Review

Cellular and Molecular Homeostatic Microenvironmental imbalances in Osteoarthritis and Rheumatoid Arthritis

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Abstract: Human movement is a complex and multifactorial process due to the interaction between the body and the environment. Movement is the result of activities of all the structures that make up a joint (i.e., ligaments, tendons, muscles, fascicles, blood vessels, nerves, etc.) and of the control actions of the nervous system on them. Therefore, many pathological conditions can affect the Neuro-Myo-Arthro-Kinetic System (NMAK). Osteoarthritis (OA) is the degenerative form of arthritis with a high incidence and a pro-longed course that affects articular and periarticular tissues such as articular cartilage, subchondral bone, and synovium, a degen-erative consequence. Instead, Rheumatoid arthritis (RA) is an immune-mediated synovial disease caused by a complex interac-tion between genetic and environmental factors. This review aims to compare Osteoarthritis (OA) and Rheumatoid Arthritis (RA) in terms of pathogenesis and microenvironment and determine the main changes in a joint microenvironment regarding immunological defense elements and bioen-ergetics which can explain the pathological development with new therapeutical opportunities.

Keywords: Osteoarthritis (OA); Rheumatoid arthritis (RA); Homeostatic imbalances; Microenviron-ment

1. Introduction

Osteoarthritis (OA) and rheumatoid arthritis (RA) are frequent forms of arthritis. Alt-hough they have different pathogenesis, both are rheumatic disorders that mainly involve the joints and show phenotypic similarities and overlapping patterns at the cellular and molecular levels (1). Despite the advantages of the overlapping features of both conditions regarding effective pharmacological or surgical therapies, the similarities also prevent re-liable discrimination of the two arthritis. Unlike fetal healing, synovial tissue may require inflammation to support and control fibroproliferation (1). Inflammation of the synovium can be seen in both pathologies (2). Patients' treatment aims to reduce pain and inflam-mation, the risk of deformities, and maintain functional abilities. Exercise (3), thermother-apy and pelotherapy (4,5), and joint protection are used in both diseases (6).

Diagnostic methods include radiography, histopathological evaluation, detection of rheumatic nodules, preclinic parameters such as rheumatoid factor and citrullinated pep-tides, and genetic assessment (1).

The dominant cell type in normal synovium is the synovial fibroblast (SF). Using SF transcriptomic data at the single-cell level, a similar transition process was identified for SF in RA and OA, with potential regulatory effects of the WNT signaling pathway, TGF-

β signaling pathway, FcεRI signaling pathway, and ERBB signaling pathways to change the functional state of the SF. These findings show that SF behaves similarly to polarized macrophages, presenting different active forms. RA is an autoimmune disease with an immune-mediated etiology, and OA has long been regarded as a degenerative cartilage disease. Still, evidence shows that inflammation also plays a critical role in its pathogenesis (2).

A living system's homeostasis is a state of constant physical, chemical, and internal conditions adjustments to an optimal functioning state that organisms should maintain. Factors regulating this include the body's temperature, pH, blood sugar levels, the concentration of nutrients and minerals, and fluid balance (7).

2. Osteoarthritis (OA)

Osteoarthritis (OA) remains one of the most prevalent chronic musculoskeletal disorders affecting synovial joint mobility, with a global prevalence of 23% among middle-aged to older people (8), affecting more than 250 million people - about 4% of the global population (9). OA affects articular and periarticular tissues, namely articular cartilage, subchondral bone, and synovium, being a cause of musculoskeletal dysfunction, especially in the elderly, as mentioned earlier (10). OA reflects the complex interplay of metabolic, epigenetic, genetic, and cellular factors leading to cartilage degradation and persistent pain (9). Synovial inflammation (synovitis) is progressive (11) and of a low-level profile. Subchondral bone erosion and osteophyte formation occur (12), ligament degeneration, joint capsule hypertrophy, and proangiogenic features leading to extracellular matrix (ECM) degradation, with structural changes in the subchondral bone, most commonly in the knee and hip joints (13).

The main symptom of OA is pain, which leads to functional limitations that consistently impact patients' quality of life (13,14). Activated synovial macrophages are involved in the pathogenesis of OA. Synovitis refers to inflammatory changes in the synovium, such as hyperplasia of the synovial mucosa, inflammatory cell infiltration, neoangiogenesis, and fibrosis. Synovitis affects about 70% of OA patients, and the severity of this condition is reflected by cartilage loss and pain (15). OA is conventionally an "attrition" disease (16).

Mechanically induced inflammation precedes cartilage degeneration. Aging, obesity, sex, chronic systemic illness, genetics, and injury are known risk factors. The cause starts from minimal mechanical factors, inflammation, and metabolic disturbances, which may interact, leading to poor curative effects for most treatments, except for end-stage joint replacement. Imaging techniques have revealed microstructural changes in subchondral bone, including loss of early-stage bone, late-stage bone sclerosis, and histopathological changes caused by subchondral bone cysts and osteophyte formation (10). These changes are induced by biological processes involving coupling and uncoupling interactions between osteocytes, osteoblasts (OB), osteoclasts (OC), endothelial cells (EC), and sensory neurons in the subchondral bone microenvironment. In particular, bone remodeling rates are altered during the development of OA due to spontaneous activation or inactivation of osteoclastic resorption activity. Activation of bone resorption may be evident in the subchondral bone microenvironment in early-stage OA, while late-stage OA is characterized by the inactivation of bone resorption activity and a derailment toward activation of bone formation activity. Subchondral bone and cartilage form a functional complex (bone-cartilage unit) involved in the pathophysiology of OA at the biochemical and mechanical levels (10). For most patients, osteoarthritis is multifactorial, reflecting aging, genetic predisposition, occupation, trauma, and obesity. Evaluation of former elite athletes who performed high-impact, high-joint-stress activities had an increased risk of hip and knee osteoarthritis compared with age-matched controls (17).

