Adipokines and inflammation: is it a question of weight?

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Abstract

Obesity has reached epidemic proportions in the Western society and is increasing in the developing world. It is considered as one of the major contributors to the global burden of disability and chronic diseases, including autoimmune, inflammatory and degenerative diseases. Research conducted on obesity and its complications over the last two decades has transformed the outdated concept of white adipose tissue (WAT) merely serving as an energy depot. WAT is now recognized as an active and inflammatory organ capable of producing a wide variety of factors known as adipokines. These molecules participate through endocrine, paracrine, autocrine, or juxtacrine cross-talk mechanisms in a great variety of physiological or pathophysiological processes, regulating food intake, insulin sensitivity, immunity, and inflammation.

Although initially restricted to metabolic activities (regulation of glucose and lipid metabolism), adipokines currently represent a new family of proteins that can be considered key players in the complex network of soluble mediators involved in the pathophysiology of immune/inflammatory diseases. However, the complexity of the adipokine network in the pathogenesis and progression of inflammatory diseases has posed, since the beginning, the important question of whether it may be possible to target the mechanism(s) by which adipokines contribute to disease selectively without suppressing their physiological functions.

Here we explore in depth the most recent findings concerning the involvement of adipokines in inflammation and immune responses, in particular in rheumatic, inflammatory and degenerative diseases. We also highlight several possible strategies for therapeutic development and propose that adipokines and their signalling pathways may represent innovative therapeutic strategies for inflammatory disorders.

Abbreviations:

ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AdipoR, adiponectin receptor; AMPK, AMP-activated protein kinase; ATMs, adipose tissue macrophages; CAIA, collagen-antibody-induced arthritis; CCL, C-C motif chemokine ligand; CIA, collagen-induced arthritis; CPCs, chondrogenic progenitor cells; DCs, dendritic cells; DMOAD, disease-modifying OA drug; ELF3, E74-like factor 3; GM-CSF, granulocyte macrophage colony-stimulating factor; IPFP, infrapatellar fat pad; LCN2, lipocalin-2; LEPR, leptin receptor; MCP-1, monocyte chemoattractant protein-1; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PGRN, progranulin; PPAR, peroxisome proliferator-activated receptor; PTP1B, protein tyrosine phosphatase 1B; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor kappa-B ligand; RASFs, rheumatoid arthritis synovial fibroblasts; SF, synovial fluid; SOCS-3, suppressor of cytokine signalling 3; STAT, signal transducer and activator of transcription; Th, T helper cells; TIMP, tissue inhibitors of metalloproteinases; Treg, T regulatory cells; VCAM, vascular cell adhesion protein; WAT, white adipose tissue.

List of Hyperlinks for Crosschecking:

Leptin: http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=5015

Adiponectin: http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=summary&ligandId=3726

TNF-α: http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=5074

Leptin receptor: http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=307#1712

Janus-family tyrosine kinase (JAK): http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=581

IL-1β: http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=4974

Adiponectin receptors:
http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=106

TNF receptors:
http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=334

IL-1R: http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1905

Introduction

Obesity, the major public health problem in the Western world has reached epidemic proportions and continues to rise in developing countries. Being itself one of the major contributors to disability, obesity is associated with several chronic autoimmune and inflammatory diseases, like type 2 diabetes mellitus, cardiovascular disease, osteoarthritis (OA) and rheumatoid arthritis (RA), thus having a high socio-economic impact (Zhang et al., 2014). For decades, researchers have focused on the identification of risk factors, preventive measures, and treatments for obesity. However, public health policies centred on diet and physical activity have been largely ineffective. Furthermore, pharmacological approaches have not provided any safe and long-term therapies (Zhang et al., 2014). Consequently, it is urgent to gain a deeper understanding of the development of obesity-associated pathologies and to focus on adipose tissue biology in this context. White adipose tissue (WAT) is now recognized as an active endocrine organ besides serving an energy storage tissue, and source of adipose tissue-derived factors (adipokines) have been reported as pleiotropic molecules that contributed to low-grade systemic inflammation in obese subjects (Tilg and Moschen, 2006). Leptin, adiponectin, lipocalin-2, and progranulin are adipokines thought to be crucial linkers between obesity and immune system, thus being attractive therapeutic targets for obesity-associated diseases, such as OA and RA.

White adipose tissue as a pro-inflammatory tissue in obesity

WAT is an active endocrine organ consisting of mature and developing adipocytes, as well as fibroblasts, endothelial cells and a broad array of immune cells, namely adipose tissue macrophages (ATMs), neutrophils, eosinophils, mast cells, T and B cells (Huh et al., 2014). Thus, WAT is now considered as a bona-fide immunometabolic endocrine organ (Vieira-Potter, 2014).

In WAT of lean individuals, the cross talk between adipocytes and immune cells maintains tissue homeostasis. In particular, eosinophils and T regulatory cells (Treg), the main resident T cell population, secreted anti-inflammatory cytokines (interleukin (IL)-10 and IL-4) that polarize ATMs towards an anti-inflammatory phenotype (i.e. M2 or alternatively activated macrophages), thus maintaining a tolerogenic environment (Exley et al., 2014; Huh et al., 2014). Moreover, “lean” WAT secretes more adiponectin that enhances the sensitivity to insulin. A positive energy balance results in adipocyte expansion, which leads to increased leptin secretion and inflammatory cells infiltration. Adipocyte hypoxia, apoptosis, and cell stress were able to induce the expression of chemoattractant molecules with the consequent recruitment of macrophages, T- and B-cells (Exley et al., 2014; Huh et al., 2014). T cells become activated, number of T reg cells were reduced and there is a macrophage phenotypic switch from M2 to M1, which accumulate around necrotic adipocytes forming 'crown-like structures' and producing large amounts of pro-inflammatory cytokines, like IL-6 and tumour necrosis factor (TNF)-α (Vieira-Potter, 2014). Additionally, obesity is characterized by a dysregulated secretion of WAT adipokines, such as leptin, adiponectin, lipocalin-2, and progranulin, which have emerged as crucial regulators of the innate and adaptive immune system (Abella et al., 2017b; Scotece et al., 2014; Tilg and Moschen, 2006). Altogether, these data revealed WAT as an important contributor to local and systemic inflammation in obesity (Figure 1).

