Inflammation and Regeneration in Osteoarthritis

Subjects: Others

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Osteoarthritis (OA) affects over 250 million people worldwide. It is a multifactorial disease characterized by cartilage loss and low-grade synovial inflammation. Focusing on these two targets together could be the key to developing currently missing disease-modifying OA drugs (DMOADs).

Keywords: osteoarthritis ; inflammation ; synovitis ; cell-free tissue engineering

1. Introduction

Osteoarthritis (OA) has long been [1][2][3] and is sometimes still [4][5] referred to as a non-inflammatory condition. Moreover, when studying “classic” inflammatory arthritides, such as rheumatoid arthritis (RA) or spondyloarthritis, researchers would often use tissue and biologic fluid samples from OA patients as negative (non-inflammatory) controls [6][7]. Although currently researchers agree that many aspects contribute to OA progression, including gender [8], it has long been regarded mainly as the consequence of cartilage wear and tear. Cartilage damage was reported to lead to joint biomechanics impairment resulting in further cartilage loss and joint deformity, while the inflammatory component was commonly underestimated.

Cartilage tissue itself, being avascular, cannot develop a classic immune response. However, when considering the joint as a whole, including synovium, ligaments, and subchondral bone, inflammation (synovitis) seems to play an important role in OA progression. There is evidence that synovitis is associated with increased OA severity [9][10], and therefore it is a promising target for currently missing disease-modifying OA drug (DMOADs) development. Most available OA management options, including lifestyle changes, pharmacotherapy, and surgery [11][12][13], also target joint inflammation to varying degrees.

Lifestyle modification is the basis of most chronic disease management and can be beneficial to compliant patients. A balanced diet and physical activity can postpone the OA onset or slow down its progression both by reducing the joint loading due to weight loss and decreasing the levels of adipokines, which are known to contribute to the inflammatory component of OA development [14][15]. Currently recommended pharmacological treatments, including non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, target inflammation and relieve pain [11], while the operative approaches aim to both reduce pain and improve joint functions [13]. However, one of the major drawbacks of all these strategies is that none of them address the problem of cartilage loss. Due to its low self-healing capacity, hyaline cartilage can only be repaired with involvement of cartilage-repair techniques, and various strategies, both scaffold-based and scaffold-free and cell-based and cell-free, are being proposed [16][17]. Unfortunately, most conventional cartilage tissue repair techniques focus on cartilage regeneration, while their effect on joint inflammation is rarely being discussed. Apparently, in order to fully address the problem of OA, a combination of cartilage repair techniques and strategies targeting inflammation should be considered.

2. Inflammation in an OA Joint

Homeostasis in a healthy joint is maintained by the synovial intima cells, namely type A macrophage-like synoviocytes, responsible for debris phagocytosis, and type B fibroblast-like synoviocytes, which produce synovial fluid components, including hyaluronan [18]. In an OA joint the products of the cartilage extracellular matrix (ECM) degradation (thoroughly reviewed elsewhere [7]) are bound to the pattern recognition receptors (PRRs) and recognized by the innate immune system as damage/danger-associated molecular patterns (DAMPs). Other groups of DAMPs in an OA joint include plasma proteins (e.g., α1 and α2 microglobulins, fibrinogen, vitamin D-binding protein), crystals of basic calcium phosphate, calcium pyrophosphate dihydrate, and uric acid [19], and so-called alarmins [6], including HMGB1 and the S100 family of proteins. There is evidence of some DAMPs’ ability to activate the complement system [19]. Some DAMPs, for example, crystals, rather bind to cytoplasmic PRRs (e.g., NLRP3), initiating inflammasomes activation [20][21]. However, it

seems that most DAMPs activate Toll-like receptors (TLRs), a large membrane-bound family of PRRs. TLRs are reported to be expressed both in the cartilage [22], being upregulated in the lesion areas [23], and in the synovium [19]. When stimulated by DAMPs, they trigger catabolic pathways in chondrocytes [23] and proinflammatory factor production by macrophages and mast cells [19]. The proinflammatory mediators can promote matrix metalloproteinases (MMP) production, directly enhancing the catabolic processes in the cartilage. They can also stimulate angiogenesis [24], increasing the influx of plasma proteins [7], which also act as DAMPs. Thus, more DAMPs are attracted to the area. Moreover, proinflammatory cytokines can boost their own production: exposure to proinflammatory cytokines promotes proinflammatory (M1) macrophage polarization, which in turn stimulates proinflammatory cytokine synthesis [25]. Thus, multiple vicious circles of further cartilage damage are established.

