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RARE BONE DISEASE (CB LANGMAN AND E SHORE, SECTION EDITORS)

Multicentric Carpotarsal Osteolysis: a Contemporary Perspective on the Unique Skeletal Phenotype

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Abstract

Purpose of Review Multicentric carpotarsal osteolysis (MCTO) is an ultra-rare disorder characterized by osteolysis of the carpal and tarsal bones, subtle craniofacial deformities, and nephropathy. The molecular pathways underlying the pathophysiology are not well understood.

Recent Findings MCTO is caused by heterozygous mutations in *MAFB*, which encodes the widely expressed transcription factor MafB. All *MAFB* mutations in patients with MCTO result in replacement of amino acids that cluster in a phosphorylation region of the MafB transactivation domain and account for a presumed gain-of-function for the variant protein. Since 2012, fewer than 60 patients with MCTO have been described with 20 missense mutations in *MAFB*. The clinical presentations are variable, and a genotype-phenotype correlation is lacking. Osteolysis, via excessive osteoclast activity, has been regarded as the primary mechanism, although anti-resorptive agents demonstrate little therapeutic benefit.

Summary This paper appraises current perspectives of MafB protein action, inflammation, and dysfunctional bone formation on the pathogenesis of the skeletal phenotype in MCTO. More research is needed to understand the pathogenesis of MCTO to develop rational therapies.

Keywords MAFB · MCTO · Carpal · Tarsal · Osteolysis · Arthritis

Introduction

Multicentric carpotarsal osteolysis (MCTO) is an ultra-rare autosomal dominant disorder (OMIM #166300) that typically presents as a skeletal dysplasia. It is characterized by the progressive destruction of carpal and tarsal bones (see Fig. 1A, B). Bones in the shoulders, elbows, and knees can also be affected by localized osteolysis. Patients often have subtle craniofacial deformities, and many patients will manifest focal segmental glomerulosclerosis (FSGS) that can lead to chronic renal insufficiency. Symptoms begin during early childhood and frequently include painful joint swelling and stiffness that are usually misdiagnosed as an inflammatory polyarthropathy. The involvement of the feet and ankle joints leads to delayed attainment of early motor milestones such as walking. Some children first learn to "walk on their knees" to avoid pain associated with typical ambulation and weightbearing. Virtually all patients with MCTO have osseous lesions and two-thirds of patients have FSGS with podocyte foot process microvillus transformation and effacement [1••, 2•]. Half of patients with renal disease progress to renal failure [2•].

In 2012, mutations in *MAFB* (V-maf musculoaponeurotic fibrosarcoma oncogene ortholog B [avian]), a single-exon gene on chromosome 20q12 that encodes the MafB transcription factor, were identified as the cause of MCTO [3, 4••]. MafB is a member of the Maf family of basic leucine zipper

