International Journal of Medical Laboratory 2025;12(3):

International Journal of Medical Laboratory
Shahid Sadoughi University of Medical Sciences

Original Article

Macrophage-Polarizing Scaffolds for Immunomodulation and Cartilage Regeneration in Osteoarthritis

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Article history
Received: 21 Jan 2026
Accepted: 2 May 2026
Available online: 18 Nov 2026

Keywords
Cartilage
Immunomodulation
Macrophage activation
Osteoarthritis
Regeneration
Tissue scaffolds

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A B S T R A C T

Introduction: Osteoarthritis (OA) is now recognized as a chronic inflammatory disease rather than a passive degenerative condition. Macrophages play a central role in OA pathogenesis, with the M1 pro-inflammatory phenotype driving cartilage degradation and chondrocyte apoptosis, while the M2 pro-regenerative phenotype promotes tissue repair. The pathological imbalance of the M1/M2 ratio in OA has emerged as a key therapeutic target. This review summarizes scaffold-based strategies for M2 macrophage polarization in OA and discusses the challenges of clinical translation

Materials and Methods: A systematic literature search was conducted using PubMed, Web of Science, and Scopus databases up to January 2026. Studies were included if they addressed scaffold-based immunomodulation, macrophage polarization, and cartilage regeneration in the context of osteoarthritis.

Results: Preclinical evidence consistently demonstrates that macrophage-polarizing scaffolds, through the integration of biomaterial selection, mechanical cues, surface topography, and controlled delivery of immunomodulatory agents, can effectively shift the M1/M2 balance toward a pro-regenerative state. These scaffolds promote chondrogenesis, reduce cartilage degradation, and improve joint functionality in animal models. However, several challenges remain, including patient-specific inflammatory profiles, spatiotemporal control of immune modulation, scalable manufacturing, and appropriate sterilization methods that preserve immunomodulatory properties.

Conclusion: Macrophage-polarizing scaffolds represent an active immunomodulatory approach for cartilage regeneration, shifting from passive supports to engaging the immune system, with future directions focused on personalized and multifunctional designs targeting both cartilage and bone.

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Introduction

Osteoarthritis is a chronic degenerative disease of the joints and is one of the main causes of global disability, affecting more than 595 million people. Osteoarthritis is currently considered as a complex disease with progressive degeneration of articular cartilage, changes in the subchondral bone, synovial inflammation and metabolic disorders [1]. Articular cartilage has no blood or nerve supply, so its inherent capacity for repair is very limited and spontaneous healing is impossible. Biological agents targeting inflammatory pathways have been effective for pain relief but have not demonstrated a capacity to reverse disease progression or regenerate damaged cartilage [2]. The development of disease-modifying therapies capable of achieving sustainable cartilage repair remains a critical and urgent unmet medical need. The failure of conventional tissue engineering strategies to achieve functional cartilage repair can be attributed largely to a fundamental oversight: they have largely ignored the inflammatory microenvironment in which the scaffolds are implanted [3]. In osteoarthritis, recruitment of macrophages leads to synovitis where the balance between pro-inflammatory M1 and anti-inflammatory M2 phenotype is pathologically disturbed. M1-type macrophages secrete pro-inflammatory cytokines, such as interleukin (IL)-1 beta, IL-6 and tumor necrosis factor alpha (TNF-α), and matrix-degrading enzymes, such as matrix metalloproteinase-3 (MMP)-3, MMP-9 and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS). This results in the destruction of cartilage and the programmed death of chondrocytes [4]. By contrast, M2-type macrophages have immunosuppressive properties and promote tissue repair via production of IL-10 and transforming growth factor-beta (TGF-β). It is worth noting that the M1/M2 ratio in the synovial membrane, blood, and synovial fluid of patients with osteoarthritis have led to osteoarthritis being as a disease resulting from wear and tear, but rather as a disease of immune origin. This shift in the conceptual framework has led to the development of a new class of immunomodulatory supportive structures which, in addition to providing structural support, effectively modulate the inflammatory environment to promote tissue repair [5]. Through the careful design of surface topography, stiffness and bioactive signals, researchers can steer macrophage behaviour towards phenotypes conducive to healing. Preclinical evidence consistently suggests that scaffolds can sometimes attenuate M1-mediated inflammatory responses whilst enhancing M2-mediated regenerative activity, thereby slowing cartilage degeneration and facilitating tissue repair [6]. This review highlights the strategies of supportive scaffolds that recruit macrophages for the treatment of osteoarthritis, focusing on how bioactive materials can effectively modulate the immune responses. Our aim is to offer a strategic framework for designing next generation scaffolds that can break the cycle of chronic inflammation and realize a durable cartilage repair. This is directly related to how severe the disease and pain are. This underlines the

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importance of macrophage recruitment in the pathophysiology of osteoarthritis.

