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Review

Activation of circulating monocytes by low-density lipoprotein—a risk factor for osteoarthritis?

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Abstract

Synovial macrophages are key mediators of OA pathology, and skewing of macrophage phenotype in favour of an M1-like phenotype is thought to underlie the chronicity of synovial inflammation in OA. Components of the metabolic syndrome (MetS), such as dyslipidaemia, can affect macrophage phenotype and function, which could explain the link between MetS and OA development. Recently published studies have provided novel insights into the different origins and heterogeneity of synovial macrophages. Considering these findings, we propose an important role for monocyte-derived macrophages in particular, as opposed to yolk-sac derived residential macrophages, in causing a pro-inflammatory phenotype shift. We will further explain how this can start even prior to synovial infiltration; in the circulation, monocytes can be trained by metabolic factors such as low-density lipoprotein to become extra responsive to chemokines and damage-associated molecular patterns. The concept of innate immune training has been widely studied and implicated in atherosclerosis pathology, but its involvement in OA remains uncharted territory. Finally, we evaluate the implications of these insights for targeted therapy directed to macrophages and metabolic factors.

Key words: OA, metabolic syndrome, LDL-cholesterol, synovitis, macrophages, monocytes, innate immune training

REVIEW

Rheumatology key messages

- Dyslipidaemia aggravates OA via pro-inflammatory skewing of the synovial macrophage population.
- Recent findings suggest that monocyte-derived macrophages can drive this pro-inflammatory shift.
- Low-density lipoprotein (LDL) can activate circulating monocytes prior to infiltration into the synovium.

Introduction

OA is a painful and debilitating disease of the joint, characterized by articular cartilage degeneration, osteophyte formation and inflammation of the synovial membrane. The old idea of OA as a wear-and-tear disease has become increasingly repressed, and although mechanical imbalances are still regarded to be important in the onset and progression of disease, many researchers consider that chronic inflammation of the synovium co-mediates and accelerates OA development. This synovitis is characterized by hyperplasia of the synovial lining and infiltration of especially monocytes, that consequently differentiate towards macrophages in the tissue. Abundance of these macrophages has been associated to increased OA pathology in humans [1].

An important risk factor for OA development in the modern-day world is the metabolic syndrome (MetS), a cluster of cardiovascular risk factors that is defined by meeting at least three out of five of the following criteria: abdominal obesity, arterial hypertension, hyperglycaemia, low serum high-density lipoprotein (HDL) and high serum triglycerides (NCEP ATPIII 2005 revision [2, 3]). Besides their increased risk of developing cardiovascular diseases (CVD) and type 2 diabetes, individuals with MetS are more susceptible to development of OA [4]. This was also found for OA in non-weightbearing joints, which

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suggests that the association is not purely a result of weight-mediated joint loading [5]. While the exact underlying mechanisms remain unclear, systemic manifestations of MetS like dyslipidaemia, hyperglycaemia, oxidative stress and low-grade systemic inflammation are thought to mediate OA pathology by promoting deleterious processes such as synovial inflammation. Lipid accumulation is the main characteristic of obesity and a large number of studies have therefore focussed on a role for lipids in OA. This has resulted in the implication of several lipid classes and lipid-derived factors in OA pathophysiology, including lipoproteins, free fatty acids, triglycerides and adipokines [6, 7].

Here, we will especially focus on the potential role of dyslipidaemia and high levels of low-density lipoprotein (LDL) in OA development in particular, one of many pleiotropic effects of dyslipidaemia subject to ongoing investigations in OA [5]. Although the dyslipidaemia component of MetS is not defined by blood levels of LDL but by levels of HDL and triglycerides, LDL is strongly related to these factors and plays a known central role in the development of CVD events [8]. In addition, the effectiveness of dyslipidaemia-modulating therapies used with the aim of lowering cardiovascular risk, such as statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, is monitored using LDL levels as a proxy measure [9–11]. PCSK9 mediates degradation of LDL, and its inhibition using novel mAbs lowers blood LDL levels by an additional 60% when used on top of statins, and further decreases risk of CVD events by 15–20% [12]. Given that atherosclerosis is strongly associated to OA and macrophages play a key role in both disease processes, this suggests they may share common biochemical pathways and patients might thus benefit from similar treatment strategies. Although some clinical trials in which the effects of statins on OA were studied showed small improvements [13–15], other studies did not [16–19]. However, the interpretation of these results is complicated by varieties in distributions of OA phenotypes, differences in treatment strategies and readouts, and the presence of dyslipidaemia in the statin non-user control group, which can result in underestimation of treatment response [16, 20].