Synovial macrophages are the key cells orchestrating the processes of inflammation and healing within the joint because of their capacity to exhibit different phenotypes ranging from proinflammatory (M1) to anti-inflammatory (M2). In an OA joint, macrophages are caught into a vicious circle, being constantly attracted to the site by the perpetuated cartilage degradation and proinflammatory cytokine production, infiltrating the synovium and impairing its functions, notably, synovial fluid component synthesis [26], although to a lesser extent than in RA [27]. Alterations in the OA synovial fluid contents influence its properties, for example, the lack of hyaluronan leads to its decreased viscosity and elasticity [28], resulting in less effective lubrication of the joint surfaces and promoting cartilage damage. Aiming to find a way to disrupt the vicious circle involving the synovial macrophages, some researchers study the consequences of their depletion when modeling OA. Local macrophage depletion using intra-articular injections of clodronate-loaded liposomes has demonstrated rather positive outcomes in murine models, such as reduced MMPs' expression in the synovial tissue and decreased osteophyte formation [29][30][31]. On the contrary, systemic depletion of macrophages in CSF-1R-GFP+ macrophage Fas-induced apoptosis (MaFIA)-transgenic mice placed on a high-fat diet induced systemic inflammation. Moreover, it led to massive infiltration of CD3+ T cells and neutrophils in the synovium [32], although neutrophil infiltration is characteristic of RA [33] and is hardly ever observed in OA [27].

3. Existing Strategies for Targeting Inflammation and Cartilage Regeneration in OA

3.1. Inflammation

OA can affect people of any age. Accidental trauma, for example, joint ligament damage, can lead to reactive inflammation and post-traumatic OA development. Even if the articular cartilage itself has not been damaged, the inflammatory process in the joint can lead to the activation of catabolic pathways in the cartilage tissue [34].

However, OA is generally discussed in the context of older adults and elderly patients, and one cannot talk about these groups of patients without mentioning comorbidities. Unfortunately, oral NSAIDs and acetaminophen (paracetamol), traditionally used for pain management in OA, are associated with adverse side effects. Those include gastrointestinal [35] and cardiovascular [36] damage for NSAIDs, while paracetamol use may be associated with liver [37] and renal [38] damage. On the other hand, topical NSAIDs are considered a safer but still rather effective option and are strongly recommended for OA patients [12]; however, their use is not enough to reverse the OA progression. Efficacy of intra-articular injections of steroids or hyaluronic acid (HA) remains debatable [11][12]. Mixed results were obtained when targeting proinflammatory cytokines as well. For example, anakinra, a recombinant human IL-1 receptor antagonist protein, was reported to perform better than placebo in patients with severe knee injury [39], and at the same time in OA patients its effect was comparable with placebo [40]. AMG 108, a monoclonal antibody binding the IL-1 receptor, also showed moderate effectiveness in OA patients with minimal clinical benefit [41]. Similarly, anti-tumor necrosis factor alpha (TNF-α) monoclonal antibodies, such as adalimumab and infliximab, despite sporadic encouraging evidence [42][43], were reported to have limited effectiveness in hand OA patients [44][45].

Speaking of arthroscopic procedures, joint lavage seems to hold promise in reducing inflammation following the removal of debris from the joint cavity; however, evidence suggests that it does not provide any significant improvement either [46].