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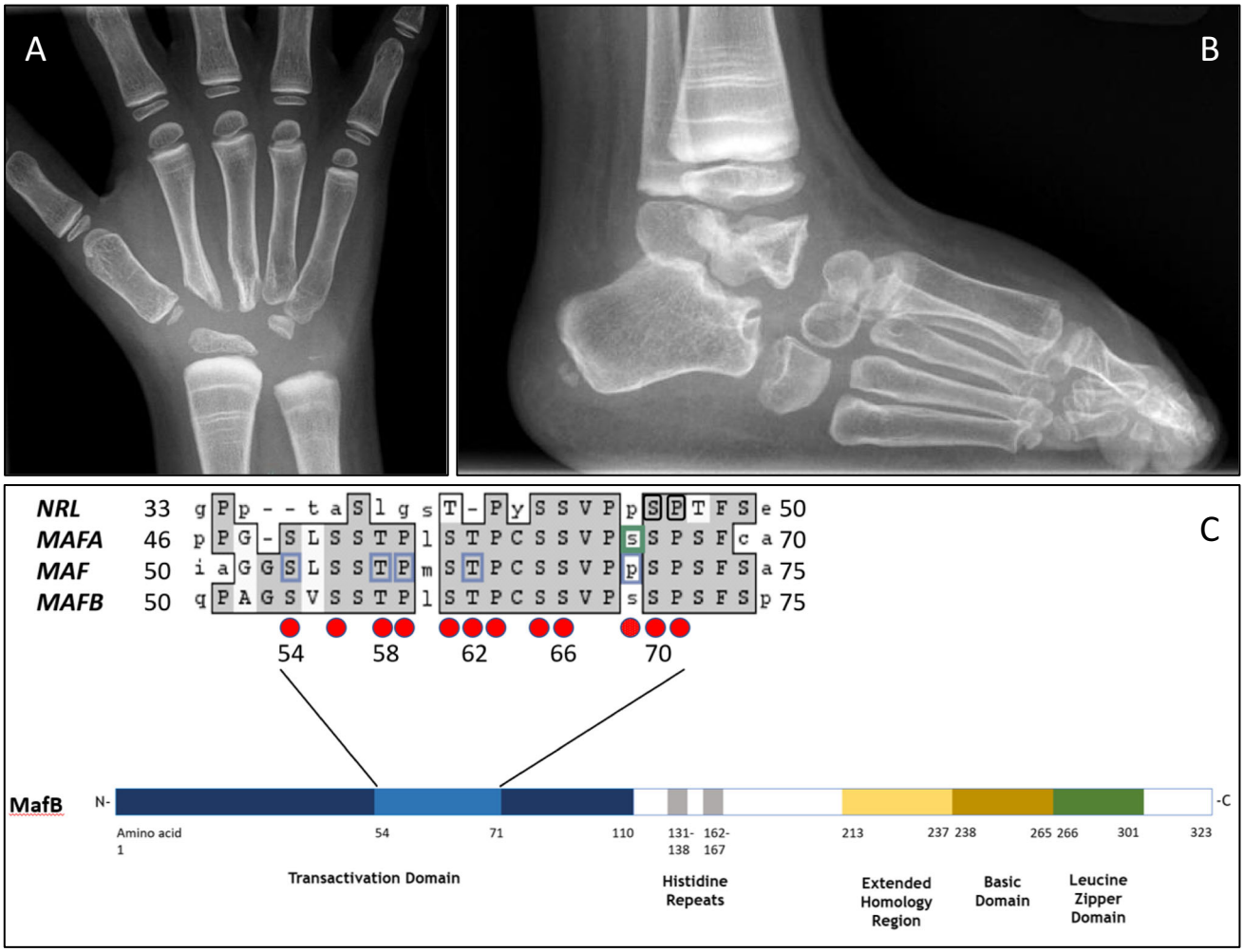

Fig. 1 **A** and **B** Radiographs of the right wrist and ankle of a 4-year–9-month-old child with MCTO. The wrist and mid-foot compartments appear small. The one carpal bone that is present (hamate) is small and irregular in shape. The erosion and tapering of the proximal second and third metacarpal bones are noted. There is a significant deformity of the talus bone and irregularity of the distal calcaneus and proximal cuboid bones. **C** *MAFB* is a single exon gene that codes for a 323 amino acid protein. Functional domains of MafB are represented by solid-colored boxes [3]. The numbered residues represent the priming Ser70 and four additional amino acids (Ser54, Thr58, Thr62, Ser66) that are phosphorylation sites. Red circles are underneath codons that are involved in MCTO-causing mutations in *MAFB* (see Table 1). The grey-shaded amino acids are conserved in proteins encoded by genes related to *MAFB* (see text) and the small blue, green, and black open boxes indicate the site of missense mutations in these other genes that cause various syndromes (see text)

(b-Zip) transcription factors. The Maf family includes seven members that are divided into two subgroups: the large and small Maf proteins. Members of the large Maf subgroup (MafA, MafB, c-Maf or v-Maf, and the neural retina-specific leucine zipper [NRL] protein) are characterized by a b-Zip structure, a motif for DNA binding and protein dimerization, and a transactivation domain [5] (see Fig. 1C). By contrast, the small Maf proteins (MafF, MafG, and MafK) lack the transactivation domain [6].

