Osteoarthritis and Cartilage 23 (2015) 22–30

Osteoarthritis and Cartilage

Review

Metabolic triggered inflammation in osteoarthritis

X. Wang †, D. Hunter ‡, J. Xu §, C. Ding † ‡ § *

† Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia
‡ Institute of Bone and Joint Research, Kolling Institute and Royal North Shore Hospital, University of Sydney, Sydney, NSW, Australia
§ Department of Rheumatology and Arthritis Research Institute, 1st Affiliated Hospital, Anhui Medical University, Hefei, China

ARTICLE INFO

Article history:
Received 22 August 2014
Accepted 6 October 2014

Keywords:
Inflammation
Metabolic factors
Obesity
Osteoarthritis

SUMMARY

Osteoarthritis (OA) is a common chronic joint disorder with a multifactorial etiology including genetic and environmental factors. Metabolic triggered inflammation, induced by nutrient overload and metabolic surplus, consists of components such as obesity, pro-inflammatory cytokines and adipokines, abnormal metabolites, acute phase proteins, vitamin D deficiency, and deregulated microRNAs that may play a role in OA pathophysiology. Obesity-related metabolic factors, especially adipokines, contribute to OA development by inducing pro-inflammatory cytokines and degradative enzymes, leading to cartilage matrix impairment and subchondral bone remodeling. Ectopic metabolite deposition and low-grade systemic inflammation can contribute to a toxic internal environment that exacerbates OA. Complement components highly expressed in osteoarthritic joints have also been proposed as causative factors. Vitamin D deficiency has been associated with obesity and is implicated to be associated with cartilage loss in OA. Metabolic microRNAs may explain the inflammatory link between obesity and OA. Therapies targeting metabolic-triggered inflammation and its components are anticipated to have potential for the treatment of OA.

Introduction

Osteoarthritis (OA) is a common disease characterized by joint pain, impaired mobility, and synovial joint structural changes[1]. It is no longer conceived as a simplex disease, but rather has a complex etiology and new discoveries have differentiated OA into several phenotypes, i.e., post-traumatic, ageing-related, genetic and symptomatic[2]. A newly defined phenotype of OA, namely 'metabolic OA', has been associated with metabolic syndrome (MetS) and obesity[3]. Metabolic triggered inflammation (also called meta-inflammation[4]), which can be a result of abnormalities in body composition, adipokines, cytokines, complements, lipids and vitamin D, has been implicated in the pathogenesis of OA (Fig. 1).

The incidence of obesity worldwide has increased dramatically during recent decades. Accordingly, obesity and associated disorders such as OA now constitute a serious threat to the current and future health of both developed and developing populations. Strategies targeting obesity-related mechanisms, e.g., meta-inflammation, may be effective in preventing and slowing disease progression of OA. The purpose of this narrative review is to examine the link between meta-inflammation and OA, discussing how the components of meta-inflammation contribute to OA, and to propose several potential therapies modifying meta-inflammation in OA.

Metabolic triggered inflammation

Meta-inflammation is mainly caused by nutrient overload and metabolic surplus[5]. Metabolic overload results in oxidative stress and inflammation, which then triggers vicious stress cycles that lead to cell dysfunction[6]. The components that make up the cluster of MetS, such as overweight, dyslipidemia and impaired glucose tolerance, have been involved in meta-inflammation. Other components as summarized in Table I also have roles to play.

Recent studies have found that centrally placed adipose tissues (e.g., visceral fat) is a crucial site in the generation of inflammatory responses and mediators[7]. Abdominal (central) obesity is associated with increased incidence of metabolic diseases, which are closely related to chronic inflammation through elevated levels of cytokines, acute-phase inflammatory components (complements and C reactive protein, CRP) and other mediators[6,8]. Furthermore, adipocytes as the key cells that regulate the interactions between endothelial cells (EC) and macrophages also synthesize numerous cytokines such as interleukin (IL)-6, IL-1, and tumor necrosis factor-α (TNF-α) and adipokines such as leptin, adiponectin, resistin, and visfatin[9].

* Address correspondence and reprint requests to: C. Ding, Private Bag 23, Hobart, Tasmania 7000, Australia. Tel: 61-3-62267730; Fax: 61-3-62267704.
E-mail address: Changhai.Ding@utas.edu.au (C. Ding).

