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Genetic Causes and Mechanisms of Osteogenesis Imperfecta

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Abstract

Osteogenesis Imperfecta (OI) is a genetic disorder characterized by various clinical features including bone deformities, low bone mass, brittle bones, and connective tissue manifestations. The predominant cause of OI is due to mutations in the two genes that encode type I collagen. However, recent advances in sequencing technology has led to the discovery of novel genes that are implicated in recessive and dominant OI. These include genes that regulate the post-translational modification, secretion and processing of type I collagen as well as those required for osteoblast differentiation and bone mineralization. As such, OI has become a spectrum of genetic disorders informing about the determinants of both bone quantity and quality. Here we summarize the known genetic causes of OI, animal models that recapitulate the human disease and mechanisms that underlie disease pathogenesis. Additionally, we discuss the effects of disrupted collagen networks on extracellular matrix signaling and its impact on disease progression.

Keywords

Osteogenesis imperfecta; collagen type I; osteoblast; extracellular matrix; TGF-β signaling

1. INTRODUCTION

Osteogenesis Imperfecta (OI) is a genetically heterogeneous skeletal dysplasia that affects approximately 1 in 10,000–20,000 births [1,2]. Patients with OI feature a prominent skeletal phenotype with a wide clinical spectrum of severities ranging from low bone mass (OI type I), to progressive bone deformities with increased incidence of fractures (OI type III/IV) and perinatal lethality (OI type II) [3,4]. Additionally, OI patients may exhibit Dentinogenesis Imperfecta (abnormal tooth development), craniofacial abnormalities and joint hypermobility, as well as extra-skeletal manifestations including blue sclerae, hearing impairment, and intrinsic and extrinsic lung abnormalities [2–4]. The majority of OI cases occur as a result of autosomal dominant mutations in the genes encoding type I collagen (*COL1A1* and *COL1A2*) [3]. In addition, approximately 10% of all OI cases are caused by

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recessive mutations in genes that regulate the post-translational modification, secretion, and processing of type I collagen, as well as those that modulate osteoblast differentiation and bone mineralization [2]. For example, defects in the prolyl 3-hydroxylase complex, which serves to convert a single proline residue at position 986 of the proα1(I) chain into 3-hydroxyproline, leads to abnormal collagen fibrillogenesis and severe OI [5]. Abnormalities in other genes that regulate the proper folding of type I procollagen molecules in the endoplasmic reticulum (ER) can delay secretion [6–8]. Additionally, recent studies have shown that defects in genes that are essential for osteoblast differentiation and function can result in recessive OI [9,10].

Anti-resorptive treatments using bisphosphonates are one of the pharmacological mainstays of OI therapy. Whereas bisphosphonates have been shown to increase bone mineral density and reduce fracture risk in pediatric OI patients, they may be less effective in treating adult patients with OI [11]. Thus, understanding the biochemical and molecular mechanisms underlying the pathogenesis of OI and OI-related diseases could significantly impact novel drug discovery for targeted-mechanism based treatments. This review summarizes the genetic causes of dominant and recessive OI, animal models, and current thinking on the biochemical and molecular mechanisms that drive disease progression. Reviews with greater emphasis on the biochemistry of collagen modifications and cross-linking [12–14] and human disease and therapeutic interventions [2,15] are discussed elsewhere.

2. GENETIC CAUSES AND MECHANISMS OF OSTEOGENESIS IMPERFECTA

2.1 Collagen genes

The fibrillar type I collagen are trimeric molecules composed of two α1(I) chains and one α2(I) chain. The helical domain type I collagen primarily consists of Gly-X-Y repeats with the X and Y frequently being occupied by proline and hydroxyproline residues, respectively [12]. The helical domain is flanked by two globular domains, the N- and C-propeptides, that are eventually removed during collagen assembly [13]. The most frequent cause of classic OI is due to glycine substitutions in the helical domain of type I collagen, which may affect helical assembly. Glycine substitutions in the α1(I) helical domains are associated with more severe phenotypes, including lethality, whereas mutations in the α2(I) helical domain are less severe. Because procollagen assembly begins from the C-propeptide, glycine substitutions in this domain can interfere with chain association and folding and cause OI [2]. Here we describe several mouse models of OI that recapitulate key features of human mutations (Table 1).

Animal models

2.1.1 Col1a1^{Mov13}—*Col1a1*^{Mov13} mice were generated by insertion of the Moloney murine leukemia virus (MoMLV) in the first intron of *Col1a1* [16,17]. Mice with homozygous insertion (*Col1a1*$^{Mov13/Mov13}$) were embryonic lethal due to the complete absence of *Col1a1* mRNA despite intact *Col1a2* expression [18,19]. *Col1a1*$^{Mov13/+}$ mice produced less but structurally normal type I collagen, with increased bone brittleness due to reduced post-yield displacement [20–22]. By 15-weeks, however, *Col1a1*$^{Mov13/+}$ mice

increased periosteal growth without significant abnormalities in biomechanical strength [23]. Thus, this model closely mimics the mild, non-deforming OI type I, which in humans is due to a heterozygous null *COL1A1* allele, resulting in a quantitative reduction of type I collagen without affecting collagen structure [24]. Also, this mouse model captures the natural history of these patients, who exhibit reduced fracture rates and a milder phenotype after puberty [4].