The adipokine superfamily

Adipokines are low molecular weight, pharmacologically active proteins that possess pleiotropic activity. Acting in the hypothalamic region as orexigenic and anorexigenic hormones, adipokines play a crucial role in energy metabolism by communicating the nutrient status of the organism (Al-Suhaimi and Shehzad, 2013). Furthermore, adipokines are currently considered as key players in inflammation and immunity, as most of them are increased in obesity and contribute to the 'low-grade inflammatory state' associated with obesity (Tilg and Moschen, 2006).

Leptin, the forerunner of adipokine family, centrally regulates body weight by linking nutritional status and neuroendocrine function. Obese individuals exhibit enhanced circulating leptin levels but, due to leptin resistance (unresponsive state to leptin) in the hypothalamus, leptin failed to increase energy expenditure and reduce food intake with consequent body weight gain (J Conde et al., 2013). Leptin can also stimulate the production of pro-inflammatory cytokines and enhance Th1 immune response, thus linking nutrition, metabolism and immune homeostasis (Abella et al., 2017b). Adiponectin is an intriguing adipokine which is related to insulin sensitivity, anti-atherogenic actions, regulation of metabolic homeostasis and modulation of the immune system (Liu and Liu, 2014). In recent years, novel adipokines, namely lipocalin-2 and progranulin, have emerged as regulators of metabolism and immune function, bridging obesity and inflammatory pathologies that affect bones and joints (Abella et al., 2017a; Villalvilla et al., 2016).

Leptin and Leptin Receptors

Leptin is a 16 kDa non-glycosylated cytokine-like hormone encoded by the *LEP* gene (the human homolog of murine ob gene) located on chromosome 7q31.3 (Green et al., 1995) and the best-characterized member of adipokine family (Scotece et al., 2014). It is mainly produced by adipocytes, and at low levels by skeletal muscle, intestine, gastric epithelium, placenta, mammary glands, brain, joint tissues and bone (Scotece et al., 2014). In physiological conditions, leptin circulating levels are positively correlated with the WAT mass and body mass index, but its synthesis is also modulated by inflammatory factors (Conde et al., 2011). This hormone has a central role in body weight homeostasis by inducing anorexigenic factors (as cocaine-amphetamine-related transcript) and suppressing orexigenic neuropeptides (as neuropeptide Y) on hypothalamus(Zhou and Rui, 2014). Therefore, central leptin resistance, caused by impairment of leptin transportation, leptin signalling and leptin target neural circuits, is considered the main risk factor for the obesity pathogenesis (Zhou and Rui, 2014). Leptin also affects other physiological functions, like bone metabolism, inflammation, infection and immune responses. Accordingly, leptin receptor is expressed throughout the cells of both innate (natural killer cells, granulocytes, monocytes, macrophages, and dendritic cells) and adaptive (B and T cells) immune system (Abella et al., 2017b).

Leptin receptors and signalling

Leptin receptors (LEPR or Ob-R) belong to the class I cytokine receptor family and are products of diabetes (*db*) gene (Münzberg and Morrison, 2015). Alternative splicing of the *db* gene produces at least six isoforms, which possess identical extracellular binding domains but differ by the length of the cytoplasmic domain: a long isoform (Ob-Rb), four short isoforms (Ob-Ra, Ob-Rc, Ob-Rd, and Ob-Rf) and a soluble isoform (Ob-Re) (Münzberg and Morrison, 2015; Zhou and Rui, 2014). Leptin exerts its biological actions through activation of the long-form receptor (OB-Rb), which has the full intracellular domain with the typical signalling elements of cytokine receptors (Münzberg and Morrison, 2015; Zhou and Rui, 2014). This receptor doesn't have intrinsic tyrosine kinase activity but, after leptin binding, Ob-Rb-associated Janus-family tyrosine kinase 2 (JAK2) becomes activated by auto- or cross-phosphorylation, which are facilitated by the formation of leptin receptor homodimers. The cytoplasmic domain of the receptor is then phosphorylated in tyrosine residues (Tyr974, Tyr985, Tyr1077, Tyr1138), each one functioning as docking sites for cytoplasmic adaptors, like signal transducer and activator of transcription (STAT), particularly STAT3 (Zhou and Rui, 2014). Besides the canonical JAK/STAT pathway, LEPR also signals via alternative pathways including extracellular signal–regulated kinase (ERK)1/2, p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), protein kinase C (PKC), SHP2/GRB2 and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/Akt pathways (Scotece et al., 2014; Zhou and Rui, 2014).

In mouse models, mutations in either *ob* or *db* gene result in leptin or LEPR ablation and severe obesity. However, in humans, common obesity is often characterized by hyperleptinemia and administration of exogenous leptin doesn't result in weight loss, indicating an unresponsive state to leptin. Possible mechanisms of leptin resistance include decreased levels of cell surface Ob-Rb, up-regulation of negative regulators and down-regulation of positive regulators. The best-characterized mechanism of leptin resistance in the central nervous system is the feedback loop inhibition of leptin signalling by binding of suppressor of cytokine signalling 3 (SOCS-3) to phosphorylated tyrosines of Ob-Rb. Protein tyrosine phosphatase 1B (PTP1B) also involved acts as negative regulator of leptin signalling through JAK2 dephosphorylation (Münzberg and Morrison, 2015; Zhou and Rui, 2014). In the periphery, leptin is increased in chondrocytes from obese OA patients (Pallu et al., 2010) and SOCS-3 expression is lower in cartilage from obese than non-obese individuals (Vuolteenaho et al., 2012). Thus, leptin responsiveness should be considered when interpreting the leptin effects in peripheral tissues and in the development of leptin-directed therapeutic approaches.

