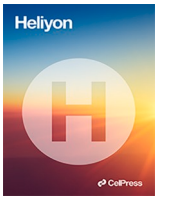
Heliyon 10 (2024) e28127

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Exosomes and exosomal miRNAs: A new avenue for the future treatment of rheumatoid arthritis

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ARTICLE INFO

Keywords:
Exosomes
Rheumatoid arthritis
Exosome mRNAs
Immunity
Mechanism of action

ABSTRACT

Rheumatoid arthritis is a chronic systemic autoimmune disease that involves mainly synovitis and joint injury and is one of the main causes of disability. The pathogenesis of rheumatoid arthritis is complicated, and the treatment cycle is long. The traditional methods of inhibiting inflammation and immunosuppression are no longer sufficient for treatment of the disease, so there is an urgent need to seek new treatments. The exocrine microenvironment is a kind of microvesicle with a lipid bilayer membrane structure that can be secreted by most cells in the body. This structure contains cell-specific proteins, lipids and nucleic acids that can transmit this information from one cell to another. To achieve cell-to-cell communication. Exocrine microRNAs can be contained in exocrine cells and can be selectively transferred to target receptor cells via exocrine signaling, thus regulating the physiological function of target cells. This article focuses on the pathological changes that occur during the development of rheumatoid arthritis and the biological regulation of exocrine and exocrine microRNAs in rheumatoid joints. Research on the roles of exocrine and exocrine microRNAs in regulating the inflammatory response, cell proliferation/apoptosis, autophagy, effects on fibroblast-like synoviocytes and immune regulation in rheumatoid arthritis was reviewed. In addition, the challenges faced by this new treatment are discussed.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by the infiltration of synovial inflammatory cells in the articular cavity and bone erosion caused by the formation of pannus [1]. RA involves mainly the small joints of the extremities and has the pathogenic characteristics of multi-joint and symmetrical joints [2]. In addition, RA can also cause extra-articular injuries, including rheumatic nodules, heart disease, kidney damage, vascular inflammation, pulmonary fibrosis, and skin and nervous system damage [3,4]. Epidemiological surveys show that the global incidence of RA is approximately 1% [5]. The exact cause of RA remains unclear, but numerous studies indicate that its development is closely linked to genetic factors [6–8]. Without prompt treatment, RA patients may experience joint deformities, restricted mobility, and in severe cases, loss of function.

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https://doi.org/10.1016/j.heliyon.2024.e28127
Received 28 August 2023; Received in revised form 12 March 2024; Accepted 12 March 2024
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These outcomes can impose significant burdens on both individuals and society [9].With the increase in the number of patients, how to diagnose and treat RA patients as soon as possible, explore new treatment strategies to control the progression of RA, and reduce or prevent the damage caused by this disease have become hot issues.

The traditional treatment for RA involves oral drugs, among which nonsteroidal anti-inflammatory drugs (NSAIDs) (including salicylic acid, diclofenac, celecoxib, and piroxicam) are used to relieve local swelling and pain, reduce periarticular inflammation and reduce patient pain [10,11]. NSAIDs can inhibit the activity of cyclooxygenase (COX) and thus reduce prostaglandin synthesis (PG) to exert anti-inflammatory and analgesic effects [12]. In addition, corticosteroids (including prednisone and methylprednisolone) also have good anti-inflammatory and analgesic effects and can bind to glucocorticoid receptors to regulate the expression of inflammatory factors and related immune genes, thereby relieving the local inflammatory response, relieving local pain and exerting immunomodulatory effects [13,14]. However, NSAIDs and corticosteroids have more side effects, including gastrointestinal reactions, ulcers, and osteonecrosis [15]. Anti-rheumatic drugs (DMARDs) are immunosuppressants that are the core drugs for the treatment of RA and can be used to prevent and slow the progressive damage of rheumatoid tissue [16]. DMARDs takes effect slowly, but they can continuously alleviate the disease activity of patients, fundamentally inhibit the progressive injury of tissues and joints, and delay or prevent the development of the disease [17]. Traditional synthetic DMARDs are indispensable classical drugs for the treatment of RA. Although the chemical structures and pharmacological mechanisms of these drugs are not the same, their clinical and pharmacological characteristics are similar, and take effect slowly. Symptoms and signs are gradually alleviated after weeks or even months of medication [18]. Representative drugs include methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), and the novel synthetic drug iguratimod (IGU), among others. Traditional DMARDs have good efficacy and a low price and can be used by a wide range of people. However, the mechanism of action of these agents is unclear, and gastrointestinal adverse reactions can easily occur [19]. Biological disease-modifying antirheumatic drugs (bDMARDs) are used to treat patients with moderate to severe rheumatoid arthritis (RA) who have shown an inadequate response or intolerance to methotrexate (MTX) and other conventional synthetic DMARDs [20]. bDMARDs include mainly tumor necrosis factor-α (TNF-α) inhibitors, interleukin-6 (IL-6) antagonists, and costimulatory factor modulators. bDMARDs are characterized by special targeting factors, but the costs are higher than those of other treatment methods, and the economic burden of patients is greater [21].

Currently, the main treatment strategy for RA is to alleviate symptoms and slow the progression of the disease; however, this approach cannot repair damaged tissue, and there have been no great breakthroughs in this treatment. Patients suffering from RA often require long-term medication, which places substantial psychological and economic strain on them [22]. With the deepening of modern medical research, many protein targets have been found to play important roles in immune regulation and inflammation and to play important roles in the prevention and treatment of RA. For example, IL-6, IL-10, IL-17, JAK and other target proteins have been found to be strongly related to the abnormal immune response in RA [23–26]. Reactive oxygen species (ROS), lipoxygenin (LXs) and other small-molecule metabolites are also important participants in the pathological progression of RA [27,28]. Exosomes are nanoscale lipid bilayer vesicles with a size range of approximately 30–150 nm that are secreted by various cells (released via fusion of intracellular multivesicular bodies with the plasma membrane) and play important roles in intercellular communication. These exosomes can carry a variety of biomolecules, including proteins, lipids, mRNAs and miRNAs, and mediate processes such as inflammation, immune regulation, cell migration, and intercellular signaling [29]. Exosomes play a vital role in the treatment of a variety of diseases, such as osteoarthritis, lumbar disc herniation, diabetes, cardiovascular disease, AIDS, chronic inflammatory diseases, and cancer [30–36]. This review provides a comprehensive overview of the latest research advancements concerning exosomes and crucial miRNAs contained within them for the treatment of RA. It explores the mechanisms underlying the actions of upregulated or downregulated exosomal miRNAs in RA, as well as the challenges anticipated in future applications.

