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Chronic Recurrent Multifocal Osteomyelitis and Related Diseases – Update on Pathogenesis

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Abstract

Purpose of the review—We focus on recent advances in the understanding of the genetic, molecular, immunologic and environmental factors implicated in the pathogenesis of autoinflammatory bone diseases including the syndromic and non-syndromic forms of chronic recurrent multifocal osteomyelitis (CRMO).

Recent findings—Evidence implicating the IL-1 pathway in the pathogenesis of the Mendelian forms of CRMO is growing. LIPIN2 can regulate the NLRP3 inflammasome by affecting P2×7 receptor activation and intracellular cholesterol can modulate P2×7R currents. Work in a mouse model of CRMO demonstrates that dietary manipulation can alter the microbiome and protect these mice from the development of sterile osteomyelitis *in vivo*.

Summary—Although the genetic and immunologic basis of non-syndromic CRMO remains only partially understood, the IL-1 pathway is central to the pathogenesis in the syndromic autoinflammatory bone disorders. Recent work implicates lipids and the microbiome in sterile osteomyelitis.

Introduction

Sterile bone inflammation is the central phenotype of the autoinflammatory bone disorders which include chronic recurrent multifocal osteomyelitis (CRMO), Majeed syndrome, and the deficiency of the interleukin-1 receptor antagonist (DIRA). In addition, there are both murine and canine models of the disease. These diseases predominantly affect children but can also occur in adults. CRMO is the most common pediatric autoinflammatory disorder, whereas in adults, the diagnosis of synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome is used. It is not clear if CRMO and SAPHO syndrome are the same disorder with slight phenotype variability depending on age (i.e. just nomenclature differences in adult and pediatric medicine) or two distinct disorders. Further complicating nomenclature is that the term CRMO and chronic non-bacterial osteomyelitis (CNO) are

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both used in the literature fairly interchangeably. In this manuscript, we will use the term CRMO and we will focus on recent advances in our understanding of sterile osteomyelitis.

CRMO – Clinical Overview

The hallmark of CRMO and all the autoinflammatory bone disorders is sterile osteomyelitis affecting one or more bones. It may have a chronic unremitting course but more often there is relapsing and remitting inflammation (1, 2). There is a strong association of CRMO with a personal or family history of inflammatory disorders of the skin, intestinal track and the joints suggesting shared disease pathogenesis. Psoriasis vulgaris, palmar-plantar pustulosis, Crohn disease and inflammatory arthritis are the most commonly co-morbidities but other associations have also been reported (2–8). There are reports of familial occurrence of CRMO but this is unusual (9, 10).

Immune dysregulation occurs in CRMO but unlike syndromic forms of CRMO, the primary pathway that is affected remains unknown. Scianaro *et al.* described significantly higher expression of Apoptosis-associated Speck-like protein (ASC), caspase-1 (CASP-1), and IL-1 β expression at the mRNA level in peripheral mononuclear blood cells from children with active disease than healthy children and those with inactive disease (11). Hofmann *et al.* reported significantly less IL-10 production by monocytes in response to TLR 4 activation by lipopolysaccharides (LPS). This down regulation likely occurs through attenuated ERK 1/2 activation, reduced expression of Sp-1, which is a transcription factor for the IL-10 promoter, and impaired phosphorylation of histone H3 serine 10 (H3S10) in children with CRMO compared to healthy children or children with juvenile idiopathic arthritis (12, 13). On the contrary, production of tumor necrosis factor (TNF)-alpha by monocytes in children with CRMO was not negatively affected suggesting that an imbalance between anti- and pro-inflammatory cytokines may contribute to the pathogenesis of CRMO. Furthermore, serum concentrations of IL-6, IL-12, RANTES, MCP-1, and sIL-2R were significantly higher in children with active CRMO than in healthy controls (14). When children with CRMO achieved complete remission, sIL-2R and IL-6 were significantly decreased, suggesting an important role for pro-inflammatory cytokines in driving active inflammation in bones from children with CRMO. Treatments targeting these pathways have not been reported in CRMO. However, the serum cytokines and chemokines described above have been proposed as biomarkers to monitor disease activity in CRMO and will need further validation through prospective studies.