In contrast to clinical trials, studies in animal models with varying degrees of inflammation have confirmed increased OA pathology in the context of dyslipidaemia, and hint at a crucial but complex role for synovial macrophages in causing these aggravated symptoms. We previously discussed this in a review published in 2016 [21]. The current review provides an updated overview of the most important and most recent literature regarding the role of synovial macrophages in MetS-associated OA development, and expands on this by proposing that especially macrophages derived from infiltrating monocytes are important in preventing the synovitis from resolving during the disease initiation stage. We substantiate this concept by speculating about how prior immune training of circulating monocytes may co-mediate this process.

Dyslipidaemia aggravates OA via skewing of the synovial macrophage population

Epidemiological evidence showing that MetS is associated with OA

In 2009, two separate studies reported an increased prevalence of MetS in the OA population, with each individual component of MetS also being more prevalent [4, 22]. Since these epidemiological studies were cross-sectional, questions concerning the longitudinal relationship between MetS and OA remain unanswered; do components of MetS drive OA development? Or, could OA also be causative for MetS via, for instance, hampered mobility and other lifestyle alterations? In the following years, multiple studies were published in favour of the former [23, 24]. Most recently, Niu and colleagues showed that in the Framingham OA study, pre-existing MetS and its components are risk factors for subsequent symptomatic knee OA [25]. These studies suggest that components of MetS can indeed drive OA, even though this does not exclude co-existence of the inverse causal relationship and of other shared risk factors that precede both.

If MetS indeed drives OA, what is the relative contribution of each individual component? In particular, is the link purely biomechanical by nature as a consequence of weight-mediated abnormal joint loading, or is it also dependent on metabolic perturbations and associated systemic inflammation? Multiple studies showed that MetS is associated to knee OA, but also OA in non-weight bearing joints, which was irrespective of BMI in some cases [26–28]. In addition, high dietary fat consumption and serum fatty acid chain length change were associated with both radiographic and symptomatic knee OA independent of BMI [29, 30]. These studies led researchers to argue that metabolic involvement in OA is likely. In contrast, the Framingham OA study showed that correction for BMI using a binary regression model nullified the association between OA and MetS, as well as most of its individual components, with only diastolic blood pressure remaining significant after correction for BMI [25]. This instinctively implies a link between MetS and OA that runs more via weight-mediated processes.

To our understanding, however, it remains unclear if correction for BMI does not also simultaneously correct for other components of MetS that correlate with BMI. In other words, whether multicollinearity occurrs. As pointed out in an editorial by Appleton and colleagues, BMI and body weight are closely correlated to abdominal obesity, which might influence OA via fat-mass driven metabolic derangement [31]. In addition to fat mass, some studies report a significant positive correlation between BMI and LDL, although this was found to be insignificant in others [32–34]. Therefore, the relative contribution of abnormal joint loading *vs* metabolic derangement remains unclear until an alternative factor can be found that adjusts for weight-mediated processes in isolation from metabolic processes.

The Framingham OA study further underlines that involvement of weight-mediated processes should always

be taken into account when considering which MetS components drive OA, expanding on literature showing obesity as the MetS component most commonly associated with OA across most studies [31]. Systemic metabolic risk factors for OA probably do not influence OA pathology completely independently, but more likely in addition of or in synergy with abnormal joint loading. The sustained plausibility of these scenarios maintains the need to investigate the role of metabolic derangement in driving OA development, especially when considering the pre-clinical studies showing involvement of dyslipidaemia in experimental OA and macrophage phenotype skewing in particular, which we will discuss in more detail later [35–41].

A pro-inflammatory macrophage phenotype shift underlies the chronicity of synovitis in OA

During initiation of inflammation resulting from cell or tissue damage, macrophages sense damage-associated molecular patterns (DAMPs) via pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), which triggers polarization towards a pro-inflammatory phenotype and release of cytokines. The eventual resolution of inflammation is dependent on a phenotypical transition of macrophages from pro-inflammatory to anti-inflammatory, commonly referred to as an M1 phenotype and M2 phenotype, respectively. Although this terminology implies that macrophage polarization status is binary, this is a drastic oversimplification of the complex phenotypic variation of *in vivo* macrophages. It is instead closer to a spectrum that includes a large number of unique and plastic phenotypes influenced by the specific microenvironment. We will refer to macrophage phenotypes as M1-like and M2-like, depending on whether it is considered to be more on the pro-inflammatory or anti-inflammatory side of the spectrum, respectively.

