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Editorial

Osteoarthritis or osteoarthrosis: the definition of inflammation becomes a semantic issue in the genomic era of molecular medicine

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Osteoarthritis (OA) or osteoarthrosis? Reports in the last decade have suggested that human OA-affected chondrocytes and activated macrophages share the release of similar inflammatory mediators. In spite of the superinduction of inflammatory mediators by OA-affected chondrocytes, the unique architecture of cartilage (avascular, aneural and alymphatic) when inflamed at the molecular level, does not qualify for the typical definition of inflammation (redness and swelling with heat and pain—*rubor et tumor cum calore et dolor*) due to the semantics and the history of the word 'inflammation'. The genomic revolution provides access to tools for examining a single event in the context of the whole genome. Use of this facility can lead to new ways of understanding complex pathophysiological conditions such as inflammation. From research laboratories to clinical settings, inflammation is now perceived differently although the molecular events remain the same. The present editorial highlights semantic issues using one example of an 'inflammatory disease': OA.

History of inflammation

Redness and swelling with heat and pain—*rubor et tumor cum calore et dolor*—were first documented as the cardinal signs of inflammation by Cornelius Celsius in the first century CE (30 BC to 38 AD). He defined inflammation as an entity using a singular rather than a plural noun, implying that it might be a single process or type of process[1]. However, the history of inflammation is long and colorful, intimately linked to that of wounds, wars and infections. In his marvelous book, *The Healing Hand: Man and Wound in Ancient World*, Majno has assembled ancient descriptions of inflammation written long before Celsius put his stamp on the field[2]. Following the rather slow development of the biological and clinical sciences in the ensuing centuries, the invention of the microscope and the discovery that there was no such thing as spontaneous generation of life forms led to a sudden burgeoning of studies on the mechanisms of inflammation in the nineteenth and early twentieth centuries. These include examination of the vascular and cellular events in thin transparent membranes *in vivo* by Cohnheim, investigation of phagocytosis by Metchnikoff, of the role of antibodies by Ehrlich, of complement by Bordet and the development of the concept of endogenous mediators by Lewis[2]. In the latter part of the twentieth century, the development of new technologies including electron and fluorescence microscopy, histopathology, biochemistry, molecular biology and genetic engineering has facilitated the remodeling of the concept of 'inflammation' in molecular medicine. The last decade has introduced several new technologies, including Real Time PCR, Gene Chip technology and Proteomics. These not only allow us to look at minor changes in pathophysiological conditions, but at global effects on gene and protein expression as they relate to expression of a single gene or protein.

The purpose of this editorial is to discuss one particular human pathophysiological condition (OA), which has certain features of inflammation but which breaks the rules for the definition of inflammation as described below.

Osteoarthritis or osteoarthrosis: which is more appropriate?

Pathologists and radiologists at the turn of the century differentiated two principal forms of chronic arthritis: (1) atrophic arthritis with synovial inflammation and erosion or atrophy of cartilage and bone (e.g. rheumatoid arthritis) and (2) hypertropic arthritis, characterized by focal loss of cartilage, little evidence of the typical form of inflammation, and by growth (hypertrophy) of adjacent bone and soft tissue[3]. The latter group became synonymous with OA. In the 1960s and 1970s major research interest increasingly focused on inflammatory arthropathies, with OA often being used in clinical and laboratory studies as a 'non-inflammatory' control, or even as a surrogate for normal joint tissue. Such usage encouraged the term osteoarthrosis to emphasize the lack of overt inflammation[4].