2. Pathogenesis of RA

The pathogenesis of RA is complex and not fully understood, but several hypotheses have been proposed. Research has shown that immune abnormalities can present several months to years before the patient becomes symptomatic [37]. Environmental factors and epigenetic interactions may lead to modifications in self-antigens. For example, histones and immunoglobulin G (IgG) can undergo citrullination [38]. Due to the strong association between RA susceptibility and the HLA-DR1 and HLA-DR4 genes, the autoimmune system in the body may recognize citrullinated proteins as foreign antigens [39,40]. Antigens are captured by antigen-presenting cells (APCs), which mainly include monocytes-macrophages, dendritic cells, and B cells [41]. Among these APCs, dendritic cells have the strongest antigen-presenting ability and can induce immune responses when activated. Air pollution is also associated with the development of RA. The mechanism involved may be that reactive oxygen species (ROS) generated by the inhalation of coarse particulate pollutants can activate nuclear factor-kappaB, leading to the activation of helper T cells and the release of inflammatory factors. These inflammatory factors promote the maturation of dendritic cells, which then present self-antigens to T lymphocytes for autoimmune reactions, resulting in local joint inflammation and bone tissue erosion [42–44]. In addition, during infection, immune cells cause local inflammation and produce a large number of inflammatory cells, reactive oxygen species, and inflammatory factors (such as prostaglandins, leukotrienes, tumor necrosis factor-alpha, interleukin-2, IL-6, and interferon-gamma). Among them, ROS can activate multiple signaling pathways related to RA disease (such as nuclear factor kappaB, protein kinase B, and c-Jun N-terminal kinase), leading to joint damage [45–47]. Cyclooxygenase-2 (COX-2) is a key enzyme involved in the synthesis of prostaglandins and leukotrienes from arachidonic acid (AA). When inflammatory factors are induced, COX-2 is highly expressed, promoting the synthesis of prostaglandins and exacerbating the inflammatory response [48]. 5-Lipoxygenase (5-LOX) catalyzes the production of leukotriene B4 (LTB4) from AA, which can upregulate the levels of TNF-alpha and IL-1beta and directly activate white blood cells to release ROS and proteinases, leading to synovial damage [49,50].

In the study of the pathogenesis of RA, the gut microbiota is believed to play an important role in the development and progression of RA [51]. Dysbiosis of the gut microbiota reportedly leads to the activation of certain autoimmune pathways, such as changes in intestinal permeability; stimulation of APCs via Nod-like receptors (NLRs); and promotion of T-cell differentiation, which exacerbates mucosal inflammation [52]. Studies have shown that the composition of the gut microbiota in early RA patients is different from that in control individuals as RA patients generally a higher abundance of *Streptococcus salivarius* and a lower abundance of Bacteroides [53–55]. In addition, the release of inflammatory cytokines stimulates the activity of osteoclasts and fibroblast-like synoviocytes (FLSs), and increased osteoclast activity leads to disruption of the bone remodeling balance, resulting in erosion of the joint surface [56,57]. FLSs also release matrix metalloproteinases (MMPs), which can degrade the extracellular matrix and damage articular cartilage, exacerbating joint deformities [58]. Furthermore, FLS can stimulate the expression of receptor activator of nuclear factor-kappaB ligand (RANKL), which allows the surface proteins of osteoclasts to bind T cells, thereby increasing osteoclast activity and damaging the bone tissue of the joint [59,60]. (Fig. 1).

3. Advancements in biologic therapy for RA

Traditional oral medications for the treatment of RA often cause numerous adverse reactions or contraindications, whereas new biologics exhibit advantages such as good efficacy, high selectivity, and fewer toxic side effects [61,62]. Representative biologics include inhibitors of tumor necrosis factor-alpha (TNF-α), the interleukin (IL) class, B-cell depletion agents, and T-cell blockers. The commonly used biologics for treating RA are presented in Table 1. TNF-α is an important cytokine that leads to bone destruction and indirectly promotes the generation of osteoclasts, which participate in the RA-related bone erosion process [63]. TNF-α inhibitors were the first biologics used for the treatment of RA and are currently the most utilized and researched biologics [64]. Recent clinical studies have shown that TNF-α inhibitors increase the risk of tuberculosis [65,66]. IL-1, IL-6, and IL-17 are expressed at high levels in RA patients and are considered key cytokines in the pathogenesis of RA, leading to pathological changes and joint damage; therefore, inhibiting or reducing the binding of ILs to their receptors is an important direction in RA drug development [67–69]. Clinical studies have shown that tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, effectively improves symptoms and signs in patients who respond poorly to TNF-α inhibitors [70–72]. Immunological tests have found higher levels of B and T cells in RA patients, which promoted the production of a large number of proinflammatory factors and stimulated autoimmune responses. B-cell depletion agents work by dissolving B cells to exert therapeutic effects; however, their efficacy is not lower than that of TNF-α inhibitors, and there is an increased risk of reactivation of hepatitis B virus in patients with hepatitis B [73,74]. Although these biologics have relatively significant effects on the treatment of RA, their excessive suppression of immune function may lead to increased susceptibility to infections and even trigger certain immune tolerance issues, and they are costly. Research on new-generation antibody biologics based on structural modifications continues to attract the attention of researchers. Certolizumabpegol is a recombinant, pegylated humanized monoclonal antibody with an antigen-binding fragment that can selectively target and neutralize TNF-α [75]. Due to the absence of an Fc fragment, this antibody has improved biosafety and can be used throughout pregnancy [75]. Another innovative biologic, vobarilizumab, is a monoclonal antibody targeting IL-6R. It comprises anti-IL-6R and anti-human serum albumin domains, exhibiting high affinity for its antigen [76]. Currently, in a phase II international clinical trial, vobarilizumab has already demonstrated significant efficacy [76].

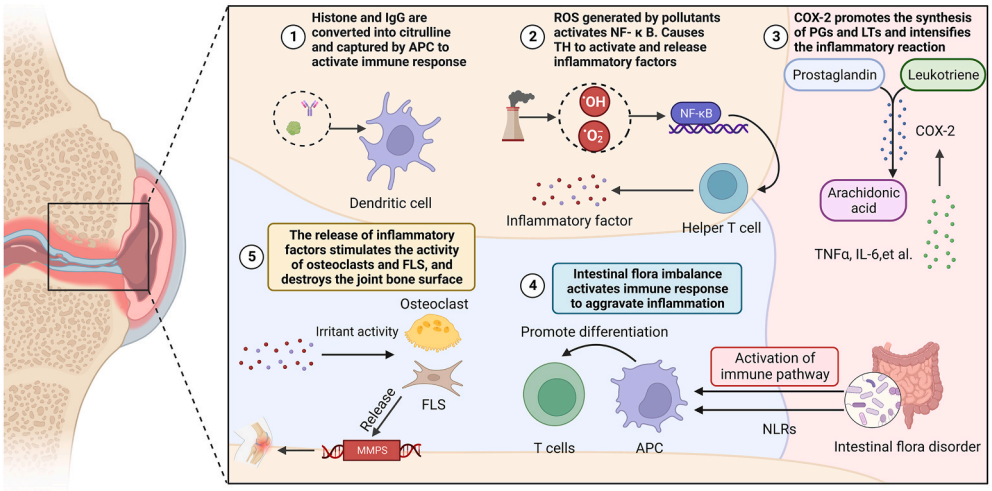

Fig. 1. Five common pathogeneses leading to the occurrence and development of rheumatoid arthritis. APC, antigen-presenting cell; ROS, reactive oxygen species; TH, helper T cell; COX-2, cyclooxygenase-2; PGs, prostaglandins; LTs, leukotrienes; NLRs, Nod-like receptors; FLS, fibroblast-like synoviocytes; MMPS, matrix metalloproteinases (created with BioRender.com).

Table 1
Biological preparation information for the treatment of RA.