http://dx.doi.org/10.1016/j.joca.2014.10.002
1063-4584/

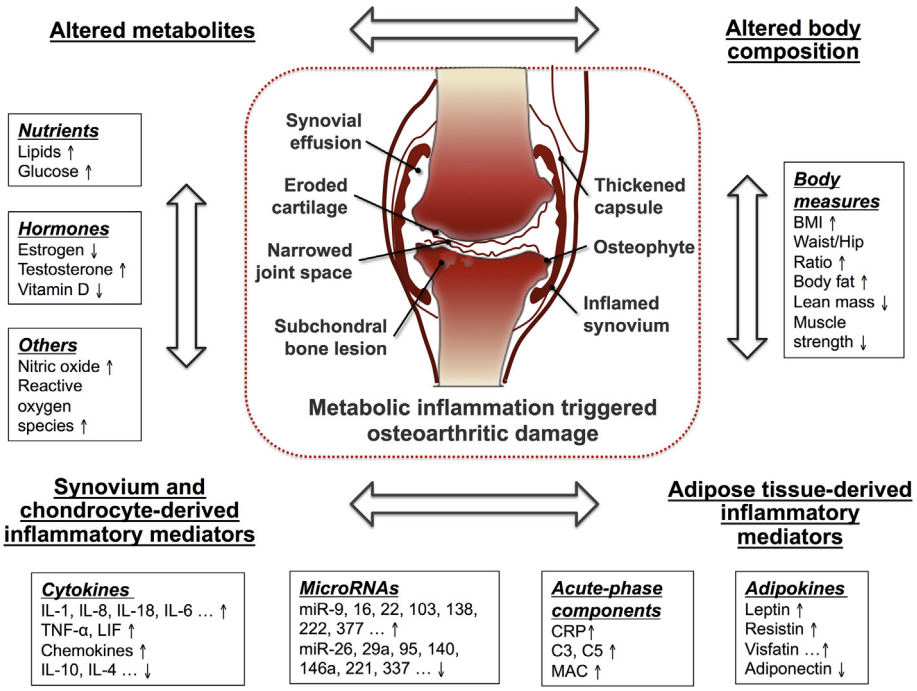

Fig. 1. Pathogenic role of metabolic triggered inflammation in OA. Abnormal dietary factors (such as lipids and glucose) and dysfunctional fat produce an excess of adipokines (leptin, resistin, visfatin *etc.*) that are able to increase risk of OA by inducing pro-inflammatory mediators (cytokines, CRP, complements). The levels of lean mass, muscle strength and anti-inflammatory mediators, including IL-10, IL-4 and adiponectin, are decreased in OA. Other common metabolites such as vitamin D not only interact with other inflammatory mediators, but also involve in cartilage and bone development and metabolism. Abnormal expressions of microRNAs are associated with meta-inflammation and joint structural alterations.

Excessive metabolites and nutrients such as lipids and glucose could disturb the integration of systemic metabolism, simultaneously leading to inflammatory responses. In addition, a group of acute phase protein such as complement components, stimulated by pro-inflammatory cytokines, could lead to a chronic inflammatory state and metabolic dysfunction[10]. Individuals with obesity and/or metabolic diseases have low circulating 25-hydroxy-vitamin D (25-(OH)D)[11], which can be induced by factors including leptin and IL-6[12]. At the molecular level, microRNAs are differentially expressed in fat depots and can regulate meta-inflammation, which potentially contribute to the pathogenesis of obesity-associated complications[13].

Direct evidence of meta-inflammation in OA

Body fat may be better than body mass index (BMI) in predicting OA

Obesity (defined by BMI > 30 kg/m^2) is a significant risk factor for the onset and progression of OA[2]. BMI was negatively associated with knee cartilage volume and cartilage thickness, and positively associated with tibial bone area and knee cartilage defects[14,15]. However, BMI is only a surrogate measure of obesity that cannot discriminate fat and lean mass, which may have different effects on OA. Indeed, central adiposity, measured by waist-to-hip ratio and waist circumference, were better predictors of OA incidence than BMI[16]. Also fat mass and skeletal muscle mass had a better statistical fit than BMI to explain both the odds of having and the severity of knee OA[17]. Furthermore, body fat adversely affects knee cartilage loss over time, whereas lean mass is protective, and body fat was better than BMI in predicting tibial cartilage loss[18]. Additionally, waist circumference and fat mass were associated with increased knee cartilage defects[19], reduced knee cartilage volume and increased bone marrow lesions (BMLs)[20]. Total body fat, trunk fat, waist-hip ratio and waist circumference were all associated with increased knee pain over 5 years[21]. In addition, some local fat tissues, such as infrapatellar fat pad (IPFP), may act as modulators in OA. IPFP was considered as a source of local inflammatory mediators and thus an active osteoarthritic tissue[22], but it also has a beneficial effect possibly through biomechanical mechanisms, as supported by a recent study suggesting that IPFP size was negatively associated with OA disease severity independent of BMI and total body fat[23]. Taken together, all these suggest that it is central adiposity, rather than extra body weight, that may play a major role in the structural and symptomatic changes of OA.

Adipokines

Adipose tissue is considered as a metabolic endocrine organ during systematic metabolic process. As obesity develops, adipocytes release active components such as leptin, adiponectin, resistin and visfatin, which lead to metabolic dysfunction in OA patients[24]. Adipokines can disrupt cartilage homeostasis through directly inducing joint structural degradation or regulating local inflammatory processes[25].

Leptin

Leptin, a small (16 kd) polypeptide encoded by the obese (*ob*) gene, is produced predominantly in white adipose tissue and regulates energy intake and expenditure at the hypothalamic level[26]. Leptin was positively correlated with BMI, fat mass and body weight among people with OA[27]. The strong synergistic relationship between leptin and pro-inflammatory cytokines has been discovered in OA, as leptin enhanced the expression of inducible nitric oxide synthase (iNOS), cyclooxygenase (COX-2), prostaglandin E2 (PGE_2), IL-6 and IL-8 in cartilage[28]. The elevated expressions of leptin and its receptor isoform (Ob-Rb) had