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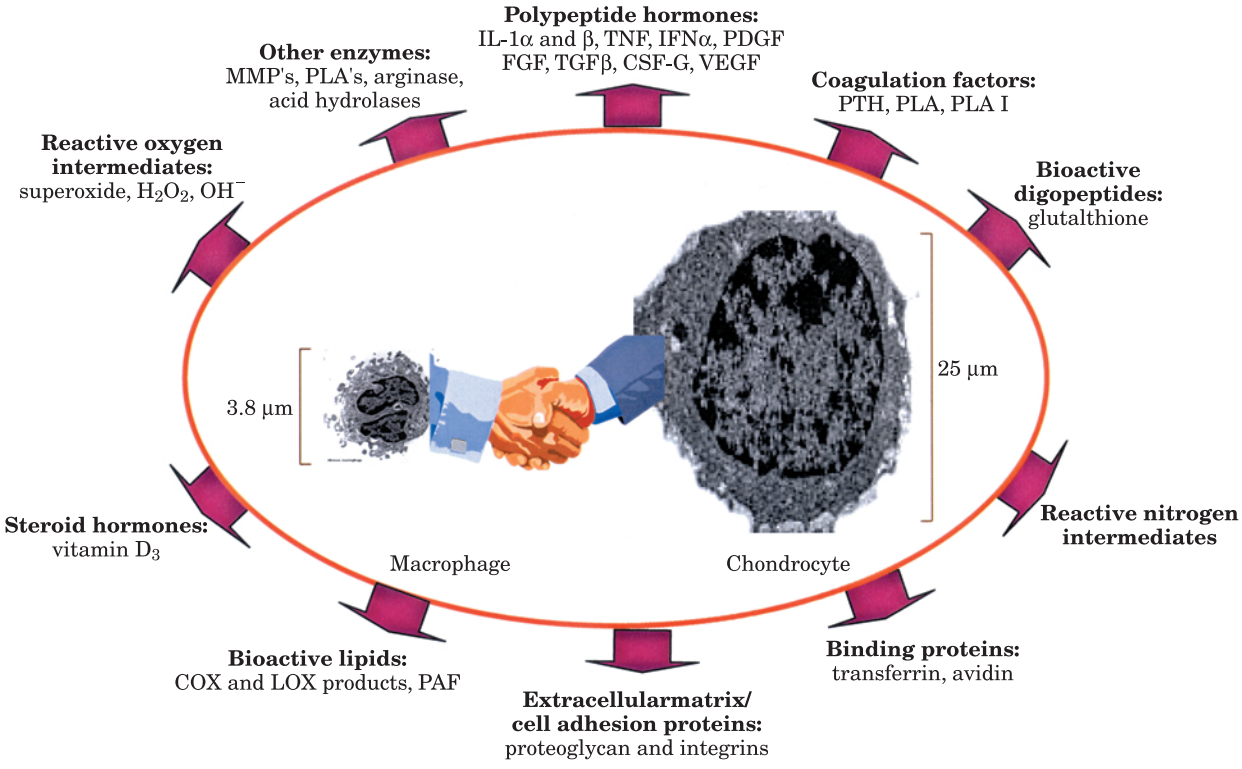

Fig. 1. Common inflammatory mediators released by activated macrophages and OA-affected cartilage. The data is compiled from References 17–24.

Classically, OA unlike rheumatoid arthritis (RA), is considered an inherently non-inflammatory disorder of movable joints characterized by deterioration of articular cartilage and the formation of new bone at the joint surfaces and margins[5]. The synovial fluid in OA, in contrast to that in RA, typically contains few neutrophils (<3000/mm^3) and, except in advanced disease, the synovium itself does not exhibit significant cellular proliferation or infiltration by inflammatory leukocytes. OA also differs from RA in that it is not a systemic disease, but one in which an 'inflammatory component' seems to be restricted in the cartilage and bone. The molecular pathogenesis of OA has been increasingly elucidated by studying events within the articular cartilage that maintain cartilage homeostasis. For example, alteration in the dynamic equilibrium between synthesis and degradation of the matrix by chondrocytes has been implicated as a first step in the degeneration of articular cartilage resulting in OA[6,7].

OA cartilage: a unique inflammatory tissue

Articular cartilage is avascular, alymphatic and aneural in nature and OA does not seem to comply with the definitions of inflammation typified by the four cardinal signs of Celsius described above. Because of its unique architecture, the cartilage in OA does not show the redness, swelling and heat that result from increases in vascular permeability and leakage during inflammation at other sites. Because there is no extravasation of body fluids and inflammatory cells, granulation tissue is not formed in OA. Because there are no nerves in cartilage, there is no painful sensation in OA cartilage during early stages of the disease.

OA-AFFECTED CHONDROCYTE: 'A LARGE ACTIVATED MACROPHAGE'

The normal size of an activated macrophage is approximately 3.8 μm, whereas that of an OA-affected chondrocyte is approximately 25 μm. Figure 1 summarizes some of the common inflammatory mediators released by activated macrophages and chondrocytes. This OA-chondrocyte may behave to some extent like a 'large macrophage' with respect to production of some of the inflammatory mediators.