Treatments for CRMO remain empirical with non-steroidal anti-inflammatory drugs (NSAIDs) as the first-line of treatment (15, 16). There are case reports describing affected children who failed NSAIDs but were treated with disease modifying anti-rheumatic drugs (DMARDs) such as TNF alpha inhibitors, IL-1 antagonists, bisphosphonates and glucocorticoids, inducing remission in many of the patients (10, 17). In some cases, a combination of treatments was utilized to manage the inflammation. One cohort study reported that infliximab and concomitant methotrexate with or without zoledronic acid significantly decreased clinical symptoms, ESR, CRP and the non-vertebral lesion number as well as the maximum bone edema score from MRI in children with CRMO after 6 months of treatment (18). But there are many studies reporting that pamidronate alone

appeared to be effective in treating children with CNO refractory to NSAIDs based on clinical evaluation and/or MRI evaluation (19–23). Based on a physician survey from a professional society in North America, after patients failed NSAIDs, physicians often used methotrexate (67%), TNF alpha inhibitors (65%), and bisphosphonates (46%) as the next-line treatments (15). Best treatment regimen(s) remain to be determined as there are no approved medications and no head-to-head comparisons of current therapeutic approaches.

CRMO – Genetics and Pathogenesis

CRMO can be genetically driven. Mutations in *LPIN2*, *Pstpip2*, *IL1RN* and *FBLIM1* have been found in human and murine models of CRMO(24–29). However, mutations in these genes explain a very small minority of patients with CRMO and for most, the genetic factors predisposing to disease remain unclear. Fortunately, despite only explaining a minority of CRMO cases, the single gene models of CRMO have been very useful for bettering our understanding of disease pathogenesis. The remainder of this manuscript will summarize recent scientific advances in the field.

Majeed Syndrome and LPIN2

Majeed syndrome (OMIM #609628) is an exceedingly rare autoinflammatory disorder that presents with CRMO and dyserythropoietic anemia with or without a neutrophilic dermatosis [Sweet syndrome or pustulosis] (24, 30–33). It is an autosomal recessive disease due to mutations in *LPIN2*, which encodes LIPIN2, a phosphatidic acid phosphatase (PAP) that is important in lipid metabolism (34). Thirteen mutation-positive patients have been confirmed in the literature (24, 30, 33, 35, 36). With each reported case, it has become increasingly apparent that there is phenotypic variability. While all have had CRMO and anemia, the classic triad including the neutrophilic dermatosis occurs in < 25% of Majeed syndrome patients. The CRMO in Majeed syndrome typically has early onset (prior to the age of 2 years), with frequent flares that can be accompanied by fever (31–33, 35, 37). However, two recent reports describe 2 cases with onset of the disease at 4 years of age and 8 years of age (30, 36). All 13 had anemia and of the 11 biopsied, all had dyserythropoiesis on the bone marrow examination. All but one had microcytic red cells and six required blood transfusions at some point in their disease course (31, 32). Two recent reports describe mutation-positive Majeed syndrome with very mild phenotypes with an older age of onset (as old as 8 years) and a milder bone disease that mimic non-syndromic CRMO (30, 36). The outcomes in Majeed syndrome are more variable than the children initially reported by Dr. Majeed and colleagues. Six different mutations in *LPIN2* have been reported in Majeed syndrome and although the numbers of affected individuals is small, there appears to be no significant genotype-phenotype correlation to disease manifestations or severity. The original report by Majeed *et al.* described a family that later was found to have a mutation in *LPIN2* that resulted in changing the highly conserved serine at amino acid 734 (that is required for the phosphatidate phosphatase activity of LIPIN2) to a leucine (24, 38). These 4 affected individuals had severe CRMO with contractures, transfusion-dependent dyserythropoietic anemia with failure to thrive and only partial improvement with available treatments of steroids and NSAIDs (31, 32). Yet the same mutation was found in the children reported by Moussa *et al.*, one of whom had only very mild normocytic anemia and

mild CRMO with onset of disease at 8 years of age (36). Treatment of Majeed syndrome remains empiric with reports of partial improvement with NSAIDs, steroids, methotrexate or pamidronate (30–33, 36). However, Herlin *et al.* report sustained clinical, laboratory and radiographic improvement in 2 Majeed syndrome patients when treated with either the recombinant IL-1 receptor antagonist anakinra or the IL-1 β blocker canakinumab (after TNF inhibition with etanercept had previously failed to produce clinical improvement) suggesting that Majeed syndrome is an IL-1 β driven disease (35, 39).