Leptin in innate and adaptive immune system

Leptin has been described as a potent enhancer of the immune system (Abella et al., 2017b). In innate immunity, leptin augments the cytotoxicity of natural killer (NK) cells, and the activation of granulocytes (neutrophils, basophils and eosinophils), macrophages and dendritic cells (DCs), thus exacerbating inflammatory responses (Abella et al., 2017b). Obese hyperleptinemic individuals have lower NK function compared to lean subjects, likely due to leptin resistance (Laue et al., 2015), neutrophils with augmented superoxide release and chemotactic activity (Brotfain et al., 2015), and eosinophils with greater adhesion and chemotaxis towards eotaxin and CCL5 (Grotta et al., 2013). Leptin-stimulated human macrophages have increased M2-phenotype surface markers but were able to secrete M1-typical cytokines (like TNF-α, IL-6, and IL-1β), indicating that leptin influences ATMs phenotype (Acedo et al., 2013). In DCs, leptin modulated their activation, chemoattraction, and survival, with possible implications for DCs maturation and migration (Moraes-Vieira et al., 2014). Moreover, Toll-like receptors (TLRs), which play a critical role in innate immune system, have been described as important players in adipose tissue, obesity-associated inflammation and leptin biology (Kim et al., 2012). In particular, leptin-deficient obese mice showed increased expression of TLR1-9 and TLR11-13 as well as downstream signalling molecules and target cytokines (Kim et al., 2012).

In the adaptive immune system, leptin augments the proliferation of naïve T cells and B cells whereas it decreases Treg cells (Abella et al., 2017b). Accordingly, morbidly obese children (congenitally leptin-deficient) had reduced number of circulating CD4+ T cells, and impaired T cell proliferation and cytokine release, which were rescued by administration of recombinant human leptin (Farooqi et al., 2002), and obese individuals presented reduced number of Treg cells (Wagner et al., 2013). Leptin also polarizes Th cells towards a proinflammatory (Th1, which secretes interferon (IFN)γ) rather than anti-inflammatory phenotype (Th2, which secretes IL-4) (Martín-Romero et al., 2000). In preclinical collagen-induced arthritis mouse model, the leptin articular injection enhanced Th17 cells in joint tissues, with consequent exacerbation of inflammation and early onset of arthritis (Deng et al., 2012). Therefore, leptin decreases Treg cell proliferation, whereas it increases Th17 cell proliferation and responsiveness, indicating the therapeutic potential of leptin system in inflammation and autoimmunity.

Leptin and osteoarthritis

Osteoarthritis (OA), the most common joint disease, is a degenerative and multifactorial pathology triggered by inflammatory and metabolic imbalances affecting the entire joint structure (articular cartilage, meniscus, ligaments, bone, and synovium) (Loeser et al., 2012). Leptin has been associated with OA and cartilage metabolism, being its levels increased in serum, infrapatellar fat pad (IPFP), synovial tissues, and cartilage of OA patients compared to healthy individuals (Javier Conde et al., 2013). Additionally, Ob-Rb is expressed in chondrocytes and is functional (Figenschau et al., 2001). Recently, a microarray analysis associated leptin-induced OA phenotype with the up-regulation of inflammatory factors, matrix metalloproteinases (MMPs), growth factors and osteogenic genes (Fan et al., 2018). Our group has demonstrated that leptin, in synergy with IL-1β, induces the expression of pro-inflammatory factors, namely nitric oxide synthase (NOS)2, cyclooxygenase (COX)-2, prostaglandin E2 (PGE2), IL-6, and IL-8 in chondrocytes (Gomez et al., 2011). Chondrocyte-synovial fibroblast cross-talk mediates leptin-induced IL-6 production in OA patients (Pearson et al., 2017). Moreover, leptin modulates the production of inflammatory mediators (IL-6, IL-8, and chemokine (C-C motif) ligand 3 (CCL3)) by CD4+ T cells in OA patients, but not in healthy subjects (Scotece et al., 2017) hence demonstrating new insights into the action of leptin in the immune system and OA pathophysiology.

Leptin can also promote OA-related joint destruction by directly inducing the expression of MMPs (like MMP-1, -2, -3, -9, and -13, A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)4 and ADAMTS5), while fibroblast growth factor 2 (FGF2) and proteoglycan were down-regulated (Scotece et al., 2014). Moreover, leptin can perpetuate the cartilage-degradation processes via vascular cell adhesion protein (VCAM)-1 induction in human primary chondrocytes, which attracts leukocytes and monocytes to inflamed joints through the action of chemoreceptors (Conde et al., 2012).

MicroRNAs (miRNAs), small single-stranded non-coding segments of RNA, are increasingly recognized as regulatory molecules involved in disease processes, including osteoarthritis, inflammation, and obesity. miR-27, which directly targeted the 3'-untranslated region (3'-UTR) of leptin, was decreased in OA chondrocytes and injection with miR-27 lentiviral overexpression vector in preclinical OA rat model resulted in decreased levels of IL-6 and -8, as well as MMP-9 and -13, thus indicating the protective action of miR-27 in OA, possibly by targeting leptin (Zhou et al., 2017).

Chondrogenic progenitor cells (CPCs) are cartilage seed cells crucial to maintain cartilage homeostasis and replace damaged tissue. Leptin reduces CPC migratory ability and their chondrogenic potential, and induces CPC senescence and osteogenic transformation, thus changing CPC differentiation fate (Zhao et al., 2016). Leptin also

regulates bone metabolism via induction of abnormal osteoblast function, which is associated with joint destruction in OA patients (Conde et al., 2015).