Neuroimmunity enables detection and response to environmental hazards and cross-talk involving dendritic cells, neutrophils, macrophages, mast cells, and T cells. Pain is vital for maintaining and restoring tissue homeostasis. After the pro-inflammatory phase,

local tissue repair and restoration of homeostasis occur during the resolution phase, in which adequate release of anti-inflammatory mediators is critical. In OA, the pro-inflammatory phase is prolonged, and the repair phase of inflammation is missing, leading to inflammatory pain (18).

3. Rheumatoid Arthritis (RA)

Rheumatoid Arthritis (RA), unlike OA, is a progressive autoimmune joint disease characterized by pronounced inflammation, usually bilaterally, with systemic features, such as fatigue or fever, of still incompletely known etiology (19). Patients with RA are generally younger than those who develop OA, with prevalence in the 20s and 30s, and the incidence peaks at 35 to 50 years, being higher in women (3.6%) compared to men (1.7%) (20). RA affects approximately 0.2–1% of the global population, and 80% of affected patients are women (21). The age of onset differs in different stages, but the most common occurs around the age of 50, with a disability rate of 61.3%, due to the destruction of the joint cartilage, bone, and joint capsule, which is why it is called "cancer that never dies" (22).

RA is also a severe erosive, destructive chronic inflammatory disease affecting almost 1% of the population (23). RA is characterized by progressive and irreversible joint damage resulting from sustained synovitis. Patients with RA present bilaterally pain, swelling, and stiffness in multiple joints (24). Patients frequently develop circulating antibodies to citrullinated peptides (anti-CCC) before disease onset, known as preclinical RA. In the synovial tissue of patients with established RA, anti-CCP antibodies are produced, and citrullinated proteins are present (25).

RA mainly involves the small joints of the limbs and results in painful swelling, stiffness, and even deformity of the joints, as well as cardiovascular, interstitial lung, connective tissue, and other systemic damage. (22). Large epidemiological studies have identified smoking, unhealthy diet, and adiposity, as well as low education and socioeconomic status, as factors that increase the incidence of RA (26). Smoking, obesity, and poor physical activity are also associated with worse treatment outcomes. Low to moderate alcohol consumption (3.5–15.2 g/day) is a protective factor in RA, as in some neurological disorders, for example (27), and have a reduced risk of RA compared with participants who drink less than 3.5 g of alcohol per day. Some components of daily foods can be considered a supplement, namely spices such as curcumin, cinnamon, garlic, and saffron, with multiple anti-inflammatory and antioxidant properties. Exposure to tobacco smoke is the leading known environmental risk factor for RA development and appears to account for 20% of all RA cases and 35% of anti-citrulline antibody (ACPA) positive RA cases. Smoking leads to lung disease and periodontitis and, thus, chronically increased inflammatory activity. Moreover, nicotine can drive autoimmunity through several pathways. There is little doubt about the beneficial effects of regular physical activity on factors such as quality of life, cardiovascular fitness, and muscle strength in patients with RA. Therefore, EULAR has made recommendations for regular exercise (28).

Most evidence, derived from genetics, tissue analyses, models, and clinical studies, points to an immune-mediated etiology associated with stromal tissue dysregulation that propagates chronic inflammation and joint destruction. A pre-RA phase lasting months to years can be characterized by circulating autoantibodies, increased concentration and range of inflammatory cytokines and chemokines, and altered metabolism. The clinical onset of the disease includes synovitis and systemic comorbidities affecting the vascular system, metabolism, and bone. Genetic factors have a role in RA's risk, severity, and progression. Monozygotic twins have RA about 12%–15% of the time, compared with 1% for the general population and about 2%–5% for fraternal twins or other first-degree relatives. This relatively low concordance involves many other factors, including the environment and the microbiome in pathogenesis. The most important genetic risk allele for RA resides in the major histocompatibility (MHC) class II locus, accounting for approximately 40% of the genetic influence. The odds ratio of developing RA in individuals with HLA-DR4

MHC class II alleles is approximately 5:1. RA has appropriately considered an immune-mediated disease with a strong genetic influence that may involve the interface between external forces and the immune system, manifested mainly at the level of mucous surfaces. Three sites were primarily associated with lung, oral mucosa, and gastrointestinal tract RA.

While the precise mechanisms that increase risk are not fully understood for each, local tissue stress likely leads to post-translational modification of peptides, with subsequent antibody formation as a common mechanism. The presence of citrullinated peptides in the lungs or other mucosa could thus represent the "original sin" in a pathway that ultimately leads to inflammatory joint diseases. ACPA and other antibody systems are detected years or perhaps even decades before clinical disease is evident. Once inside the joint in an established condition, autoantibodies can bind antigens, fix complement, release chemotactic fragments, and initiate a cascade of events that activate other resident cells, recruit new innate and adaptive immune cells, and promote stromal cell activation. These, in turn, can produce additional cytokines and chemokines to create a positive feedback loop and, ultimately, a self-perpetuating process with inadequate negative regulators needed for termination. The intimal synovial lining, which forms the surface of the synovium and contains macrophage- and fibroblast-like synoviocytes (FLS), is not an effective barrier because there are no tight junctions or an organized basement membrane. Once in the joint, the antibodies can be displayed on the cartilage to promote complement fixation (29).