1. the immunopathological landscape of osteoarthritis

1.1. Synovitis: The inflammatory engine of osteoarthritis progression

Synovitis is very common in osteoarthritis and can be detected in more than 90% of patients, even in the early stages of the disease. The synovium is a specialized and highly vascularized membranous lining of the diarthrodial joint that normally acts as a semipermeable barrier, regulating the two-way exchange of nutrients, cytokines, and metabolic byproducts between the avascular cartilage and the systemic circulation [7]. However, in the setting of osteoarthritis, this barrier is structurally and functionally disrupted, manifesting as immune cell leakage, aberrant neovascularization, and accumulation of a wide range of proinflammatory mediators in the synovial fluid and tissue. Furthermore, the subpatellar fat pad is not the only intracapsular fatty structure but is an active participant in this inflammatory cascade [8]. This gland secretes bioactive adipokines, including leptin and prostaglandin E2, which stimulate the activation of synovial fibroblasts and perpetuate the positive feedback loop of chronic inflammation, thereby exacerbating cartilage degradation and the destruction of joint tissues.

1.2. Damage-associated molecular patterns (DAMPs): Initiators of synovial inflammation

Imaging studies confirm that synovitis actively drives the progression of osteoarthritis magnetic resonance imaging shows a correlation between the severity of synovitis and cartilage loss [7, 9]. Pieces of damaged cartilage, DAMPs, stimulate immune receptors and promote inflammation. This creates a positive feedback loop of destruction; inflammation damages cartilage and releases more DAMPs, which stimulates more inflammation [10]. DAMPs are associated with disease severity and are biomarkers. A subset of $TIMD4^{+}IL1\beta^{+}$ macrophages proliferate with disease progression [11]. These cells are driven by endoplasmic reticulum stress and blocking this stress in mice reduces inflammation and joint damage [12].

1.3. Macrophages as the hub of osteoarthritis immunopathology

Macrophages are the predominant immune population in the arthritic synovium and represent approximately 65% of the leukocytes. These cells display a continuum of polarization states classically divided into a proinflammatory M1 phenotype and an anti-inflammatory M2 phenotype. Under physiological conditions, the synovial homeostasis is maintained by the phagocytic activity, immune surveillance and paracrine regulation of synovial fibroblasts by tissue-resident macrophages of embryonic origin [13, 14]. These long-lived cells are capable of self-renewal, and together form a protective immunological barrier in the synovial lining. However, in the arthritic joint this homeostatic TRM population is progressively lost and correlates with the expansion of proinflammatory subsets of macrophages [15]. This combined change represents a critical pathological turn that accelerates the transition to chronic synovial inflammation, leading to catabolism of downstream cartilage and destruction of the joint structure.

M1 macrophages secrete pro-inflammatory cytokines including TNF-α, IL-1β, IL-6 and matrix degrading enzymes including MMPs to induce

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catabolism, apoptosis and destruction of cartilage [16, 17]. Besides the direct effects on chondrocytes, M1-derived inflammatory mediators can also activate synovial fibroblasts. This results in amplification of the local inflammatory response through reciprocal signalling loops [18]. Osteoarthritis patients have a high M1/M2 ratio in both the peripheral blood and the synovial fluid. In contrast, M2 macrophages have anti-inflammatory and tissue repairing functions through the release of mediators such as IL-10, TGF-β and vascular endothelial growth factor (VEGF), which together promote angiogenesis, extracellular matrix remodelling and tissue regeneration [19]. There are different types of M2, including the M2a, M2b, M2c and M2d subtypes. Each of these have different functional profiles. In the arthritic joint, the homeostatic balance between M1/ M2 is pathologically shifted to a dominant proinflammatory M1 state owing to the confluence of several factors, including reduced availability of M2-polarizing cytokines (IL-4 and IL-10), persistent activation of M1 responses by DAMPs, and age-related immune dysregulation, often called immune sensitization [20]. Mechanistically, M2-derived TGF-β promotes chondrogenic differentiation and matrix synthesis, IL-10 inhibits inflammatory signalling cascades, and M2-derived exosome microRNAs (mirRNAs) including miR-146a and miR-223, negatively regulate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, thus attenuating the inflammatory transcriptional program and promoting the establishment of a pro-regenerative articular microenvironment [21]. Macrophages play a key role in the inflammation that is a hallmark of osteoarthritis, but they do not act in isolation. In the proinflammatory environment, $CD4^+$ and $CD8^+$ T lymphocytes are important players secreting interferon gamma (IFN-γ) and IL-17 that enhance the polarization of macrophages toward a destructive M1 phenotype and increase the expression of MMPs [22]. Furthermore, Thelper (Th)17 cells aggravate joint pathology and regulatory T cells (Tregs) are reduced in number and function and their reduction correlates with increased disease severity [23]. The humoral immune response is mediated by B lymphocytes and plasma cells, which produce antibodies and form lymphoid aggregates in the synovium [24]. In addition, natural killer (NK) cells, mast cells and dendritic cells in the synovial inflammatory network also enhance the local immune response [25]. This interconnected immune perspective suggests that combination approaches targeting multiple immune cell subsets and their signalling pathways simultaneously may provide a more effective path to sustained disease modification.