In OA, the inflammatory response does not seem to resolve and rather turns into a chronic inflammation that causes deregulation of both catabolic and anabolic processes. Phenotype skewing of the synovial macrophage population in favour of the M1-like phenotype is thought to underlie the chronicity of inflammation in OA [7, 42, 43]. This is supported by clinical studies showing that the CD11c/CD206 expression ratio in SF and the quantity of activated macrophages in the synovium is associated to severity of radiographic knee OA, although it remains an area of ongoing investigation [1, 44]. The exact cause, or causes, of the phenotype shift remains unclear. Possible scenarios include sustained presence of DAMPs as a result of re-occurring or continued cell and tissue damage, such as extracellular matrix components leaking from damaged cartilage (including fibronectin, hyaluronan and Tenascin-C [45]). In addition, the macrophage phenotype could be skewed under the influence of other factors, such as circulating metabolic factors and metabolic intermediates. Numerous pre-clinical studies have linked a phenotype shift of synovial macrophages towards the M1-like phenotype to increased pathology of experimental OA in the context of dyslipidaemia, which includes a long list of potential mediators including LDL-cholesterol.

Dyslipidaemia causes a pro-inflammatory macrophage phenotype shift and aggravates experimental OA

In mice, a MetS-like phenotype is often simulated by feeding of a calorie-rich diet like a high-fat diet (HFD) or a Western diet (WD), a variation of a HFD that aims to reproduce human high caloric fast-food feeding. Wu and colleagues reported in 2015 that obese mice fed HFDs rich in saturated and omega-6 fatty acids, which enhance systemic inflammation, developed more severe OA and more macrophage infiltration during a destabilization of the medial meniscus (DMM) model of OA compared with mice fed HFDs rich in omega-3 fatty acids [35]. Interestingly, weight-matching and multivariate models showed that injury-induced OA was not associated with body mass, but was associated to dietary fatty acid content and serum adipokines leptin and resistin. In addition, two studies in rats showed that HFD-feeding caused increased M1-like macrophage infiltration and accelerated OA progression [36, 37]. However, the specific metabolic factors responsible for these effects remain unanswered.

Gierman and colleagues presented convincing evidence that high cholesterol has the potential to mediate OA. They showed increased cartilage damage with higher percentages of dietary cholesterol, which was ameliorated by the cholesterol-lowering drug atorvastatin in a humanized dyslipidaemia mouse model [38]. Further highlighting a role for cholesterol, and LDL-cholesterol in particular, our group has previously shown that WD-feeding of WT, *Ldlr*$^{-/-}$ and *Apoe*$^{-/-}$ mice—genetic models commonly used in combination with a WD to induce hypercholesterolaemia—leads to aggravated OA, indicated by increased osteophyte formation combined with increased synovial activation as shown by enhanced S100A8 expression [39, 40]. Presumably, synovial inflammation characterized by local production of reactive oxygen species (ROS) is a prerequisite for making high blood LDL a risk factor for worsened OA symptoms. ROS can oxidize LDL to form oxidized LDL (oxLDL), which has the potential to locally stimulate macrophages to activate tumour growth factor-β (TGF-β) [41]. Interestingly, monocyte-derived macrophages that have differentiated in presence of oxLDL adopt a unique phenotype, different from macrophages polarized towards an M1 or M2 phenotype [46]. This phenotype has shown increased PPARγ activity, which promotes fatty acid oxidation, OXPHOS and oxLDL uptake via scavenger receptors such as CD36 and SR-A. Atypical to an M2-like macrophage however, it has also shown increased NF-κB activity and secretion of cytokines such as IL-1β [46–50]. In addition to macrophage skewing in the local inflammatory environment, oxLDL exposure in solely the monocyte stage can train monocyte-derived macrophages to react more strongly to a secondary TLR4 stimulus [51]. We will elaborate on the possible

involvement of monocyte training in OA later in this review.