Altogether, this evidence indicated a key role of leptin in OA pathophysiology by influencing pro-inflammatory status, cartilage catabolic activity, as well as cartilage and bone remodelling.

Leptin and rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease defined by synovial membrane inflammation and hyperplasia ("swelling"), production of autoantibodies – autoimmune disease, and destruction of cartilage and bone ("deformity") (Smolen et al., 2016). Leptin levels were augmented in RA patients, and its serum and SF levels were associated with disease duration,parameters of RA activity and radiographic joint damage (Olama et al., 2012; Rho et al., 2009), although there are controversial results and large cohort studies are necessary. Leptin-deficient mice demonstrate a less severe antigen-induced arthritis, decreased levels of TNF-α and IL-1β in knees synovium, a defective cell-mediated immunity and a shift towards Th-2 cell response (Busso et al., 2002). Moreover, reducing leptin levels in RA patients by fasting improves the clinical symptoms of the disease (Fraser et al., 1999). Leptin protein mutants with antagonist activity and monoclonal antibodies against human leptin receptor or leptin itself are promising therapeutic approaches to RA (Tian et al., 2014). Of note, clinical studies evaluating the effect of insulin sensitivity modulators (affected by leptin levels), like PPARγ agonists, are ongoing as a new potential treatment to improve the inflammatory status and cardiovascular outcome in RA patients (Chimenti et al., 2015). Further knowledge on the leptin mechanisms would be important for RA treatment.

Therefore, leptin can be pointed as a linker between immune tolerance, metabolic function, and autoimmunity, and approaches directed to leptin signalling could provide future innovative therapies for autoimmune disorders like RA.

Adiponectin and Adiponectin Receptors

Adiponectin, also called GBP28, apM1, Acrp30, or AdipoQ, is a 244-residue protein with structural homology to collagen type VIII and X, and complement factor C1q. It is mainly synthesized in adipose tissue and exists in several configurations: the globular adiponectin (gAPN), the full-length adiponectin (fAPN), the low molecular weight adiponectin (LMW), the medium molecular weight adiponectin (MMW), the high molecular weight adiponectin (HMW), and the serum albumin bounded LMW form (Alb-LMW) (Liu and Liu, 2014; Sun et al., 2009). In morbidly obese patients, circulating adiponectin levels tend to be low,

increasing with weight loss and with use of thiazolidinediones (PPAR agonists), which enhance insulin sensitivity (Liu and Liu, 2014). Adiponectin acts as an endogenous insulin sensitizer by stimulating glucose uptake through its ability to increase fatty acid oxidation and to reduce the synthesis of glucose in the liver. Human adiponectin is encoded by ADIPOQ gene, which is located on chromosome 3q27 a locus linked with susceptibility to diabetes and cardiovascular disease (Liu and Liu, 2014).

Adiponectin receptors and signalling

Adiponectin acts specifically via two receptors, AdipoR1 predominantly found in skeletal muscle and AdipoR2 mainly present in the liver. AdipoRs signalling leads to activation of AMP-activated protein kinase (AMPK), PPAR-α, and PPAR-γ (Liu and Liu, 2014). AMPK activation by adiponectin has been implicated in its insulin-sensitizing activity in liver and muscles, while AMPK, Ca^{2+}, and PPAR-α are involved in the regulation of glucose and fatty acid metabolism by adiponectin. Ceramide and MAPK signalling pathways also mediate the adiponectin action (Liu and Liu, 2014). Increasing evidence reveals the importance of adiponectin in inflammation-related pathologies, like cardiovascular disease, endothelial dysfunction, type 2 diabetes, metabolic syndrome, OA and RA (Liu and Liu, 2014), likely due to its ability to modulate innate immune response, as well as B and T cells (Luo and Liu, 2016).

Adiponectin in innate and adaptive immune system

Adiponectin has been recognised as a key regulator of the immune system, playing a major role in the progression of inflammatory and metabolic disorders (Luo and Liu, 2016). Nevertheless, whether adiponectin behaves as an anti- or pro-inflammatory factor is still a matter of intense debate. This adipokine suppresses the differentiation and the classical activation of M1 macrophages by down-regulating pro-inflammatory cytokines (TNF-α, monocyte chemoattractant protein (MCP)-1, and IL-6), while it promotes M2 macrophage proliferation and expression of anti-inflammatory M2 markers (arginase (Arg)-1, Mgl-1, and IL-10) (Luo and Liu, 2016). Adiponectin also modulated the eosinophils, neutrophils, NK cells, and DCs activity (Luo and Liu, 2016; Tilg and Moschen, 2006) but it remains unclear whether adiponectin positively or negatively regulates their function. These paradoxical dual effects might result from different functions of different adiponectin configurations (Sun et al., 2009). For example, HMW and gAPN but not MMW and LMW adiponectin increased NF-κB activity in monocytic cells while gAPN but not fAPN decreased LPS-stimulated ERK1/2 pathway in Kupffer cells (Sun et al., 2009).

In the adaptive immune system, adiponectin activates plasma B cells and stimulate the secretion of the B cell-derived peptide PEPITEM, which inhibits the migration of memory T cells (Chimen et al., 2015). In T cells, AdipoRs are up-regulated after its activation and adiponectin decreased antigen-specific T cell proliferation and cytokines production, via enhancement of T cell apoptosis (Procaccini et al., 2013). Adiponectin also enhances Th1 differentiation and adiponectin-treated DCs significantly induced both Th1 and Th17 responses in allogenic T cells, contributing to enhanced pro-inflammatory responses (Procaccini et al., 2013). A deeper knowledge of adiponectin's effects on B and T cells and its mechanism of action will be important for developing new therapeutic strategies aimed at the adiponectin system.