Figure 1 illustrates the M1/M2 imbalance in osteoarthritis, where proinflammatory M1 macrophages drive cartilage destruction while M2 macrophages promote tissue repair. Macrophage-polarizing scaffolds have been designed to reverse this pathological imbalance toward a regenerative M2 phenotype. The osteoarthritis synovium harbors a diverse array of immune cells, with macrophages being the most abundant population. As shown in Table 1, synovial macrophages include protective tissue-resident macrophages, pro-inflammatory M1 macrophages that drive cartilage degradation, and anti-inflammatory M2 macrophages that promote tissue repair.

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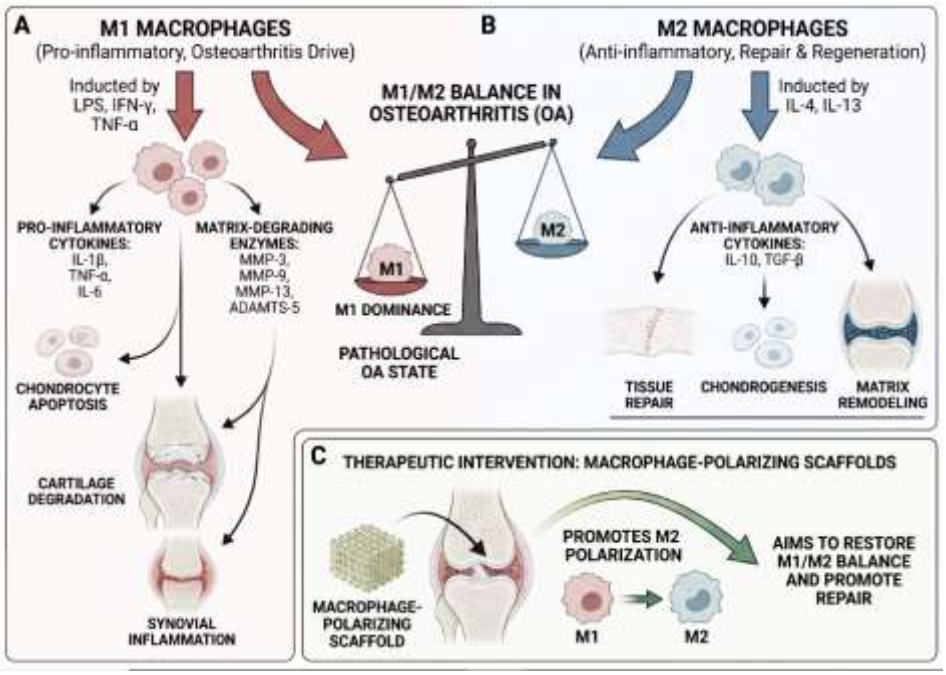


Fig. 1: Schematic representation of the M1/M2 macrophage polarization in osteoarthritis pathogenesis

Table 1. Immune cell populations and their role in the osteoarthritic synovium.

Cell type	Phenotype	Key markers	Secreted factor	Role in osteoarthritis
Tissue-resident macrophages	Protective	CX3CR1$^+$, TREM2$^+$, MerTK$^+$, LYVE1	IL-10, TGF-β	Maintain homeostasis; clear debris; form a protective barrier
M1 macrophages	Pro-inflammatory	CD86$^+$, CD80	IL-1β, TNF-α, IL-6, MMP-3, MMP-9, MMP-13	Drive cartilage degradation; induce chondrocyte apoptosis; amplify inflammation.
M2 macrophages	Anti-inflammatory	CD163$^+$, CD206$^+$, Arg-1$^+$	IL-10, TGF-β	Promote tissue repair; suppress inflammation; support angiogenesis
CD4$^+$ T cells	Helper	CD4$^+$	IFN-γ, IL-17	Promote M1 macrophage polarization
Th17 cells	Pro-inflammatory	CD4$^+$, IL-17$^+$	IL-17, IL-22	Enhance MMP production; degrade cartilage
Regulatory T cells	Immunosuppressive	CD4$^+$, CD25$^+$, FOXP3$^+$	IL-10, TGF-β	Suppress inflammation; maintain immune tolerance
B cells / Plasma cells	Antibody-producing	CD19$^+$, CD20$^+$, CD138$^+$	Autoantibodies	Form ectopic lymphoid structures in advanced disease
NK cells	Cytotoxic	CD56$^+$, NKp46$^+$	IFN-γ, perforin	Contribute to synovial inflammation
Mast cells	Inflammatory	FcεRI$^+$, CD117	Histamine, tryptase, TNF-α	Contribute to pain and angiogenesis
Dendritic cells	Antigen-presenting	MHC-II$^+$, CD11c$^+$	IL-12, IL-23, TNF-α	Promote T-cell activation