Altogether, these *in vivo* studies present convincing evidence that the dyslipidaemia component of MetS can mediate OA pathology. Interestingly, increased pathology was commonly accompanied by an increase in M1-like macrophages, or M1-like macrophages were speculated to be involved. The exact molecular drivers of macrophage skewing and the origins of these macrophages remain unclear. *In vitro* and *in vivo* studies have shown that metabolic factors can cause skewing of macrophages towards a pro-inflammatory M1-like phenotype, which suggests that this can occur locally in the synovium. Several of these mechanisms are described in detail in an excellent review by Dickson and colleagues, focussing on the role of metabolic sensors AMPK, mTOR1 and HIF-1α in particular [7]. In addition to local macrophage skewing, the pro-inflammatory phenotype shift could be partly driven by increased influx of monocytes from the circulation.

Can metabolic activation of circulating monocytes drive a synovial macrophage phenotype shift?

Resident vs monocyte-derived macrophages

Recent studies have contested the idea that tissue macrophages exclusively originate from the bone marrow, and have shown that yolk sac–derived macrophages populate organs during early development and self-sustain their numbers via proliferation [52–55]. A comprehensive study by Culemann and colleagues has clarified the structural organization and origins of different types of synovial macrophages in a healthy mouse knees, and how this changes during inflammation [56]. Using fate mapping techniques in mice, they identify a distinct population of CX3CR1+ tissue resident macrophages which form a dense physical barrier that secludes IA structures from the capillary network of healthy synovium. This protective macrophage barrier was shown to be locally renewed by proliferating CX3CR1– interstitial macrophages, which were derived from early embryonic haematopoiesis and maintained its numbers independent of monocyte-derived macrophages. These resident macrophages were shown to have anti-inflammatory M2-like properties. During the onset of experimental arthritis, the resident lining macrophages rapidly changed their morphology and abrogated cell–cell contacts, but stably maintained their anti-inflammatory phenotype. Meanwhile, a cluster of monocyte-derived macrophages displaying an M1-like expression profile expanded during progression. Considering that the resident macrophages showed a more anti-inflammatory and monocyte-derived macrophages a more pro-inflammatory phenotype, the latter seems to be the most likely suspect in pushing the overall phenotype of synovial macrophages towards the M1-like phenotype, as seen in MetS mouse models and during OA [35–51]. It is unknown whether MetS may also skew a pro-inflammatory phenotype shift in residential synovial macrophages, which could work in conjunction with influx of monocytes to push the overall synovial macrophage phenotype towards pro-inflammatory.

Monocyte infiltration into OA synovium is associated to clinical disease parameters

Recently published studies are in support of the idea that especially monocytes and monocyte-derived macrophages are important drivers of OA pathology. Zhao and colleagues reported higher expression of the chemokines CCL2, CCL3 and CCL4 in SF of knee OA patients compared with isolated knee meniscus injury patients [57]. Further evaluating the pathogenic role of the CCL3/CCR1 and CCL2/CCR2 axes, the authors used the collagenase-induced OA (CiOA) mouse model to show that blockade of these pathways resulted in decreased synovial lining thickness and number of F4/80$^+$ cells in the synovium. It is noteworthy that the decrease in F4/80$^+$ cells caused by chemokine and chemokine receptor blocking was observed in both the lining and the sub-lining, with the numbers of F4/80$^+$ cells in the sub-lining being lower but reflective of the numbers in the lining. Given that blood-derived monocytes infiltrate the synovium in the sub-lining, this could suggest that the thickening of synovial lining is, at least in part, a result of monocyte-infiltration as opposed to resident macrophage proliferation. Although speculative, this could mean that thickened OA synovium has a higher content of monocyte-derived macrophages, thereby making the lining more pro-inflammatory.

Since monocyte-derived macrophage precursors largely develop in bone marrow and blood, exposure to MetS-associated factors at this stage might already skew their phenotype prior to entry into the synovium. Related to this, a study focussing on circulating monocytes in knee OA patients showed increased monocyte activation compared with healthy controls, demonstrated by increased CD16, HLA-DR and CCR2 cell surface expression and increased TNF-α and IL-1β production on a per cell basis following stimulation with DAMPs [58]. High serum TNF and BMI were positively correlated with CCR2 expression on circulating classical monocytes, and monocyte CCR2 expression was correlated with worse pain. Whether these effects were mediated by BMI or other MetS-associated aspects was not investigated here. The results led the authors to suggest that the circulating monocytes of OA patients are activated prior to their entry into the synovium. Also, studies focussing on MetS patients and patients with familial hypercholesterolemia have shown that their circulating monocytes show a pro-inflammatory phenotype and increased migratory capacity, as shown by increased expression of chemokine receptors, monocyte chemotactic protein-1 (MCP-1) and activation markers compared with healthy individuals [59–61]. Interestingly, several studies have shown that this was downregulated after treatment with the LDL-lowering drugs atorvastatin and PCSK9 inhibitors

[60–62], suggesting that LDL is a MetS-associated factor that mediates activation of circulating monocytes. Providing this, it is surprising that studies showing an association between familial hypercholesterolemia and OA are scarce.