2.1.2 Aga2$^{+/-}$—The *Aga2*$^{+/-}$ mice were generated by N-ethyl-N-nitrosourea (ENU) mutagenesis that caused a C-terminal frameshift mutation in *Col1a1*. While a significant number of *Aga2*$^{+/-}$ mice died after birth, likely due to cardiorespiratory defects [25], non-lethal mutants displayed reduced size and low bone mass, owing to increased bone turnover [26]. In the same study, an increase in endoplasmic recitulum (ER)-retention of procollagen was observed in *Aga2*$^{+/-}$ primary dermal fibroblasts. Furthermore, *Aga2*$^{+/-}$ osteoblasts significantly increased apoptosis, both *in vitro* and *in vivo*, which was associated with elevated levels of unfolded protein response (UPR) genes such as BiP, Hsp47 and Ddit3 [26] that may be induced by ER stress (See "Collagen secretion and ER stress"). *Aga2*$^{+/-}$ mice also manifests with frequent fractures, and kyphosis/scoliosis, which, together with the variation in phenotypic severity, provides a model of OI type III [26,27].

2.1.3 Brtl$^{+/-}$ (Brittle IV)—The *Brtl*$^{+/-}$ knockin mouse carries a glycine to cysteine substitution at amino acid position 349 of the *Col1a1* allele, which was previously characterized in a patient with a moderately severe OI type IV. 40–60% of *Brtl*$^{+/-}$ mice died shortly after birth due to respiratory distress [17]. The remaining non-lethal *Brtl*$^{+/-}$ mice were significantly smaller in size and showed reduced bone mineral density, cortical thickness, cross-sectional area and biomechanical properties until 6-months of age, which were largely corrected by 12-months of age [28]. Consistent with these observations, histomorphometric analyses revealed a significant reduction in osteoblast function with a concomitant increase in osteoclast numbers in *Brtl*$^{+/-}$ mice at 6-months of age [29]. Taken together, *Brtl*$^{+/-}$ mice are phenotypically heterogeneous in severity, ranging from moderate to perinatal lethality, and show the classic OI symptoms of low bone mass, bone deformities and fragility. Hence, this mouse model recapitulates the phenotype of moderate to severe forms of human OI type IV, in which there is variable expressivity as is seen in patients with the same mutation [30].

2.1.4 Oim$^{-/-}$—The *oim*$^{-/-}$ mouse model has a recessively inherited mutation in the C-terminal propeptide of *Col1a2*, which prevents its incorporation into the collagen triple helix and generates α1(I) homotrimers [31]. *Oim*$^{-/-}$ mice were smaller in size and had reduced bone mineral density when compared with either wild type or *oim*$^{+/-}$ mice [32]. The reduction in bone mass is likely due to high bone turnover, as *oim*$^{-/-}$ mice show increased osteoblast and osteoclast numbers by histomorphometry [33]. Bones from *oim*$^{-/-}$ mice have altered mineral content with dense and disordered apatite crystals, which likely contribute to increased brittleness [32,34–38]. Furthermore, collagen cross-linking is altered in *oim*$^{-/-}$ mice. Specifically, stabilizing enzymatic lysyl oxidase-mediated cross-links between fibrils are decreased whereas non-enzymatic glycation-induced cross-links are increased in *oim*$^{-/-}$ mice, both of which may contribute to the increase in bone fragility [39]. Despite the lack of

change in bone mineral density, *oim*$^{+/-}$ mice also showed abnormalities in biomechanical properties including reduced ductility, which measures the degree of bone to deform preceding a fracture [39,40]. Thus, these results suggest that *oim*$^{+/-}$ mice have qualitative bone defects independent of bone mass. Because *oim*$^{-/-}$ mice develop low bone mass, bent bones, and frequent and early fractures, this model phenotypically resembles the moderate to severe OI type III [31,33,41] while *oim*$^{+/-}$ represents a less severe form of OI [40]. *Oim*$^{-/-}$ mice displayed increased numbers and branching of canaliculi concomitant with increased numbers and greater spherical morphology of osteocyte lacunae compared to controls [42], which indicates that the alterations in type I collagen may affect osteoblast and osteocyte differentiation.

2.1.5 Col1a2$^{tm1.1Mcbr}$—*Col1a2*$^{tm1.1Mcbr}$ mice were generated by insertion of a knockin allele carrying a G-to-T substitution that converts the triple-helical codon for glycine-610 to cysteine, which is identical to a *COL1A2* variant that was identified in an Amish population [43]. *Col1a2*$^{tm1.1Mcbr}$ mice showed reduced bone mass and cortical thickness as well as decreased biomechanical properties [43,44]. In the same study, an increase in mineral-to-collagen ratio was observed, indicating more brittleness in *Col1a2*$^{tm1.1Mcbr}$ bones [43,44]. Similar to the Aga2$^{+/-}$ model, increased expression of Ddit3 and Hsp47 was observed in *Col1a2*$^{tm1.1Mcbr}$ mice, indicating that high ER stress and UPR activation may potentially account for osteoblast dysfunction in mutant mice [45]. Taken together, the *Col1a2*$^{tm1.1Mcbr}$ mouse model recapitulates the moderately deforming OI type IV [43].