Adiponectin and osteoarthritis

Adiponectin has been implicated in OA pathophysiology. Serum and plasma adiponectin levels are increased in OA patients, compared to healthy individuals, and its levels in OA SF were correlated with aggrecan degradation. Moreover, adiponectin could be expressed by synovial fibroblasts, IPFP, osteophytes, cartilage and bone tissues within the joint (Scotece et al., 2014). Adiponectin has been associated with erosive OA and with OA severity assessed radiologically, thus being pointed as a potential OA biomarker (Poonpet, 2014). However, a recent study reported no association between serum adiponectin levels and erosive or non erosive hand OA, while resistin and visfatin were pointed as possible OA biomarkers (Fioravanti et al., 2017).

Spontaneous animal models of OA (STR/Ort mice) present with lower serum adiponectin levels than controls. Adiponectin has been reported to have a protective action by inhibiting IL-1β-induced MMP-13 expression and to up-regulate tissue inhibitors of metalloproteinases (TIMP)-2 production in human chondrocytes (Scotece et al., 2014). However, most of the data indicated a pro-inflammatory and catabolic role for adiponectin in OA cartilage by increasing the production of NO, IL-6, IL-8, VCAM-1, TIMP-1, MMP-1, -3 and -13 (Kang et al., 2010; Scotece et al., 2014), which lead to cartilage degradation and OA pathogenesis. Furthermore, adiponectin modulates bone metabolism by stimulation of human osteoblast proliferation and mineralization, via p38 MAPK signalling pathway and bone morphogenetic protein (BMP)-2 (Scotece et al., 2014). Nevertheless, there are contradictory results in the literature and further studies are of the utmost importance to clarify the exact role of adiponectin in the joint cartilage and bone and in the pathogenesis of OA.

Adiponectin and rheumatoid arthritis

Clinical evidence suggests that adiponectin levels are increased in serum and SF of RA patients compared to healthy subjects, and that baseline serum adiponectin levels are predictive of RA radiographic progression (Chen et al., 2013; Giles et al., 2009; Rho et al., 2009). Adiponectin, alone or in combination with IL-1β, induces IL-6, IL-8 and PGE_2 production in RA synovial fibroblasts (RASFs), being the IL-6 production dependent of AdipoR1 receptor/AMPK/p38 MAPK/NF-κB signalling pathway (Chen et al., 2013; Scotece et al., 2014). Of note, anti-IL-6 receptor monoclonal antibody has been approved in several countries for the RA treatment. Adiponectin also increased the production of MMP-1, MMP-13, and vascular endothelial growth factor (VEGF) in synovial cells, and promoted joint inflammation via attraction of immune cells into the synovium and induction of cytokine production (Scotece et al., 2014); thus indicating a crucial role of adiponectin in synovitis and joint destruction in RA.

Although *in vitro* data indicates adiponectin as a potential RA, in *in vivo* models this adipokine exhibits quite different effects. In preclinical collagen-induced arthritis mouse model, adiponectin treatment mitigated the severity of arthritis along with a decrease in the expression of TNF-α, IL-1β, and MMP-3 in joint tissues (Lee et al., 2008). Future data in basic research and clinical observations in large-scale cohort studies are important to deeper elucidate the role and mechanisms of adiponectin in inflammatory-related pathologies, such as RA.

Other Adipokines

Lipocalin-2

Lipocalin-2 (LCN2), also named neutrophil gelatinase-associated lipocalin (NGAL), 24p3, p25, migration-stimulating factor inhibitor, human neutrophil lipocalin, α-1-microglobulin-related protein, siderocalin or uterocalin, is a glycoprotein encoded by a gene located at the chromosome locus 9q34.11 (Abella et al., 2015). Originally identified in mouse kidney cells and human neutrophil granules, adiponectin is also expressed in immune cells, liver, spleen, and chondrocytes, although WAT is its major source (Abella et al., 2015). Two receptors for LCN2 have been proposed: solute carrier family 22 member 17 (SLC22A17 or 24p3R) that binds to mouse Lcn2 and the megalin/glycoprotein GP330, a low-density lipoprotein receptor that binds human LCN2 protein. LCN2 circulates as a 25 kDa monomer, a 46 kDa homodimer and in a covalent complex with MMP-9, thus preventing MMP-9 auto-degradation (Villalvilla et al., 2016) The members of lipocalin family contain a hydrophobic ligand binding pocket, which confers the ability to bind and transport steroids, lipopolysaccharides (LPS), fatty acids, iron, and in the case of LCN2, siderophores. LCN2

has also been involved in the induction of apoptosis in hematopoietic cells, modulation of inflammation and metabolic homeostasis (Abella et al., 2015). Of note, thiazolidinedione treatment reverses obesity-induced LCN2 expression (Abella et al., 2015) and there is increasing evidence suggesting that LCN2 contributed to obesity-related disorders, like type 2 diabetes mellitus and non-alcoholic fatty liver disease (Moschen et al., 2017).

LCN2 binds to enterobactin, a siderophore present in gram-negative bacteria, and transport iron into mammalian cells where it is stored. By depleting bacterial iron stores necessary for their growth, LCN2 exhibits bacteriostatic effects (Abella et al., 2015), which have been implicated in the protection of gastrointestinal tract against various pathogens (Moschen et al., 2017). The promoter region of LCN2 contains binding sites for key inflammatory transcription factors, like NF-κB, STAT1, STAT3, and C/EBP. Accordingly, LCN2 acts as an anti-inflammatory regulator of M1/M2 macrophage polarization via NF-κB/STAT3 loop activation (Guo et al., 2014). In adaptive immunity, LCN2 induced human leukocyte antigen G (HLA-G), a well-known tolerogenic mediator, on CD4+ T cells, and up-regulated the expansion of Treg cells in healthy subjects (Abella et al., 2015). Taking into account the role of LCN2 in the modulation of inflammatory and immune response, future studies should investigate the LCN2 therapeutic potential to immunosuppressive therapy efficacy, tolerance induction in transplanted patients, and to other inflammatory/immune system disorders, such as OA and RA.

