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Autoinflammatory bone disorders: update on immunologic abnormalities and clues about possible triggers

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Abstract

Purpose of the review—To provide an update on the genetics and immunologic basis of autoinflammatory bone disorders including chronic recurrent multifocal osteomyelitis including the monogenic forms of the disease.

Recent findings—Ongoing research in murine, canine and human models of sterile bone inflammation has solidified the hypothesis that sterile bone inflammation can be genetically driven. Mutations in *Pstpip2*, *LPIN2* and *IL1RN* have been identified in monogenic autoinflammatory bone disorders that have allowed more detailed dissection of the immunologic defects that can produce sterile osteomyelitis. Recent studies in murine chronic multifocal osteomyelitis, deficiency of the interleukin-1 receptor antagonist (DIRA), Majeed syndrome and SAPHO syndrome reveal abnormalities in innate immune system function. IL-1 pathway dysregulation is present in several of these disorders and blocking IL-1 therapeutically has resulted in control of disease in DIRA, Majeed syndrome and in some cases of SAPHO and CRMO. Basic research demonstrates the importance of the innate immune system in disease pathogenesis and offer clues about potential disease triggers.

Summary—Research and clinical data produced over the last several years support the important role of innate immunity in sterile osteomyelitis. Based on what has been learned in the monogenic autoinflammatory bone disorders, IL-1 is emerging as an important pathway in the development of sterile bone inflammation.

Keywords

Chronic recurrent multifocal osteomyelitis (CRMO); Synovitis; acne; pustulosis; hyperostosis and osteitis syndrome (SAPHO); Majeed syndrome; Osteomyelitis; Deficiency of the interleukin-1 receptor antagonist (DIRA)

Introduction

Autoinflammatory disorders of the innate immune system typically present with recurrent bouts of inflammation. Chronic recurrent multifocal osteomyelitis (CRMO) [also known as chronic nonbacterial osteomyelitis (CNO)] is an autoinflammatory bone disease that predominantly affects children and presents with bone pain, sometimes accompanied by

fever (1–4). Histologically and radiographically, the bone lesions mimic infectious osteomyelitis but biopsies are typically sterile and disease manifestations improve with the use of anti-inflammatory medications. CRMO is frequently associated with inflammatory disorders of the skin or intestine(5–10). Associated skin conditions include palmar plantar pustulosis (PPP), psoriasis vulgaris, severe acne, generalized pustulosis, and Sweet syndrome (2, 4, 11–21). Intestinal inflammatory co-morbid disorders occur in approximately 10% of patients; most often Crohn disease, ulcerative colitis and less commonly celiac disease(2, 4, 7, 22–26). Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome occurs predominately in adults and has considerable phenotypic overlap with CRMO(27–29). It remains unclear if these are distinct clinical entities or if CRMO and SAPHO are the same disease with varying features that depend on age of onset. Evidence points to a genetic susceptibility to disease and the genes for several rare autoinflammatory bone disorders have been identified(17, 18, 30, 31). Immunologic defects in innate immunity, particularly dysregulation of IL-1 pathway function, are beginning to emerge as clues to disease triggers.

Non-syndromic CRMO

Evidence strongly supports a genetic component to CRMO susceptibility(32). Although having two individuals with CRMO in one family is rare, 50% of those affected have a 1st or 2nd degree relative with a chronic inflammatory disorder most often psoriasis, inflammatory bowel disease or inflammatory arthritis(2, 33). In humans with sporadic CRMO, Golla et al. reported the identification of a disease susceptibility locus on chromosome 18(34) and Hofmann et al. reported an association with IL-10 promoter polymorphisms consisting of the -1082G/G alleles and GCC haplotype(35). However, CNO peripheral blood monocytes did not hyper-produce IL-10 as would be predicted based on the identified promoter polymorphism; yet the IL-10 pathway was dysregulated resulting in a pro-inflammatory response(35). These are intriguing associations which await replication in an independent cohort.

Monogenic disease models

Monogenic disorders that have CRMO as a subphenotype occur in mice, large breed dogs and humans. Each model offers unique insight into disease pathogenesis with the human models strongly implicating IL-1 pathway dysregulation in disease pathogenesis.

Canine hypertrophic osteodystrophy

Hypertrophic osteodystrophy (HOD) is a rare canine disorder that occurs in large breed dogs with Weimaraners being particularly susceptible(36, 37). HOD phenotypically resembles human CRMO. It predominantly affects juveniles, presents with recurrent fever and bone pain(36, 37). The disease has a predilection for the metaphyses of the long bones but it can also affect the vertebral bodies and the jaw(36). For many dogs with HOD, the disease is mild and self-limiting but for some dogs it can be life threatening(36). Sixty percent develop diarrhea and nearly a quarter develop skin involvement typically in the form of pustules(36). The disease is relapsing in ~ 50% of the cases and may continue until the closure of the

epiphyses(36). Osteolytic lesions are seen radiographically associated with histologic features of osteitis and osteonecrosis(36). Bone cultures are typically sterile and the treatment is with anti-inflammatory medications with recent data demonstrating that corticosteroids were superior to NSAIDs (36).