To this day, activation of circulating monocytes has not been linked to OA development. However, recent developments in the research field investigating other non-communicable diseases have provided intriguing insight into this process and the factors involved, which might prove to also be relevant for OA. Atherosclerosis, for example, is comparable to OA in the sense that it is strongly associated to MetS and is mediated by local DAMP-induced inflammation and consequent infiltration and differentiation of monocytes and monocyte-derived macrophages. A process termed innate immune training, which involves reprogramming of monocytes, has been studied in the context of atherosclerosis and is suggested to be involved in the disease process [63, 64].

Metabolic activation of circulating monocytes: innate immune training

The concept of trained immunity is relatively new, and initially was used to explain how the innate immune system has evolved non-specific adaptive mechanisms that provides protection against future infections. More specifically, an initial activation of innate immune cells by specific pathogen associated molecular patterns (PAMPs), like β-glucan, primes the cells to stay in an activated state for a prolonged period of time, during which they will respond more vigorously to a secondary pro-inflammatory stimulus [65, 66]. In contrast, some other types of PAMPS, like lipopolysaccharide (LPS) and tuberculosis vaccine Bacille Calmette-Guerin (BCG), have shown to induce immune tolerance, dampening the inflammatory response to a secondary stimulus [67, 68].

In addition to PAMPs, non-infectious triggers like DAMPs or WD-associated factors such as oxLDL also have the ability to prime innate immune cells. Bekkering and colleagues showed in 2014 that *in vitro* oxLDL-priming of human monocytes induces memory responses via epigenetic programming [51]. Some years later, Christ and colleagues showed *in vivo* that short-term WD feeding of *Ldlr*$^{-/-}$ mice led to functional reprogramming of innate immune cells as shown by an increased TNF-α and keratinocytes-derived chemokine (KC) response to TLR ligands, which persisted for several weeks after switching back to a standard diet [69]. The NRLP3 inflammasome was identified as a crucial mediator of this systemic process. Furthermore, other studies showed that dyslipidaemia caused higher expression of the ROS-producing enzyme NOX2 and increased oxidative stress. Besides being able to induce immune activation via various pathways including NLRP3 [70, 71], NOX2-derived ROS may potentially also facilitate LDL oxidation in the joint [72–74].