4. Homeostatic imbalances

4.1. Vascular homeostatic imbalances in Rheumatoid Arthritis and Osteoarthritis.

Adult articular cartilage is a specialized avascular joint tissue consisting of the extracellular matrix (ECM), proteoglycans, chondrocytes, collagen and non-collagen proteins, and water. It receives nutrients and oxygen by diffusion from the dynamic synovial fluid and subchondral bone flow. Articular cartilage's specific function is to provide a smooth, lubricated surface for the joint and facilitate load transmission with a low friction coefficient (30). Once adult articular cartilage is damaged, its regeneration and repair are limited because of its hypovascularity (31). However, the avascularity of cartilage tissue has allowed the establishment of time-conserved mechanisms by which chondrocytes can survive under such conditions (32).

Synovium is the crucial tissue in which pathogenic events develop in OA and RA. Molecules in the extracellular matrix ECM provide environmental signals that determine programmed cellular behavior. Stromal cells, extracellular matrix (ECM) molecules, and other tissue-resident cells comprise the synovial tissue microenvironment. The composition of stromal cells is heterogeneous and includes fibroblasts, blood, lymphatic endothelial cells, and epithelial cells. The synovial fibroblasts and synovial macrophages are the primary stromal cells in the synovium. The synovium is highly innervated and vascularized (33).

Pathological remodeling processes in OA and RA are associated with angiogenesis (34), nerve growth, and inhibition of osteoclast activity. Osteogenesis and angiogenesis are coupled through H-type vessels and multiple cytokines in bone metabolism. A positive feedback loop was revealed between the functions of mesenchymal stem cells and H-type vessels. Angiogenesis is another homeostatic physiological process involved in endochondral bone formation, knowing that initially, the hyaline cartilage is non-vascularized with resistance to vessel formation, suggesting that vessels may be responsible for cartilage digestion. Hypertrophic chondrocytes are a major Vascular Endothelial Growth Factor (VEGF) source, which links cartilage resorption, ossification, and angiogenesis. Osteoblast-derived VEGF can recruit osteoclasts and stimulate osteogenesis and angiogenesis (9).

Interactions between vascular cells and surrounding tissues involve paracrine or juxtacrine signaling, also called "angiocrine signaling". Angiocrine signals involve growth

factors, extracellular matrix components, secreted signaling molecules such as cytokines and chemokines, and gaseous, physical, or cell-cell communication through cell surface molecules. The central player in the invasion of blood vessels in bone tissue is hypoxia, where hypoxia-inducible factors (HIFs) signal the oxygen level. While in hypoxia, due to limiting oxygen levels for hydroxylation, HIF1-α subunits are stabilized and activate downstream signaling pathways, including VEGF signaling (35).

VEGF signaling from avascular regions, which have high levels of VEGF receptors, recruits ECs and causes blood vessel growth. VEGF signaling plays a central role in coupling angiogenesis and osteogenesis through its effect on endothelial cells and by influencing chondrocytes, osteoblasts, and osteoclasts. Wnt5a is a secreted glycoprotein that mediates the β-catenin signaling pathway, a central osteogenesis regulator. VEGF overexpression conditions lead to β-catenin stabilization and excessive bone ossification, indicating antagonism between angiogenesis and bone formation via Wnt signaling (35). In addition, VEGF activates the phosphatidylinositol-3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways (ERK1 and ERK2). In addition, PI3K activates serine/threonine kinase (AKT), and AKT activates rapamycin-associated protein FKBP12, mTOR, and RAFT (FRAP), which induces HIF-1α expression. Under low oxygen conditions (hypoxia), PHD activity decreases, which stabilizes HIF-1α and accumulates in the cytoplasm to be phosphorylated by MAPK. Once phosphorylated, HIF-1a translocates to the nucleus and binds to HIF-1 (subunit 3) to form the HIF-1a/HIF-1 complex, complex through the HRE binds to specific DNA sequences 51TAGCGTGH31 present in the promoter regions of genes for further expression. Some of these target genes include nitric oxide synthase 2 (NOS2), vascular endothelial growth factor (VEGF), erythropoietin (EPO), some glucose transporters (GLUT1, GLUT3), insulin-like growth factor type 2 (IGF2), which potentially act to maintain chondroprotective functions caused by the harmful conditions that occur in the OA joint environment (32).

4.2. Oxygen homeostatic imbalances in Rheumatoid Arthritis and Osteoarthritis.

Without a direct blood supply, the synovial fluid is the leading supplier of chondrocytes. (36). Under healthy conditions, the oxygen concentration in articular cartilage ranges from 0.5 to 10% (32). However, conditions that reduce the oxygen supply to the joint can cause changes in the concentration of oxygen in the synovial fluid (37). For instance, due to the effects of ischemia-reperfusion syndrome and the accumulation of abnormal strains, the level of oxygen that the joint receives is lower, but chondrocytes display an adapted metabolism to this hypoxic microenvironment (38).