2.2 Post-translational modification and cross-linking

During collagen synthesis, nascent type I procollagen molecules are translocated into the endoplasmic reticulum where they are subject to various post-translational modifications (e.g. lysyl and prolyl-hydroxylation), which are important for proper collagen synthesis, transport and stability. These modifications are subsequently used as substrates for lysyl oxidases to convert specific lysine residues to lysyl-pyridinoline (LP) or hydroxylysine residues to hydroxylysyl-pyridinoline (HP) to generate inter-collagen cross-links [14,46]. Overall, post-translational modification of collagen can influence the formation of covalent cross-links between the collagen telopeptide and helical domains, which can govern its tensile properties.

2.2.1 Prolyl 3-hydroxylase complex (P3h1/Crtap/CypB)—Prolyl 3-hydroxylase 1 (P3H1, encoded by *LEPRE1*) belongs to a group of prolyl 3-hydroxylases (P3H) which makes up the larger 2-oxoglutarate dioxygenase domain containing family of enzymes. Initially purified from chick embryos, P3h1 was observed to co-purify with cartilage associated protein (Crtap) and Cyclophilin B (CypB, encoded by *Ppib*) [47]. The P3h1 complex converts a single proline in the helical region of type I procollagen (Pro986 of chain α1(I) and Pro707 of chain α2(I)) to 3-hydroxyproline (3Hyp) [48]. However, the biological significance of this modification was not completely understood. Interestingly, homozygous deletion of *Crtap* downregulates 3Hyp and results in reduced bone mass, increased bone brittleness and impaired biomechanical parameters in mice. Consistent with this observation, loss of function mutations in *CRTAP*, *P3H1* and *PPIB* have been identified in patients with severe recessive OI [47,49–52]. Similarly, *Lepre1*$^{-/-}$ mice displayed skeletal

abnormalities, including reduced growth, osteopenia and decreased bone strength, indicating that loss of the P3h1 complex and 3Hyp may account for the skeletal phenotypes in these mouse models [53]. Interestingly, knockin mice containing a single amino acid substitution of the P3h1 catalytic site, which abolished enzymatic activity while retaining the ability to bind with Crtap and form the P3h1 complex, caused osteopenia without discernible effect on mouse growth [54]. These observations support the notion that P3h1 enzymatic activity and 3Hyp may be an essential requirement for fibrillar collagen in mineralized tissues, and that defects in either Crtap or P3h1, may cause recessive OI. In addition, homozygous deletion of the peptidyl-prolyl isomerase, *Ppib*, resulted in mice of smaller size, kyphosis and decreased bone mass [55]. In the same study, *Ppib* deletion reduced P3h1 but not Crtap levels, indicating that Ppib is essential for P3h1 stability [55]. Whereas the lack of 3Hyp does not affect collagen stability, it may allow prolonged access to other collagen-modifying enzymes, which leads to overmodification of the helical domain of type I procollagen and increased cross-linking [47]. Interestingly, overmodification is observed in *Lepre1*$^{-/-}$ and *Crtap*$^{-/-}$ mice but not in *Ppib*$^{-/-}$ mice, which may be in part due to the mutual requirement of P3h1 and Crtap to maintain the trimeric complex [5,56].

2.2.2 Lysyl-hydroxylase complex (Plod2/Fkbp10)—Lysyl hydroxylase 1-3 (LH1-3) are encoded by procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1-3 (*PLOD1-3*), respectively, and serve to convert lysine to hydroxylysine (Hyl) residues, which are subsequently used as substrates by the family of lysyl oxidases (LOX) to generate pyridinoline cross-links. Hyl residues are generated by specific enzymes depending on the location of the lysine residue within the procollagen molecule. For example, *PLOD1* regulates helical Hyl formation whereas *PLOD2* governs Hyl formation in the telopeptide regions [57]. In humans, loss of function mutations in *PLOD2* results in OI combined with congenital joint contractures, known as Bruck syndrome [58,59]. Similarly, mutations in *FKBP10* causes OI and Bruck syndrome that is accompanied by a significant decrease in telopeptide lysyl-hydroxylation and subsequent inter-chain cross-linking [60–63]. Due to the similarities in phenotypic features, cellular localization and the lack of intrinsic lysyl-hydroxylase function of FKBP65, it was speculated that FKBP65 and LH2 may need to form a complex to exert enzymatic function [2,12]. Indeed, a recent study has shown that physical interaction between FKBP65 and LH2 promotes dimerization and activation of LH2 in cell culture [64]. This interaction was specific to LH2 as FKBP65 did not bind with either LH1 or LH3, corroborating the observation that loss of *Fkbp10* does not reduce helical lysyl hydroxylation [63,64]. Similar observations have been made by an independent group (D. Krakow submitted). Still, whether the biochemical interaction between FKBP65 and LH2 is biologically important calls for further investigation. Future studies warrant genetic evaluation between *Fkbp10* and *Plod2* to determine the physiological relevance of its interaction. Unlike the human mutation, *Fkbp10*$^{-/-}$ mice died before birth due to embryonic lethality, possibly due to vasculature defects, generalized tissue fragility or poor lung function [65]. In this regard, a conditional knockout mouse model for *Fkbp10* would be useful to determine the bone and tendon functions of *Fkbp10* removal in postnatal mice.