REGULATION OF INFLAMMATORY MEDIATORS IN NORMAL AND OA-AFFECTED CARTILAGE

When compared with normal cartilage, OA-affected cartilage shows superinduction of inflammatory mediators in *in vitro* and *ex vivo* conditions. A summary of inflammatory mediators increased in OA-affected as compared with normal cartilage is presented in Fig. 2. Real Time PCR has been used to demonstrate upregulation of various proinflammatory genes in human OA-affected as compared with normal cartilage (Fig. 2A). As can be seen in the figure, the scale for expression of various mRNAs in normal human cartilage is very broad and can vary from 2 to 50,000 transcripts for a particular gene. Up-regulation of the IL-1 gene, normally transcribed in low abundance, and the IL-6 and IL-8 genes, normally transcribed in high abundance, is clearly demonstrated. There is significant up-regulation of TNFα convertase (TACE), which regulates the release of soluble TNFα but little change in aggreganase mRNA (ADMP-2). There is a reduction in the amount of mRNA

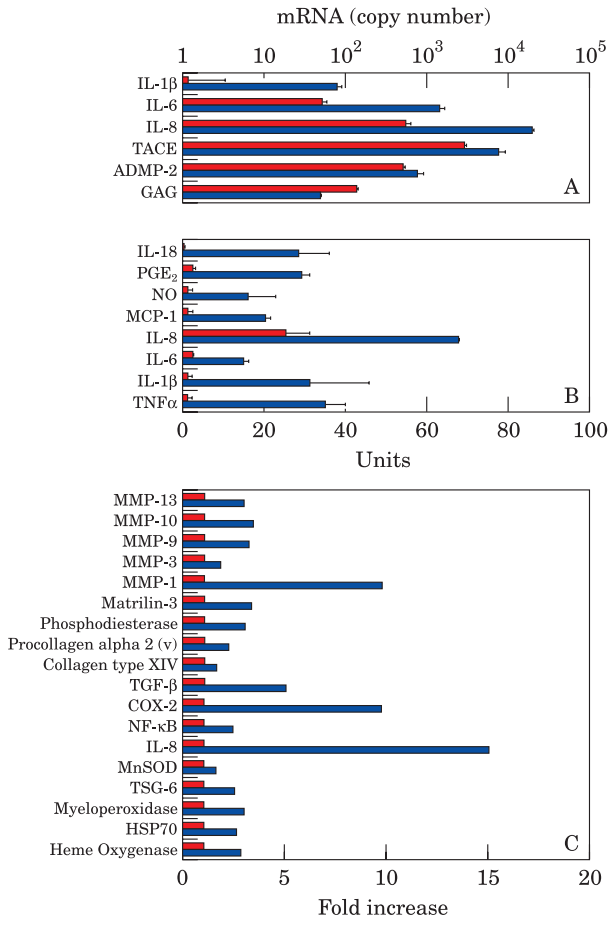

Fig. 2. Up-regulation of inflammatory mediators in human OA-affected cartilage. (A) Real time PCR of mRNA transcripts in normal and OA-affected cartilage. Equal amounts of DNAase treated total RNA were used to prepare cDNAs, which were PCR amplified in triplicate using specific primers by the TaqMan Method[25]. Fluorescence was measured during cycling reactions and the increase in fluorescence after subtraction of baseline fluorescence was plotted. The numbers of mRNA transcripts were estimated [pre-developed assay reagents (PDARs), fluorescent labeled], after normalization to GAPDH. Quantification of the transcripts was performed assuming there is a single copy of a gene using genomic DNA. Statistical analysis of the data was performed on grouped individual data where $N=10$ (Fig. 2(A), (B)). The P values were <0.01. (B) Spontaneous production of inflammatory mediators by normal and OA-affected cartilage *in vitro*[17]. Human normal and OA cartilage was incubated in *ex vivo* conditions in triplicate as previously reported[18]. IL-1β and TNFα were estimated by ELISA and represented as pg/ml/100 mg of cartilage. IL-6, IL-8, MCP-1 and IL-18 were represented as ng/ml/g of cartilage. PGE_2 was represented as ng/ml and NO as μM/g of cartilage. $N=3$, $P\leq0.01$. (C) Gene chip analysis of selected proinflammatory mediators and stress genes in normal and OA-affected cartilage. The human Affymetrix U95 gene chip was probed with a pool ($N=10$) of normal and OA-affected cartilage RNAs. The data is presented as fold increase, normalizing the values to those of GAPDH. The levels of OA transcripts that showed a minimum of 1.75-fold increase above normal are summarized.