When the oxygen concentration decreases and the environment becomes increasingly hypoxic, HIF-1a plays a critical role in maintaining homeostasis by inducing the expression of a variety of protein-coding genes to increase the availability of oxygen and nutrients to homeostatic levels (32). Hypoxia and oxidative stress may be essential factors in the inflammatory process in arthritic joints. Hypoxia and inflammation are characteristic of RA and OA synovitis. Several previous studies have shown that synovitis in RA is characterized by severe hypoxia. A method of measuring oxygen tension (pO2) in synovial tissue directly uses an arthroscope and a combined pO2 and temperature probe and reveals severe hypoxia in inflamed synovial joints (median synovial oxygen levels of 3.2% [range 0.46 –7%]). pO2 levels in synovial tissue negatively correlate with CD3+ and CD68+ cell counts in the synovial sub-lining (39). The proliferation of synovial cells and secretion of inflammatory substances in RA leads to increased oxygen demand in the joint cavity, and synovial cells switch from phosphorylation to glycolytic pathways to maintain energy supply (22).

Articular cartilage survives in an oxygen-deprived microenvironment regulated by hypoxia-inducible factor (HIF-1a). HIF-1α is the primary transcriptional regulator of the cellular and developmental response to hypoxia (27,40). The relevance of HIF-1a in the evaluation of cartilage has increased since its participation is essential in the homeostasis of this tissue (41). Chondrocyte viability is compromised by several phenomena, such as

oxidative stress, inflammatory mediators, biochemical damage, and hypoxic conditions (32). The active site of this protein is an oxygen-dependent degradation domain (ODDD) that functions as an oxygen sensor. Under normoxia and in the presence of Fe^{2+} and 2-oxoglutarate, specific proline residues 402 and 564 are hydroxylated on the ODDD domain by oxygen-dependent prolyl hydroxylases (PHDs) to form a complex with von Hippel-Lindau factor (VHL); in turn, this complex binds to ubiquitin (Ub) and is subsequently degraded in the proteasome (32).

The oxygen consumption of the rheumatoid synovial membrane per gram of excised tissue is about 20 times that of ordinary (42). Hypoxia plays a significant role in the metabolism of articular cartilage. It induces changes in proteoglycan synthesis, expression of extracellular matrix (ECM) components, growth factors, glucose transporters, and ATP levels in chondrocytes. Since oxygen molecules are involved in forming inflammatory mediator NO, the level of inflammation is associated with oxygen tension in the articular cartilage. For example, when exposed to pro-inflammatory cytokines, NO production in the articular cartilage was significantly changed under hypoxic conditions. Incubation of cartilage explants for 72 h at low oxygen levels (1% O_2) resulted in significantly reduced NO production when exposed to 10 ng/mL IL-1α or 10 ng/mL TNF-α as compared to samples incubated in 20% oxygen. On the contrary, reoxygenation with 20% oxygen in previously hypoxic cartilage explants exposed to IL-1α or TNF-α resulted in significantly increased production of NO (43).

Under normal conditions, the oxygen concentrations in articular cartilage vary between 0.5 and 10%, with 6% oxygen in the superficial zone and less than 1% oxygen in the deep zone of the cartilage layer. Chondrocytes develop specific mechanisms to maintain normal tissue function under hypoxic environments. One of the mechanisms is by inducing increased expression of cartilage ECM components. It was found that culturing articular cartilage at a low oxygen concentration of 5% significantly increased proteoglycan and collagen synthesis compared to the culture at 20% oxygen. Moreover, hyaluronan synthesis was significantly increased after culturing articular cartilage for 12 h at 5% oxygen compared to 20% oxygen [36]. Another mechanism involves the regulation of metabolic homeostasis by mitochondria in the chondrocytes. Hence, hypoxia may serve as another treatment option for OA based on its effects on restoring the chondrocytes (43).

4.3. Homeostatic imbalances of the Synovial Fluid in Rheumatoid Arthritis and Osteoarthritis.

Synovial fluid in all joint cavities protects the articular cartilage surfaces (44) and facilitates the transport of nutrients and wastes, including proteins, water, ions, and metabolites. Synovial fluid components are derived from blood plasma. Synovial fluid also contains proteins secreted by articular cartilage and synovium (45). Synovial fluid protein concentration from healthy knee joints is about 25 mg/mL, ~1/3 of the concentration in blood plasma, and albumin makes up about 12 mg/mL (45).

The synovium consists of two layers, the intimal lining layer, and the sublining layer, with the FLS residing primarily in the former compartment. In the healthy joint, the intimal mucosa forms a thin porous barrier at the interface between the sublining and the synovial fluid space. FLS controls the composition of the extracellular matrix (ECM) and synovial fluid, thereby lubricating and nourishing cartilage surfaces. In RA, FLS have unique aggressive behaviors active in disease pathogenesis and progression. Although cytokines and growth factors are essential regulators of stromal cells, FLS in RA are not simply "passive responders" reacting to the inflammatory environment. Instead, these cells are epigenetically imprinted with an aggressively activated phenotype. FLS contributes directly to the composition of the synovial fluid, producing hyaluronic acid and other joint lubricants such as lubricin (also known as proteoglycan 4). As a result, synovial fluid nourishes the underlying articular cartilage and decreases the adhesion of cells and proteins. Synovial fluid also contains proteins, blood plasma constituents, and limited leukocytes. FLS also help shape and maintain the synovial ECM by producing matrix components (such as fibronectin, collagen, tenascin, proteoglycans, and laminin) and ECM-

degrading enzymes (such as proteases, matrix metalloproteinases (MMPs, and cathepsins) (46).