MafB is a member of the activator protein 1 (AP-1) superfamily of transcription factors, which form homo- and heterodimers via their leucine zipper domains with other AP-1 family members (*e.g.,* Fos and Jun) [7, 8]. Large Maf proteins regulate the transcription of their target genes by binding to two types of palindromic sequences in DNA called TRE- or CRE-type Maf-recognition elements (MAREs) [9]. The basic domain that precedes the leucine zipper enables the interaction of the Maf protein dimers with these recognition elements on target genes (see Fig. 1C).

Since 2012, fewer than 60 subjects with MCTO have been reported. Although the precise incidence and prevalence of MCTO are unknown, MCTO is considered to be exceedingly uncommon and is recognized as a rare disease in Orphanet (ORPHA: 2774) and the National Institutes of Health, National Center for Advancing Translational Sciences (Genetic and Rare Diseases [GARD]: 13042). Affected patients carry heterozygous missense mutations, each changing one of 12 amino acids within a short region of the MafB transactivation domain (residues 54–71) that is highly conserved in all large Maf proteins (see Table 1 [2•, 4••, 10–20,

Table 1 Summary of missense variants in *MAFB* reported to cause MCTO

Nucleotide change	Amino acid change	Reference [2•, 4••, 10–20, 21•, 22, 23]
161 C>G	Ser 54 Trp	Mehawej 2013
161 C>T	Ser 54 Leu	Zankl 2012, Zhuang 2017, Wu 2021, Chen 2021
167 C>T	Ser 56 Phe	Dworschak 2013
173 C>G	Thr 58 Arg	Li 2020
176 C>T	Pro 59 Leu	Zankl 2012, Mehawej 2013, Mumm 2014, Sun 2016
183 C>A	Ser 61 Arg	Park 2018
184 A>C	Thr 62 Pro	Zankl 2012
185 C>T	Thr 62 Ile	Mumm 2014
188 C>G	Pro 63 Arg	Zankl 2012, Mehawej 2013, Narhi 2021
188 C>T	Pro 63 Leu	Mehawej 2013, Stajkovska 2018
188 C>A	Pro 63 Gln	Wu 2021
194 G>T	Ser 65 Ile	Mehawej 2013
197 C>G	Ser 66 Cys	Zankl 2012, Choochuen 2018
206 C>T	Ser 69 Leu	Zankl 2012, Upadia 2018, Regev 2021, Mumm 2014
208 T>G	Ser 70 Ala	Zankl 2012
209 C>T	Ser 70 Leu	Zankl 2012, Mumm 2014
211 C>G	Pro 71 Ala	Park 2018
211 C>T	Pro 71 Ser	Zankl 2012, Mumm 2014
212 C>G	Pro 71 Arg	Ma 2020
212 C>T	Pro 71 Leu	Zankl 2012, Park 2018

21•, 22, 23] and Fig. 1C). This small region contains five serine and threonine residues (numbered in Fig. 1C) that when phosphorylated result in both increased transactivating function and decreased stability of all large Maf proteins [24–27]. Phosphorylation of these residues occurs through a hierarchal process that is highly conserved among all the large Maf proteins as well as other transcription factors that have transforming potential (*e.g.,* Kruppel-like factor 5) [28, 29]. In the case of MafB, a priming phosphorylation at Ser70 by an unknown kinase first occurs. Next, glycogen synthase kinase-3 (GSK3) catalyzes sequential phosphorylation of four serine/threonine residues proceeding toward the N-terminus (Ser66, Thr62, Thr58, and Ser54 in MafB; see Fig. 1C), which are organized in four tandemly arranged phosphorylate-able motifs [24–27]. GSK3-mediated phosphorylation of Maf proteins may lead to increased transactivation activity via the recruitment of accessory proteins such as p300 and CREB-binding protein [25, 30]. At the same time, phosphorylation decreases protein stability via increased ubiquitination and proteosomal degradation [24, 25, 31–33]. Phosphorylation also decreases the association of Maf proteins with the ubiquitin-specific protease 7, which blocks polyubiquitination and degradation [34].

Six MCTO mutations result in the replacement of residues (Ser54, Thr58, Thr62, and Ser66) that are GSK3 phosphorylation target sites [2•, 4••, 10–15]. In addition, other mutations are predicted to impair GSK3-mediated phosphorylation by altering residues adjacent to phosphorylation sites or the C-terminal priming site (Ser70) that is required as the priming phosphorylation [27] (see Table 1 and Fig. 1C).

