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Minireview

Leptin in osteoarthritis: Focus on articular cartilage and chondrocytes

Morena Scotece [a,b,*], Ali Mobasheri [b,c,d]

[a] SERGAS, Research Laboratory 9 (NEIRID LAB: Neuroendocrine Interactions in Rheumatology and Inflammatory Diseases), Institute of Medical Research (IDIS), Santiago University Clinical Hospital, Santiago de Compostela 15706, Spain
[b] The D-BOARD European Consortium for Biomarker Discovery, Department of Veterinary Preclinical Sciences, School of Veterinary Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, United Kingdom
[c] Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, Arthritis Research UK Pain Centre, Medical Research Council and Arthritis Research UK Centre for Musculoskeletal Ageing Research, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, United Kingdom
[d] Center of Excellence in Genomic Medicine Research (CEGMR), King Fahd Medical Research Center (KFMRC), King AbdulAziz University, Jeddah 21589, Saudi Arabia

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ABSTRACT

Osteoarthritis (OA) is a complex joint disorder with a number of underlying physical, biochemical, biomechanical and genetic causes. Obesity is considered to be one of the major risk factors for the development and progression of OA. It actively contributes to the inflammatory status and to cartilage degradation in the OA joints. Recent data suggests that metabolic factors produced by white adipose tissue, such as leptin, may provide a mechanistic link between obesity and OA, providing an explanation for the high prevalence of OA among obese and over-weight individuals. The unbalanced production of catabolic and anabolic mediators by chondrocytes, the only cell type present in cartilage, determines cartilage degradation, which is the central pathological feature of OA. Evidence is accumulating to support a key role for leptin in the pathogenesis and/or progression of OA. The goal of this focused review is to summarize the current knowledge on the role of leptin in OA with particular emphasis on the effects of this adipokine in cartilage and chondrocyte pathophysiology.

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1. Introduction

Osteoarthritis (OA) is one of the most common disorders of load-bearing synovial joints. Its incidence is steadily increasing worldwide and it is associated with a significant economic burden in the developed and developing countries. A study published in 2006, reported that OA affects more than 37% of US citizens whose age were over 60 years [1]. The destruction and loss of articular cartilage have long been considered to be the central pathological feature of OA. However, this concept has been challenged in recent years and OA is now considered as a global joint disorder that may affect the whole joint (including subchondral bone, muscle, peri-articular ligament and synovium). Advancing age is another strong risk factor for OA development. The age-dependent deterioration of chondrocytes, termed “chondrosenescence”, is a consequence of replicative and stress-induced factors, resulting in the development of a “senescent secretory phenotype” [2]. Physicochemical

* Corresponding author.
E-mail addresses: morena.scotece@sergas.es (M. Scotece), anerom84@hotmail.it (A. Mobasheri).

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and biomechanical stimuli also are reported to reduce extracellular osmolarity, resulting in reduced viscoelastic tissue properties contributing to cartilage deformation [3–5]. However, other factors, such as obesity, trauma and physically demanding occupations also increase the risk of OA [6,7].

It has long been recognized that excess body weight may lead to cartilage degeneration by increasing the mechanical forces across weight-bearing joints. Nevertheless, several studies have reported the association between obesity and OA also in non-weight-bearing joints (fingers and wrists) [8]. Moreover, recent results suggest that additional metabolic factors, produced by white adipose tissue (WAT), may also be responsible for the high prevalence of OA among overweight people [9]. Adipocyte-derived molecules, better known as "adipokines", are closely associated with obesity and play an important role in cartilage and bone homeostasis. Thus, adipokines are likely to be important mediators linking obesity and adiposity with inflammation and OA (Fig. 1).

In the present review, we summarize the current knowledge on the first identified adipokine, leptin, focusing our attention on its effects on articular cartilage and chondrocyte function.

1.1. Leptin and leptin receptors

Leptin was the first adipocyte-derived hormone to be described in 1994 by Zhang et al. [10]. Human leptin is a 16-kDa protein encoded by the gene located on chromosome 7q31.3 [11]. Other tissues, such as intestine, placenta, mammary glands, gastric epithelium, skeletal muscle, brain [12], joint tissues and bone [13–18] also produce various quantities of leptin. This hormone acts in the brain as an appetite-regulating factor that induces a decrease in food intake and an increase in energy consumption by inducing anorexigenic factors and suppressing orexigenic neuropeptides [19]. Leptin signals through specific binding to the leptin receptors (OBR). OBRs are encoded by the diabetes (db) gene and belong to the class I cytokine receptor superfamily, which also includes receptors for IL-6, LIF, CNTF, OSM, G-CSF and gp130. Six alternatively spliced isoforms of OB-R have been identified. These isoforms contain identical extracellular binding domains but differ by the length of their cytoplasmic domains: a long isoform (OB-Rb), 4 short isoforms (OB-Ra, OB-Rc, OB-Rd and OB-Rf), and soluble isoform (OB-Re). However, only the long form (OB-Rb), which has the full intracellular domain, with the typical signaling elements of cytokine receptors, is able to transduce the leptin-binding signal to the nucleus. Leptin circulates both as a biologically active free form and a presumably inactive bound form associated with plasma proteins and the soluble leptin receptor isoform OB-Re [20].