Normal human synovial fluid contains trace amounts of phospholipids and cholesterol. Arthritic synovial fluid contains increased phospholipids, cholesterol, and neutral lipids (47).

Water is a vital substance for normal function as a generator of hydro electrolytic energy stored in ATP. Extracellular water comprises one-third of the body's fluids, including the synovial fluid. It maintains an optimal viscosity level, supports transporting all vital elements, acts as a lubricant, shock absorber, and carrier for nutrients and waste products, and in thermoregulation (48).

Na+, Ca2+, and H+ levels are higher than in synovial fluid, with the extracellular pH reduced to about 6.6–6.9 (36). Sodium ions widely exist in extracellular fluids and are the most abundant cations in the human body (49), closely related to liquid osmotic pressure. The voltage-gated sodium ion channel is a highly glycosylated complex consisting of an alpha subunit and two beta subunits. There are two sodium channels in osteoblasts, namely voltage-sensitive sodium channels (Nav) and epithelial sodium channels (ENaC) (49).

As the basic anions in the human body, chloride ion plays an essential role in the electrochemical balance between the intracellular and extracellular side. It also regulates intracellular and extracellular functions through the active transport of chloride channels, which can control the physiological process by changing its channel currents, such as liquid secretion, cell volume regulation, transmembrane transport, excitatory conduction, and intracellular acidification. It is reported that various chloride channels exist in the cell membrane or organelles. For example, in osteoblasts, Clcn7 is expressed by wrinkles formed by the fusion of vesicles containing H+-ATPase, and then protons are secreted into the voids in the osteoblast (49).

It is well known that external Ca2+ and intracellular Ca2+ signaling are critical to bone homeostasis. First, the normal function of bone depends on normal serum calcium levels, while bone also plays an essential role in maintaining systemic calcium homeostasis. 99% of the calcium in the body is stored in bone, contributing to its mechanical structural properties. Therefore, bone needs enough calcium to maintain bone integrity. Moreover, intracellular Ca2+ is also an essential second messenger in bone. Intracellular Ca2+ signaling in osteoblasts, osteoclasts, chondrocytes, and nerve endings has been shown to regulate many functions, including differentiation, signal transduction and mechanical transport, permeation, and perception of painful stimuli. Therefore, fine-tuning intracellular Ca2+ levels is critical for normal bone homeostasis (49)

4.4. Homeostatic imbalances of the Bioenegetic Microenvironment in Rheumatoid Arthritis and Osteoarthritis.

Age-related gut disorders and dysbiosis contribute to tissue inflammation and oxidative stress, affecting immune responses and cellular metabolism. Dysregulation of intestinal microflora correlates with the development of osteoarthritis. Gut microorganisms produce metabolites, including short-chain fatty acids, bile acids, trimethylamine N-oxide, and liposaccharides, affecting mitochondrial function, metabolism, biogenesis, autophagy, and redox reactions in chondrocytes and bone cells to regulate joint and bone tissue homeostasis (50).

In the arthritic synovial microenvironment, excessive synoviocyte proliferation and massive infiltration of immune cells into the synovial tissue cause synovial pannus and metabolic disturbances with abnormal vascularization and inappropriate accumulation of metabolic intermediates such as lactic acid, derived from ineffective aerobic glycolysis, similar to the Warburg effect in cancer. These abnormal pathological events lead to acidification of the arthritic synovial microenvironment, causing polarization of anti-inflammatory M2 macrophages into pro-inflammatory M1 macrophages and subsequently stimulating synoviocytes to progress to invasive phenotypes (51).

Mitochondrial fitness is particularly important in RA, where bioenergetic and biosynthetic flux deviations affect T cells function. In the early stages of RA, mitochondrial deficiency (52) allows naïve T cells to lose self-tolerance, influencing fundamental choices of the immune system toward immune-mediated tissue damage. Mitochondrial abnormalities at late stages shape the response patterns of effector T cells involved in the inflammatory injury, allowing remodeling and chronic damage. T cells are remarkably adaptable to microenvironmental conditions, given their high proliferation capacity, complex differentiation patterns, and portfolio of cytokines and cytotoxic effector molecules (53).

Glucose quantification in synovial tissues showed distinctly low glucose concentrations, forcing tissue-resident cells to switch to alternative energy sources (53). In addition to abnormal energy metabolism due to mitochondrial damage, mitochondrial peptides can activate the adaptive immune response by presenting MHC molecules. In contrast, mitochondrial homeostasis imbalance induces mtDNA mutations and damage, causing peptide sequence changes that can mediate immune cell activation (22). AMPK is a key protein that senses energy changes and coordinates mitochondrial energy metabolism. AMPK can directly activate PGC-1α expression to induce mitochondrial neogenesis or catalyze the deacetylation of PGC-1α by stimulating SIRT1 signaling, which promotes mtDNA replication in mitochondria and indirectly mediates mitochondrial neogenesis. At the same time, AMPK is a potent inhibitor of ROS and can reduce mtROS production and mtDNA oxidative damage, inhibiting the inflammatory response (22).