IL= Interleukin; TNF-α = Tumor necrosis factor-alpha; MMP= Matrix metalloproteinase; TGF-β = Transforming growth factor-beta; IFN-γ = Interferon-gamma; NK= Natural killer

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2. Principles of design for immunomodulatory scaffolds

To rationally design macrophage-polarizing scaffolds, construction alone is insufficient; rather, it requires the systematic and synergistic integration of biophysical, biochemical, and biomolecular cues that collectively orchestrate the host immune microenvironment toward a pro-regenerative phenotype. In contrast to traditional scaffolds that serve mainly as inert scaffolds for cell adhesion and tissue in-growth, immunomodulatory scaffolds are intentionally engineered to engage with the inflammatory microenvironment and re-educate the macrophage polarization from destructive pro-inflammatory phenotypes to regenerative, tissue-healing phenotypes [26]. This conceptual change underscores the importance of spatiotemporal control of material properties to achieve targeted immune modulation and durable cartilage repair.

2.1. Choice of biomaterials and assessment of biocompatibility

Selection of a suitable biomaterial is a key factor that affects scaffold performance and determines the subsequent biological activities. Natural polymers, such as collagen, gelatin, hyaluronic acid, and chitosan, possess inherent bioactivity and ligand motifs recognized by cell receptors, which lead to positive cell-material interactions. Synthetic polymers like poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL) and polyethylene glycol (PEG) offer advantageous mechanical properties and highly adjustable degradation profiles to adapt to the biomechanical requirement of a specific target tissue [27]. Decellularized extracellular matrix (ECM) scaffolds are a novel biomimetic platform that preserve the architecture of the tissue of origin, as well as a variety of growth factors, matricellular proteins, and bioactive peptides, providing an inherent capacity for immune modulation and tissue-specific repair. However, even the most advanced biomaterial composites are subject to failure if the protocols for processing and quality control are not adequate. Factors such as purity, endotoxin contamination, and sterilization method have a profound impact on the host immune response; low levels of contaminants can inadvertently bias macrophages toward a proinflammatory M1 phenotype, thereby counteracting the intended immunomodulatory effects of the scaffold.

2.2. Biodegradation kinetics and byproduct management

The degradation kinetics should be in harmony with tissue regeneration, which typically maintains the integrity for 3–6 months before gradual absorption [28]. Degradation byproducts should be nontoxic and preferably bioactive. However, polyester-based materials (e.g., PLGA, PCL) undergo hydrolysis and generate acidic metabolites (e.g., lactic and glycolic acids) that may decrease the local pH and worsen inflammation [29]. Mitigation strategies include incorporating basic salts (e.g. calcium carbonate, hydroxyapatite) to buffer pH changes, or blending synthetic materials with natural polymers to control degradation and mitigate pro-inflammatory effects [30].

2.3. Mechanical properties and mechano-transduction

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Macrophages show heightened sensitivity to the mechanical rigidity of their microenvironment. This property influences their polarization state. Scaffolds with stiffness in the physiological range of normal soft tissues (~1–100 kPa) have been shown to promote M2 polarization via mechanotransduction signalling pathways including RhoA/ROCK and YAP/TAZ. On the other hand, substrates that are either too stiff or too soft tend to promote a proinflammatory M1 phenotype of macrophages [31]. Besides static stiffness, dynamic mechanical forces, such as compressive and shear stresses, also modulate macrophage behaviour [32]. To provide sufficient mechanical stability, the ideal scaffold for cartilage repair should have a compressive modulus that closely matches that of the natural articular cartilage (0.5–2 MPa). It should also provide topographical and stiffness signals that promote macrophage polarization toward a tissue-reparative state and enhance matrix deposition.