In joint tissues, LCN2 is produced as a mechano-responsive adipokine whose expression can be induced by inflammatory mediators. In osteoblasts, the absence of mechanical loading stimulates LCN2 expression, likely contributing to bone metabolism via stimulation of pro-osteoclastogenic factors, receptor activator of nuclear factor kappa-B ligand (RANKL) and IL-6, and inhibition of anti-osteoclastogenic factor osteoprotegerin (Abella et al., 2015). The LCN2 expression is also augmented by inflammatory factors TNF-α and IL-17 in osteoblasts, whilst in chondrocytes, it is induced by stimulated osteoblast conditioned medium, IL-1β, adipokines (leptin and adiponectin), LPS and dexamethasone (Villalvilla et al., 2016). Interestingly, NO is able to exert a control on LCN2 expression in chondrocytes, suggesting the existence of a feedback loop regulating its expression.

In OA patients, LCN2 levels are increased in SF and cartilage, where it is involved in cartilage degradation via blocking of MMP-9 auto-degradation and reduction of chondrocyte proliferation (Abella et al., 2015; Gupta et al., 2007). Recently, glucocorticoids (commonly used to treat OA and RA), alone or in combination with IL-1, have been reported to induce LCN2 expression through corticoids receptors and PI3K, ERK1/2 and JAK2 pathways in mouse chondrogenic cell line (Conde et al., 2017). The transcription factors E74-like factor 3 (ELF3) and NF-κB were also reported as modulators of LCN2 expression in chondrocytes

(Conde et al., 2016). Altogether, these data reveal that LCN2 acts as a sensor of mechanical load and inflammatory status of the joint, leading to alterations in subchondral bone, cartilage and bone-cartilage crosstalk underlined to OA pathophysiology. Nevertheless, one study verified that LCN2 overexpression in mouse cartilage does not cause OA pathogenesis and that Lcn2-knockout mice had no alteration in OA cartilage destruction induced by destabilization of the medial meniscus (Choi and Chun, 2017). Thus, LCN2 seems to contribute to OA pathophysiology but it's not sufficient by itself to induce OA cartilage destruction in mice. Further studies are necessary to fully elucidate the role of LCN2 in human OA development.

Patients with RA clinically exhibit higher levels of LCN2 in SF than OA patients (Katano et al., 2009). Using proteome analysis, it has been demonstrated that granulocyte macrophage colony-stimulating factor (GM-CSF) contributed to RA pathophysiology through upregulation of LCN2 in neutrophils, followed by induction of TERA, cathepsin D and TG2 in synoviocytes, with potential implications in the proliferation of synovial cells and infiltration of inflammatory cells into the synovium (Katano et al., 2009). Nevertheless, the action of LCN2 in RA pathophysiology remains largely unknown.

Progranulin

Progranulin (PGRN), also known as granulin-epithelin precursor (GEP), proepithelin, GP88, PC-cell-derived growth factor (PCDGF), or acrogranin, is a cysteine-rich secreted protein encoded by the *GRN* gene, located on chromosome 17q21.32 (Abella et al., 2017a). It is a 68-88kDa secreted glycoprotein that can undergo enzymatic proteolysis into small homologous subunits - granulins or epithelins (Wei et al., 2016), and that is produced by a wide range of cells, including epithelial cells, macrophages, chondrocytes and also adipocytes. Recently identified as an adipokine, PGRN has been implicated in inflammation, wound healing, obesity, and rheumatic diseases, like OA and RA, thus having a potential role as therapeutic target and biomarker in inflammatory diseases (Abella et al., 2017a).

PGRN is a key regulator of inflammation, at least in part, due to direct interaction with TNF receptors (possessing higher affinity than TNF-α, especially for TNFR2), and consequently acting as an antagonist of TNF/TNFR pro-inflammatory signalling (Jian et al., 2016; Wei et al., 2016). PGRN also bind to death receptor 3 (DR3), which is involved in various inflammatory disorders (Jian et al., 2016). Furthermore, PGRN suppressed the production of chemokines, like CXCL9 and CXCL10, through the TNFR1 pathway, and induced Treg populations and IL-10 production (Jian et al., 2016; Wei et al., 2016). PGRN can be degraded by several proteinases, like MMP9, 12, and 14, ADAMTS-7, elastase and proteinase-3, originating granulins, which have pro-inflammatory activity and may counteract

the anti-inflammatory action of intact PGRN's (Jian et al., 2016). Atsttrin, an engineered PGRN-protein, effectively prevents the onset and progression of inflammatory arthritis in several preclinical animal models (Liu and Bosch, 2012). Hence, identification of PGRN and the discovery of atsttrin as antagonists of TNF-α/TNFR pathway may lead to new therapeutic interventions for TNF-α-mediated pathologies, including rheumatic diseases.

PGRN expression is augmented during chondrocyte differentiation *in vitro*, as well as in cartilage, synovial and IPFP samples from OA patients (Abella et al., 2016). Deficiency of PGRN results in OA-like phenotype in aged mice, and both recombinant PGRN and atsttrin protect against OA development (Jian et al., 2016). PGRN exhibits anti-inflammatory properties in OA by promoting anabolic metabolism via TNFR2, and by inhibiting IL-1β-mediated catabolic metabolism (suppression of NOS2, COX-2, MMP13 and VCAM-1) through TNFR1 binding and blocking of TNF-α mediated activation of NF-κB, thus inhibiting MMPS and ADAMTS expression, and cartilage degradation (Abella et al., 2016; Jian et al., 2016). PGRN also exerts a crucial role in the differentiation and proliferation of chondrocytes, and in endochondral ossification of growth plate during development (Feng et al., 2010). Intra-articular injection of mesenchymal stem cells that express recombinant atsttrin prevents the progression of degenerative changes in a surgically induced preclinical OA mouse model (Xia et al., 2015). Moreover, intra-articular injection of etanercept (a fusion-soluble TNFR2 protein that inhibits TNF-α and has therapeutic activity in RA patients) induces more severe joint destruction in preclinical OA mouse model, because it blocks PGRN binding to TNFR2 (Jian et al., 2016). Therefore, PGRN directed therapeutic approaches seem to be promising for OA treatment.