Autophagy is a degenerative process that involves several stages of recycling essential components of cells, which enter the senescence phase. It has a prominent role in the pathogenesis as well as the homeostasis of cells involved in RA and OA. Chondrocyte health is maintained by autophagy, and dysregulation of autophagy is a major contributor to chondrocyte death. The autoimmune response to chondrocytes and synovium is a significant trigger leading to cell apoptosis and autophagy. Autophagy is a complex process by which cells break down their components and can be positively or negatively governed by various factors starting from the initiation and maturation of autophagosomes. Autophagy can be positively regulated by beclin-1, AMPK, and ULK-1, while negatively regulated by mTOR and PI3K/AKT (54). Autophagy is believed to be a survival mechanism that helps protect cells from the harmful effects of ER stress. The presence of various stress markers in the tissue of the RA joint significantly increased the chances of developing osteoarthritis. In vitro studies revealed increased autophagy levels in the ER stress response (19).

Iron is found in the synovial membrane of lesions and is known to be a catalyst for ROS production via the Fenton reaction. The degenerative process of RA development may be aided by ferroptosis related to lipid peroxidation. Synovial fluid hypotonicity causes Ca2+ entry through the TRPV4 channel, which increases ATP release and ROS generation, thereby exacerbating synovial fibroblast proliferation. ROS and reactive nitrogen species are known to be produced by RA synovial tissues and can induce mutations in critical genes. The genome maintenance protein p53, widely known as the "guardian of the genome", inhibits the proliferation of cells with damaged DNA (39).

4.5. Homeostatic imbalances of the Immunitary Microenvironment in Rheumatoid Arthritis and Osteoarthritis.

A hallmark of RA is the production of autoantibodies, including rheumatoid factors (RF), antibodies against the Fc portion of immunoglobulin G (IgG), and antibodies against modified proteins, especially citrullinated and carbamylated (ACPA and anti-CarP antibodies). The production of autoantibodies depends on the help of T cells (55). Abnormal adaptive immunity, including synovial mucosal immune responses, begins years before RA onset. The invasive synovial membrane is also known as pannus tissue. In addition, a large amount of ROS is produced by phagocytes, recruited immune cells, and proliferating synovial stromal cells in the RA synovitis microenvironment (56).

Fibroblast-like synoviocytes (FLS) are specialized mesenchymal-derived cells which release components of the extracellular matrix (ECM) and synovial fluid to lubricate and nourish cartilage surfaces, thereby maintaining joint homeostasis. FLSs in RA display a unique aggressive behavior resulting from their reduced rate of apoptosis; dysregulated proliferation, migration, and invasion; and an enhanced ability to secrete inflammatory mediators and matrix metalloproteinases (MMPs) into the synovial fluid. In addition, researchers detected constitutive overexpression of the tumor suppressor p53 and mutations of the gene encoding p53 in FLSs from RA patients (24).

Specific and non-specific leukocytes migrating into the joints interact with resident cells in the synovial tissue and each other, thereby creating synovitis. Numerous cytokines have been shown to play a pivotal role in RA, including TNF (tumor necrosis factor), IL-1 (Inter-Leukin 1), IL-6 (Interleukin 6), and IL-12. The disease mainly damages synovial membranes, cartilage, and bone but also causes systemic threats, threatening other organs and tissues. In addition, RA affects the cardiovascular system, psychological health, and the risk of developing cancer (23).

Activated macrophages can show 2 phenotypes: M1 macrophages with pro-inflammatory properties and M2 macrophages with waterproof properties (57). The induction of M2 macrophages improves the microenvironment that supports tissue repair and regeneration in inflammatory diseases such as OA. Transforming growth factor $\beta1$ (TGF-$\beta1$) has been shown to possess potent immunosuppressive and anti-inflammatory properties by regulating the ability of monocytes/macrophages to release inflammatory cytokines (13). Specifically, higher synovial macrophage expression levels of OX40L were associated with enhanced development of follicular helper T cells in the joint microenvironment, thereby contributing to the pathogenesis of RA. Furthermore, OX40L expression by synovial macrophages is required to support Tfh differentiation in joint tissues, thus providing new insights into the etiological basis of RA progression (21). Mediators of osteoimmune interactions are direct cell-cell contacts, cytokines, other chemical mediators, and extracellular vesicles 30–150 nm in diameter with a lipid bilayer. After release by exocytosis, they interact with target cells and transport intracellular components, including proteins, lipids, messenger RNA (mRNA), and microRNA (12).

Synovial tissue from early OA patients shows increased production of pro-inflammatory mediators. Toll-like receptors recognize pathogen-associated and damage-associated patterns, including extracellular matrix (ECM) degeneration and cellular stress products. Activation of Toll-like receptors induces the production of pro-inflammatory cytokines: Tumor necrosis factor-α (TNF-α), IL-1, IL-6, IL-8, matrix metalloproteinases (MMP)-1, MMP-3, and MMP-13, which degrade the structural components of cartilage extracellular matrix (15).