The leptin receptor (Ob-Rb) does not have intrinsic tyrosine kinase activity but upon leptin binding, it recruits cytoplasmic kinases like JAK2 to start leptin signaling [21,22]. The ability of leptin receptor to form homodimers facilitates the autophosphorylation of JAK2 [23,24]. Once JAK2 is activated, it is phosphorylated in three tyrosine residues (Tyr985, Tyr1077, Tyr1138) and each tyrosine phosphorylation site is involved with the recruitment of other different signaling proteins [25]. Among these proteins there are STAT members such as STAT3. In addition to the canonical JAK/STAT pathway, leptin receptor signals through other alternative pathways including the ERK1/2, p38, JNK, PKC, SHP2/GRB2 and PI3K/AKT pathways [25–33].

1.2. Leptin and OA

Plasma leptin levels in OA patients correlate positively with BMI. Plasma leptin concentrations are 3 times higher in premenopausal women than men [13,34,35]. The group of Karvonen-Gutierrez showed a positive association between plasma leptin levels and knee OA in middle-aged women [36].

Leptin has been detected also in the synovial fluid (SF) obtained from OA patients and interestingly, leptin levels measured in the joint fluid exceed those found in serum [15]. In addition, Ku et al. reported that SF leptin levels correlate positively with the radiographic severity of OA [37] and also with MMP-1 and MMP-3 levels in OA patients [33], suggesting the possible use of leptin as a potential biomarker for quantitative detection of OA [37]. In a recent study, SF leptin concentrations are associated also with knee and hip pain in OA patients [38].

Griffin and co-workers further investigated the relationships between leptin, obesity and OA in mice. They demonstrated that obesity *per se* is not a sufficient condition for the development of obesity-associated OA [39]. Actually, adiposity in the absence of leptin signaling is insufficient to induce systemic inflammation and knee OA. This is an important point that is often neglected when this issue is discussed in the literature.

In spite of the results obtained in rodent models, correlations that have been observed were between radiographic OA and leptin in patients with hand OA [8,40]. On the contrary, in another study involving 170 patients with knee and hand OA, baseline leptin was associated with increased levels of bone formation biomarkers (osteocalcin and PINP) over 2 years of followup, while OB-Re was associated with

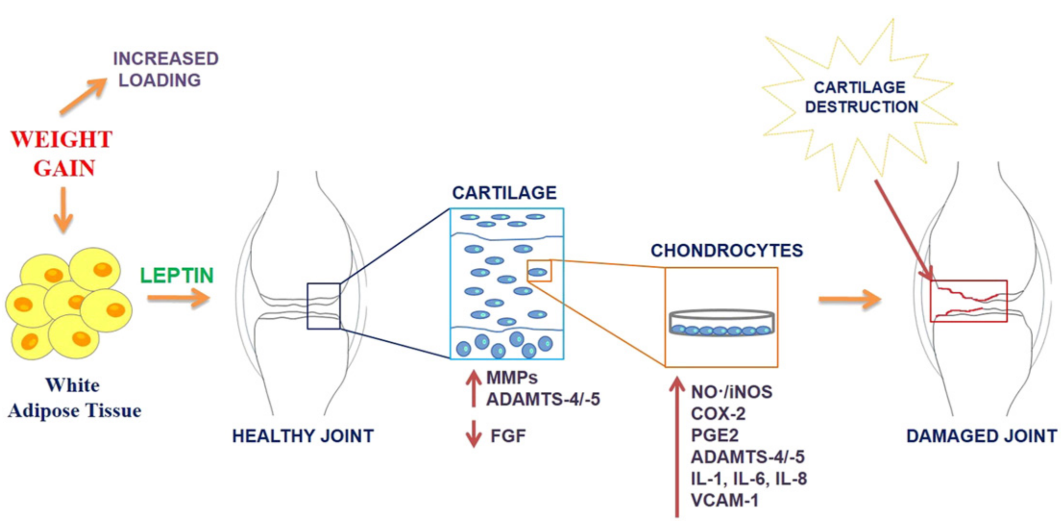

Fig. 1. Schematic representation of the effects of leptin on articular cartilage and chondrocytes.