MCTO has been reported in patients of various ethnic groups and nations around the world. The majority of MCTO cases are sporadic, but autosomal dominant transmission with variable expressivity does occur [4••, 10, 12, 14, 16, 17]. Moreover, although *MAFB* mutations have high penetrance, rare cases of incomplete penetrance have been reported. For instance, the *MAFB* variant, c.167C>T, p.Ser56Phe, was identified in an index case with typical features of MCTO. However, the patient's mother, sister, and maternal grandmother carried the same genetic mutation but were clinically unaffected [18]. These and other authors have suggested that modifier genes, epigenetic mechanisms, or environmental factors may influence the MCTO phenotype.

There does not appear to be an obvious genotype-phenotype correlation. For example, clinical heterogeneity and even intrafamilial variability are observed in the clinical presentation of MCTO among patients who carry the same *MAFB* mutation [4••, 10]. Genetic mosaicism may partially explain some of the clinical heterogeneity although there has been only one reported case of mosaicism so far. In this case [21•], the father required kidney transplantation at the age of 27 years due to renal failure from FSGS but did not have osteolysis on radiographs of the hands or feet. His son was diagnosed with MCTO at a young age with classical skeletal features as well as FSGS. While they both carried the same

mutation in the transactivation domain of *MAFB* (c.188 C>G, p.Pro63Arg), the father's DNA sequencing chromatograph showed an unequal ratio of wild-type to mutant allele and the son's chromatograph showed an equal ratio. The unequal allele ratios in the father were confirmed by sequencing DNA that was extracted from hair obtained from different body parts.

Current Perspectives on Pathogenesis of MCTO

MafB Protein Function and MCTO

Large Maf transcription factors are expressed in multiple tissues and regulate gene transcription by binding to MAREs in target genes as homo- or heterodimers [9]. MafB has diverse biological functions and is involved in the segmentation of the hindbrain [35, 36], in the differentiation and survival of pancreatic α- and β-cells [37–40] and parathyroid glands [41], in the survival of podocytes in the kidney [1••, 42–44], and in the differentiation of monocytes [45–47]. Within the murine myeloid lineage, MafB is preferentially expressed in most tissue-resident macrophages whose specific enhancers contain an over-representation of MARE sequences [48]. MafB restricts the ability of M-CSF to instruct myeloid cell proliferation, promotes macrophage differentiation [49] through repression of self-renewal enhancers in macrophages *in vivo* [50], and (paradoxically from the perspective of MCTO) prevents osteoclast generation via inhibition of c-Fos, Mitf and NFATc1 [45]. In addition to these physiological and developmental processes, the large Maf proteins also have transformational potential and can act as oncogenes. Notably, the *MAF* gene is upregulated in over 50% of human multiple myelomas and 60% of angioimmunoblastic T-cell lymphomas [51, 52]. In addition, recurrent translocations that lead to the high expression of MafA, MafB, and c-Maf are present in 5–10% of patients with multiple myeloma and predict a poor clinical outcome [26, 51].

Missense mutations affecting homologous residues of the closely related Maf, MafA, and NRL proteins have also been identified (see Fig. 1C), leading to the hypothesis that these are dominant, gain-of-function mutations that share a common pathophysiological mechanism by which they cause disease. For example, the *MAFA* missense mutation, p.Ser64Phe (corresponding to p.Ser69Phe in MafB), is present in patients with familial insulinomatosis and diabetes mellitus and was shown to impair phosphorylation within the transactivation domain [38]. The mutant MafA protein shows increased stability and enhanced activity in pancreatic β-cell lines but not in non-β HeLa cells, suggesting that the mutation can cause a cell-specific increase in oncogenic potential [38]. Patients with *MAFA* mutations do not have a skeletal phenotype, which may be explained by the absence of a role for MafA in chondrocyte differentiation or bone development. By contrast, skeletal defects do occur in patients with *MAF* mutations that cause the Aymé-Gripp syndrome (AYGRPS) [53–55]. Patients with AYGRPS have *MAF* gene mutations that replace residues Ser54, Thr58, Pro59, Thr62, and Pro69 that are also affected in *MAFB* in patients with MCTO [27]. In contrast to MafA, Maf is highly expressed in cartilage and bone cells, and patients with AYGRPS manifest skeletal abnormalities, some of which (*e.g.,* midface hypoplasia and carpal/tarsal development defects) also occur in MCTO. The overlapping skeletal findings in AYGRPS and MCTO are not unexpected as Maf is expressed in hypertrophic chondrocytes of the femur epiphysis and in embryonic rib and limb cartilage [56], and *MAF* and *MAFB* both control the expression of the *CTGF* gene encoding connective tissue growth factor [57], which has been implicated in endochondral ossification defects by perturbing the transforming growth factor-β pathway [58]. Finally, patients with similar mutations in *NRL* develop autosomal dominant retinitis pigmentosa 27 (OMIM #613750) [59], further highlighting the critical role of this phosphorylation domain.