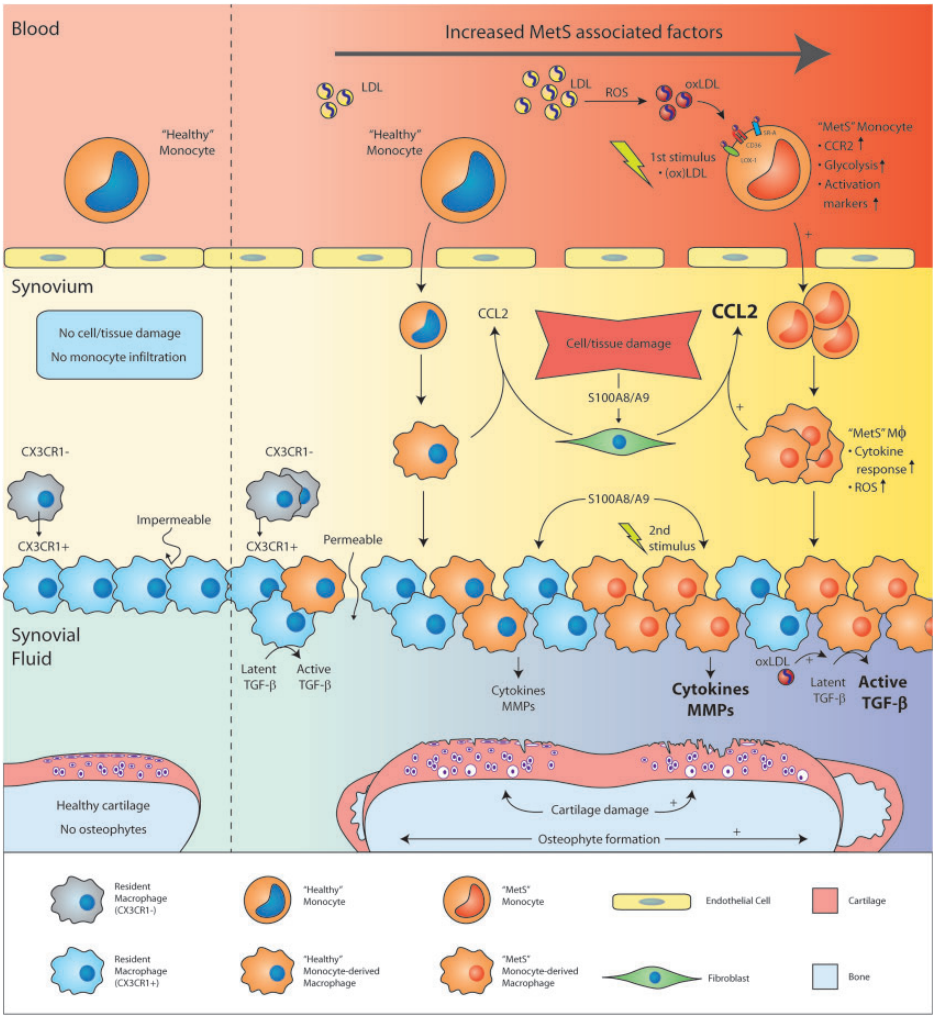
Do resident macrophages contribute to oxLDL-mediated OA symptoms?

The previous paragraphs describe how metabolic factors like (ox)LDL can prime monocytes in the circulation to become more sensitive to chemokines and DAMPs, and may consequently infiltrate the synovium in higher numbers and respond more strongly when locally encountering OA-related stimuli such as S100A8/A9 (Fig. 1). These particular macrophages may thus promote OA development by further stimulating the chronic inflammation of the synovium via continued production of chemokines, catabolic factors and pro-inflammatory factors, which can simultaneously mediate OA-associated cartilage breakdown. However, solely an increase in monocyte-derived macrophages would not explain the increase in ectopic bone formation that was observed in the context of high LDL in several previously mentioned studies [39, 40]. This is a process mediated by growth factors, most importantly being TGF-β, which is more produced by M2-like macrophages than M1-like macrophages. Preclinical studies in which synovial macrophages were selectively depleted using clodronate-filled liposomes have demonstrated that macrophages in particular mediate osteophyte formation during experimental OA [75]. Osteophyte size was severely reduced in macrophage-depleted joints (56–85% reduction among all locations), and this was accompanied with a strong reduction in TGF-β. In addition, the generation of pro-inflammatory cytokines and MMPs was significantly decreased in the absence of synovial macrophages in both human and mouse OA synovium [76, 77].

It remains unclear whether it is primarily resident macrophages or monocyte-derived macrophages that mediate these processes. Interestingly though, other macrophage-depletion studies showed that IA TGF-β injection led to osteophyte formation also in naïve mice joints, whereas this was drastically reduced in macrophage-depleted joints (70% and 64% histological score reduction with 20 and 200 ng of TGF-β, respectively) [78]. In addition, repeated IA oxLDL injections led to increased TGF-β activation in naïve mice joints but not in macrophage-depleted joints [41]. Given that in these studies, macrophages were depleted before injection of TGF-β and oxLDL in naïve mice joints, there is no reason to assume that high numbers of monocyte-derived macrophages were present in the synovium at this stage. This would suggest that (oxLDL enhanced) TGF-β activation is mediated mostly by resident lining macrophages in a non-inflamed microenvironment. However, it remains possible that monocyte-derived macrophages are also involved, despite their lower numbers, but that they are depleted by the clodronate-filled liposomes along with the residential macrophages.