3.2. Cartilage Regeneration

Despite undeniable progress in the field, cartilage regeneration remains a challenge. There are multiple approaches to cartilage repair depending on the size of the defect, and unfortunately each of them has some drawbacks. For example, bone marrow stimulating techniques, such as subchondral drilling and microfracturing, lead to the formation of fibrocartilage, whose mechanical properties are inferior to those of hyaline cartilage [47]. The use of bone marrow stimulation technique with hydrogel implantation into the defect provides the appropriate environment for hyaline cartilage

formation [48]. Localized co-delivery of agents inducing hyaline cartilage formation such as bone morphogenic protein 2 (BMP2) and vascular endothelial growth factor (VEGF) receptor antagonist [49] in a hydrogel has also been proposed.

Another group of approaches is based on autologous chondrocyte implantation (ACI), sometimes applied together with collagen-based scaffolds (matrix-induced ACI, or MACI), and is used for larger cartilage defects. These approaches are reported to result in repair with hyaline-like cartilage; however, those are expensive multi-stage procedures requiring long-term rehabilitation [50].

In contrast, autologous stem cell transplantation may be performed in one stage, has a shorter rehabilitation period, and is less expensive than ACI. However, this approach requires longer-term studies to be recommended as a first-line treatment [50].

Osteochondral autografts or allografts are used for the largest cartilage lesions [51]. The osteochondral autograft transfer system (OATS, also known as mosaiplasty) has demonstrated good clinical outcomes, but even though the grafts are harvested from low-bearing regions in the joint, donor-site morbidity cannot be fully avoided. On the other hand, allografts, taken from deceased donors, seem to solve the problem of donor-site morbidity, but despite consensual cartilage immune privilege, some histocompatibility concerns cannot be ignored [52].

4. Inflammation Management in Tissue Engineering

In tissue engineering inflammation is mostly regarded as an adverse effect and a challenge to overcome. All the components of the tissue engineering triad (i.e., biomaterials, cells, and biochemical factors) are therefore being discussed in the context of biocompatibility. Furthermore, various modifications promoting better engraftment as well as minimizing the undesired immune reactions are being proposed for the existing approaches.

4.1. Biomaterials

Both natural and synthetic biomaterials used in tissue engineering have some strong advantages and some critical issues. For example, when assessing biomechanical properties or reproducibility, synthetic biomaterials, such as polycaprolactone (PCL), poly(glycolic acid) (PGA), polylactide (PLA), or poly(lactic-co-glycolic acid) (PLGA), are superior to natural biomaterials. On the other hand, when speaking about biocompatibility, natural biomaterials take precedence. It was reported that most synthetic polymers induce considerable inflammation in vivo [53][54], while natural biomaterials such as collagen [55] or silk [56][57][58][59] cause a significantly lower immune response. Still, synthetic polymers remain attractive substrates for tissue engineering and can be functionalized to enhance their biocompatibility. For example, magnesium hydroxide nanoparticles may help to neutralize pH changes by PLGA degradation acidic products, alleviating inflammation [60].

Hydrophilicity or hydrophobicity of the scaffold is another important characteristic affecting the protein adsorption and therefore the host immune response. Most synthetic polymers are hydrophobic, which correlates with high immunogenicity, but hydrophilic molecules such as polyethylene oxide (PEO) [61], polyethylene glycol (PEG) [61], or graphene oxide (GO) [62] can be used to modify their surface chemistry [63]. There is evidence that compound scaffolds consisting of both synthetic and natural biomaterials show rather good biocompatibility, for example, collagen from micronized porcine cartilage alleviated the inflammatory effect of a PLGA scaffold in a rat model [54]. However, the best available option in terms of biocompatibility remains decellularized ECM (dECM). Not only does dECM provide a perfect microenvironment for cells, it was also repeatedly reported to have immunomodulatory properties, including the influence on the macrophages, namely their polarization to the anti-inflammatory M2 phenotype [63][64][65][66]. Unsurprisingly, many researchers try to mimic ECM properties when designing biomaterials [67].

