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Inflammatory Biomarkers in Osteoarthritis

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Summary

Osteoarthritis (OA) is highly prevalent and a leading cause of disability worldwide. Despite the global burden of OA, diagnostic tests and treatments for the molecular or early subclinical stages are still not available for clinical use. In recent years, there has been a large shift in the understanding of OA as a “wear and tear” disease to an inflammatory disease. This has been demonstrated through various studies using MRI, ultrasound, histochemistry, and biomarkers. It would of great value to be able to readily identify subclinical and/or sub-acute inflammation, particularly in such a way as to be appropriate for a clinical setting. Here we review several types of biomarkers associated with OA in human studies that point to a role of inflammation in OA.

Keywords

Inflammation; biomarker; osteoarthritis

Introduction

Inflammatory osteoarthritis (OA) is a debilitating and highly prevalent disease, but is often sub-clinical. There is an increasing body of evidence that inflammatory and destructive responses of the synovium play a major role in OA(1). Moreover, the role of inflammation in the illness of OA has been recognized through the association of joint effusion with joint pain(2). It is still unclear to what extent inflammation is an initiator versus an outcome of the joint destructive process(3). Of particular interest is the emerging evidence that the degree to which the immune and wound healing responses can be activated in part controls the predisposition of an individual to chronic diseases, among them OA. Despite the global burden of OA, diagnostic tests and treatments for the molecular or early subclinical stages are still not available for clinical use. It would of great value to be able to readily identify subclinical and/or sub-acute inflammation, particularly in such a way as to be appropriate

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for a clinical setting. Here we review several types of biomarkers associated with OA in human studies that point to a role of inflammation in OA.

Genetic and Genomic Markers

Increasingly, enrichment strategies are being used in clinical trials to select a study population in which detection of a drug effect is more likely than it would be in an unselected population (prognostic enrichment), or to increase the likelihood of predicting a response (predictive enrichment). In December 2012, the US Food and Drug Administration (FDA) published a draft guidance describing enrichment strategies to support approval of drugs and biological products(4). To date, labeling of more than 100 approved drugs contain information on companion diagnostics, all in the form of genomic biomarkers(5). Genomic selection to predict a response has primarily been used in hematology/oncology and only 4% of the companion diagnostics are currently in the field of rheumatology(6). However, a genomic strategy to identify a subset (4%) of patients with cystic fibrosis likely to respond to ivacaftor (via specific mutations of the CFTR gene) led to the recent FDA approval of this drug(7). In addition, the FDA has recently approved several new drugs and drug combinations(8–10) for the treatment of specific hepatitis C genotypes on the basis of companion genomic tests. A number of genetic/genomic markers are emerging in OA that relate to inflammatory phenotypes that might be similarly exploited in the future for enriching for specific patient subsets for trials and eventually selecting patients for specific clinical treatments.

For instance, several studies suggest that a proportion of the genetic susceptibility to OA may be encoded by variations in innate cytokine activity(11–15). Interestingly, it is possible that our access to antibiotics has shifted the role of the innate immune system from being protective against infectious diseases to intensifying age-related chronic diseases(16, 17). The fact that this may be the case has recently been demonstrated by the emerging story related to the forkhead-box class O (FOXO) genes, which have been found to mediate the inflammatory, apoptosis, and barrier function responses of keratinocytes exposed to bacteria(18). In particular, FOXO1 promotes wound healing by regulating the expression of transforming growth factor-beta (TGF-β) and playing a protective role against oxidative stress (19). FOXO1 and FOXO3 were also found to be expressed in human cartilage, and exposure of pro-inflammatory cytokines suppressed the activity of FOXO1 in chondrocytes(20). In addition, chondrocytes with reduced expression of FOXO transcription factors were more susceptible to apoptosis when exposed to oxidative stress(21). The injury of articular cartilage induces changes in genes associated with cell signaling, response to injury, and wound healing(22). Recently, the pro-apoptotic gene, PUMA, has been shown to be activated by the c-Jun N-terminal kinase (JNK)/c-Jun pathway in the regulation of chondrocyte apoptosis in cartilage of patients with OA(23). Moreover, the Wnt signaling pathway, which is involved in both cartilage and bone tissue homeostasis(24), was found to be up-regulated while its inhibitor (FRZB) was down-regulated in cartilage from joints with moderate to severe OA damage(22). Wnt signaling and DNA repair pathways have also been identified to be significantly correlated with articular cartilage healing(25).