Biological preparation	Molecular target	Biological function	The most common side effects	Reference
Bucillamine	Other	In the presence of Ca++, gamma globulin can be inhibited	Nonspecific mucosal and skin reactions	[77]
Actarit	Other	Inhibition of T lymphocyte activation	Abnormal digestive system and kidney function	[78]
Leflunomide	Other	Inhibits the proliferation of lymphocytes and B cells	Diarrhea, pruritus and reversible elevated liver enzymes	[79]
Tacrolimus	Calcineurin	Inhibits the release of interleukin-2 (IL-2) and completely inhibits the effect of T lymphocytes	Hypertension	[80]
Iguratimod	COX-2	Anti-inflammatory, inhibition of immunoglobulin and cytokine production, anti-bone resorption and bone formation	Gastrointestinal reaction and elevated aminotransferase	[81]
Tofacitinib citrate	JAKs	Inhibition of Janus kinase	Infectious disease	[82]
Baricitinib	JAK1,JAK2	Selective inhibition of JAK1 and JAK2	Headache, upper respiratory tract infection	[83]
Adalimumab	TNF-α	Specifically bind to TNF- α and block its interaction with TNF receptors on the surface of P55 and p75 cells	Infection, injection site reaction	[84]
Enbrel	TNF-α	Inhibition of biological activity of tumor necrosis factor	Infection	[85]
Certolizumab pegol	TNF-α	Inhibition of biological activity of tumor necrosis factor	Injection site reaction, headache, nausea	[86]
Infliximab	TNF-α	Inhibition of biological activity of tumor necrosis factor	Infection and infusion reaction	[87]
Golimumab	TNF-α	Targeting and neutralizing TNF to prevent inflammation and destruction of cartilage and bone	Upper respiratory tract infection, nasal and throat stimulation	[88]
Tocilizumab	IL-6R	Bind soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibit sIL-6R and mIL-6R-mediated signal transduction	Upper respiratory tract infection	[89]
Sarilumab	IL-6R	Inhibits the activity of IL-6R	Infection	[90]
Satralizumab	IL-6R	Inhibits the activity of IL-6R	Infection	[91]
Anakinra	IL-1	Competitive binding of type 1 and type II IL-1 receptors partially blocked the cellular response mediated by IL-1a and IL-1	Sinusitis, headache, gastrointestinal reaction	[92]
Canakinumab	IL-1	Block IL-1-mediated inflammatory response	Infection, abdominal pain and injection site reaction	[93]
Secukinumab	IL-17A	Selectively bind human interleukin-17A (IL-17A) and neutralize the biological activity of this cytokine	Nasopharyngitis, rhinitis	[94]
Xekizumab	IL-17A	It can specifically bind to cytokine IL-17A and inhibit the interaction between cytokine IL-17A and IL-17 receptor.	Injection site reaction and upper respiratory tract infection	[95]
Ustekinumab	IL-12,IL-23	Inhibiting the activation of Th1 and Th17 cells through specific binding with p40 subunit of IL-12/IL-23	Joint pain, cough, headache	[96]
Abatacept	CD80,CD86	Inhibition of T-cell activation by binding to CD80 and CD86 on antigen presenting cells	Headache, upper respiratory tract infection, nasopharyngitis and nausea	[97]
Rituximab	CD20	Specifically bind to the transmembrane antigen CD20	Infection, blood and lymphatic system abnormalities	[98]
Bevacizumab	VEGF	Inhibition of biological activity of human vascular endothelial growth factor(VEGF)	Gastrointestinal reaction, hypertension	[99]

4. Exosomes and exosomal miRNAs

4.1. Biogenesis and function of exosomes

Exosomes are all kinds of vesicles with membrane structures released by cells. Because of their different diameters and modes of occurrence, exosomes can be divided into four subgroups: exosomes (exosomes, diameter 30–150 nm), microvesicles (diameter 100–1000 nm), apoptotic bodies (apoptotic bodies, diameter 100–5000 nm) and carcinosomes (oncosomes, diameter 1–10 μm) [100]. Among them, the study of exosomes is the most common. Exosomes were first found in reticular cells more than 30 years ago and have a phospholipid bilayer structure similar to that of the cell membrane [101]. One of the most common sources of exosomes is various cell lines, including tumor cells, immune cells (such as lymphocytes and macrophages), stem cells, and epithelial cells, among others [102]. Additionally, extracellular vesicles can be found in plasma and various body fluids and have been identified in cerebrospinal fluid (CSF), serum, breast milk, saliva, urine, synovial fluid, and other body fluids [103]. Exosomes originate from multivesicular bodies (MVBs) within the endocytic system and are released into the extracellular environment after MVBs come into contact with and fuse with the plasma membrane [103]. In addition, in T cells, exosomes can be released directly from discrete regions of the plasma membrane to the extracellular space [104]. Recent studies suggest that the key regulatory molecules affecting the formation and release of MVBs/exosomes include the endosomal sorting complex required for transport (ESCRT), which is required for transport, and members of the RabGTPase family (such as Rab11, Rab27 and Rab35) [105,106]. The specific process of exosome biogenesis is as follows: Intraluminal vesicles (ILVs) are initially formed within the lumen of endosomal compartments through endosomal membrane invagination. ILVs further internalize to form MVBs via ESCRT. MVBs can subsequently follow three pathways: 1. They can move toward the plasma membrane and fuse with it, leading to the release of exosomes into the extracellular space, thus generating

exosomes; 2. MVBs can participate in the synthesis of intracellular organelles, such as melanosomes; 3. MVBs can fuse with lysosomes under the regulation of relevant genes for recycling and reutilization [107–109].

Exosomes consist of a wide range of cellular molecules, such as lipids, proteins, carbohydrates, DNA and RNA [110], and the structure of the lipid bilayer protects active molecules from extracellular degradation and smooth transmission to recipient cells to perform a variety of biological functions [111]. The exosome bilayer is rich in a variety of transmembrane proteins, such as CD9, CD63, CD37, CD81, and CD82; heat shock proteins, such as Hsp60, Hsp70, Hsp90, and ALG-2 interacting protein X (Alix); and the tumor susceptibility gene 101 protein (Tsg101). In addition, the exosome bilayer also contains specific proteins that reflect its parent cells to a large extent. These proteins include adhesion molecules, membrane transport molecules, cytoskeleton molecules, cytoplasmic enzymes, signal transduction proteins and cell-specific antigens [112–116]. Currently, studies have shown that almost all cells can transfer specific nucleic acids, proteins and lipids between cells by secreting exosomes to play an important role in intercellular communication and play a key role in the maintenance of protein and lipid homeostasis [117,118]. Exosomes may be beneficial or harmful in the process of exerting their biological effects. For example, exosomes are involved in basic physiological processes, such as neuronal communication, antigen presentation, immune response and organ development [119–122]. Exosomes also play an important role in the occurrence and development of diseases, including the progression of cancer, cardiovascular disease and inflammation [123–125]. Research indicates that exosome secretion is a naturally occurring process, and the intensity of this process also changes correspondingly when cells are in a stressed or signal-activated state [126–128]. Exosomes are stably present in almost all body fluids, and the heterogeneity in the size and cargo of extracellular vesicles reflects the cellular status and type differences of their originating cells [129]. Therefore, exosomes have extremely important clinical significance in the diagnosis and prognosis of patients and in the monitoring of disease progression (Fig. 2).