Some researchers propose scaffold-free approaches to avoid any possible adverse immune reactions to the biomaterials. Both chondrocyte-based [68] and synovial mesenchymal stem cells (MSCs)-based [69] cell sheets were demonstrated to promote good cartilage regeneration without any undesired inflammatory response in vivo. However, although considered “scaffold-free”, both constructs contained the ECM synthesized by the cells [70], and therefore these data may speak in favor of the use of ECM as well.

4.2. Cells

MSCs from different sources, the cell type the most extensively used in tissue engineering, are appreciated for their low immunogenicity and certain immunosuppressive capacity [71]. However, it was reported that in the process of

differentiation in vivo their immunogenicity is induced due to MHC-I and MHC-II expression [72], and there is evidence that MSCs can cause a memory T-cell response in immunocompetent hosts [73].

MSCs' therapeutic potential has long been discussed in the context of their differentiation capacity, i.e., ability to replace damaged tissues. However, a growing body of evidence suggests that MSCs exert their regenerative effect via paracrine activity [74]. Cytokines, chemokines, and, most importantly, extracellular vesicles (EVs) secreted by MSCs are now considered the key players in MSC-based therapies. EVs are heterogeneous membrane nanoparticles providing intercellular communication. Their research and use in various fields of regenerative medicine have been boosted over the past years, and they were demonstrated to possess all the advantages of MSCs without considerable drawbacks. For example, MSC-derived EVs exhibit no risk of tumor formation and demonstrate even lower immunogenicity than MSCs [75]. Moreover, they have lower storage demands and are therefore a promising agent for biomedical product development. Summing up, this makes cell-free approaches more and more prevalent in tissue engineering, including cartilage repair [76].

4.3. Biochemical Factors

Cytokines and growth factors control inflammation as well as cell proliferation, migration, and differentiation, thus orchestrating tissue remodeling and regeneration. Biochemical factors are naturally synthesized by the cellular component of tissue-engineered constructs: for example, MSCs are known to produce a variety of both growth factors and cytokines [77][78]. Moreover, cell cultures can be transfected or transduced so that the cells will secrete the desired bioactive molecules. In a study conducted by Holladay and colleagues, transfected rat bone-marrow-derived MSCs over-expressing an anti-inflammatory cytokine interleukin 10 (IL-10) demonstrated a good retention rate within collagen scaffolds in vivo for up to 7 days in comparison to unmodified cells, while the number of inflammatory cells during this period was decreased [79]. However, the authors reported that IL-10 modified the MSCs' retention rate to reduce almost to the same level as unmodified cells by day 21, with an unexpected increase in inflammatory cell number on day 7, speculating that prolonged culturing might have altered the MSCs' phenotype to become more immunogenic. Thus, given the difficulty to control implanted cells in vivo as well as the growing popularity of cell-free approaches, scaffold loading with bioactive factors has been developed. For example, in the same study, Holladay and colleagues proposed an alternative method where rat bone-marrow-derived MSCs were implanted in scaffolds loaded with IL-10 plasmid–polymer complexes, or "polyplexes", allowing in vivo transfection [79]. This approach increased the MSCs' retention rates for up to 21 days, which led to prolonged IL-10 release and decreased number of inflammatory cells. Although the idea of scaffold loading with bioactive molecules is not a new one [80], their delivery remains a challenge and ranges from chemical [81][82] or physical [83] incorporation to the use of micro- [84][85][86] or nanoparticles [87]. In this light, ECM as a natural source of bioactive molecules, such as VEGF [88], granulocyte-macrophage colony-stimulating factor (G-MCSF) [66], hepatocyte growth factor (HGF) [66][88], transforming growth factor-beta (TGFβ) [66][88], interleukin 3 (IL-3) [66], or interferon-gamma (INFγ) [66], is of great interest. Moreover, while state-of-the-art approaches suggest EVs' integration into scaffolds as a powerful tool for cell signaling [89][90][91], ECM-based scaffolds are a natural source of matrix-bound nanovesicles (MBVs), a subgroup of EVs known for their unique immunomodulatory properties [92].

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