HOD clusters in families and in specific large dog breeds which suggests a genetic component to disease susceptibility. However, the inheritance of HOD is not completely clear. Several Weimaraner pedigrees had multiple affected pups with unaffected parents suggesting either autosomal recessive inheritance or autosomal dominant with incomplete penetrance(37, 38). In Safra's review of clinical disease in 53 affected Weimaraners, ~ 50% of the dogs had at least one affected littermate (36). Linkage to the DLA-DRB1*01501 (DLA is the dog equivalent of the HLA) was reported by Abeles et al. (38) but no association could be found with the DLA locus when expanded DLA SNP analysis was performed (39) nor in another study assessing the role of DLA-DQA1 locus(40). The search for the disease causing gene is ongoing using a next generation sequencing approach. Once identified, HOD gene(s) will be an excellent candidate for human CRMO susceptibility.

HOD triggers remain unknown. The canine distemper virus was initially implicated in disease however, experimental attempts at transmitting the disease failed. Vaccination has also been implicated as a disease trigger(41). Safra's review, found that all 53 dogs had received live virus vaccine within 30 days of disease onset(36). However, Safra points out that HOD occurs in juvenile dogs at the time when all puppies are getting vaccinated. Dogs immunized with recombinant instead of live virus vaccine also developed HOD which is evidence against the live virus vaccine trigger(36).

Murine chronic multifocal osteomyelitis

There are 2 murine CRMO models, both due to missense mutations in the proline-serine-threonine phosphatase interacting protein 2 (*pstpip2*) gene(31, 42). The chronic multifocal osteomyelitis (cmo) mouse is a spontaneous mutant mouse and the lupo mouse was created by ENU mutagenesis. The disease in both murine models is hematopoietically driven and occurs in the absence of a functional adaptive immune system consistent with an autoinflammatory disorder(42, 43). The mice develop sterile osteomyelitis, extramedullary hematopoiesis in the spleen, and skin inflammation(31, 42, 44). *Pstpip2* is expressed in cells of the monocytic lineage and mutations in this gene result in elevated levels of proinflammatory serum cytokines (42, 43, 45). In addition to localized osteomyelitis, both cmo and lupo mice develop diffuse osteopenia suggesting a more widespread bone disease than was previously reported(45). Evidence suggests that the osteopenia is caused by enhanced osteoclast function(45). To demonstrate this, the investigators implanted dentin discs into the muscles of cmo mice and found enhanced disc resorption accompanied by increased circulating levels of pro-osteoclastogenic factor MIP-1 α without elevation of IL-1 α , IL-1 β , TNF- α or RANKL(45). The immunologic abnormalities were CSF-1 receptor (CSF-1R) dependent. These findings suggested that CSF-1R regulated *Pstpip2* tyrosine phosphorylation is required for suppression of osteoclastogenesis and that *Pstpip2* acts as a negative regulator of osteoclastogenesis(45).

Deficiency of the Interleukin-1 Receptor Antagonist (DIRA)

DIRA is a recently identified autoinflammatory disorder that affects the skin and bone(17, 18). Infants with DIRA present in the first weeks of life with pustular skin rash and systemic inflammation with or without fever(17, 18, 46–49). The chronic sterile multifocal bone inflammation becomes clinically apparent several weeks later. Radiographically, there are osteolytic lesions with varying degrees of sclerosis, widening of the medial clavicles, widening of the anterior rib ends and marked periosteal elevation(17, 18, 46, 49). The inflammatory bone disease can result in bone destruction and vertebral body fusion(17). The disease is autosomal recessive; the majority of mutations have been frameshift, non-sense or deletions, which are predicted to result in the lack of a functional protein or its complete absence(17, 18, 46–51). One DIRA mutation is a 175Kb deletion, which involves *IL1RN* plus 5 additional IL1 family members(17, 18, 46, 51, 52). Evidence points to founder populations for the E77X Dutch mutation, the 15 base-pair Brazilian mutation, the 175-kb Puerto Rican deletion and the Q54X Lebanese mutation(18, 46, 48, 50–52). All are predicted to result in the absence of production of the interleukin-1 receptor antagonist (IL-1Ra) protein. IL-1Ra is a critical down regulator of the IL-1 pathway and WBC from individuals with DIRA hyper-produce proinflammatory cytokines when exposed to IL-1 *in vitro*(17). Although bone and skin inflammation are the prominent clinical characteristics of DIRA, dysregulated IL-1 pathway mediated inflammation can cause interstitial lung disease, vasculitis and thrombosis(17, 18). DIRA has a high mortality rate if not recognized and adequately treated with mortality resulting from interstitial lung disease or from systemic inflammatory response syndrome(17). Treatment with the recombinant IL-1 receptor antagonist (IL-1ra), anakinra, results in rapid and sustained improvement in all aspects of disease and is life-saving(17, 18, 46, 48, 50–53). DIRA clearly demonstrates the importance of IL-1 in sterile bone inflammation.