4.2. Exosomes and miRNAs

Exosome miRNAs are miRNA molecules that exist within extracellular vesicles. These miRNAs can be disseminated in body fluids through the release of extracellular vesicles, thereby influencing the gene expression and biological functions of other cells. Due to the significant regulatory role of miRNAs in gene expression, exosomal miRNAs have also been extensively investigated. In 2007, VALADI et al. [130] first described the presence of miRNAs in exosomes, which can be transferred to receptor cells to play a related role. To date, 2838 kinds of miRNAs have been found in exosome bodies, and the expression levels of these exosome miRNAs differ according to disease and physiological conditions [131,132]. The types of exosomal miRNAs mainly include cell-derived miRNAs, which originate from cells and are released into the extracellular environment through the secretion of exosomes [133]. These cell-derived miRNAs may be involved in the cellular regulation of gene expression; environment-responsive miRNAs; the release of several exosome miRNAs is regulated by environmental stimuli, and these miRNAs may play important roles in responding to environmental stress; signaling-regulatory miRNAs and exosome miRNAs are considered to be molecules that can transmit signals between cells and can influence the gene expression and function of target cells; and disease-associated miRNAs and some exosome miRNAs are associated

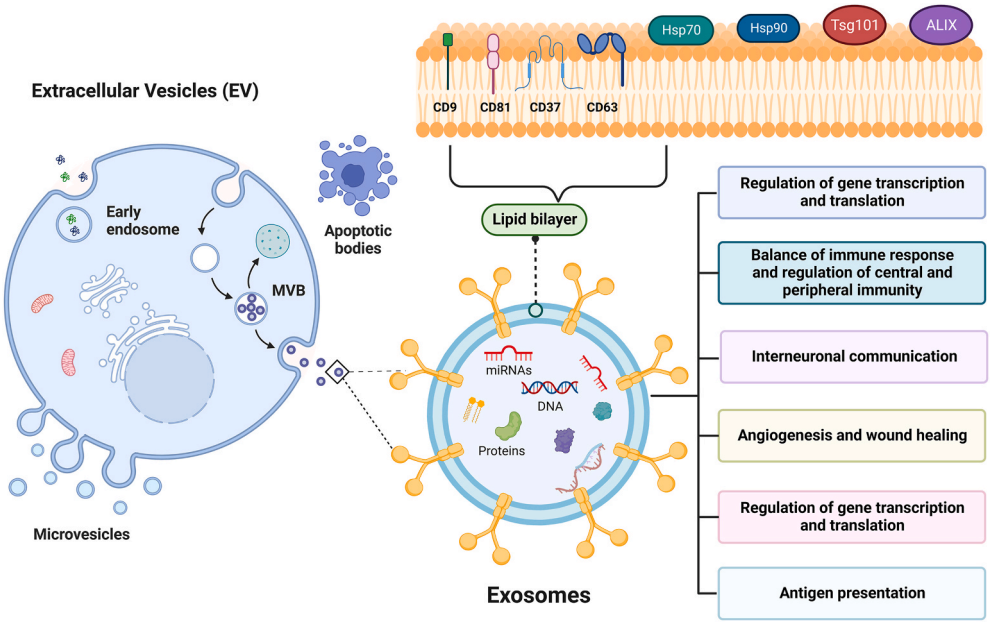

Fig. 2. Biogenesis and biological characteristics of exosomes. Exosomes are secreted and generated by extracellular vesicles with a lipid bilayer in which a variety of transmembrane proteins, such as CD9, CD63, CD37, CD81, and CD82, and heat shock proteins, such as Hsp60 and Hsp70, are present and are able to perform multiple immune functions. These genes are involved in the regulation of gene transcription and translation, homeostasis of the immune response, regulation of central and peripheral immunity, antigen presentation, etc. (created with BioRender.com).

with the occurrence and development of diseases; therefore, they are studied as potential biomarkers or therapeutic targets [134]. MicroRNAs (miRNAs) are a class of endogenous noncoding small RNA molecules ranging in length from 18 to 25 bp, that exist in eukaryotic organisms. Most mature miRNA molecules specifically bind to the 3′ untranslated region (3′-UTR) of downstream target mRNAs through base pairing, resulting in degradation and translational inhibition of the targeted mRNA. This posttranscriptional regulation of gene expression plays a role in cellular-level regulation [135,136]. In addition to their intracellular functions, miRNAs can also be secreted through exosomes, allowing them to be transferred to nearby or distant cells for gene expression regulation [137]. A single miRNA can regulate the expression of multiple mRNA molecules, and the expression of a single mRNA molecule can be regulated by multiple miRNAs, forming a complex miRNA regulatory network [138]. This multidirectional regulation enables miRNAs to have multifunctional effects on tissue microenvironment homeostasis, pathological progression, mechanistic effects, and therapeutic aspects [139]. With the advancement of molecular research, exosomal miRNAs have been actively studied in the field of rheumatoid arthritis (RA) in recent years. It has been confirmed that exosomal miRNAs play a role in immune regulation, cell proliferation and apoptosis, autophagy, inflammatory responses, and ferroptosis in RA [140–142]. The pathological progression of RA is closely associated with the imbalance of exosome-related miRNAs and their regulated mRNAs [143].

5. The function of exosomal and exosomal miRNAs in rheumatoid arthritis

Intracellular miRNAs play a crucial role in regulating gene expression. Additionally, miRNAs can be transferred through extracellular vesicles, known as exosomes, and they also play a significant role in RA. These upregulated or downregulated miRNAs have significant impacts on the development of RA. miR-155 has been demonstrated to be upregulated in the exosomes of RA patients, and it enhances inflammatory responses by promoting the expression of proinflammatory factors such as tumor necrosis factor-α (TNF-α) [144]. Upregulated miR-155 is associated with disease activity and severity in RA [145]. Upregulated miR-16 in RA promotes the invasion of fibroblast-like synoviocytes, which has negative effects on joint destruction and sustained inflammation [146]. It has been found that miR-146a is upregulated in the exosomes and synovial tissues of RA patients and participates in regulating inflammatory responses by targeting multiple components of the NF-kB signaling pathway [147]. Although miR-146a seems to play a proinflammatory role in the early stage of this disease, it may also have negative regulatory effects on immune responses [147]. In addition, studies have confirmed the upregulation of miR-203 in RA patients, which enhances the secretion of MMP-1 and IL-6 through the NF-κB pathway, thereby promoting the activated phenotype of synovial fibroblasts in RA [148]. miR-223 is considered to be a potential protective factor in RA, and its downregulation is commonly observed in RA patients and may lead to increased activation of synovial fibroblasts and exacerbation of inflammation [149]. In recent years, exosomes and exosomal miRNAs have become the research focus of RA therapy. The results of the existing studies of exosomes and exosomal miRNAs in RA were summarized and classified according to the underlying mechanisms involved, and the progress of related research on the roles of exosomes and exosomal miRNAs in extracellular matrix inflammation, cell proliferation, apoptosis, autophagy, angiogenesis, oxidative stress, immune regulation and effects on FLSs was reviewed (Fig. 3, Table 2).

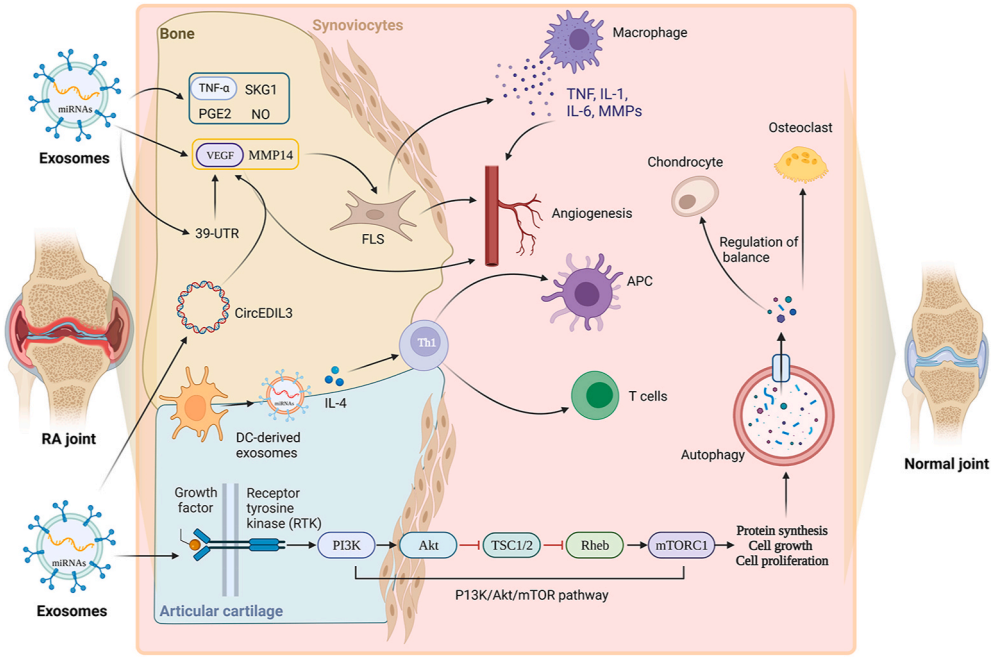

Fig. 3. Exosomes and exosomal miRNAs ameliorate RA by regulating local oxidative stress, the inflammatory response, angiogenesis, and cellular autophagy in joints.