Until recently, the role of LIPIN2 in inflammation was unknown, however, two groups recently reported findings that demonstrate the importance of LIPIN2 in inflammation (40, 41). LIPIN2 is a phosphatidic acid phosphatase (PAP) that plays an important role in triglyceride synthesis and dephosphorylation of phosphatidic acid (PA) to generate diacylglycerol (34, 42–44). Despite its critical role in fat metabolism, the role of LIPIN2 in inflammation remained obscure. In 2012, Valdearcos *et al.* studied the role of lipin2 in the inflammatory response to excessive saturated fatty acids using human and murine macrophages (40). They found increased expression of pro-inflammatory cytokine genes (including *tnf* and *Il6*) in monocytes that under-express *lipin2* and decreased proinflammatory cytokine gene expression in cells that overexpressed *Lpin2* when exposed to high levels of saturated fatty acids *in vitro* (40). In 2016, they expanded on the mechanism that LIPIN2 plays in inflammation, reporting that not only did LIPIN2-deficient human macrophages produce higher amounts of TNF mRNA but also produced higher amounts of *Il1b* mRNA and biologically active IL-1 β (41). They demonstrated that bone marrow derived macrophages (BMDM) from *Lpin2* deficient mice increased the release of mature Caspase-1 after inflammasome activation (41). Further, they demonstrate that the Lipin2-deficient BMDM have increased ASC oligomerization and inflammasome assembly with subsequent increase IL-1 β production (41). Lipin2-suppression of NLRP3 inflammasome activation occurs upstream by altering intracellular K⁺ levels and membrane permeability during P2 $\times$ 7R activation (41). Taken together, Lorden *et al.*'s work demonstrates that Lipin2 reduces ATP-promoted K⁺ efflux that leads to downstream IL-1 β production, as well as P2 $\times$ 7R pore formation, during classical Nlrp3 inflammasome activation (41). These findings confirm that Majeed syndrome is an autoinflammatory disease and is more specifically an NLRP3 inflammasomopathy. This provides additional support for the use of IL-1 β blockers in the treatment of Majeed syndrome.

Murine chronic multifocal osteomyelitis (cmo) and the microbiome

The *cmo* mouse develops sterile osteomyelitis due to recessive mutations in *Pstpip2* which encodes proline-serine-threonine phosphatase interacting protein -2 (Pstpip2 or PPIP2) (25, 26). Pstpip2 deficient mice develop sterile osteomyelitis with 100% penetrance with majority being affected by 8 to 12 weeks of age (25, 26). The disease in the *cmo* mouse is hematopoietically driven and occurs independent of a functional adaptive immune system (45). Our group and others demonstrated that disease in the *cmo* mice is an IL-1 dependent disorder and that it is IL-1 β (not IL-1 α) mediated using double mutant mice (46, 47). Despite being IL-1 β dependent, the disease in *cmo* mice can occur independent of a functional Nlrp3 inflammasome as *cmo* mice that are also deficient in either Nlrp3, ASC or caspase-1 continue to develop osteomyelitis (46, 47). However, others suggest that caspase-1

and caspase-8 may play a redundant role in the processing of IL-1 β in the cmo model (47), and cmo mice that are deficient in both caspase-1 and caspase-8 are partially protected from disease (48). Furthermore, Nlrp3 may be playing a redundant role with caspase 8 in osteomyelitis in the cmo model because cmo mice that are deficient in Nlrp3, Ripk3 and caspase-8 (cmo.Nlrp3^{-/-}.Ripk3^{-/-}.caspase8^{-/-}) are also partially protected from disease (48).