2.4. Porosity, architecture of pores and mass transport

A porosity of 70–90% with an interconnected pore architecture with pore diameters of 100–300 μm is an ideal scaffold design for good transport of nutrients and removal of metabolic waste and allow for cellular infiltration [33]. Gradient pore structures mimicking the hierarchical structure of natural tissues can induce specific cell responses. Chondrogenic differentiation is promoted with smaller pore sizes while larger pore sizes promote angiogenesis and immune cell recruitment [34]. In addition, pore geometry has a direct effect on macrophage morphology and polarization. It has been demonstrated that elongated pore morphology and aligned topographic features can induce macrophages to adopt an M2 phenotype through cytoskeletal reorganization and mechanism-sensitive signalling pathways [35]. Furthermore, hypoxic conditions increase mass transfer efficiency and oxygen tensions between 1–5% O 2 have been shown to drive M2 polarization and chondrogenic differentiation, creating a more regenerative progenitor microenvironment [36].

2.5. Surface topography and bio-chemical signals

Micro- and nanoscale surface topographies act as contact cues, significantly impacting macrophage adhesion, morphology, and polarization. Engineered surfaces with grooved aligned or nano topographic patterns have been shown to promote M2-like polarization via enhanced integrin clustering and cytoskeletal reorganization leading to the activation of mechanotransduction signalling cascades [37]. At the same time, biochemical functionalization of scaffold surfaces with bioactive moieties such as RGD peptides, glycosaminoglycans, and ECM proteins improves cell matter interactions and actively modulates the local immune response [38]. These physical and biochemical approaches thus offer complementary routes to achieving sustained and efficient immunomodulation in cartilage repair scaffolds.

2.6. Design considerations for osteochondral applications

The two tissue compartments of an osteochondral defect, articular cartilage and subchondral bone, have different mechanical properties, biochemical composition and biological needs. This complexity has driven the development of

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multiphase scaffolds with spatially graded properties, including region-specific mechanical properties, biochemical signatures, and porosity profiles, for each tissue layer [39]. The inflammatory response in osteoarthritis do not respect the tissue. Thus, the immunomodulatory function must be systematically incorporated into all scaffold compartments to ensure synchronized and complete healing of the osteochondral unit and to prevent discordant remodelling between adjacent tissues.

3. Sterilization and effects on immunomodulatory properties

The choice of sterilization technique is an important, yet often under-appreciated, factor in scaffold-based immunomodulation. Table 2 indicates that each technique has its own implications for the performance of the scaffold and these implications can be of great importance. Sterilization can change the surface chemistry, mechanical properties, degradation behaviour and bioactivity and all these can influence the responses of macrophages. Toxic residues of ethylene oxide treatment can activate Toll-like receptor (TLR)4 and skew macrophages toward a pro-inflammatory M1 phenotype [40]. However, irradiation with gamma and electron beam generally damages the mechanical integrity and decreases the ability of the scaffold to promote M2 polarization. Although autoclaving is the most used method, it denatures heat sensitive biomolecules such as collagen and gelatine, thereby reducing their biological activity critical for facilitating repair. Ultraviolet irradiation is a low-cost alternative but may reduce the bioactivity of cues functionalized on the surface. The choice of method is not a trivial technical aspect, as it essentially determines whether a scaffold is supporting healing or provoking inflammation [41]. On the contrary, sterilization with supercritical carbon dioxide ($scCO_2$) maintains the physicochemical properties of the scaffold and the polarizing ability of M2 and does not generate toxic residues [42]. The results show that scCO2 is the best sterilization technique to preserve the immune-modulating function of scaffold-based systems.

4. Scaffolds for engineering macrophage polarization

Finally, the macrophage-polarizing scaffolds for osteoarthritis are conducive to the recovery of the M1/M2 balance. To achieve this, there are three complementary strategies: incorporating agents that actively direct polarization, using biomaterials with intrinsic immunomodulatory properties, or combining both to achieve a more durable and superior therapeutic benefit.

4.1. Intrinsically immunomodulatory biomaterials

Some biomaterials promote macrophages toward a healing M2 phenotype inherently without the addition of any biological agents. Chitosan stimulates mannose receptors and TLR2 and increases IL-10 and arginase-1 and suppresses TNF-α [43]. M2 polarization by high molecular weight hyaluronic acid (HMW-HA) is mediated via CD44 while low molecular weight HA (LMW-HA) induces inflammation [44]. The conserved triple helical structure of collagen favors M2 polarization via integrin and DDR signaling. This is further supported by antioxidants that decrease oxidative stress-induced M1 activation and scavenge ROS [45]. Together, these intrinsically active biomaterials

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offer a powerful drug-free platform for the design of immunomodulatory scaffolds.

