP1* result in the collagen processing defects of OI type XII. Defects in the relatively novel OI genes *SP7/OSX, WNT1, TMEM38B* and *CREB3L1* result in osteoblast differentiation defects of separate, currently unclassified OI cases/types.

	OI Type	Defective Gene	Defective Protein	Defective Mechanism	
Autosomal Dominant	I	*COL1A1*	α1(I) collagen	Col Quantity	85-90% of OI cases
	II	*COL1A1 or COL1A2*	α1(I)/α2(I) collagen	Col Structure	
	III	*COL1A1 or COL1A2*	α1(I)/α2(I) collagen		
	IV	*COL1A1 or COL1A2*	α1(I)/α2(I) collagen		
	V	*IFITM5*	BRIL	Matrix Mineralization	10-15% of OI cases
Autusomal Recessive	VI	*SERPINF1*	PEDF		
	VII	*CRTAP*	CRTAP	Col 3-hydroxylation	
	VIII	*LEPRE1*	P3H1		
	IX	*PPIB*	CyPB		
	X	*SERPINH1*	HSP47	Col Chaperoning Telopeptide hydroxylation	
	XI	*FKBP10*	FKBP65		
	XII	*BMP1*	BMP1/mTLD	Col Processing	
	Unclassified	*SP7/OSX*	SP7/OSTERIX	Osteoblast development	
		WNT1	WNT1		
		TMEM38B	TRIC-B		
		CREB3L1	OASIS		