encoding the matrix component glucosamine glycans (GAG) confirming a previous report that this is down-regulated in OA[8]. Enzyme linked immunosorbent assay (ELISA) or radio immunoassay (RIA) have been used to measure the amount of mediators released (Fig. 2B). These vary from pg/g of cartilage for IL-1β to ng/g for IL-8 and IL-6. Significantly increased levels of IL-18, PGE_2, NO, monocyte chemoattractant protein-1 (MCP-1), IL-8, IL-1β and TNFα are also observed. Increased levels of NO, PGE_2, IL-6, IL-1 and TNFα have been reported by others to have detrimental effects on cartilage homeostasis including collagen metabolism and to impact on cartilage repair *in vitro* and *in vivo*[9]. As assayed by gene chip technology (Fig. 2C), various other genes are found to be over-expressed. These include matrix metalloproteases (MMP)-1, 3, 7, 9, 10 and 13, and stress induced genes such as TNF stimulated gene-6 (TSG-6) and heat shock protein 70 (HSP70), heme oxygenase, manganese superoxide dismutase (MnSOD) and myeloperoxidase. Many of these are known to alter cartilage homeostasis by up-regulating a network of pleiotropic inflammatory mediators, such as IL-1 and TNFα together with their interleukin 1 converting enzymes (ICE) and TACE, as well as cytokine receptors including IL-1RI, TNFα-p55 and TNFα-p75[10]. Other investigators have also reported up-regulation of membrane type (MT)-MMP, plasminogen activators/plasmin system and cathepsin B[11]. One of our most intriguing findings utilizing the gene chip array was the two-fold increase in induction of the signaling transcription factor, NFκB, in OA as compared with normal cartilage. Activated NFκB routes various inflammatory pathways induced by IL-1, TNFα, biochemical and mechanical/oxidative stress pathways[12]. Inhibition of NFκB *in vitro* in OA cartilage in *ex vivo* conditions inhibits much of the action of the inflammatory mediators[13].

At least two connections have been made between elevation of biochemical markers of inflammation and progression of structural changes in OA joints. It has been suggested that elevation in cartilage oligomeric protein (COMP) may reflect synovitis[14] while elevation in C-reactive protein (CRP) may be associated with long term radiographic progression[15]. Conversely, intraarticular injection of corticosteriods in OA joints with consequent reduction in output of the inflammatory components are clearly associated with short-term improvement. The improvements include reduction of symptoms, minimization of functional disabilities and limitation of progression of structural changes[16].

Claude Bernard first suggested that the purpose of all physiological processes is to keep the internal environment the way cells like it. This responsibility of maintaining cartilage homeostasis is entrusted to chondrocytes. It seems the 'activated chondrocytes' observed in OA may not only be a target, but also an instigator in the disease process, due to autocrine production of inflammatory mediators.

In conclusion, we have entered a new era in the conceptualization of the pathogenesis of OA. The debate, 'Osteoarthritis vs osteoarthrosis', must be reframed. If we require of *inflammatory* processes all of the classical signs of inflammation (e.g., rubor, color, dolor, etc.), then the narrow concept of OA as a biomechanically driven process interrupted by brief and episodic inflammation will prevail. However, in the modern genomic era, 'inflammation' can alternatively be seen as a process characterized by the release and activation of toxic cellular mediators which promote tissue injury, resulting in some, but not all, of the classical signs of inflammation, including 'functia laesa', loss of function. OA cartilage is a rich source of such inflammatory mediators, a site of activated cytokine production and of prodigious amounts of both NO and PGE_2. OA cartilage can be viewed as an inflamed tissue, brimming with phylogistic products that could serve as targets for future pharmacological intervention. Which conceptual

framework shall we choose, Osteoarthritis or osteoarthrosis? The implications are clear: exciting interventional 'antiinflammatory' strategies for the former, pharmacological nihilism for the latter.

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