4.2. Mechanical cues and topography

Mechanotransduction is a process in which the physical properties of the scaffold actively participate in shaping macrophage fate, in which mechanical cues are converted into intracellular signals that direct polarization. Topographical features such as grooves, alignment or nanoscale patterns enhance M2 polarization by clustering integrins, modulating the cytoskeleton and activating YAP/TAZ signaling [37]. Stiffness adds another dimension: macrophages cultured on substrates in the physiological stiffness window (1–100 kPa) are more likely to adopt an M2 phenotype, while stiffer substrates drive M1 polarization through NF-κB and MAPK cascades. Even cell shape is important, with micropatterned surfaces that have elongated morphologies being associated with increased expression of M2 markers. This suggests that controlling the design of scaffold physics can be used to direct immune responses predictably.

Table 2. Effects of sterilization methods on scaffold properties and immunomodulatory capacity.

Sterilization method	Principle	Effect on scaffold properties	Effect on immunomodulatory capacity
Ethylene oxide	Alkylation of microbial DNA	Toxic ethylene chlorohydrin residues may require extended aeration	Promotes M1 polarization; activates toll like receptor 4 signaling induces interleukin-1 beta and tumor necrosis factor-alpha secretion.
Gamma irradiation	DNA damage via free radicals	Polymer chain scission; reduced mechanical properties; accelerated degradation; free radical generation	Reduced M2 polarization; increased inflammatory cytokine production; altered cell adhesion
Electron beam	DNA damage via high-energy electrons	Polymer chain scission and crosslinking; altered degradation kinetics	Reduced bioactivity of incorporated growth factors may alter M2 polarization
Autoclaving (Steam)	Heat denaturation	Thermal degradation, melting, and denaturation of collagen/ gelatin	Loss of triple-helical structure; loss of integrin-binding sites; impaired M2-polarizing capacity
Supercritical carbon dioxide	Sterilization using CO_2 under supercritical conditions	Preserves scaffold structure, mechanical properties, and bioactivity; no toxic residues	Maintains M2-polarizing capacity; retains incorporated growth factors
Ultraviolet sterilization	DNA damage via UV radiation	Limited penetration; protein crosslinking; photo-oxidation	Alters scaffold bioactivity; reduces M2 polarization; induces protein damage

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4.3. Scaffolds incorporating immunemodulatory cargo

Controlled drug delivery systems including nanoparticles, microspheres, and hydrogels allow for sustained, localized release of immunomodulatory agents to maintain macrophage polarity over time [18]. Pro-M2 cytokines (IL-4, IL-10) and small anti-inflammatory molecules (dexamethasone, rapamycin, curcumin) promote regenerative phenotypes, while IL-1 receptor antagonists, TNF-α inhibitors, and cytokine-blocking antibodies suppress M1 activation [46].

Together, these approaches provide a localized, tunable approach for sustained immunomodulation and overcome the limitations of bolus injections.

4.4. Exosome-functionalized scaffolds

M2 macrophage-derived exosomes were reported to transfer miR-146a and miR-223 to recipient cells and inhibit NF-κB signaling [47]. Engineered vesicles with targeting ligands enhance uptake by macrophages. Exosomal miRNAs induce anti-inflammatory responses and inhibit the TLR/NF-κB and STAT1 pathways to promote M2 polarization. Chondroprotective miRNAs delivered by mesenchymal stem cells-derived exosomes suppress ADAMTS-5 and MMP-13, stimulate matrix synthesis, and decrease inflammation [48]. Exosomes on scaffolds facilitate prolonged local delivery, increasing persistence and efficacy over bolus injection.

4.5. Stimuli-responsive and smart scaffolds

Rather than deploying their cargo indiscriminately, “smart” scaffolds respond to the local inflammatory state. pH-sensitive systems are triggered by the acidic pH of inflamed joints, enzyme-sensitive platforms are triggered by increased MMP activity in osteoarthritis, and ROS-responsive release is triggered by oxidative stress [49]. Dual responsive systems with pH and ROS sensitivity allow improved spatiotemporal control, while thermoresponsive polymers allow temperature dependent control [50]. The result is a set of sophisticated delivery systems that localize immunomodulation to the site of inflammation, enhancing efficacy with decreased systemic exposure.

5. Nanotechnologies development for immune-modulation mediated by scaffolds

Osteoarthritis immunotherapy mediated by scaffolds has two synergistic approaches available: nanocarrier-based drug delivery systems and design of nanostructured scaffolds.

5.1. Nanocarrier systems for delivery of immunomodulatory drugs

Nanocarriers represent a versatile and powerful means of targeted delivery of immunomodulatory agents to inflamed joints. Polymeric, lipid and inorganic analogs have distinct advantages, including sustained release, great biocompatibility, antioxidant properties or imaging capabilities, depending on the formulation [51]. Intelligent scaffolds and stimuli-responsive systems release their payload in a controlled manner only in response to inflammatory stimuli such as acidic pH, oxidative stress or elevated MMP activity. Specificity is provided by the targeting ligands that direct the carriers specifically to activated macrophages or inflamed synovium. These design features allow immunomodulation to be long-lasting, site-

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specific, and responsive to the changing inflammatory environment of the joint.