2.2.3 Serpinh1/Hsp47—Hsp47 is an ER-chaperone that contributes to proper assembly of the collagen triple helix. *Hsp47*$^{-/-}$ mice are embryonic lethal at E11.5 due to defects in

collagen synthesis [66]. Mechanistically, Hsp47 regulates triple-helix stability via direct binding to specific arginine residues that lie at the interface between Hsp47 and collagen [66–68]. Loss of function mutations in *HSP47* causes recessive OI due to aggregation and delayed secretion of procollagen molecules [69,70]. While Hsp47 is not directly involved in the post-translational modification of collagen, loss of function mutations of *HSP47* (p.L326P) in a dog OI model caused overmodification of type I collagen and increased cross-linking without affecting 3Hyp (Pro986) [71]. This indicates that structural defects of collagen may contribute to abnormalities in post-translational modification. Given that FKBP65 and HSP47 co-eluted in a velocity sedimentation experiment [47] and were also shown to interact by proximity ligation assay, it is possible that HSP47 associates with the FKBP65/LH2 complex, albeit in a weak or transient fashion [69].

2.3 Collagen secretion and ER stress

Newly synthesized proteins must undergo proper conformational change prior to secretion. This process occurs in the endoplasmic reticulum (ER), a eukaryotic organelle that is important for calcium homeostasis, protein folding and secretion. Protein misfolding or excess protein synthesis can cause ER stress and elicit the unfolded protein response (UPR), which activates specific transcriptional programs to cope with ER stress. The most well studied UPR mechanisms include the PERK-eIF2α-ATF4, IRE1α-Xbp1 and ATF6α pathways [72]. Novel recessive OI genes for which the pathogenic mechanisms may involve ER stress and UPR have now recently been identified.

2.3.1 Creb3l1/OASIS—The cAMP response element-binding protein 3-like 1 (Creb3l1) is a basic leucine zipper (bZIP) transcription factor belonging to the CREB/ATF family. Creb3l1, also known as old astrocyte specifically induced substance (OASIS), shares high structural similarities with ATF6. Creb3l1 is highly expressed in osteoblasts and homozygous deletion in mice causes severe osteopenia due to reduced osteoblast function [73]. The molecular function of Creb3l1 known thus far is two-fold: Creb3l1 directly binds to a UPRE-like sequence in the Col1a1 promoter region to drive its expression, and it also appears to regulate the secretion of matrix proteins [6]. Loss of function mutations in *CREB3L1* have been shown to cause recessively inherited severe OI with spontaneous fractures in human [74].

2.3.2 Mbtps2—Membrane-bound transcription factor protease, site 2 (Mbtps2) is localized in the Golgi membrane where it cleaves substrates involved in the ER stress response, including Creb3l1/OASIS, ATF6 and sterol regulatory element binding protein (SREBP). A novel missense mutation in *MPTBS2* which affected a motif that is important for protease catalytic function caused moderate/severe X-linked recessive form of OI in two independent families [7]. In the same study, OI patient osteoblasts showed reduced cleavage of Creb3l1/OASIS and decreased LH1 levels concomitant with lower levels of hydroxylation of helical lysine (K87) and higher LP/HP ratio [7].

2.3.3 Tric-b—Trimeric intracellular cation channel subtype B (Tric-b, also known as TMEM38B in human) is expressed ubiquitously at low levels and functions to regulate intracellular calcium release [75]. *Tric-b*$^{-/-}$ mice die soon after birth due to lung defects. At

birth, *Tric-b*$^{-/-}$ mice display significant loss of bone mineralization [8]. Primary calvarial osteoblasts from *Tric-b*$^{-/-}$ mice showed reduced mineralization despite an increase in collagen protein accumulation in the ER upon recombinant BMP-2 treatment, indicating defects in collagen secretion [8]. Loss of function mutations in *TRIC-B* cause moderate to severe recessive OI [76–80]. Similar to what is observed in mice, human fibroblasts from OI patients with *TRIC-B* mutations showed decreased synthesis, secretion and deposition of type I collagen [79]. Further studies are needed to determine how loss of *TRIC-B* causes defects in collagen biogenesis.

2.4 Collagen processing

Procollagen molecules must undergo proteolytic processing of the N- and C-terminal domains preceding fibril formation [13]. Removal of the C-propeptides is particularly important as it is necessary and sufficient for collagen fibril formation [13,81]. Key cross-linking evens then occur via oxidation of telopeptide hydroxyl-lysines by the family of lysyl oxidases (LOX) [12].