Amino acid replacements within the phosphorylation domain of large Maf proteins generate proteins with increased stability, but the basis for a putative gain-of-function phenotype remains speculative. For example, Niceta and colleagues [27] showed that variant Maf proteins lacking full phosphorylation exhibited more rapid migration as well as an increased expression on immunoblots, but that these mutant proteins have decreased ability to activate an IL4-luciferase reporter gene when expressed in COS1 cells. By contrast, Rocques and colleagues [25] showed that overexpression of normal Maf proteins in multiple myeloma and other tumors leads to increased transforming potential and oncogenesis.

Phosphorylation of Maf proteins is an important mechanism for regulating protein abundance and activity. Tanahashi and colleagues demonstrated (in COS7 cells) that proteosomal degradation of MafB is promoted by c-Jun N-terminal kinase (JNK) phosphorylation and the introduction of JNK phosphorylation target site mutations in the transactivation domain of MafB (amino acid positions 58, 62, 70, and 74) increased MafB protein stability [60]. A separate study by Cuevas and colleagues demonstrated that MafB activation domain mutations resulted in increased MafB protein with an extended half-life when expressed in HEK293T cells [47].

Phosphorylation increases the association of Maf proteins with coactivator P/CAF which prevents ubiquitination while non-phosphorylated proteins are also not ubiquitinated. GSK3-mediated phosphorylation may provide diversity in Maf biological responses by differentially affecting gene expression. For example, microarray analysis of chick embryonal fibroblasts transfected with wild-type MafA or a MafA mutant (4A protein), in which all four amino acids

phosphorylated by GSK3 had been replaced by alanine, showed unanticipated effects on transcription of target genes. Although many transcripts were induced more by the phosphorylated wild-type MafA than by the non-phosphorylated 4A protein, the expression of many genes was insensitive to MafA phosphorylation. For a few genes, expression was increased more by the 4A protein than by wild-type MafA [25]. Whereas similar effects of GSK3 on MafB stability have recently been reported [26], potential target genes that may be affected have not been identified. These results suggest that the hypo-phosphorylated Maf proteins could be more active on some promoters. Moreover, since hypo-phosphorylated Maf proteins are more abundant due to their stabilization, it is possible that this increase compensates for a weaker transactivation activity in some instances (see above). These observations may provide an explanation for the apparently restricted gain-of-function phenotypes that occur in patients with missense mutations that replace the conserved amino acids within this phosphorylation domain in widely expressed *MAF* genes. These findings support the idea that, besides promoting degradation, GSK3-mediated Maf phosphorylation impacts protein activity through other mechanisms, as previously demonstrated for MafA, and suggest a complex pathogenetic mechanism involving protein stability and functional dysregulation. Taken together, the overabundance of Maf proteins may lead to a greater biological effect despite the reduced specific activity of the variant protein. Thus, cell-specific gain-of-function may be dependent upon the accumulation of variant proteins as well as interactions with other proteins and MAREs that can affect transactivation of target genes.