Intriguingly, oxLDL injection led to an increase in MCP-1 and macrophage inflammatory protein 1-α (MIP-1-α) production, and increased monocyte infiltration only in macrophage depleted joints. OxLDL injection in these joints led to development of a thicker synovial lining that produced higher protein levels of S100A8 compared with

Fig. 1 Metabolic activation of circulating monocytes aggravates OA development via an increase of pro-inflammatory synovial macrophages



Schematic overview of the theoretical mechanism that describes how MetS-associated factors, such as oxLDL, can activate circulating monocytes to obtain an increased migratory capacity and cytokine response. In the event of cell/tissue damage, alarmins such as S100A8/A9 are released in the synovium, which can attract these monocytes from the circulation by promoting chemokine production. This consequently leads to an increase in more reactive monocyte-derived macrophages in the synovium (coloured red), which are pro-inflammatory and contribute to degradative processes and the chronicity of inflammation. In contrast, resident synovial macrophages (colored blue) maintain their protective and anti-inflammatory phenotype during inflammation, but may still contribute to OA symptoms via, for instance, activation of TGF-β. MetS: metabolic syndrome; LDL: low-density lipoprotein; oxLDL: oxidized LDL; ROS: reactive oxygen species.

PBS and LDL injection 7 days post-depletion [41]. This suggests a dual role for oxLDL, in which it stimulates TGF-β activation when interacting with residential macrophages, but initiates chemokine-mediated monocyte attraction and thickening of the lining when interacting with cells in the sub-lining such as fibroblasts. The latter alludes to the idea that the newly attracted, potentially primed, monocyte-derived macrophages repopulate the lining and thereby compromise its natural protective and anti-inflammatory function, and rather turn it pro-inflammatory. It would be interesting to investigate if this indeed occurs, and if so, how this repopulated lining mediates OA-related processes like TGF-β activation and MMP production compared with the resident lining.

Implications for therapeutic options

Although it should be more thoroughly investigated whether metabolic training of monocytes indeed plays a role in OA, the current evidence provides interesting opportunities to speculate on the possibility to therapeutically target MetS components, or monocyte-derived

macrophages, to treat or slow down OA progression. Cholesterol lowering or anti-oxidative drugs in individuals with MetS may help to prevent oxLDL-mediated monocyte and macrophage skewing. Indeed, statin use was associated to reduced clinical OA outcome in some studies [19, 79], although other studies were unable to find this association [17, 18]. Besides therapeutic options, the call for a shift towards individual responsibility to prevent and self-manage disease is increasing [80]. Weight reduction and dietary interventions should be applied by both healthy individuals and OA patients to limit the risk for OA development and progression. For management of serum levels of LDL-cholesterol specifically, individuals should focus on reducing intake of saturated fat while having sufficient intake of LDL-lowering nutrients such as plant stanols and sterols [43, 80, 81].

In this review, we particularly focussed on LDL-cholesterol as a MetS-associated factor that could underly the link between MetS and OA because of its known involvement in OA pathology in mice and atherosclerosis pathology in humans. This, of course, does not exclude the possibility that other components of MetS, such as hyperglycaemia, could also be involved in similar processes and likewise form interesting factors to be investigated further as potential therapeutic targets. Indeed, hyperglycaemia is known to cause systemic macrophage activation [82], and the glucose-lowering drug metformin was shown to limit progression of injury induced OA [83]. The purpose of this review is to explain the role of LDL in MetS-associated without dismissing a possible role for other aspects of MetS and dyslipidaemia. Additional studies and reviews should be consulted in order to get a complete understanding of the processes underlying the link between MetS and OA.

Aa an alternative to targeting metabolic factors, systemic inflammation could be dampened using anti-inflammatory drugs. In this context, a retrospective exploratory analysis of the CANTOS study (Canakinumab Antiinflammatory Thrombosis Outcome Study)—a large clinical trial involving 10 061 patients with previous myocardial infarction and high systemic inflammation—provided interesting results; the rate of total knee and hip replacements was lower in patients treated with mAb against IL-1β, canakinumab [84].

The increasing evidence showing an important role for synovial macrophages in OA, and MetS-associated OA in particular, appeals to the idea to target macrophages specifically as means to alleviate OA symptoms. However, attempts to do this have had limited success so far. Specifically targeting monocyte-derived macrophages might be a more efficient strategy, due to their supposedly important role in skewing synovial macrophage phenotype as shown by the evidence presented in this review. Using factors that stabilize PPARγ could aid in skewing macrophage phenotype to become more anti-inflammatory [85]. Alternatively, inhibiting monocyte infiltration by blocking CCL2 or CCR2 (a phase 2 clinical trial using CCR antagonist CNTX-6970 is currently ongoing), or inducing innate immune tolerance via vaccination with BCG, are some of many possible options to interfere in this process in an attempt to find a novel therapy for OA.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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