2.4.1 Bmp1—Bone morphogenetic protein 1 (Bmp1) encodes a secreted procollagen C-proteinase that is closely related to the tolloid family of proteases and is functionally distinct from other bone-inducing BMPs [82]. In addition to procollagen, BMP1 has also been shown to exhibit protease activity on LOX and other extracellular matrix (ECM) proteins [83,84]. *Bmp1*$^{-/-}$ embryos showed reduced ossification of the frontal, parietal and interparietal bones of the skull but no discernible abnormalities in the axial or appendicular skeleton [82]. The lack of a robust skeletal phenotype in *Bmp1*$^{-/-}$ mice are likely due to residual C-proteinase activity of tolloid-like 1 (Tll1) as simultaneous deletion of *Bmp1* and *Tll1* in postnatal mice significantly reduced bone mass, length and biomechanical properties owing to increased bone turnover [84]. In human OI patients, mutations in *BMP1* had variable effects on bone mass but all cases reported frequent fractures that are associated with decreased cleavage of the collagen C-terminal domain [85–89]. Interestingly, the cleaved C-terminal carboxy propeptide has been reported to influence cellular behavior [90], but further studies are needed to determine whether these functions can contribute to OI pathogenesis.

2.5 Osteoblast differentiation and mineralization

Osteoblasts are derived from mesenchymal lineage cells and are the primary source of collagen deposition in bone [91]. Abnormalities in osteoblast proliferation, differentiation and function significantly impacts the quality and quantity of bone. Once mature osteoblasts secrete collagen into the ECM, multiple factors regulate the mineralization process. Emerging evidence has shed light on the relevance of genes that are important for osteoblast differentiation and mineralization in the context of OI in human patients.

2.5.1 Wnt1—The WNT signaling pathway has critical roles in regulating osteoblast differentiation and function. Upon binding of WNT ligands to Frizzled receptors and co-receptors including the low-density lipoprotein receptor-related protein 5 or 6 (LRP5, LRP6), β-catenin is localized to the nucleus and activates downstream target genes [91]. The first evidence of the importance of WNT signliang in human was demonstrated by reports on

loss of function mutations in *LRP5*, which causes osteoporosis-pseudoglioma syndrome (OPPG) [92]. In contrast, activating mutations in *LRP5/6* or mutations in molecules that block ligand-receptor interaction, including Dickkopf-related 1 (*DKK1*) and sclerostin (*SOST*), lead to high bone mass [93–97]. In addition, WNT signaling regulates β-catenin-independent pathways in bone [98–100]. While the mechanism by which WNT signaling regulates bone formation is well documented, less is known about which WNT ligands are most critical for regulating bone formation. Interestingly, recent studies have shown that loss of function mutations in *WNT1* cause OI, whereas heterozygous *WNT1* mutations can lead to early onset osteoporosis [9,101,102]. Here, the semidominant inheritance (i.e. homozygous mutations causing a more severe phenotype than the heterozygous mutation), supports a critical time and dose dependent requirement for this ligand. In mice, the Swaying mouse model (*Wnt1*$^{sw/sw}$) which has a spontaneous loss of function mutation in *Wnt1*, showed frequent fractures, low bone mass and decreased bone strength, recapitulating the phenotypes of human patients [103].

2.5.2 Sp7/Osx—*Sp7/Osterix* (*Osx*) is a zinc finger-containing transcription factor that is essential for osteoblast differentiation [104]. *Sp7/Osx*-null mice completely lack bone formation due to defects in osteoblast differentiation [104] whereas postnatal deletion mildly reduces bone mass due to impairment of osteoblast numbers and function [105]. Mechanistically, Sp7/Osx is recruited to AT-rich enhancers of osteoblast target genes by regulatory complexes containing Distal-less homeobox (Dlx) genes [106]. Interestingly, a frameshift mutation in *OSX* caused recessive OI in human with mild bone deformities and recurrent fractures [10].

2.5.3 Serpinf1/Pedf—*Serpinf1* encodes pigment epithelium-derived factor (PEDF), a secreted glycoprotein originally known for its neurotropic and antiangiogenic features. Loss of function mutations in *SERPINF1* causes recessive OI type VI, which features long bone fractures and deformities due to impaired mineralization (i.e., osteomalacia) [107,108]. *Serpinf1*$^{-/-}$ mice display a mild decrease in bone mass and reduced biomechanical strength accompanied by increased brittleness [109]. Because PEDF is a secreted protein that is primarily produced in the liver and at lower levels in bone, it was hypothesized that restoration of circulating PEDF levels may correct the bone phenotype in OI type VI. In one study, which used a helper-dependent adenovirus (HDAd) to drive human SERPINF1 expression in mouse liver, overexpression of PEDF did not improve the bone phenotype in *Serpinf1*$^{-/-}$ mice despite restoring biologically active PEDF serum levels [110]. In a separate study, however, intraperitoneal injection of PEDF-containing microspheres markedly increased bone mass and partially improved biomechanical parameters [111]. One possible explanation for this apparent difference in efficacy between the two methods may be the ability of PEDF to inhibit Wnt signaling at high levels [111], but this warrants further investigation.

2.5.4 Ifitm5/Bril—The interferon inducible transmembrane protein family 5 (*Ifitm5*), also known as Bone restricted Ifitm-like protein (*Bril*), is a member of the Ifitm family of proteins. Unlike other Ifitm genes that were initially known to regulate germ cell specification [112], *Ifitm5* expression is most prominent in osteoblasts [113,114].