Table 2
The role of exosomal miRNAs in RA.

Exosomes miRNAs	Donor	Regulation and control approach (Targets)	Biological function	Upward/ downward (in RA)	MiRNA types	Reference
miR-155	Serum	SHP-1,SOCS1	Targeted inhibition of SHP-1 and SOCS1 to enhance STAT3 activity	Upward	Signaling-regulatory	[144]
MiR-146a	Synovial tissue/fluid	TRAF6, IRAK1	Regulating TLR and cytokine signaling pathways to inhibit their target genes TRAF6 and IRAK1	Upward	Disease-associated	[147]
miR-150-5p	MSCs	MMP14,VEGF	The migration and invasion of synovial fibroblasts (FLS) in RA were reduced by targeting MMP14 and VEGF	Downward	Disease-associated	[150]
miR-204-5p	Plasma	Not mentioned	Inhibits the activation of FLS by targeting genes related to cell proliferation and invasion	Upward	Signaling-regulatory	[151]
miR-124a	MSCs	Not mentioned	Inhibits the proliferation and migration of FLS and promote the apoptosis of the cells during coincubation.	Downward	Signaling-regulatory	[152]
miR-125b	LGMSC	PRDM1	Significantly reduces the proportion of $CD19^{+}$, CD20 -, $CD27^{+}$, CD38+plasma cells in peripheral blood mononuclear cells	Downward	Signaling-regulatory	[153]
miR-6089	MSCs	TLR4	Inhibits lipopolysaccharide (LPS)-induced cell proliferation and activation of macrophage-like THP-1 cells, and reduce inflammatory response	Downward	Signaling-regulatory	[154]
miR-223	BMSCs	NLRP3	Targeting NLRP3 to regulate the activation of inflammatory bodies	Downward	Signaling-regulatory and environment-responsive	[155]
miR-205-5p	BMSCs	MDM2,MMP, MAPK,NF-κB	Inhibition of pro-inflammatory cytokines, MMP, MAPK and NF- κ B pathways in RA	Downward	Signaling-regulatory	[156]
miR-140-3p	HUCMSCs	SGK1	Inhibits inflammation, oxidative stress and fibrosis, inhibits the growth of FLS and reduces joint injury	Downward	Signaling-regulatory	[157]
miR-486-5p	RA-FLSs	Tob1/BMP/Smad	Activation of BMP/Smad signaling pathway and inhibition of Tob1 to promote osteoblast differentiation	Downward	Signaling-regulatory	[158]
miR-103a	Macrophage	HNF4A,JAK/ STAT3	Promote inflammation and angiogenesis	Upward	environment-responsive	[159]
miR-106b	RA-FLSs	PDK4	Inhibition of proliferation and migration of chondrocytes	Downward	Signaling-regulatory	[160]
miR-424	RA-FLSs	FOXP3	T-cell differentiation was significantly induced, in which Th17 cells increased and Treg cells decreased.	Upward	Signaling-regulatory	[161]
miR-192-5p	BMSCs	RAC2	Reduces joint destruction and inflammation	Downward	Signaling-regulatory	[162]
miR-548a-3p	Not mentioned	TLR4/NF-κB	Inhibits the proliferation and activation of pTHP-1 cells and regulate inflammatory response	Downward	Signaling-regulatory	[163]
miR-17	Not mentioned	TGFBR II	Destroys the homeostasis of Tregs to promote the pathogenesis of RA	Upward	Disease-associated	[164]
miR-203	MSCs	VEGF and its receptors	The potential involvement of regulating angiogenesis by modulating VEGF and its receptors	Upward	Disease-associated	[195]
miR-17-5p	Not mentioned	TGF-β	By targeting multiple genes associated with angiogenesis, it exerts its effects	Upward	Signaling-regulatory	[196]
miR-124	Plasma	Not mentioned	Regulating oxidative stress response to protect bone tissue	Downward	environment-responsive	[207]

5.1. Exosomes and exosomal miRNAs participate in the inflammatory response during the development of RA

During the occurrence and development of RA, inflammatory reactions are closely related to the pathological state [165]. Inflammatory reactions are caused by a variety of proinflammatory factors and oxidative stress factors in the body and lead to disorders of bone metabolism, increased osteoclast activity and bone destruction [166]. An increasing number of studies have shown that exosomes and exosomal miRNAs play important roles in the development and progression of RA [141,167]. Exosomes in the NF-κB signaling pathway regulate inflammation by affecting the polarization of macrophages [168]. On the other hand, inflammation further affects the release of cytokines and the internalization of secreted exosomes. These proinflammatory signals regulate osteoclast differentiation through receptor activators of the NF-κB pathway and affect the activity of osteoblasts through the Wnt pathway, resulting in the destruction of the metabolic balance in bone [169]. HUCMSC-exos carrying miR-140-3p improved the pathological changes observed in RA; inhibited inflammation, oxidative stress and fibrosis; and inhibited the growth of synovial fibroblasts by inhibiting the expression of SKG1 [157]. Similarly, RAC2 was found to be an important hub in the analysis of the RA molecular interaction network.

MiR-192-5p is found in high amounts in exosome bodies derived from bone marrow mesenchymal stem cells (MSCs) and targets RAC2. MiR-192-5p inhibits the inflammatory response by downregulating the release of the proinflammatory factors TNF-α, prostaglandin E2 (PGE2), and nitric oxide (NO) in RA serum and synovial tissue [162]. The expression levels of exosome-related miR-155 are increased in the blood and synovial tissues of RA patients and are associated with disease activity [144]. miR-155 can promote the production of inflammatory cytokines, such as TNF-α, by targeting inhibitory signaling molecules such as SHP-1 and SOCS1 to increase the activity of the signaling transducer and transcription activator STAT3, thereby promoting the progression of RA-related inflammation [144]. In addition, miR-146a is upregulated in synovial cells and exosomes from RA patients. miR-146a can regulate Toll-like receptor (TLR) and cytokine signaling pathways by blocking its target genes TRAF6 and IRAK1, thus limiting the inflammatory response [147].

5.2. Exosomes and exosomal miRNAs are involved in regulating cell proliferation, apoptosis and autophagy in RA

An imbalance in apoptosis regulation is an important mechanism in the pathogenesis of RA and often leads to abnormal cell proliferation or excessive death [170]. Although synovial tissue cells can induce apoptosis and inhibit cell proliferation by regulating the Fas/FasL pathway, this mechanism is obviously defective in RA [171]. Exosomes contain cell-specific factors that can mediate their selective targeting [172]. Therefore, exosomes can effectively transfer miRNAs to targets, which is a potential tool for the treatment of RA. MSC-derived exosomal miR-150-5p has been shown to be involved in T-cell maturation, so miR-150-5p is closely related to autoimmune diseases [173]. In recent studies, it has been found that the extracellular vesicle miR-150-5p is capable of downregulating the proliferation of MMP14 and VEGF cells, promoting their apoptosis [150]. Exosome bodies harboring miRNA-221 mediate inflammation and TLR4 signal transduction through fusion with chondrocytes, resulting in abnormal chondrocyte proliferation [174]. Reducing the expression of miR-221 can promote the apoptosis of FLSs and regulate the normal growth of chondrocytes [174]. In addition, studies have shown that T lymphocytes from normal humans release exosomes containing a large amount of miR-204-5p in vitro, which can be transferred to FLSs and inhibit cell proliferation [151].