5.2. Nanostructured scaffold design

Nanoscale features of scaffolds affect macrophage behavior through physical cues. The aligned electrospun nanofibers mimic the architecture of natural matrix and induce M2 polarization via cytoskeletal tension and mechanical transduction. Nanoparticle-containing scaffolds can be used to achieve sustained drug delivery or continuous reactive oxygen species scavenging while maintaining the structural integrity. Nanopatterning techniques, including nanopillar arrays and nanogrooves, regulate macrophage polarization through integrin signaling and YAP/TAZ pathways, while also improving chondrocyte function [52]. The inclusion of nanomaterials in hydrogels results in mechanically reinforced architectures that can either sequester inflammatory cytokines or induce chondrogenesis. Thus, physical cues can be as effective as biochemical cues in steering macrophages towards a repair phenotype.

6. Immunomodulation and osteochondral regeneration together

Osteochondral defects require a coordinated repair of cartilage and bone, two tissues with very different mechanical and biological properties. Since both components and their interfaces are involved in inflammation, any successful strategy should target the entire osteochondral unit, not an individual tissue [53]. This complexity can be addressed by multiphase scaffolds that integrate spatially graded designs, where each zone is designed to match the target tissue in terms of porosity, stiffness and biochemical signatures [54]. Immunomodulatory factors are distributed accordingly, promoting the polarization of M2 in the cartilage phase and modulating osteoclast activity in the bone phase.

6.1. Considerations on vascularization of osteochondral constructs

A unique paradox of chondro-osseous tissue engineering is that angiogenesis is required for bone but avascularity is required for cartilage. Hence, osteochondrosis scaffolds should stimulate angiogenesis in the bone phase and prevent the invasion of blood vessels into the cartilage phase. New angiogenesis at the chondro-osseous junction may initiate intrachondral bone formation and cartilage integrity [55]. In osteoarthritis, the inflammatory environment compounds the problem by promoting pathological angiogenesis via VEGF and other mediators, thus worsening synovitis and cartilage destruction. Strategies include the combination of anti-angiogenic agents in the cartilage phase and pro-angiogenic agents in the bone phase. Vascularization control must be paired with immunomodulation, since inflammation-triggered angiogenesis can upset the fragile balance that cartilage requires to withstand long-term degradation [56]. The current strategies for engineering macrophage-polarizing scaffolds are summarized in Figure 2 and include intrinsic biomaterials, physical and mechanical cues, and immunomodulatory cargo delivery. These complementary approaches share a common goal: rebalancing M1/M2 polarization and encouraging a pro-reparative microenvironment in the osteoarthritic joint.

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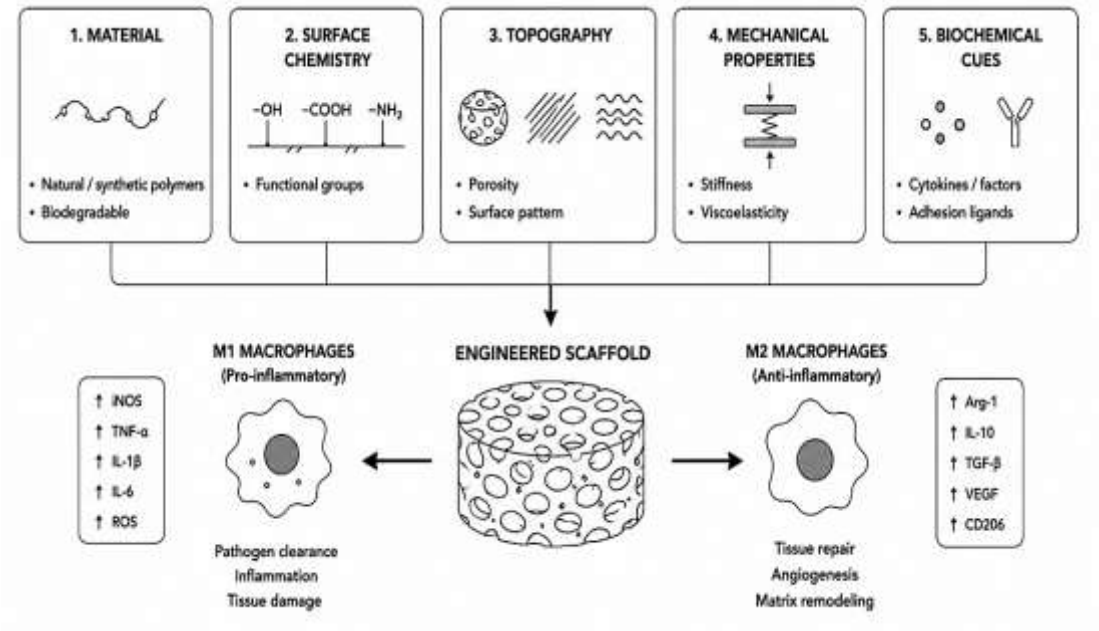