Majeed syndrome

Majeed syndrome is an autosomal recessive disease caused by mutations in *LPIN2*. Majeed syndrome presents in the first 2 years of life with CRMO and congenital dyserythropoietic anemia(30, 54–58). Some individuals with Majeed syndrome also have a chronic neutrophilic dermatosis (Sweet syndrome) but this is not a uniform finding(32, 55, 56). The CRMO associated with Majeed syndrome is often more severe than that seen in sporadic cases of CRMO and has more frequent exacerbations(32, 56). Failure to thrive, hepatomegaly in infancy and long term sequelae in the form of permanent joint contracture may occur(55–57). It is an exceedingly rare disorder, to date, it has been reported in 4 inbred families each with a unique or “private” deleterious mutation in *LPIN2*(30, 57, 58). *LPIN2* variations have been reported in individuals with psoriasis and obesity associated type II diabetes suggesting that *LPIN2* may be a disease susceptibility gene in these disorders(59, 60).

Majeed syndrome improves with IL-1 blockade but not TNF- α blockade

Recently, Herlin et al. described the clinical presentation, cytokine profiles and response to cytokine blockade in 2 brothers with a novel 2 base-pair deletion in *LPIN2*(58). The boys

presented with early onset CRMO (at 3 and 6 months of age), anemia and one had recurrent fevers lasting 1 to 3 days with exacerbations of the disease. The metaphyseal areas of the long bones were involved and biopsy revealed chronic non-granulomatous inflammation. Both had marked elevation of inflammatory markers and elevated levels of pro-inflammatory cytokines including IL-1 β , IL-6, TNF- α and INF- γ (58). Bone marrow showed dyserythropoiesis (58). The disease in these boys was refractory to treatment with corticosteroids and the TNF- α blocking agent etanercept(58). However, rapid improvement in bone inflammation, systemic inflammatory markers and proinflammatory cytokine levels occurred with treatment of anakinra which blocks IL-1 receptor signaling and with canakinumab which blocks IL-1 β (58). Anemia improved but it was unclear if dyserythropoiesis resolved as a repeat bone marrow biopsy was not performed. The response to IL-1 blocking agents in these 2 boys strongly supports the hypothesis that Majeed syndrome is an IL-1 β mediated disorder.

Could saturated fats be a trigger for inflammation in Majeed syndrome?

LIPIN2 is a phosphatidate phosphatase that plays an important role in lipid biosynthesis (61–63). Reue et al. demonstrated that the serine at amino acid 734 is important in the phosphatidate phosphatase (PAP) activity of LIPIN2 and PAP activity is abolished when the Majeed syndrome causing mutation S734L is studied *in vitro* (64). But the role of LIPIN2 in controlling chronic inflammation remains less clear. Saturated fatty acids, like LPS, can activate toll-like receptors TLR2 and TLR4 which leads to down-stream activation of MAPK particularly JNK1 and ultimately leads to NF- κ B mediated up regulation of pro-inflammatory cytokine production (65, 66). Valdearcos et al. sought to determine if LIPIN2 plays a role in controlling inflammation induced by this pathway. They assessed the difference in proinflammatory cytokine production when human or murine monocytic cells that either over- or under-expressed *LPIN2*, were exposed to excessive quantities of the saturated fatty acid palmitic acid (67). Decreased expression of *LPIN2* resulted in enhanced secretion of proinflammatory cytokines including TNF- α , IL-6 and Ccl-2, whereas over-expression of *LPIN2* blunted the inflammatory response (67). Further, they showed that the increased cytokine production is mediated through JNK-1/c-Jun leading to increased transcription of these proinflammatory cytokines (67). Thus, chronic inflammation in *LPIN2* deficiency may be triggered by exposure to excessive saturated fatty acids. This question has not been assessed *in vivo*, but is a very intriguing hypothesis. To date, the few children with Majeed syndrome that have been tested have not had evidence of dyslipidemia (57).