Autophagy is an endogenous self-protective mechanism that occurs under stress conditions. Autophagosomes encapsulate damaged organelles, misfolded proteins and intracellular pathogens to form autophagic lysosomes, which are degraded, recycled and reused for cellular energy and function. This dynamic cycle process is called autophagy flow and plays an important role in maintaining intracellular homeostasis [175,176]. The expression of autophagy-related proteins (Beclin1 and ATG5) in the joint synovium of patients with RA was significantly increased [177]. BMSC-exos can regulate autophagy through the miRNA-146a-mediated PI3K/Akt/mTOR signaling pathway, thus inducing the proliferation and apoptosis of FLSs [178]. Another study found that MSC-exos improved the degree of inflammation in vivo, inhibited apoptosis, enhanced cell matrix synthesis, and downregulated the expression of catabolic factors in vitro [179]. In addition, MSCs-exos can also affect the autophagy level of chondrocytes by regulating the mTOR inhibition pathway [180]. Activation of serum exosome bodies modified by transcription Factor 4 (ATF4) can alleviate cartilage degeneration or injury and inflammation in RA [181]. In addition, autophagy in the knee cartilage decreased. Further studies found that ATF4-modified exosomes can promote TNF-α-induced autophagy in chondrocytes and inhibit chondrocyte apoptosis, thus protecting cartilage and delaying the progression of this disease [181,182]. A recent study found that activating autophagy can promote the release of MSC exosomes, thus enhancing the therapeutic effect of MSCs on cartilage repair in patients with arthritis [183]. Autophagy in RA is closely related to apoptosis. Autophagy can antagonize apoptosis [184]. FLS-related exosomes can induce the formation of RA autophagosomes by enhancing the expression of Beclin-1. To promote autophagy in FLSs, apoptosis is inhibited, and the proliferation ability of FLSs is increased [185]. Therefore, the results of some studies on autophagy are contradictory and may be caused by differences in cell types and exosome sources.

5.3. Exosomes and exosomal miRNAs participate in angiogenesis during RA

A significant number of FLSs are found in the synovial tissues of RA patients, and these FLSs have been demonstrated to generate various angiogenic factors, such as VEGF [186]. Angiogenesis not only provides a channel for the transport of inflammatory cytokines but also provides a source of nutritional supply for inflammatory cells [187]. Prolonged angiogenesis can lead to chronic alterations in the synovial tissue of rheumatoid arthritis (RA) patients [188,189]. Therefore, angiogenesis is considered to play a key role in the progression of RA. It is particularly important to explore the molecular factors that can inhibit angiogenesis in RA. VEGF is overexpressed in RA and promotes disease progression, and is regulated by miRNAs during angiogenesis [190]. The extracellular vesicle miR-150-5p directly inhibits VEGF upregulation by binding to its 3′UTR, reducing angiogenesis and alleviating local joint swelling [150]. In RA, synovial tissue produces a large number of cytokines that cause inflammatory cells to migrate to joints under inflammatory conditions, thus promoting the formation of new microvessels [191]. Moreover, the formation of new blood vessels exacerbates the local inflammatory response. It has been found that macrophage-derived exosomal miR-103a can target hepatocyte nuclear factor 4α (HNF4α). Macrophage-derived miR-103a can also upregulate the expression of MMP14, VEGF and CD31 in membrane tissue by inhibiting the expression of HNF4α and activating the JAK/STAT3 signaling pathway, thus promoting the inflammatory response and angiogenesis in patients with RA [159]. Similarly, in another study, macrophage-derived exosomal miR-103a in cancer patients was shown to promote tumor angiogenesis [192], suggesting that macrophage-derived exosomal miR-103a may be a new target for blocking angiogenesis. In addition, studies have confirmed that the process of angiogenesis in the synovial tissue of RA patients is related to an imbalance between autophagy and immune function [193]. Exosome CircEDIL3 from SMSCs can target VEGF through the miR-485-3p/PIAS3/STAT3 axis, inhibit the expression of downstream VEGF, and slow local inflammation and angiogenesis [194]. Therefore, exosomal CircEDIL3 derived from SMSCs may be a new therapeutic drug for RA and has great potential for the treatment of RA and other diseases. The expression of miR-203 derived from MSCs is increased in the serum and synovial fluid of RA patients,

suggesting its potential involvement in regulating angiogenesis through the modulation of VEGF and its receptors [195]. Additionally, miR-17-5p is upregulated in exosomes from RA patients and may exert its effects by targeting multiple angiogenesis-related genes, such as TGF-β [196].

5.4. Exosomes and exosomal miRNAs participate in oxidative stress in the RA process

Oxidative stress, also known as redox imbalance, is closely related to chronic inflammation [197]. In this case, reactive oxygen species (ROS) will continue to increase with time, and an increase in ROS will lead to the enhancement of oxidative stress and damage of redox signals, resulting in the destruction of cell or tissue function [198]. RA is an autoimmune disease characterized by chronic systemic inflammation. Therefore, there is a potential correlation between RA and oxidative stress. Neutrophils in the synovium in RA patients exhibit obvious expression of oxidative stress genes [199]. Mitochondrial DNA in patients with RA can directly stimulate isolated neutrophils and induce the expression of RANKL. This biological process regulates the proliferation of osteoclasts, disrupts the balance of bone formation and causes bone erosion in RA joints [200]. As an endogenous danger signal induced by oxidative stress, exosomes play an important role in the occurrence and development of chronic inflammatory osteoarthrosis [201]. It has been found that exosomal miR-140-3p from human umbilical cord mesenchymal stem cells (HUCMSCs) can inhibit the oxidative stress response in RA and reduce the release of intercellular inflammatory factors by silencing the expression of SGK1 [157]. Moreover, miR-140-3p, an exosome from HUCMSCs, promotes the apoptosis of FLSs by inhibiting SGK1 [157]. Similarly, exosomes derived from HUCMSCs have been used in previous studies to reduce inflammation and oxidative stress in mouse models of spinal cord injury [202]. Exosomes derived from HUCMSCs reportedly slow chondrocyte apoptosis and inhibit oxidative stress in inflammatory joint diseases [203]. In addition, miR-140-3p plays a positive role in oxidative stress in acute renal injury and liver injury [204,205]. Exosomes derived from HUCMSCs can be used as carriers of mi-140-3p to play a targeted role in the treatment of RA and delay its progression. MiR-146a is another miRNA found in the exosomes of RA patients. Research has shown that miR-146a may influence the oxidative stress pathway by regulating TNF receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase 1 (IRAK1) [206]. Exosome-associated miR-223 has been found to affect oxidative stress by reducing the expression of RhoB [155]. Although exosomal miR-124 has been studied more extensively in various central nervous system diseases, it has been suggested that miR-124 potentially regulates the host immune response and is associated with oxidative stress pathways in RA pathology [207].