Fig. 2. Engineering strategies for macrophage-polarizing scaffolds

Results

The reviewed studies (n=56) were categorized according to the major scaffold-based strategies for macrophage polarization. Intrinsically immunomodulatory biomaterials, including chitosan, high molecular weight hyaluronic acid, and collagen, demonstrated inherent capacity to promote M2 polarization through receptor-mediated pathways (mannose receptors, CD44, integrins) and ROS scavenging. Physical cues, including substrate stiffness (1–100 kPa) and topographical features (grooves, nanoscale patterns, aligned fibers), enhanced M2 polarization through mechanotransduction pathways (RhoA/ROCK, YAP/TAZ) and cytoskeletal reorganization. Controlled delivery systems, including nanoparticles, microspheres, and hydrogels, enabled sustained release of pro-M2 cytokines (IL-4, IL-10), anti-inflammatory agents (dexamethasone, rapamycin), and cytokine inhibitors, achieving localized immunomodulation superior to bolus injections. Exosome-functionalized scaffolds transferred miR-146a and miR-223 to inhibit NF-κB signaling and promote M2 polarization, while suppressing ADAMTS-5 and MMP-13. Stimuli-responsive "smart" scaffolds (pH-sensitive, MMP-sensitive, ROS-responsive) provided spatiotemporal control of cargo release. Nanotechnology-based approaches, including nanocarriers and nanostructured surfaces (electrospun nanofibers, nanopillars, nanogrooves), enabled targeted delivery and physical immunomodulation. Multiphase scaffolds with spatially graded properties addressed osteochondral defects by promoting M2 polarization in the cartilage phase and modulating osteoclast activity in the bone phase, with controlled vascularization strategies.

Conclusion

Osteoarthritis is no longer seen as a simple wear-and-tear disease; it is now understood as a

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chronic inflammatory condition driven in large part by abnormal macrophage behavior. This shift in thinking has forced us to rethink how we design scaffolds for cartilage repair. This review focuses on macrophage-polarizing scaffolds, a new class of constructs that depart sharply from traditional tissue engineering approaches. Where older scaffolds were designed mainly to provide passive structural support, these newer systems are built to actively intervene to reshape the inflammatory environment through careful material choice, physical cues, and controlled delivery of bioactive signals. The promise is real: by reprogramming macrophages toward a reparative state, these scaffolds may be able to break the cycle of chronic inflammation and tissue loss that defines osteoarthritis. The immunopathology of osteoarthritis is a complex network of immune cells in which synovial macrophages play a dominant role. Disease progression is linked to the pathological shift to a proinflammatory M1 phenotype. This imbalance has been understood to enable development of scaffolds that drive macrophages toward an M2, regenerative state. Through the manipulation of biophysical factors, nanotechnology has enabled targeted delivery, stimulus-responsive release and the formation of nanostructured surfaces. But even with positive preclinical results, there are still a number of hurdles to overcome before these scaffolds can be used in clinical applications. Technical challenges remain in the precise control of timing and site of immune modulation and further advances in fabrication technologies are needed for scalable manufacture of complex, multiphase scaffolds.

In conclusion, macrophage-polarizing scaffolds represent a novel approach to osteoarthritis by targeting the immune dysfunction. Instead of just filling a defect or providing temporary support, they actively engage with the inflammatory environment and steer it toward repair. That shift, from passive replacement to active immune engagement, may finally open the door to something that has remained out of reach for decades: durable, biological cartilage restoration. Looking ahead, the real progress in osteoarthritis therapy will probably come not from implanting new tissue, but from creating conditions that allow the joint to heal itself. And immunomodulatory scaffolds, if the evidence holds, are well-positioned to lead that effort.

Ethical Considerations

This review required no ethical approval as it involved no original research, animal studies, or human subjects.

Funding

This manuscript is a review and did not receive any specific grant from any funding agency.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgments

The authors declare that they have no acknowledgments to make.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

H.D. conceptualized and supervised the manuscript. M.S.N., E.Y., and S.N. contributed to the literature review and drafting. All authors reviewed and approved the final manuscript.

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