Interestingly, *Ifitm5*$^{-/-}$ mice displayed bent bones in newborn mice (which was later corrected in adulthood) and shorter appendicular elements but no apparent effects on bone mass [114]. The majority of human mutations in *IFITM5* are caused by a unique heterozygous mutation (c.-14C>T) in the 5′-untranslated region, which results in autosomal dominant OI type V featuring hyperplastic callus formation [115–119]. Transgenic mice overexpressing the mutant form of *Ifitm5* showed delayed mineralization, *in utero* fractures and severe skeletal malformation, but postnatal bone mass could not be determined due to perinatal lethality [120]. In the same study, transgenic mice overexpressing the wildtype form of *Ifitm5* showed normal growth and development, indicating that the human mutation (c.-14C>T) likely has a neomorphic effect in bone [120]. It is worth noting that another heterozygous mutation (c.119C>T) which causes S40L substitution in BRIL protein, showed phenotypic features of type VI OI but not that of type V OI [121]. In this study, serum PEDF levels were significantly reduced, indicating that the S40L substitution in *SERPINF1* affects PEDF stability [121]. Thus, IFITM5 may regulate bone formation through interaction with PEDF in a context dependent manner.

2.6 OSTEOGENESIS IMPERFECTA AND TGF-β SIGNALING

The collagen network in skeletal elements serves as a scaffold for its growth and houses a diverse number of proteoglycans, growth factors and cytokines that regulate tissue organization and function. Thus, it is conceivable that defects in collagen structure may adversely affect the extracellular microenvironment leading to dysregulation of cell-matrix interactions and cell signaling.

The transforming growth factor beta (TGF-β) signaling modulates cell proliferation, lineage determination and differentiation in a variety of tissues [122]. The TGF-β ligand is secreted as an inactive latent form, whereas active TGF-β is non-covalently associated with its propeptide LAP (latency-associated peptide) to form the small latent complex (SLC) [123]. The SLC can bind to the latent TGF-β binding protein (LTBP) that can modulate sequestration of the TGF-β complex in the ECM [124,125]. Activated TGF-β signaling is primarily transduced via kinase cascades. Upon ligand binding, TGF-β receptors form a heterotetrameric receptor complex that induces phosphorylation of Smad2/3, which subsequently localizes into the nucleus and interacts with co-activators and co-repressors to modulate gene expression [126].

In bone, TGF-β is secreted by osteoblasts and stored in the bone matrix, primarily in association with SLC, while it often binds with LTBPs in non-skeletal tissues [124,127]. Additionally, TGF-β bioactivity can be modulated by small leucine-rich proteoglycans (SLPRs) such as decorin, which binds to active TGF-β and collagen fibrils [128–130]. TGF-β can be released from the bone matrix and activated during bone resorption by osteoclasts [131], upon which it can locally attract osteoblast precursor cells and stimulate their proliferation and differentiation to facilitate new bone formation [132]. Hence, TGF-β is an important factor that locally couples bone resorption with bone formation to properly maintain bone mass [132]. However, continuous activation of TGF-β signaling has been shown to inhibit terminal osteoblast differentiation and function, leading to low bone mass while increasing osteocyte density [122,133,134].

Interestingly, bones of *Crtap*$^{-/-}$ and *Col1a2*$^{tm1.1Mcbr}$ mice show a phenotypic overlap with a genetic model of increased TGF-β signaling, including increased numbers of osteoblasts and osteoclasts with impaired osteoblast function, low bone mass and increased osteocyte density [132,133,135–137]. Furthermore, *Crtap*$^{-/-}$ mice demonstrate lung abnormalities similar to those observed in Marfan-syndrome, where increased TGF-β activity has been identified as a contributing pathogenic mechanism [138,139]. Interestingly, Smad2 phosphorylation and TGF-β target gene expression were increased in both *Col1a2*$^{tm1.1Mcbr}$ and *Crtap*$^{-/-}$ mice [135]. Furthermore, TGF-β-reporter activity was elevated in *Crtap*$^{-/-}$ mice, *in vivo* [135]. Importantly, TGF-β neutralizing antibody (1D11) treatment reduced osteoblast and osteoclast numbers, normalized the osteocyte density and improved bone biomechanical strength in both *Col1a2*$^{tm1.1Mcbr}$ and *Crtap*$^{-/-}$ mice to wildtype levels [135]. Furthermore, 1D11 partially corrected the lung defects in *Crtap*$^{-/-}$ mice. Collectively, these findings indicate that increased TGF-β signaling may be a common mechanism that contributes to the skeletal and extraskeletal phenotypes in dominant and recessive forms of OI.