5.5. Effects of exosomes and exosomal miRNAs on synovial fibroblasts

FLSs are involved in joint injury and inflammation during the progression of RA. It has been reported that FLS-derived exosomes may stimulate $CD4^+$ T cells by inhibiting cytokine activation-mediated cell death and caspase3 cleavage, upregulating interferon secretion and IL secretion, and enhancing the activation of the NF-kappa B pathway and AKT pathway [208]. Moreover, exosome bodies derived from FLSs can directly lead to bone degradation and destruction by secreting MMP1 [209]. Moreover, TNF-α can stimulate FLS-derived exosomes to secrete miR-221-3p. Exosome miR-221-3p can enter osteoblasts by regulating the Wnt signaling pathway and regulating bone metabolic bone formation-related genes (TCF4, Dkk2, Runx2, and ESR1) and inhibit osteoblast differentiation and maturation via molecular mechanisms, thus affecting bone repair [208]. Moreover, studies have shown that exosomes in the plasma of patients with RA also have negative effects on disease progression and can stimulate monocytes in peripheral blood to release chemokines and proinflammatory factors, such as ILs and TNF [210]. Furthermore, plasma-derived exosomal miR-92a has an antiapoptotic effect on FLSs, which further leads to articular cartilage damage and bone destruction in patients with RA [211]. In addition, the FLS-derived exosome miR-106b has been confirmed to be able to be transferred to chondrocytes to affect chondrocyte production; inhibit chondrocyte proliferation and migration; and affect the RANKL/RANK/OPG system, ultimately interfering with cartilage formation by downregulating the expression of PDK4 [160]. Studies have shown that exosomal miRNA-124a derived from MSCs can inhibit the proliferation and migration of FLSs and promote their apoptosis. Importantly, the present study found that exosomes derived from MSCs are ideal tools for loading therapeutic miRNAs, which provides an idea for the development of new therapeutic models for RA [152]. In a drug intervention study, curcumin-loaded MSC-derived exosomes were shown to promote FLS apoptosis by altering cell membrane permeability and decreasing the membrane potential [212].

5.6. Immunomodulatory effects of exosomes and exosomal miRNAs in RA

Exosomes derived from follicular-like dendritic cells (DCs) can regulate the adaptive immune response and innate immune response in humans [213]. Exosomes derived from DCs can effectively reduce the humoral immune response in a CIA model, which is an effective method for treating this disease [214]. Studies have shown that exosomes derived from DCs directly or indirectly induce immune cell subsets by releasing IL-4, which reduces the production and activity of antigen-reactive Th1 cells, thus improving the function of endogenous APCs and T cells and slowing the progression of RA [214]. To explore a new approach to the treatment of RA, Kim et al. [215] used DC-derived exosomes in a CIA mouse model after treatment with IL-10. DC-derived exosomes downregulated the expression of the heat shock protein HSP70 and inhibited the release of TNF-α and IL-1, thus inhibiting the autoimmune response and reducing the level of inflammation. In addition, exosomes derived from BMSCs can reduce the release of macrophage inflammatory factors, inhibit the autoimmune response, and mediate the activation of the NLR family pyrin domain-containing 3 (NLRP3) [216]. Moreover, exosomal miR-223 derived from MSCs has been shown to play an anti-inflammatory role and downregulate the immune response by targeting NLRP3 [155]. One study found that extracellular vesicle miRNA-125b derived from labial gland mesenchymal stem cells (LGMSCs) can significantly reduce the proportion of $CD19^+$, $CD20^-$, $CD27^+$, and $CD38^+$ plasma cells among peripheral

blood mononuclear cells by directly binding to its target gene PRDM1 [153]. It is well known that the T-cell activation-mediated immune response can accelerate the progression of RA. Therefore, eliminating T-cell activation is very important in the treatment of RA [217]. Regulatory T cells (Tregs) are a functional subset of suppressor T cells, and studies have shown that MSC-derived exosomes can enhance Treg cells and stimulate paracrine signaling in CIA mice (Fig. 4). Based on the findings of the present study, the use of MSC-derived exosomes could lead to a more effective immunosuppressive method for RA therapy [218]. In addition, studies have shown that extracellular vesicles derived from RA FLSs and macrophages can influence adaptive and innate immune responses. For instance, these extracellular vesicles may affect the activation and differentiation of lymphocytes, promote the production of inflammatory factors such as TNF-α and IL-1β, and enhance immune-related inflammatory processes.

6. Discussion

With the deepening of research on RA, new therapeutic concepts have been proposed. The study of noncoding RNAs, especially microRNAs (miRNAs), which have gradually transitioned from animal experiments to clinical trials, is of particular interest. Due to the ability of exosomes and miRNAs to serve as mediators of intercellular communication and regulate immune responses by altering the gene expression of target cells, these molecules have the potential to become novel therapeutic approaches for RA treatment. Currently, multiple studies have shown that exosomes from MSCs are ideal carriers of miRNAs and have high biological stability, good immune tolerance, and biological targeting potential. Exosomes from different sources have different biological functions. For example, in RA lesions, exosomes produced by synovial cells may induce excessive proliferation of FLSs and inhibit their apoptosis, leading to local inflammation and cartilage destruction. Exosomes can carry a variety of substances, including proteins, lipids, and nucleic acids, and transmit signals between cells through their double-layered lipid membrane structure without being cleared by the immune system, suggesting that they have great potential as biomarkers and for targeted drug delivery. Current research has focused mainly on exploring how exosomes and their miRNAs regulate inflammatory responses and affect the activity of FLSs in RA, and little attention has been given to their role in improving the immune microenvironment [219–221]. Given the diversity of miRNAs and their close relationship with the pathogenesis of RA, miRNAs carried by exosomes from various sources show great therapeutic potential as carriers of targeted therapy or as targets themselves. However, this new therapeutic concept has not yet demonstrated its full potential or advantages, as it faces many challenges, and research on the role of exosomes and their miRNAs in RA is relatively limited. Based on the progress of the current research, how to better eliminate abnormal immune inflammatory responses and repair damaged bone tissue depends on the improvement of the immune microenvironment and the balance of cell proliferation and apoptosis. In this process, screening for exosomal miRNAs with high biological activity and broad selectivity that can participate in various pathological stages of RA is crucial. Moreover, increasing the half-life of exosomes in the body and enhancing their targeting specificity are important and difficult tasks. In addition, long noncoding RNAs (lncRNAs) contained in exosomes and lncRNAs associated with exosomal miRNAs are worthy of further research and attention.

Exosomes and exosomal miRNAs have demonstrated immense potential in alleviating symptoms of RA. However, as therapeutic tools, their core issues remain unresolved. These issues can be solved by enhancing the targeting efficiency and duration of action of exosomes, establishing criteria for selecting appropriate sources of exosomes, standardizing the extraction process, and addressing relevant ethical concerns. Currently, no clinical trials have been conducted on the use of exosomes and their miRNAs in the treatment of RA. In summary, this novel therapeutic concept and strategy present challenges in the treatment of RA patients, and it is imperative to urgently address these issues.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Nos. 82,274,481 and 81874449) and the Natural Science Foundation of Shandong Province (ZR2022LZY004).

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because it does not involve any animal or human experimental research.

Data availability statement

No data were used for the research described in the article.

CRediT authorship contribution statement

Yuan Liu: Writing – review & editing, Writing – original draft. **Ping Jiang:** Funding acquisition. **Yuan Qu:** Project administration. **Chuanguo Liu:** Project administration. **Di Zhang:** Visualization, Conceptualization. **Bing Xu:** Visualization. **Qian Zhang:** Visualization, Funding acquisition.