SAPHO syndrome and the question of *P. acnes* as an infectious trigger

Although it is uniformly taught that bone inflammation in CRMO and SAPHO syndrome is sterile, there are reports of individuals with typical CRMO and SAPHO with bone cultures that were positive for various organisms (4, 23, 68–76). In the CRMO literature, these are often discounted as contaminants. Supporting the sterile nature of CRMO, Girschick et al. studied 12 CRMO/CNO biopsies that histologically revealed chronic osteomyelitis but utilizing standard culture techniques failed to detect fungi, mycobacteria, aerobic or anaerobic bacteria(3). Analysis of the specimens for bacterial ribosomal DNA by PCR using

universal 16S ribosomal DNA primers failed to identify a microbial signature supporting the sterile inflammation theory of CRMO/CNO(3).

Yet in SAPHO syndrome, the role of infectious agent as a trigger has gained more traction, particularly in regards to the role of *Propionibacterium acnes* (*P. acnes*) in disease pathogenesis (69–71). Rozin, as well as, Assmann and Simon recently reviewed the role of *P. acnes* in SAPHO syndrome (69, 70). They identified 11 manuscripts addressing the issue and found that 42% of 90 SAPHO bone cultures were *P. acnes* positive (69, 70). Recently, Assmann et al. reported on a cohort of 21 SAPHO patients that had all had bone biopsies and bone cultures. They found that 66% (14 out of 21) of bone biopsies from this cohort of patients grew *P. acnes*, suggesting that the role of *P. acnes* in SAPHO should be reconsidered if not as an infectious agent but as a trigger of inflammation (71). In support of an infectious etiology, *P. acnes* has been isolated from the anterior chest wall, spine, synovial fluid and skin pustules in some individuals with SAPHO. But more compelling are the reports of its isolation from bone biopsy samples of patients with SAPHO. In one case report, 6 surgically obtained bone cultures from a single individual all grew *P. acnes* as the only microbe recovered(77).

P. acnes is a Gram-positive, motionless, non-spore-forming, slow growing bacillus that prefers anaerobic conditions(78, 79). It is a part of the normal flora of the intestinal tract and skin. It does not typically cause clinical or laboratory manifestations of infection but it can cause serious, even life threatening infections(78, 80, 81). However, data from the neurosurgery and orthopedics fields is compelling to implicate *P. acnes* as a true pathogen rather than a mere contaminant(82–84). It is not eliminated by the preoperative antibiotics or standard pre-operative skin preparation(85). It synthesizes biofilms on implants and hardware where it is protected from the host microenvironment(79). The organism is able to survive within phagocytes, reducing the host's immune response ability to clear the organism(79).

P. acnes activates the innate immune response via Toll-like receptor (TLR)-9, as well as TLR9 independent, pathways (86, 87). In mice, *P. acnes* induces the development of splenomegaly and granuloma formation. It leads to heightened production of pro-inflammatory cytokines responses when the immune system is simultaneously triggered with TLR agonists including lipopolysaccharide (LPS)(86, 88). Mice primed with killed *P. acnes* have a more robust inflammatory response to TNF- α (4, 89). More recently, TLR9 independent mechanisms have been described to produce a delayed, but similar phenotype, which is dependent on IFN- γ and on MyD88 (an adaptor molecule that is required for signaling through most of the TLRs)(86). Given these findings, it is possible that involvement of TLR2 and TLR4 explain the TLR9 independent findings. These TLRs can respond to both microbial and non-microbial ligands which could allow them to participate in both infectious and sterile inflammatory disorders (86).

Sahdo et al. recently reported that *P. acnes* may activate the inflammasome(90). They reported increased caspase-1 activity from neutrophils but not monocytes (isolated from healthy blood donors) when stimulated with *P. acnes* compared to stimulation with ATP + LPS(90). This was associated with enhanced production of IL-1 β and IL-18 but there was

significant variability from donor to donor(90). Additional studies are needed to determine the role of *P. acnes* and IL-1 in CRMO/CNO and SAPHO.

Conclusions

Progress has been made in our understanding of the pathogenesis chronic sterile osteomyelitis by studying human, murine and canine models of the disease. Innate immune system dysregulation is a common feature and IL-1 dysregulation is important in the monogenic human forms of the disease. The role of IL-1 in murine cmo is currently under study. *P. acnes* may play a role in SAPHO syndrome pathogenesis via its ability to trigger the innate immune system through both TLR9-dependent and -independent mechanisms. LIPIN2 may play a role in regulating inflammation associated with abnormal fat metabolism.

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Key Points

- Advances have been made in understanding the genetic basis of chronic non-bacterial osteomyelitis
- Both murine and human data strongly implicate aberrant activation of the innate immune system in disease pathogenesis
- Dysregulation of the IL-1 pathway results in sterile bone inflammation in DIRA and in Majeed syndrome.
- *In vitro* data suggests that LIPIN2 plays a role in controlling inflammation in the setting of excessive saturated fatty acids.
- *P. acnes* continues to be implicated as a potential disease trigger in SAPHO syndrome; *P. acnes* stimulated proinflammatory immune response is dependent on both TLR9 and TLR-9 independent mechanisms.