Further evidence that *MAFB* mutations in MCTO may represent a gain-of-function comes from studies of inactivating missense mutations or deletions in Maf family genes that reduce protein expression or DNA binding properties. *MAF* mutations cause congenital cataracts, microcornea, and iris coloboma [61–64]. In addition, similar mutations in *MAFB* that truncate MafB protein and prevent binding to MAREs lead to Duane Retraction Syndrome (DRS), a congenital oculomotor disease that is characterized by impaired horizontal eye movement and FSGS [65–67]. Loss of Mafb function in humans with DRS due to haploinsufficiency and dominant-negative *MAFB* mutations does not cause osteolysis. This emphasizes the conundrum that although MafB has been shown to negatively regulate receptor activator of nuclear factor kappa-β ligand (RANKL)-mediated osteoclast differentiation [45], putative gain-of-function mutations in MCTO are associated with increased osteoclastic bone resorption.

Inflammation

Patients with MCTO are frequently diagnosed with juvenile idiopathic arthritis (JIA) due to the overlapping clinical features of MCTO and JIA and the greater prevalence of JIA than MCTO. This results in an estimated delay in diagnosis of MCTO of 3.82 years (range 0–35 years) [2•]. Early recognition of the localized destruction of the carpal and tarsal bones and the frequent coexistence of nephropathy and subtle craniofacial differences should prompt genetic testing and earlier diagnosis of MCTO.

Elevated levels of biomarkers of systemic inflammation are not typical features of MCTO. Nevertheless, magnetic resonance imaging and musculoskeletal ultrasound have documented localized joint inflammation [16, 23]. Moreover, patients with MCTO report symptomatic relief of joint pain with anti-inflammatory therapy, further supporting the notion that joint inflammation is present. More evidence is needed to support the potential benefit of anti-inflammatory treatments because of their side effects and toxicities, particularly to renal health in a cohort of patients already at-risk for terminal renal insufficiency. However, it is plausible that there could be an adjunctive role for anti-inflammatory therapies with careful supervision in a subset of patients with inflammatory joints [16, 68]. In a 21-month-old child with MCTO, methotrexate and IL-6 receptor antagonist combination therapy helped relieve pain and improve range of motion and joint function such that she began to weight bear and walk independently [23]. It is uncertain how common joint inflammation is in MCTO, but the consistent observation that patients present with arthritic symptoms is intriguing and may offer insights into the underlying pathophysiology.

Patients with MCTO typically receive anti-inflammatory therapies (*e.g.,* IL-6 or TNF inhibitors) when they are initially diagnosed with JIA. It is common for them to discontinue these anti-rheumatic treatments after a diagnosis of MCTO is made due to a perceived lack of clinical effectiveness of treatment on the progressive nature of their bone and joint disease. The significance of inflammation in the pathogenesis of MCTO is unclear, but there is an urgency to understand its role since inflammation of any cause may aggravate bone destruction in affected joints.

Many aspects of the inflammation hypothesis remain unknown. It is uncertain whether the inflammation occurs before, during, or after the onset of osteolysis and joint destruction. Prospective studies are needed to better characterize the joint disease over time to learn if joint inflammation occurs at initial presentation only and is self-limited, or could it be chronic and recurrent. The larger joints such as the elbows and knees are less frequently involved, compared to the wrists and ankles. A better understanding of the natural history of the arthritic presentation of MCTO will inform future studies that examine the safety and efficacy of potential treatments for MCTO.

Dysfunctional Endochondral Ossification

MCTO is characterized by aggressive osteolysis of the carpal and tarsal bones, and MafB has been shown to play a role in

RANKL-mediated osteoclast differentiation [45]. MafB is specifically expressed in the monocytes and macrophages of the myeloid lineage that includes osteoclasts. MafB induces the differentiation of multipotent progenitor cells into monocytes and macrophages, but paradoxically MafB inhibits the differentiation of these cells into osteoclasts. The proposed mechanism for MafB-dependent inhibition of osteoclast differentiation is via inhibition of RANKL-mediated osteoclastogenesis at the transcriptional level by binding to the related transcription factors c-Fos, Mitf, and NFATc1 [45]. However, these observations obtained *in vitro* using cell models may not be relevant to conditions *in vivo* where additional paracrine, autocrine, and endocrine factors may modify the effect of the *MAFB* mutation.