In RA patients, circulating and SF levels of PGRN are elevated and are associated with disease activity (Cerezo et al., 2015). Furthermore, TNF-α-driven inflammation and cartilage destruction are a critical event in the development of RA pathology, and TNF biological therapies are considered as the most effective treatments for this autoimmune disease (Jian et al., 2016). As TNF/TNFR inhibitor, PGRN-derived atsttrin has been extensively studied on RA pathophysiology. In particular, atsttrin administration reduced the disease severity in preclinical collagen-induced arthritis (CIA) and collagen-antibody-induced arthritis (CAIA) mouse models, being even more effective than PGRN, possibly due to the absence of a complete granulin domain with pro-inflammatory activity (Abella et al., 2017a; Jian et al., 2016). Interestingly, atsttrin was more effective in reducing inflammation than etanercept and demonstrated high stability and was well absorbed when administered intraperitoneally in mice (Jian et al., 2016). Regardless the promising therapeutic data of atsttrin for RA, so far no clinical trials have been performed.

Future Prospects for Therapy

Great strides have been made in recent years to elucidate the role of adipokines as mechanistic drivers of obesity, inflammation, and immunity. This review has summarized the increasing evidence of the role of classical adipokines leptin and adiponectin, as well as lipocalin-2 and progranulin in obesity-associated inflammatory and autoimmune diseases, namely osteoarthritis and rheumatoid arthritis (Figure 2). Current OA drug therapies used in clinical practice are mainly based on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular administration of corticosteroids, and no disease-modifying OA drug (DMOAD) therapies exist with the ability to inhibit structural damage of articular cartilage (Glyn-Jones et al., 2015). RA treatment options include anti-TNF-α and anti-IL-1/IL-1R biologics, but their high cost, and short half-life prompted the development of alternative strategies against new therapeutic targets, such as adipokines, multiligand receptor for advanced glycation end products (RAGE) as well as inflammatory mediators and signalling pathway components (Alghasham and Rasheed, 2014). In fact, the development of promising therapeutic approaches targeting adipokine network are already underway.

Compelling evidence has demonstrated that elevated leptin levels are linked to immune system derangements and obesity-associated disorders (Abella et al., 2017b). Therefore, control of bioactive levels of leptin, by high-affinity leptin-binding molecules, monoclonal humanized antibodies blocking leptin receptor, administration of leptin receptors antagonists, or miRNAs targeting leptin, are likely to be feasible therapeutic options (Otvos et al., 2011). In the case of adiponectin, only a few protein-based biological modulators have been developed due to the extreme insolubility of C-terminal domain and larger peptide fragments thereof (Otvos et al., 2014). LCN2 has been implicated in articular cartilage degradation (Villalvilla et al., 2016). Silencing RNAs or miRNAs, promotion of protein sumoylation and nanoparticle delivery systems for drug administration may be useful approaches to regulate LCN2 levels and activity (Meszaros and Malemud, 2012). Moreover, the PGRN-derived engineered protein atsttrin was able to prevent inflammation in arthritis models (Liu and Bosch, 2012). However, given the pleiotropic action of adipokines, a systematic approach to modulate their levels and thus prevent obesity-associated disorders, namely osteoarthritis and rheumatoid arthritis, might be, for the moment, unavailable. Instead, the local inhibition of adipokines at sites of joint injury or targeting of specific receptor isoforms could be a potential viable option.

Given the role of adipokines in OA and RA pathophysiology, these molecules have been singled-out as possible biomarkers for monitoring disease onset and progression, as well as the efficiency of therapeutic interventions (Abella et al., 2015; Poonpet, 2014). However, further evaluations will be necessary to establish adipokines as OA and RA

biomarkers for use in clinical practice.

Altogether, the data presented and reviewed in this paper proposes adipokines as emerging biomarkers and therapeutic targets for immune disorders. However, the adipokine network is complex and further insights into the pathophysiological role of adipokines in the immune system as well as in the development of obesity-associated disorders will be crucial for the development of novel therapeutic approaches.

Nomenclature of Targets and Ligands:

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander et al., 2017)

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VF and JP have made a substantial contribution to acquisition and analysis of data and critically revised it. These two authors equally contributed to the realization of this work. MAGG, AM, FL, RG and AM have been involved in drafting the manuscript and revising it critically for important intellectual content. OG made a substantial contribution to conception and design of the review article, drafting the manuscript and critically revising it. All authors approved the final version to be published.