The mechanisms leading to abnormal TGF-β signaling in OI are incompletely understood. *In vitro*, binding of recombinant decorin to type I collagen of *Crtap*$^{-/-}$ mice is reduced compared with wildtype collagen, which raises the possibility that the abnormal collagen in OI impairs the ability of decorin, and potentially other SLRPs, to modulate TGF-β signaling [135]. Abnormalities in TGF-β signaling were also observed in *Brtl*$^{+/-}$ mice, which exhibit phenotypic variability with either a moderately severe or lethal phenotype [140]. Bones from lethal *Brtl*$^{+/-}$ mice showed increased expression of TGF-β, but no change in the phosphorylation of Smad2/3, whereas bone from non-lethal *Brtl*$^{+/-}$ mice demonstrated no increased TGF-β expression, but increased Smad2/3 activation. Furthermore, lethal *Brtl*$^{+/-}$ mice showed abnormal cytoskeletal structure and function, which affected intracellular trafficking and integrin-mediated signaling. Because integrins have been shown to activate TGF-β in the ECM, it is possible that defects in integrin function may be a contributing factor to abnormal TGF-β signaling in OI [140,141]. Together, these findings indicate roles for dysregulated matrix-cell signaling in the pathogenesis of OI. Future clinical studies warrant evaluation of the therapeutic safety and value of targeting altered signaling pathways for the treatment of OI patients.

The potential contributions of another important class of ECM proteins, such as proteoglycans may be underscored by these abnormalities in extracellular-matrix signaling. Specifically, SLRPs interact with collagens as a class and may mediate complex protein-protein interactions which are redundant in nature. In support of this notion, loss of function models of single SLRP mutations often have minimal phenotypes, while more severe bone and connective tissue phenotypes are revealed when they are intercrossed in combination [142]. Hence, the future understanding of how classes of SLRPs and proteoglycans can regulate collagen function and matrix-cell signaling will be critical in delineating the mechanistic basis of these disorders.

3. CONCLUSIONS AND FUTURE DIRECTIONS

The past decade has seen explosive growth in the discovery of novel genes that cause OI, and our understanding of the underlying molecular mechanisms. Beginning with the identification of *CRTAP*, 14 new genes that cause OI have been discovered, primarily owing to significant advances in genomic technology. In this review, we described genetic causes of OI, mouse models that recapitulate the human disease to varying degrees (Table 1, 2), as well as common mechanisms that contribute to OI pathophysiology (Figure 1).

The fundamental understanding of the mechanisms that underlie disease pathogenesis is essential to devise specific treatment options for the various OI symptoms. Still, investigating both general and specific mechanisms of OI pathogenesis is important to reach this goal. In this regard, the identification of altered TGF-β signaling in both dominant and recessive OI matrix has emerged as a targetable pathway for therapy. It will be of interest to determine whether other matrix signaling pathways are altered in unique OI cases. To this end, using modern technology to massively screen altered gene expression and cell signaling pathways may provide a useful platform to discover pharmacological targets for treatment of OI.

Recent studies have shown that OI has tissue-specific effects. For example, mutations in *FKBP10* causes joint contractures in conjunction with deforming OI while other forms of OI cause skin abnormalities. Thus, future studies warrant further investigation in the pathogenic mechanisms and consequence of OI in extraskeletal tissue, including tendons, muscles and skin. Given that human fibroblasts in OI patients do not completely reflect the molecular changes in bones or the affected tissue, generation of animal models that recapitulate the human phenotype is crucial to overcome the limitations studying patient samples originating from unaffected tissues.

Lastly, in OI, alterations in the complex post-translational modifications and residue-specific cross-linking is associated with changes in bone mass and mineral-to-matrix content (Table 1). However, the regulatory mechanisms by which they control bone formation is not completely understood. Further studies will be critical for identifying the specific mechanisms and to develop new treatment options to improve bone quantity and quality and pave way for the next generation of therapies to treat OI and OI-related connective tissue disorders.

As a collection of disorders, the study of OI has not only impacted our understanding of the genetic determinants of bone mass and bone quality in the context of disease but also in physiological bone homeostasis. Moreover, the disorders currently identified to date point to important common pathophysiological mechanisms that contribute differentially to the integration of bone mass and quality. They include broadly, defects in intracellular trafficking and UPR in response to ER stress, abnormalities that affect collagen cross-linking, and finally, disorders that affect cellular-matrix signaling (Figure 1). The future challenge will be to develop mechanistic therapies that will deliver on genotype specific treatments in the form of personalized medicine.

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Highlights

- Osteogenesis Imperfecta is a genetic disorder of skeletal and connective tissues
- Defects in collagen assembly and matrix quality can affect extracellular signaling
- Development of mechanistic therapies can benefit genotype-specific treatments