A well-validated gene expression method has identified higher levels of interleukin (IL)-1β expression in peripheral blood leukocytes (PBLs) in patients with knee OA in association with increased pain and greater risk of radiographic progression of OA(26). The expression of four microRNAs (miRNAs) (miR-146a, miR-155, miR-181a, and miR-223), which have been reported to be expressed in immune cells and are responsible for regulating inflammation, were significantly higher in the peripheral blood mononuclear cells (PBMCs) of patients with OA compared to the PBMCs of healthy controls(27). In another study, plasma concentrations of miR-132 were significantly higher in healthy controls compared to patients with either OA or rheumatoid arthritis (RA)(28). In addition, microarray analysis of blood samples from healthy controls and patients with OA identified six genes significantly down-regulated in mild OA (heat shock 90kDa protein 1, alpha; inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein; IL-13 receptor, alpha 1; laminin, gamma 1; CXCL4; and tumor necrosis factor-inducible gene (TSG)-6)(29), many of which play an important role in inflammatory cascades. Given the role that genomic companion testing has had in personalized treatments, these genetic markers may pave the path for the development of novel therapeutic targets to treat a subset of patients with OA.

Macrophages

The human body swiftly reacts in response to acute foreign intrusions or injury in a very complex and organized manner via the innate immune system(30). However, low-level inflammatory stimulation may also affect the body and cause a state of chronic inflammation. OA is increasingly recognized as a process involving low grade inflammation, often subclinical (31), that is predictive of articular chondropathy and OA progression (32–35).

A critical aspect of joint inflammation in OA involves synovial macrophages and macrophage-produced cytokines that drive aggrecanases, matrix metalloproteinases, and other destructive and inflammatory responses(36). These critical mediators of joint destruction may be used as tools to assess disease activity and severity. We demonstrated that the profile of cytokines in the OA joint is consistent with macrophage-mediated inflammasome activation(37). Interestingly, the synovial fluid (SF) concentration of uric acid in these OA knees was strongly associated with the concentration of several inflammatory cytokines. Uric acid is the canonical trigger of the macrophage-mediated inflammasome activity in gout(38) and is able to induce cytokine production by macrophages(39). Additional supporting evidence for a potential role of uric acid in OA has been demonstrated by the effect monosodium urate crystals have on decreasing chondrocyte viability and function in gout(40).

Targeting activated macrophages as a treatment for OA has been previously proposed(41–43). Similarly, the released proteins and cytokines of activated macrophages have great potential to become diagnostic biomarkers for OA. Our recent etarfolatide imaging study, which targets activated but not resting macrophages(44), demonstrated the preferential localization of activated macrophages to painful and more severely affected osteoarthritic knees(33). The macrophage markers CD14 and CD163 measured in the blood sera/plasma

and SF were associated with etarfolatide uptake, radiographic OA severity and progression, and joint symptoms(34). YKL-40, a member of the chitinase family, is a glycoprotein that is secreted mostly from macrophages(45, 46) and chondrocytes(47) and has been found to be elevated in the SF of patients with rheumatoid arthritis (RA) and OA(48). Moreover, the median value of SF YKL-40 was greater in patients with moderate/severe arthritis when compared to those with none/mild arthritis(48). Taken together, these results support the involvement of macrophages in OA with activation of the innate immune response in OA pathology and progression.

Complement

As part of the innate immune system, the complement system, as inferred in its name, complements and assists antibodies and phagocytic cells with the clearance of foreign objects(49). The complement system can be activated by several different pathways, including by many components of the cartilage extracellular matrix (reviewed by Hsueh et al.(50)). One proteomic study identified several complement proteins that were differentially expressed between healthy and OA knee SF samples(51). In another proteomic study, complement components were found to be modulated in sera of patients with moderate and severe OA(52). In particular, concentrations of C3a and C5b-9 have been found to be significantly higher in the SF from patients with early-stage OA in comparison to those from healthy individuals(53). In addition, expression of transcripts encoding the complement effectors C7, C4A, factor B, C9, and C5 was significantly higher, while factor H, C4-binding protein, C1 inhibitor, and clusterin, which are complement inhibitors, were lower in synovial membranes of patients with OA in comparison to those from healthy individuals(53). Interestingly, cartilage oligomeric matrix protein (COMP), which is elevated in the sera(54–56) and SF(57, 58) of patients with OA, can also activate the complement system (59, 60). The involvement of complement activation in OA is consistent with its involvement in several other chronic inflammatory diseases, including RA(61, 62), atherosclerosis(63, 64), Alzheimer's(65–67), and age-related macular degeneration(68, 69).