T cell subsets have different immune roles. Th1, Th2, Th17, and Treg interfere in bone repair and regeneration. Th17 cells, known as T cells that support osteoclastogenesis, secrete IL-17 activate osteoclast precursor cells, and inhibit osteoblast function. Conversely, Th1, Th2, and Treg inhibit osteoclastogenesis by secreting the cytokines IFN-γ, IL-4, IL-10, and CTLA-4. B cells block the effect of RANKL by synthesizing osteoprotegerin (OPG) and induce osteoclast apoptosis by secreting TGF-β (58). Regulatory T cells (Treg) are a distinct subpopulation of T cells involved in maintaining and regulating self-tolerance and homeostasis (59). Anti-inflammatory cytokines in OA refer to cytokines that can inhibit the actions of IL-1β and TNF-α and any other cytokine that mainly inhibits the cellular effects of pro-inflammatory cytokines in OA. Currently, the main anti-inflammatory cytokines in OA are IL-4, insulin-like growth factor (IGF), IL-10, and TGF-β. Intra-articular pro-inflammatory and anti-inflammatory cytokines maintain a dynamic balance following the physiological metabolism of articular cartilage. (60)

4.6. Bone and Biomechanic homeostatic imbalances in Rheumatoid Arthritis and Osteoarthritis.

The concept of biomechanics includes the assembly of the structural reaction of joint tissues to mechanical stimuli. Typically, a reduced bone density of the subchondral bone

is observed in the early stages of OA. However, at a later stage, subchondral bone sclerosis and higher bone density are seen radiologically.

Joints connected serially act as a kinematic chain. This construct allows motion and provides stability, congruency, and shock absorption. Adequate mechanical loading provides the essential stimulus to maintain physiological joint homeostasis, whereas excessive mechanical stress and unloading the joint are crucial for disease onset and progression. Over the last two decades, it has been shown that altered joint biomechanics of the knee, such as loss of cruciate ligaments, removal of menisci, posttraumatic cartilage damage, changes in bone alignments, unloading through casting and overloading through intense exercise, may cause disease initiation and progression of cartilage degradation (61).

Chondrocytes play a critical role in the production of the extracellular matrix. Chondrocyte senescence is one of the prominent cellular events (62), accelerating chondrocyte loss, underproduction of extracellular matrix, and production of proteolytic enzymes, which progressively accelerate cartilage degradation. Noxious circumstances in the OA microenvironment also induce epigenetic changes, which disrupt the transcription of genes related to cartilage anabolism, including aggrecan, collagen, nuclear factor of activated T cells (NFAT1), and Sox9 (sex-determining Y box 9 region). Moreover, it regulates catabolic processes by increasing aggrecanases, collagenases, inflammatory cytokines, and Runx2 (runt-related transcription factor 2) that increase ECM (extracellular matrix) proteolysis or calcified matrix production in chondrocytes, the development of cartilage erosion and the formation of osteophytes (50).

Normally, cartilage undergoes a remodeling process stimulated by joint movement or use. This process is altered by a combination of mechanical, cellular, and biochemical processes, resulting in abnormal cartilage repair and increased cartilage degradation. In addition, vascular invasion and subsequent calcification of nearby articular cartilage may occur, leading to decreased articular cartilage thickness and, over time, bone remodeling and cartilage damage (20).

5. Chaotic Complexity vs. Homeostasis regarding Microenvironment in Rheumatoid Arthritis and Osteoarthritis

Holism as a subsystem has unique characteristics which are not common in any other part of a unit. It is something new, emergent, created from the mutual interaction of elements (facets). The equilibrium state represents the most favorable state in which a system can survive long (63). "Health" may then be defined as the harmonious interaction of all hierarchical components, while "disease" is the result of a force that perturbs or disrupts hierarchical structure (64). Several regulatory mechanisms are continuously activated in a living being to produce homeostatic responses (65). The neocybernetic model is a balanced model of balances (or higher-order balance – figure 1), considering the environment's properties. The neocybernetic model is a map of the relevant behaviors corresponding to the observed environment. (7).
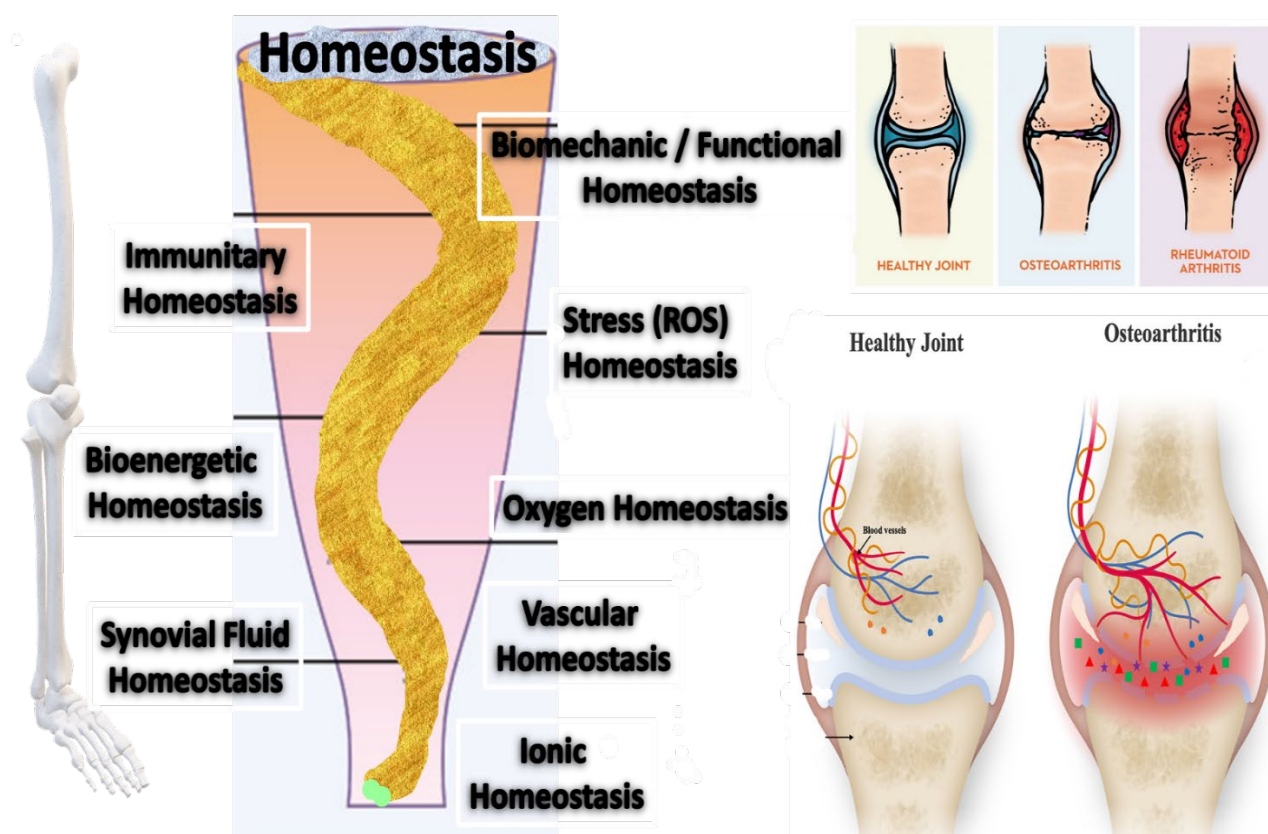
Figure 1. Hierarchical homeostasis facets of the microenvironment in healthy joints, OA and RA, starting from a basic ionic and water homeostasis level and reaching biomechanics/functional homeostasis. Angiogenesis is especially underlined.