Based on the presence of progressive and debilitating osteolysis, anti-resorptive agents such as bisphosphonates and denosumab have been administered in an attempt to prevent or reduce osteoclastic activity [2•, 11, 16, 17, 20, 23]. Unfortunately, these agents have not proven to be effective and bone destruction usually continues with further loss of carpal and tarsal bones. On the other hand, anti-resorptive therapy does seem to improve generalized osteopenia and increase bone mass at other skeletal sites [17]. It is uncertain whether higher doses or more frequent administration of anti-resorptive agents than are typically used for other bone disorders may be necessary to inhibit the intense, localized osteoclastic bone destruction in patients with MCTO. The limited benefit of denosumab (RANKL inhibitor) in MCTO may indicate that there is a cell-autonomous defect in the osteoclast or that post-RANK pathways are involved in driving the osteoclast. On the other hand, bisphosphonate treatment that inhibits bone resorption by impairing osteoclasts has also shown limited benefit in preventing site-specific osteolysis in MCTO. The limited efficacy of bisphosphonates suggests that other bone cells involved in endochondral bone formation may be affected by *MAFB* mutations (see below).

The site-specific distribution of MCTO may provide additional insight into the molecular pathways contributing to carpal and tarsal bone growth and development. MCTO and two other osteolysis disorders share a similar site-specific skeletal phenotype. Multicentric osteolysis, nodulosis, and arthropathy (MONA; also called Torg syndrome; OMIM #259600) is characterized by osteolysis in the hands and feet, subcutaneous nodules on the palms and soles, osteopenia, and arthropathy. Additional features may include coarse facial features, cardiac defects, and corneal opacities [69]. Winchester syndrome (OMIM #277950) presents similarly to MONA, except without subcutaneous nodules. MONA and Winchester syndrome are caused by recessive mutations in matrix metalloproteinases (MMP), *MMP2* and *MMP14*, respectively [70–72]. MMPs are endopeptidases that hydrolyze the extracellular matrix and are involved in collagen remodeling. MMP-2 is a gelatinase and type IV collagenase, and MMP-14 is an upstream activator of MMP-2. This interaction between MMP-14 and MMP-2 explains how mutations in these genes lead to decreased MMP-2 activity and the shared clinical features of MONA and Winchester syndrome.

MafB has been shown to be expressed in the proliferative and hypertrophic chondrocytes of the growth plate in neonatal rats and to regulate cartilage formation [73]. MMP-2 is expressed in adult human articular chondrocytes and is suggested to play a role in early skeletal development [74, 75]. To that end, MafB, MMP-2, and MMP-14 were hypothesized to play important roles in carpal, tarsal, and epiphyseal bone development, and that altered bone formation (rather than osteolysis) contributes to the anatomic distribution of osseous abnormalities in carpotarsal osteolysis syndromes. Lazarus and colleagues [76] demonstrated that in normal mice, the carpal bones as well as the distal ulna and radius and second to fifth proximal metacarpals undergo a distinct variation of (subarticular) endochondral ossification compared with classic growth plate ossification. Also, MafB, MMP-2, and MMP-14 were highly expressed in areas of new bone formation, supporting the hypothesis that dysfunctional bone development and modeling may be the driving pathophysiology in the affected bones of carpotarsal osteolysis syndromes.

Children with MCTO are observed to have narrow joint compartments starting at a very young age [23]. This suggests dysfunctional cartilaginous template and defective preparedness of the joint space for carpal and tarsal bone formation during the early stages of endochondral bone formation. In a preliminary report, *MAFB* mutations causing MCTO were shown to disrupt osteoblast and chondrocyte development in a MCTO patient-derived induced pluripotent stem cell line (with patient mutation Pro59Leu) [77]. When comparing patient-derived osteoblasts to control cells, osteoblast markers, *OPN*, *OCN*, *OSX*, and *RUNX2* were decreased, while *COL1A1* was expressed similarly and *ALPL* was increased in the *MAFB* mutant cells *vs.* control cells. When comparing patient-derived chondrocytes to control cells, *SOX9* expression was similar, but *COL2* and aggrecan expression were reduced in the patient-derived cells compared to the controls. These preliminary findings add further support that bone formation may be affected by *MAFB* mutations causing MCTO.