C-Reactive Protein

C reactive protein (CRP) is a central component of the innate immune inflammatory response; by binding to the cell surface of dead or dying cells and some bacteria it leads to the activation of the complement system(70). The synthesis of CRP is mediated by factors released by macrophages and adipocytes. CRP also leads to the promotion of pro-inflammatory cytokines, which increases the inflammatory response(71). CRP was elevated in patients with acute heart failure(72), and has been associated with the risk of developing coronary artery disease(73), head and neck squamous cell carcinoma mortality(74), and inflammatory bowel disease(75). Several studies have also sought to establish a connection between levels of serum CRP and OA(76). A recent meta-analysis of 32 studies revealed statistically significant differences in serum CRP between patients with OA and healthy controls. The study also revealed that CRP was significantly associated with pain and decreased physical function, but not radiographic OA (77). In studies that have adjusted for body mass, CRP has been shown to be independently associated with OA(78), while other studies have not proven CRP to be independently associated with OA(79, 80). The meta-

analysis study by Jin and colleagues(77) also compared studies that accounted for BMI from those that did not and concluded that the association of CRP with OA was independent of BMI.

Cytokines

Cytokines are small proteins released from a wide array of cells, including immune cells (macrophages, B lymphocytes, T lymphocytes, mast cells, natural killer cells, epithelial cells, endothelial cells, dendritic cells, fibroblasts, and stromal cells)(81, 82). Various cells utilize cytokines, chemokines (chemotactic cytokines), and adipokines (cytokines released by adipose tissue) as part of the inflammatory response to regulate cell signaling and interactions within the cell itself and between other cells(83, 84). Cytokines can have either pro-inflammatory or anti-inflammatory properties and often work concordantly to maintain cell homeostasis(85). We have shown that the concentrations of key SF cytokines (IL-1α, IL-18 and tumor necrosis factor (TNF)-α) were associated with the level of OA severity; baseline IL-18 also predicted OA progression(37). Serum levels of IL-6 and TNF-α have also been associated with the prevalence of joint space narrowing and prediction of knee cartilage loss(86). Serum TNF-α levels have effectively been used to monitor the efficacy of various OA treatments in rabbits(87). However, in a multi-center, randomized, double blind, placebo-controlled trial, injection of anti-TNF-α agents did not show any improvement in patients with unmanageable hand OA(88). Soluble TNF-α receptor levels were decreased in the SF and plasma of patients with OA in comparison with healthy controls, with SF levels being negatively correlated with joint symptoms(89) evaluated by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire. Recently, the activity of the protein encoded by TSG-6, which is an anti-inflammatory protein that is upregulated in response to the pro-inflammatory cytokines TNF and IL-1(90), and was previously detected in patients with arthritis(91), has been shown to be associated with progression of OA after 3-year follow up in a study of 91 patients(92). In a small pilot study, Vangsness et al. (93) showed that higher levels of SF IL-2, IL-5, and monocyte chemoattractant protein (MCP)-1 were associated with greater degrees of OA severity. SF levels of IL-6, IL-13, and macrophage inflammatory protein (MIP)-1β were elevated in patients with end-stage knee OA while granulocyte colony-stimulating factor (G-CSF) levels were lower when compared to SF levels of healthy controls(94).

From a prospective population-based study of 908 healthy middle-aged British women, individuals with higher age and baseline body mass index (BMI) and increased serum IL-6 after 5-year follow-up were more likely to be diagnosed with radiographic knee OA at their 10-year follow-up(95). Given the association of obesity with OA(96, 97), it is of interest that patients with knee OA have increased levels of IL-6 and soluble IL-6 receptor released from the infrapatellar fat pad of the knee compared with subcutaneous adipose tissue(98). Weight loss and increased physical activity in obese elderly patients with OA decreased levels of soluble TNFα Receptor 1 and increased physical function(99). Exercise has also been shown to increase both intraarticular and peri-synovial concentrations of anti-inflammatory IL-10 in women with knee OA(100).