In addition to demonstrating that disease in the cmo mouse is an IL-1 β mediated disease, there is new data that the cmo microbiome is altered and that dietary changes can modulate the development of sterile osteomyelitis in this model. Cmo mice fed with a standard low fat diet have an expansion of 'pro-inflammatory' or 'inflammation-associated' microbes like *Prevotella* species relative to wild-type mice fed the same low fat diet (49). When cmo mice are fed with a high fat diet, there was an expansion of protective [i.e. *Lactobacillus* species] and suppressed growth of disease-associated microbes [i.e. *Prevotella* species] (49). Transfer of stool from a cmo diseased mouse fed with low fat diet into a young, disease-free cmo mouse accelerates disease. However, transfer of stool from a cmo mouse fed with high fat diet into a young, disease-free cmo mouse decreases the *Prevotella* species and protects the recipient from disease (49). Cmo neutrophils from high fat diet fed cmo mice produced less IL-1 β compared to cmo mice on a low fat diet (49). Antibody mediated depletion of neutrophils *in vivo* in the cmo mice completely protects from disease (49), demonstrating their importance in the development of osteomyelitis.

CRMO and *FBLIM1*

Recently, we reported on a South Asian child with consanguineous parents who presented with CRMO and psoriasis (29). Whole exome sequencing detected a rare, homozygous missense mutation in the gene *FBLIM1*, which codes for FBLP1, a filamin-binding protein that anchors cytoskeletal adhesion proteins at cell-extracellular matrix (ECM) and cell-cell contacts (50, 51). In mice, FBLP1 is essential for balanced bone remodeling; *Fblim1*^{-/-} mice have increased RANKL expression, osteoclast activation and subsequent osteopenia (52). In macrophages, *FBLIM1* expression is significantly increased in IL-10 treated cells compared to untreated cells, and this upregulation is a function of regulation by STAT3 as part of the anti-inflammatory response (53). We performed a microarray experiment measuring gene expression among bone marrow-derived macrophages from cmo mice, cmo *IL1R*^{-/-} mice and cmo *IL1R*^{+/-} mice, and *Fblim1* was the most significantly differentially expressed gene, downregulated 26-fold in the cmo mouse (29). Sequencing *FBLIM1* in a large cohort of CRMO patients identified a second child harboring compound heterozygous functional mutations, a novel frameshift mutation and a rare variant in the third intron (29). The intronic variant (rs41310367) is in an enhancer and a STAT3 binding region, as characterized by ENCODE (54), and disrupts an NR4A2 recognition site (29). Functional validation of rs41310367 in osteoblast-like cells showed that the region surrounding the variant exhibited significant enhancer activity, and that the mutation completely negated the activity (29).

FBLP1 binds to filamin (FLN) in competition with integrin β ; FBLP1-filamin binding releases and thereby promotes integrin β activation (55, 56). Integrin β is a component of macrophage-1 (mac-1), a complement receptor whose activation contributes to neutrophil

recruitment during sterile inflammation (57). The homozygous mutation in the South Asian child is in the FLN-binding domain of FBLP1, so while experimental validation is necessary, it is likely that the mutation disrupts FBLP1-FLN binding, impacting integrin β activation and neutrophil infiltration. *FBLIM1*'s involvement in both sterile inflammation and the regulation of bone remodeling coincide with the CRMO phenotype, and the sequencing results combined with *Fblim1*'s dysregulation in the *cmo* mouse led to its identification as a gene contributing to the pathogenesis of CRMO. Sequencing of other families with non-syndromic CRMO will identify other genes in humans, potentially those involved in the same pathway impacted by *FBLIM1*.

Conclusions

Over the last several years, experiments using both human subjects and animal models have resulted in significant progress regarding the understanding of CRMO pathogenesis. Mechanisms underlying immune dysregulation have been clarified. Specifically, aberrant IL-10 production was identified in LPS-stimulated monocytes from CRMO patients, and the suspected involvement of the IL-1 pathway in sterile bone inflammation was supported with definitive genetic and experimental data from sporadic CRMO patients, families with Majeed syndrome, and the *cmo* mouse. Genetic analysis of two families combined with expression data from the *cmo* mouse led to the identification of *FBLIM1* as a new CRMO susceptibility gene. Experiments using the mouse model also demonstrated that the environment can significantly alter disease susceptibility, as *cmo* mice develop an altered gut microbiome and marked disease protection when fed a high fat diet. The role of the diet in pathogenesis needs to be explored in human CRMO as this is a potentially highly applicable discovery that could alter how we approach treatment.

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