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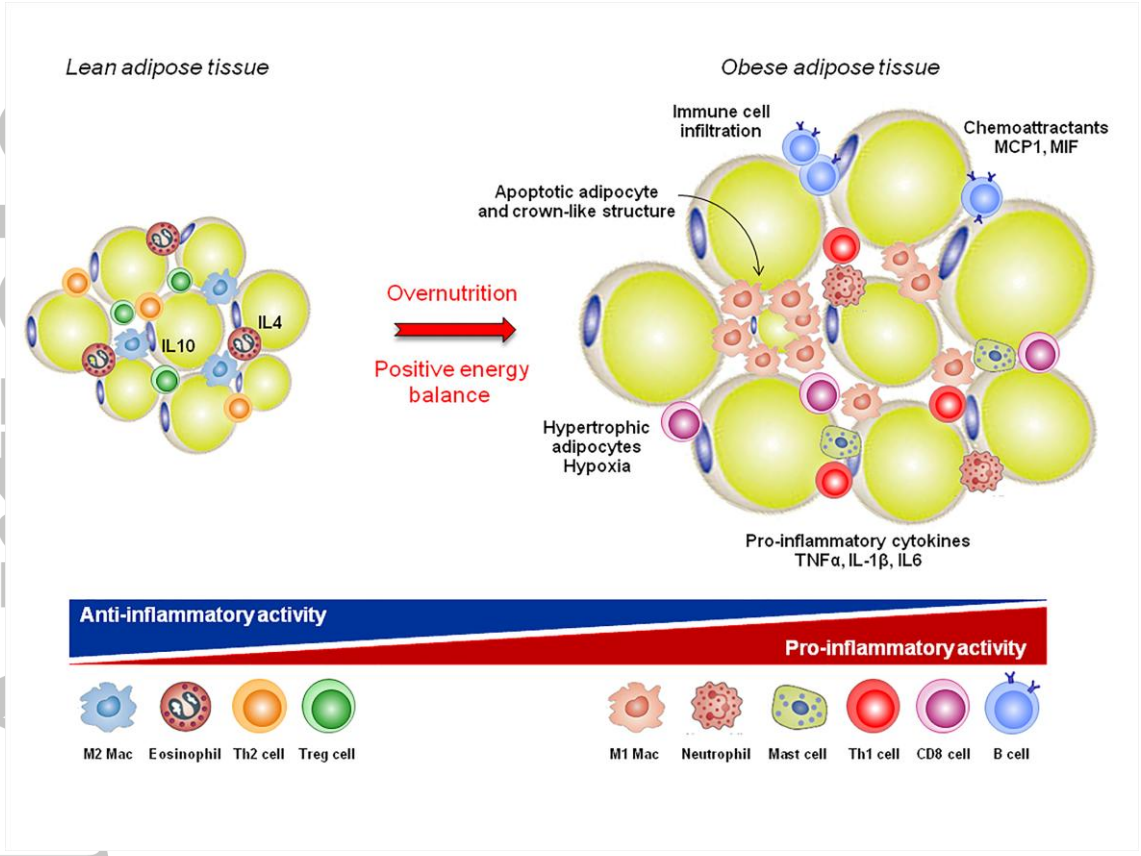

Figure 1. White adipose tissue as a pro-inflammatory tissue. In lean adipose tissue, the cross-talk between adipocytes and immune resident cells maintains tissue homeostasis. In particular, Treg cells secreted anti-inflammatory cytokines (IL10 and IL4) that promotes M2 macrophage phenotype. Overnutrition results in WAT expansion and adipocyte hypoxia, with consequent production of chemoattractants and infiltration of immune cells. B and T cells cells become activated, and there is a phenotypic switch from M2 to M1 macrophages, which accumulate around necrotic adipocytes forming “crown-like structures”

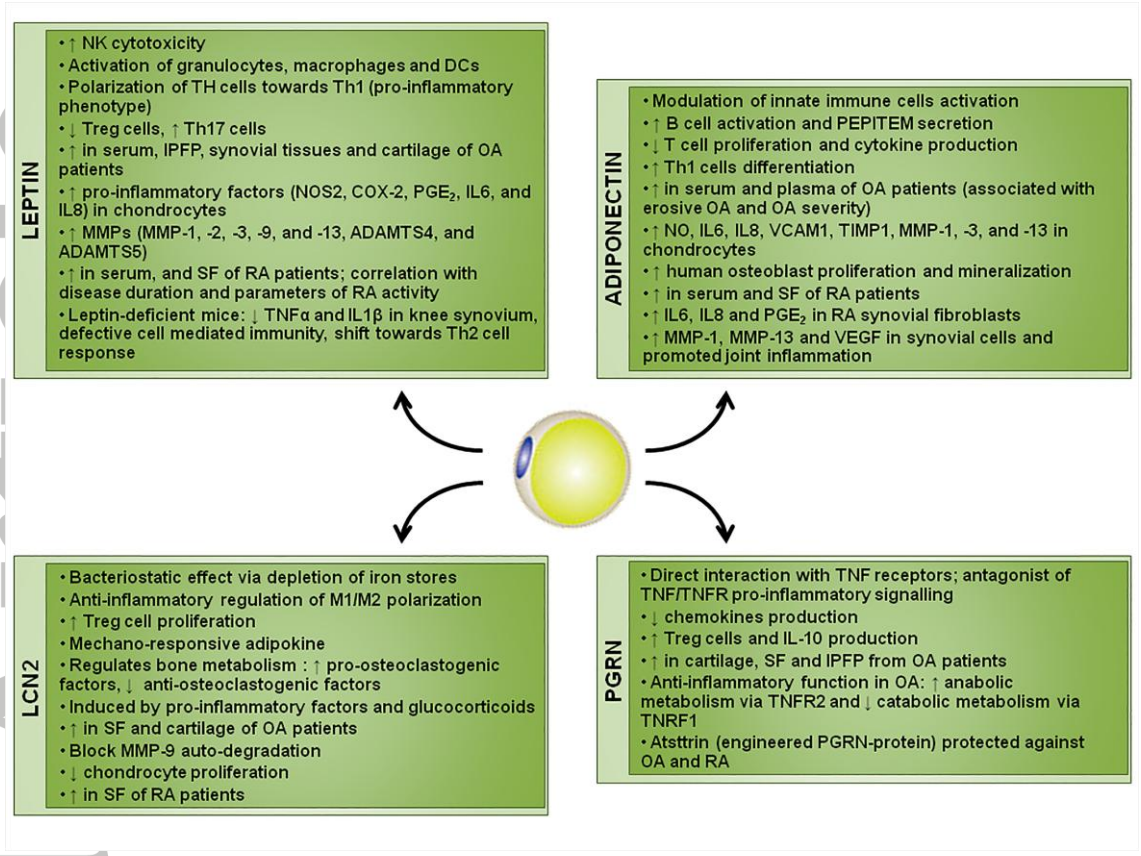

Figure 2. Schematic representation of the adipokines effects on inflammatory diseases