A mouse model developed from the homologous human *MAFB* mutation Pro59Leu exhibits renal failure resembling the FSGS nephropathy seen in human patients with MCTO [1••]. $Mafb^{MCTO/MCTO}$ mice demonstrate higher urine albumin to creatinine ratios than wild-type from four weeks of age. However, the body weights of these $Mafb^{MCTO/MCTO}$ mice are already reduced from postnatal day zero, and the growth deficiency persists as the mice age [1••]. The reduced body weights at birth may be from an early developmental bone defect in MCTO. The skeletal phenotype of the MCTO mouse model requires further analysis.

A zebrafish model with a *mafbb* mutant line has been developed and analyzed for the bone phenotype [78]. Zebrafish have two paralogs of human *MAFB*, *mafba* and *mafbb*. *Mafbb* is preferentially expressed in myeloid cells, which are

precursors of osteoclasts, so this gene was targeted [78]. The 11 bp coding region deletion results in a frameshift mutation, giving a haploinsufficiency phenotype. The zebrafish demonstrated enhanced osteoclast cell differentiation and morphological defects such as abnormal tail bending during embryogenesis, and protruding lower jaw, asymmetric caudal fin, and curved spine in adult zebrafish. While giving insight into the function of *mafbb* in zebrafish, this model does not fully recapitulate MCTO. However, the early timing of abnormal tail bending during embryogenesis may suggest an early developmental deficit in cartilage and bone formation.

Taken together, if it is correct that MCTO is a disorder of bone formation rather than bone resorption, or, more likely, a combination of both defective bone formation and excessive osteolysis, it may make sense why anti-resorptive therapies have shown minimal benefit.

Conclusion

MCTO is a rare skeletal dysplasia that presents during early childhood with joint pain and swelling, site-specific osteolysis of the carpal and tarsal bones, and nephropathy that progresses to terminal renal insufficiency. There may also be subtle craniofacial changes and the involvement of larger joints such as the knees and elbows. Due to the rareness of this condition, a diagnosis of MCTO is delayed on average by 3–4 years, with some adults not receiving a diagnosis of MCTO until after their child undergoes genetic testing. It is critically important to raise awareness of MCTO across various pediatric and adult disciplines to decrease the time to diagnosis. An earlier diagnosis of MCTO may enable screening for nephropathy and preventative measures to avoid nephrotoxic medications and preserve renal function for as long as possible. Also, the bone and joint destruction that progressively worsens over time can result in substantial debilitation and crippling of joints that are used for activities of daily living. Early recognition of MCTO as a chronic condition may prompt sooner referrals to physical and occupational therapy to assist patients as they adapt to changes in their mobility and joint function.

The pathophysiological underpinnings of MCTO are not well understood. Patients with MCTO are frequently diagnosed with JIA initially when they present with arthritic symptoms (*e.g.,* pain, swelling, stiffness). There are documented reports of joint inflammation in imaging studies and pain relief with anti-rheumatic therapies. Also, osteolysis has traditionally been viewed as the primary mechanism underlying bone destruction in MCTO. However, anti-resorptive agents have offered minimal benefit to prevent the eventual disappearance of the carpal and tarsal bones. Mouse studies and preliminary human cell studies suggest other bone cells are also impacted by *MAFB* mutations. Taken together, these observations suggest that a reappraisal is warranted of our current understanding and treatment approach to MCTO.

In the presence of MafB protein overabundance, targeted molecular strategies to decrease its expression or facilitate protein clearance may help modulate the clinical phenotype. Patients commonly discontinue anti-rheumatic treatments after receiving a diagnosis of MCTO. However, this class of drugs may play an adjunctive role in the treatment of joint pain and inflammation in some patients with MCTO. More research is desperately needed to better understand the natural history of disease progression across the lifespan. More detailed clinical phenotyping and examination of the mechanistic pathways and biological underpinnings are crucial to inform better-targeted therapies and to guide the development of prudent and cost-effective screening and monitoring practices. Meanwhile, a multidisciplinary approach to care would include coordinated evaluations by primary care, genetics, endocrinology, rheumatology, or other provider experienced with pediatric bone disorders, nephrology, orthopedics, physical and occupational therapy, and social work teams.

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Declarations All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- •• Of major importance

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