6. Discussion

With age, the joints become subject to chronic inflammatory processes that lead to the degeneration of the articular cartilage. Cytokines are small molecules initially identified for their chemoattractant properties and central role in promoting cell mobilization but are now recognized for their many roles in recruitment, development, homeostasis, and tissue engineering (66). Medications play an essential role in the management of RA and osteoarthritis. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) decrease joint inflammation, reducing joint swelling, warmth, and pain (67). Recent single-cell studies have shown the importance of homeostasis when degeneration progresses (68). The infrapatellar fat pad (IFP) has recently been considered a source of stem cells for cartilage regeneration in osteoarthritis (OA) due to their ability to differentiate into chondrocytes. For a long time, this particular extrasynovial adipose tissue was simplistically held to be a deformable space filler endowed with shock-absorbing properties in the knee joint and a bystander in knee OA; on the contrary, it is now considered an emerging player in knee OA with a multifunctional role in knee joint homeostasis, also mediating joint pain and inflammation. This is caused by the active secretion of cytokines and adipokines, whose sex-dependent levels are usually, after adjusting for body mass index (BMI), higher in women than men (69).

OA patients experience chronic pain, swelling, deformity, and joint stiffness, leading to progressive disability and deterioration of the patient's quality of life (70). Many factors influence the risk of developing RA. The impact of environmental stressors, particularly smoking and exposure to chemicals (e.g., silicate), on genes is thought to drive the processes that induce autoimmune reactions that lead to the inflammation seen in RA (20). Long non-coding RNAs (lncRNAs) regulate various biological processes during gene transcription, being considered essential regulators in bone homeostasis because they can regulate the expression of key related enzymes and proteins (71).

Physical examination, laboratory tests, radiographs, and other assessments (e.g., functional status, disease activity) are frequently helpful in confirming a diagnosis. RA usually affects several joints, although it may affect only a few places during its initial presentation. Unlike OA, joint involvement in RA is usually symmetrical and frequently affects small distal joints (i.e., wrists, proximal interphalangeal joints, and metacarpoph-alangeal joints) (20).

The proper functioning of the joint depends on the maintenance of joint homeostasis, a dynamic balance between anabolic and catabolic processes within all joint components. The joint is a complex multi-tissue organ comprising articular cartilage, subchondral bone, synovial membrane, and, in some joints, additional intra-articular structures such as ligaments and menisci. Changes in the composition and structure of subchondral bone can affect the behavior of the overlying cartilage, suggesting the existence of physical and molecular crosstalk between the two tissues (72).

An in vitro 3D microsystem model of the osteochondral unit was developed by mounting a multi-chamber bioreactor in a microfluidic base to reconstitute the articular joint microenvironment. It is becoming clear that the synovium and the osteochondral unit, menisci, tendons, and adipose layer are essential components for developing an advanced in vitro model of the joint. However, a significant limitation is an inability to precisely target synovial cells without affecting whole-body physiology. (72). The recent advent and accessibility of both transcriptional and proteomic single-cell technologies have enabled a high-resolution understanding of tissue composition, architecture, and function by analyzing the contribution of single cells in tissues in tissues in tissues in tissues in tissues in health and disease. (73).

7. Conclusions

Living systems are autonomous and complex and exist in a state of bounded instability in which there is an ever-present dynamic balance between order and disorder at the edge of chaos. Living systems are open to their environment, interact with it, and have flows of information, energy, and physical material with it. However, they are also self-organizing, maintaining internal order that contributes to their viability. The latter ensures their survival through efficacious adaptation to changing environmental conditions. In the view of the entire homeostatic paradigm, neoangiogenesis, connected with inflammatory events, is the main pathological trigger, which can be influenced by physical therapy, thermotherapy, or pelotherapy.

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