Chemokines

Chemokines are a class of small protein cytokines that act as chemoattractants to guide cells to migrate to a specific location, and in the context of inflammation, toward the site of injury or pathogenic invasion(82). Interferon gamma inducible protein 10, also known as CXCL-10, is a chemokine that has been shown to be inversely associated with radiographic knee OA in both plasma and SF(62). Serum fractalkine, or CX3CL1, has also been shown to be significantly elevated in patients with knee OA in comparison to the sera from healthy individuals, while both serum and SF concentrations of the chemokine were associated with KL scores(101). SF CXCL12, but not serum CXCL12, was associated with radiographic severity of OA(102). A recent study has demonstrated the feasibility of using serum and SF MCP-1, also known as chemokine ligand 2 (CCL2), as a biomarker for self-reported pain and physical disability in patients with knee OA(103). To further support the role of macrophages in OA-related inflammation, MCP-1 has been shown to increase the recruitment of macrophages into adipose tissue(104) and atherosclerotic lesions(105). SF levels of macrophage derived chemokine (MDC) and interferon gamma-induced protein (IP-10) were elevated in patients with end-stage knee OA, while eotaxin levels were lower when compared to SF levels of healthy controls(94).

Adipokines/Hormones

A number of adipose tissue-secreted hormones mediate inflammatory effects(106, 107) and cartilage catabolism(108–110) in OA. Plasma adipokines adiponectin, which is responsible for modulating metabolic processes, and leptin, a regulator of fat storage, have been shown to be positively associated with joint symptom burden, while the glucose modulating adipokine, adipsin, was lower in patients with hip and knee OA(111). Adipsin is also known as complement factor D and is responsible for activating the alternative pathway of the complement system(112). Serum adiponectin levels have also been associated with radiographic hand OA progression after 6-year follow-up(113). Leptin is believed to play an important role in the pathogenesis of OA via its stimulation of anabolic functions of chondrocytes in cartilage(114). Serum leptin levels were also associated with prevalent and incident knee OA in the Study of Women's Health Across the Nation (SWAN) cohort(115). Serum leptin measured at baseline has been associated with increased levels of bone formation biomarkers (osteocalcin and procollagen type I N-terminal propeptide (PINP)) after two-year follow-up(116). In addition, baseline soluble leptin receptor was associated with lower levels of procollagen type II N-terminal propeptide (PIIANP) and decreased cartilage volume(116). Visfatin (also known as nicotinamide phosphoribosyltransferase (Nampt)), which is an adipokine and enzyme involved in the metabolism of nicotinate and nicotinamide, has recently been suggested to be a therapeutic target for OA given its role in chondrocyte and osteoblast activation(117). As an inflammatory biomarker, levels of SF visfatin were significantly greater in patients with knee OA compared to control subjects(118). In addition, SF visfatin was positively correlated with the cartilage degradation markers collagen II (CTX-II) and aggrecan (AGG1 and AGG2) and was significantly elevated in more severe knee OA grades (Kellgren Lawrence 4 versus 3)(118). In middle-aged women, lower levels of serum estradiol, which is a hormone that has anti-

inflammatory properties(119), and the urinary estrogen metabolite 2-hydroxyestrone were associated with both the prevalence and incidence of knee OA(120).

Conclusions

Given the inverse association of OA susceptibility with the ability of cartilage to repair itself(121), the subset of patients with inflammatory OA phenotypes are likely the ones most at risk for progression and symptoms. Moreover, given the wealth of agents available for treating autoimmune arthritides characterized by flagrant inflammation, there is a high likelihood that some of these agents, in appropriate dosing schemes, could be employed to treat the subset of patients with inflammatory OA. This OA subgroup would therefore seem to be an ideal one for which to develop algorithms and tools for reliable identification such as the artificial neural network model recently developed by Heard and colleagues(122). The descriptions above briefly summarize associations of inflammatory components with OA that could in future be exploited to assist with identification of patients for the most appropriate therapy. This however, will require tests with known precision and predictive capability (sensitivity, specificity, positive and negative predictive value) that represents a long developmental pathway before any of the research findings described above could be translated into use in clinical trials or practice. Nevertheless, a biomarker qualification project in OA is ongoing(123) that could serve as a paradigm for the qualification of inflammatory markers is OA. Although a number of OA-related biomarkers emanating from joint tissue have been identified, only a minority have been qualified in the context of inflammation due to the limitation of phenotyping tools to identify the subclinical inflammation in OA(1). Nevertheless, it has been possible to identify numerous inflammatory molecules and pathways in association with OA. This underscores the generalizability of inflammation in OA, albeit often subacute or subclinical. As we learn more about the genetic control of inflammation and wound healing in OA we will undoubtedly discover key targets for therapy in addition to being able to better subset patients for trials and eventually, specific therapies.

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