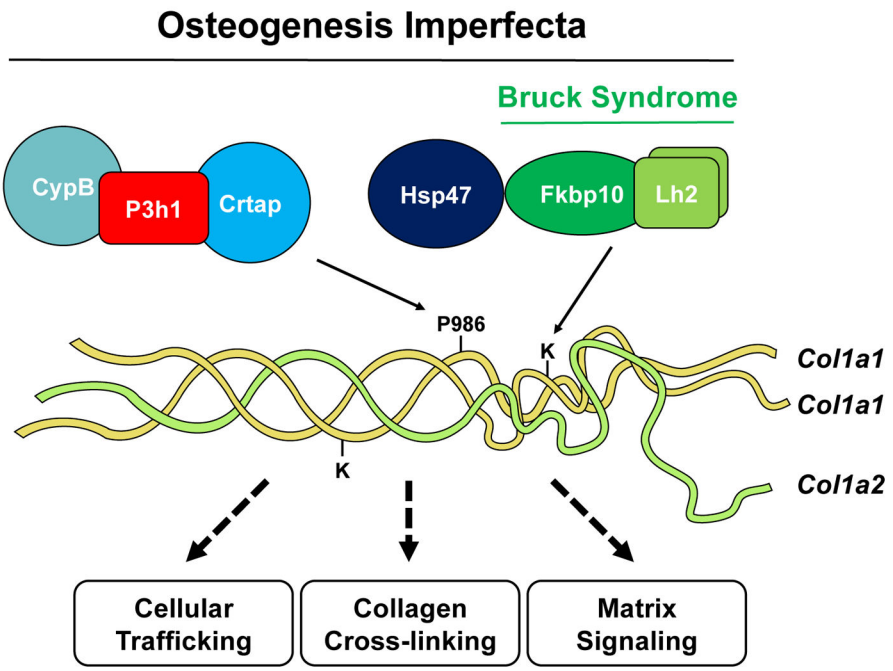

Figure 1.

Genes involved in the post-translational modification of type I collagen. The P3h1 complex serves to generate 3Hyp at P986 of the α(I) chain and the Lh2 complex lysyl hydroxylates telopeptide lysine residues. Defects in members of the P3h1 complex causes OI, whereas Lh2/Fkbp65 mutations cause Bruck syndrome in conjunction with OI. In addition to dominant mutations in *Col1a1* or *Col1a2*, common causes of OI encompass altered collagen trafficking, cross-linking and extracellular matrix signaling.

Table 1

Summary of mouse genetic models of dominant OI with type I collagen mutations.

Gene	Mouse model	Skeletal Phenotype	Type	Reference
Col1a1	*Col1a1*$^{Mov13/+}$	Reduced bone mass but recovers by 15 weeks	I	[16,17,23]
	Aga2$^{+/-}$	Reduced bone mass with fractures	III	[26]
	Brtl$^{+/-}$	Reduced bone mass and strength but recovers by 12 months	IV	[28,143]
Col1a2	*Oim*$^{-/-}$	Reduced bone mass and strength with fractures	III-like	[31,32,34–38]
	Col1a2$^{tm1.1Mcbr}$	Reduced bone mass and strength	IV	[43]

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Table 2

Summary of mouse genetic models of dominant and recessive OI.

Gene	Mouse model	Modification	Cross-linking	Skeletal Phenotype	Type	Reference
POST-TRANSLATIONAL MODIFICATION AND CROSS-LINKING						
Crtap	*Crtap*$^{-/-}$	3Hyp↓ Overmodification	HP/LP↑	Reduced bone mass and strength	VII	[47]
Lepre1	*Lepre1*$^{-/-}$	3Hyp↓ Hyl↑ Overmodification	HP/LP↑	Reduced bone mass and strength	VIII	[53]
CypB	*CypB*$^{-/-}$	3Hyp↓ Hyl (K87)↓	HP/LP↓ HP+LP↑	Reduced bone mass and strength	IX	[55,56]
Fkbp10	*Fkbp10*$^{-/-}$	Hyl (telo) ↓	HP/LP↓*h* HP+LP↓*h*	Embryonic lethal	XI, Bruck syndrome	[63,65]
Plod2	n.a.	Hyl (telo) ↓*h* Hyp↑*h*	HP+LP↓*h*	No mouse model available	Bruck syndrome	[59]
Serpinh1	*Hsp47*$^{-/-}$	Overmodification	HP/LP↑*d*	Reduced bone mass	X	[66,71]
COLLAGEN SECRETION AND ER STRESS						
Creb3l1	*Creb3l1*$^{-/-}$	n.d.	n.d.	Reduced bone mass with fractures	XVI	[6]
Mbtps2	n.a.	Hyl (K87) ↓	HP/LP↓*h*	No mouse model available	n.a.	[7]
Tric-b	*Tric-b*$^{-/-}$	3Hyp↓*h* Hyl (helical) ↓*h* Hyl (telo)↑*h*	n.d.	Reduced bone mass	XIV	[8,79]
COLLAGEN PROCESSING						
Bmp1	*Bmp1*$^{-/-}$	n.d.	n.d.	Skull defects	XIII	[82]
	Bmp1$^{-/-}$;; *Tll1*$^{-/-}$	n.d.	n.d.	Reduced bone mass and strength		[84]
OSTEOBLAST DIFFERENTIATION AND MINERALIZATION						
Wnt1	*sw/sw*	n.d.	n.d.	Reduced bone mass and strength with fractures and increased ductility	XV	[103]
Sp7/Osx	*Sp7/Osx*$^{-/-}$	n.d.	n.d.	No bone formation	XII	[10,104]
Serpinf1	*Pedf*$^{-/-}$	n.d.	n.d.	Reduced bone mass	VI	[109]
Ifitm5	*Ifitm5*$^{-/-}$	n.d.	n.d.	Bone mass unchanged	V	[114]
	Tg(Col1a1-Ifitm5$^{c.-14C>T}$*)*	Unchanged	Unchanged	Embryonic lethal		[120]

3Hyp 3-hydroxyproline, *Hyl* hydroxylysine, *telo* telopeptide, *HP* hydroxylysylpyridinoline, *LP* lysylpyridinoline,

[h] data from human patients.

[d] data from dog model.