Commentary

A possible cause of joint destruction in septic arthritis

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There are many unanswered questions regarding the mechanisms of joint damage in the only real rheumatologic emergency, septic arthritis. Aside from antibiotic therapy, clinical studies in this area have shown that the single most important element in the successful treatment of septic arthritis is early adequate drainage of the joint [1]. For joints, the outcome from septic arthritis is frequently poor, with moderate to severe damage to the joint in more than a third of patients, regardless of whether treatment was with aspiration alone, or surgical. Progress in this field has been hindered by a lack of knowledge concerning the mechanism of destruction in the infected joint. Pus in the joints can mediate chondrolysis, at least in part because of the presence of numerous activated host leukocytes [2]. But how does the presence of bacteria in the joint initiate the inflammatory process? Our understanding of this process has been essentially limited to vague notions of 'evil humors' from the bacteria. The 'evil humors' cannot be bacterial endotoxins, since septic arthritis from gram positive bacteria is at least as damaging to joints as that from gram negative. What then could the 'evil humors' be, and how does this inform us about the optimal management of this potentially devastating condition?

A recent study from Deng *et al* at the University of Göteborg in Sweden provides new insight into a previously overlooked potential etiologic factor in septic arthritis [3]. These investigators showed that the mere introduction of bacterial DNA into the knee joints of mice triggered rapid and severe inflammatory arthritis with an influx of monocytes and the production of intra-articular tumor necrosis factor-α. Joint damage was independent of B or T cells, suggesting that it involved instead the activation of the more evolutionarily primitive innate immune system.

At first glance, it may seem quite surprising that highly purified bacterial DNA could trigger such profound immune effects in the absence of infection, especially since injection of vertebrate DNA into the joints had no pro-inflammatory activity. However, in recent years it has become clear that DNA serves not just as the genetic material for encoding genes, but also can have direct immunostimulatory effects (reviewed in [4]). In vertebrate DNA, the combination of bases in which a cytosine is followed by a guanine, termed a CpG dinucleotide (the 'p' refers to the phosphate bond linking the C and the G), occurs less frequently than would be predicted assuming a random combination of all possible bases in the genome. Moreover, when CpGs occur in vertebrate genomes, the C is almost always modified by the addition of a methyl cap. In contrast, bacterial DNA generally has the expected frequency of CpG dinucleotides that are not methylated. This subtle structural difference in the DNA of vertebrates and bacterial pathogens is apparently used by our immune system as a 'danger signal' indicating the presence of infection. Indeed, recent studies showed that immune recognition of this elegantly simple unmethylated 'CpG motif' has evolved as a relatively simple way for the immune system to detect the presence of bacteria or other pathogens without necessarily recognising the identity of the specific pathogen [5]. CpG motifs in bacterial DNA or synthetic oligonucleotides rapidly stimulate macrophages, dendritic cells, B cells, and natural killer cells to become activated, to secrete pro-inflammatory cytokines, and to initiate protective immune responses [6]. The molecular mechanism of action of CpG DNA involves cell uptake, followed by activation of intracellular mitogen-activated protein kinases and transcription factors, including nuclear factor κB and activator protein-1 [7–9]. Intriguingly, antimalarials such as chloroquine and quinacrine have been found to specifically block all of the pro-inflammatory effects of CpG at very low concentrations that do not inhibit responses to other microbial substances, such as endotoxins [9–11]. CpG DNA can be used therapeutically as a vaccine adjuvant against infectious diseases, cancer, or allergy, or as a broad spectrum

immunotherapy. As would be expected for an immune defense mechanism, Deng *et al* have shown that injection of CpG DNA systemically into mice had no adverse effects on the joints. It is only when the CpG DNA (or the infection) actually enters the joint that the pro-inflammatory effects of CpG DNA appear to trigger harmful inflammatory responses as opposed to protective responses. On the other hand, CpG motifs present in chlamydia DNA can act as adjuvants to trigger immune responses to self antigens, causing heart disease [12].

Limitations of the present study include the fact that it is not a realistic model of septic arthritis, and that the inflammation resolves spontaneously if the injection of CpG DNA into the joint is not repeated. In addition, it seems intuitively likely that there is not just a single trigger for joint damage in infected joints, but that this must be the result of a complex interaction between multiple microbial signals and the host's responses. Of course, results in mice cannot always be extrapolated to humans, though recent studies have shown that CpG DNA activates human immune cells in a similar fashion to those of mice [6].

These new findings provide an insight into what must happen early in the course of septic arthritis. When bacteria begin multiplying in a joint, the products of the bacteria such as the CpG DNA will activate inflammatory host defense mechanisms to control the infection and destroy the invading bacteria even at the expense of causing permanent joint damage. The CpG DNA is not toxic in and of itself, but only because of its stimulatory effect on host immune mechanisms. This understanding has important potential implications for rheumatologic care. This model would certainly reinforce the need for early recognition and treatment of septic arthritis. However, it also suggests the possibility that joint aspiration alone may not be the optimal therapy for septic arthritis, and that more aggressive closed joint lavage may result in improved outcomes. This question seems apposite as a subject for future clinical investigations.

It has long been suspected that unidentified chronic microbial infection may underlie at least some cases of chronic inflammatory arthritis. Several groups have reported the presence of DNA from chlamydia and other bacteria in joints of patients with inflammatory arthritis, particularly reactive [13,14] (reviewed in [15]). These data are of particular interest given the association of chlamydia with autoimmune heart disease [12]. If these findings are confirmed, the presence of CpG DNA in inflammatory arthritic joints would finally provide a rationale for the therapeutic use of antimalarials, which specifically block CpG-induced inflammation [9–11]. Moreover, the identification of more potent small molecule inhibitors of CpG DNA [16] may offer interesting new therapeutic options for the treatment of inflammatory arthritis. Thus, DNA is more than the key to the genetic blueprint, it may also help to unlock a better understanding of infectious and reactive arthritis.

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