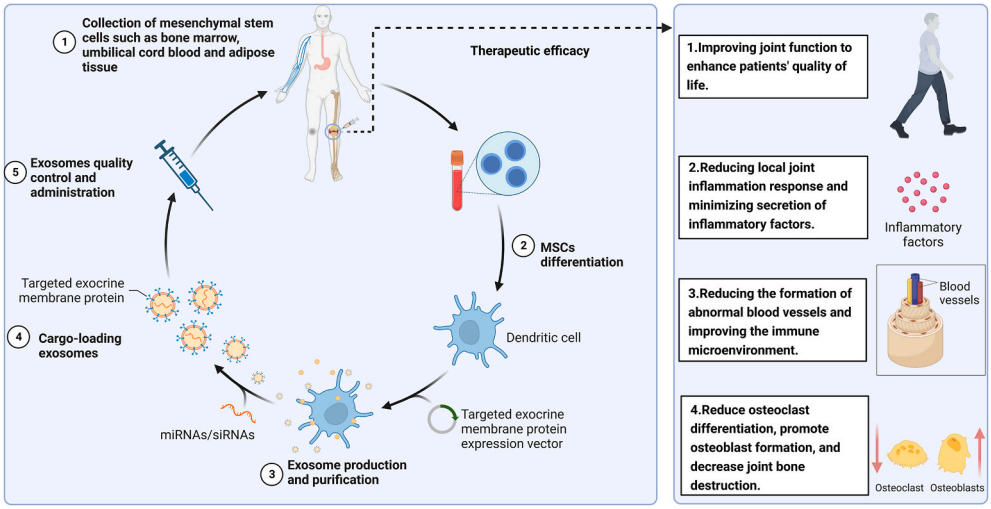

Fig. 4. Mesenchymal stem cell-derived exosomes as immunomodulatory carriers in the treatment of disease (generated with BioRender.com).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A.F. Radu, S.G. Bungau, Management of rheumatoid arthritis: an overview, Cells 10 (11) (2021) 2857, https://doi.org/10.3390/cells10112857.
[2] J.S. Smolen, D. Aletaha, I.B. McInnes, Rheumatoid arthritis [published correction appears in Lancet, 2016 Oct 22;388(10055):1984], Lancet 388 (10055) (2016) 2023–2038, https://doi.org/10.1016/S0140-6736(16)30173-8.
[3] K. Sharif, A. Sharif, F. Jumah, R. Oskouian, R.S. Tubbs, Rheumatoid arthritis in review: clinical, anatomical, cellular and molecular points of view, Clin. Anat. 31 (2) (2018) 216–223, https://doi.org/10.1002/ca.22980.
[4] D.M. Lee, M.E. Weinblatt, Rheumatoid arthritis, Lancet 358 (9285) (2001) 903–911, https://doi.org/10.1016/S0140-6736(01)06075-5.
[5] R.C.D.E. Santo, J.F. Baker, L.P. Dos Santos, et al., Changes in physical function over time in rheumatoid arthritis patients: a cohort study, PLoS One 18 (1) (2023) e0280846, https://doi.org/10.1371/journal.pone.0280846. Published 2023 Jan 23.
[6] M.H. Smith, J.R. Berman, What is rheumatoid arthritis? JAMA 327 (12) (2022) 1194, https://doi.org/10.1001/jama.2022.0786.
[7] K. Klein, S. Gay, Epigenetics in rheumatoid arthritis, Curr. Opin. Rheumatol. 27 (1) (2015) 76–82, https://doi.org/10.1097/BOR.0000000000000128.
[8] D.S. Mikhaylenko, M.V. Nemtsova, I.V. Bure, et al., Genetic polymorphisms associated with rheumatoid arthritis development and antirheumatic therapy response, Int. J. Mol. Sci. 21 (14) (2020) 4911, https://doi.org/10.3390/ijms21144911.
[9] E. Mollard, K. Michaud, Mobile apps for rheumatoid arthritis: opportunities and challenges, Rheum. Dis. Clin. N. Am. 45 (2) (2019) 197–209, https://doi.org/10.1016/j.rdc.2019.01.011.
[10] D.S. Pisetsky, Advances in the treatment of rheumatoid arthritis: costs and challenges, N. C. Med. J. 78 (5) (2017) 337–340, https://doi.org/10.18043/ncm.78.5.337.
[11] A.M. Wasserman, Diagnosis and management of rheumatoid arthritis, Am. Fam. Physician 84 (11) (2011) 1245–1252.
[12] L.D. Kumar, R. Karthik, N. Gayathri, T. Sivasudha, Advancement in contemporary diagnostic and therapeutic approaches for rheumatoid arthritis, Biomed. Pharmacother. 79 (2016) 52–61, https://doi.org/10.1016/j.biopha.2016.02.001.
[13] S. Pirmardvand Chegini, J. Varshosaz, S. Taymouri, Recent approaches for targeted drug delivery in rheumatoid arthritis diagnosis and treatment, Artif. Cells, Nanomed. Biotechnol. 46 (sup2) (2018) 502–514, https://doi.org/10.1080/21691401.2018.1460373.
[14] I. Haro, R. Sanmartí, Rheumatoid arthritis: current advances in pathogenesis, diagnosis and therapy, Curr. Top. Med. Chem. 13 (6) (2013) 697, https://doi.org/10.2174/1568026613139990091.
[15] J. Huang, X. Fu, X. Chen, Z. Li, Y. Huang, C. Liang, Promising therapeutic targets for treatment of rheumatoid arthritis, Front. Immunol. 12 (2021) 686155, https://doi.org/10.3389/fimmu.2021.686155.
[16] A.E. Koch, New concepts in the pathogenesis and treatment of rheumatoid arthritis, Curr. Opin. Rheumatol. 18 (3) (2006) 261, https://doi.org/10.1097/01.bor.0000218946.35107.36.
[17] T. Dervieux, D. Furst, D.O. Lein, et al., Pharmacogenetic and metabolite measurements are associated with clinical status in patients with rheumatoid arthritis treated with methotrexate: results of a multicentred cross sectional observational study, Ann. Rheum. Dis. 64 (8) (2005) 1180–1185, https://doi.org/10.1136/ard.2004.033399.
[18] M.K. Demoruelle, K.D. Deane, Treatment strategies in early rheumatoid arthritis and prevention of rheumatoid arthritis, Curr. Rheumatol. Rep. 14 (5) (2012) 472–480, https://doi.org/10.1007/s11926-012-0275-1.
[19] M. Yang, X. Feng, J. Ding, F. Chang, X. Chen, Nanotherapeutics relieve rheumatoid arthritis, J. Contr. Release 252 (2017) 108–124, https://doi.org/10.1016/j.jconrel.2017.02.032.
[20] J.A. Singh, Treatment guidelines in rheumatoid arthritis, Rheum. Dis. Clin. N. Am. 48 (3) (2022) 679–689, https://doi.org/10.1016/j.rdc.2022.03.005.
[21] H. Malhotra, V. Garg, G. Singh, Biomarker approach towards rheumatoid arthritis treatment, Curr. Rheumatol. Rev. 17 (2) (2021) 162–175, https://doi.org/10.2174/1573397116666201216164013.
[22] J. Dale, Advances in the management of rheumatoid arthritis, Scot. Med. J. 60 (3) (2015) 108–114, https://doi.org/10.1177/0036933015592761.
[23] M. Narazaki, T. Tanaka, T. Kishimoto, The role and therapeutic targeting of IL-6 in rheumatoid arthritis, Expet Rev. Clin. Immunol. 13 (6) (2017) 535–551, https://doi.org/10.1080/1744666X.2017.1295850.
[24] Y. Degboé, B. Rauwel, M. Baron, et al., Polarization of rheumatoid macrophages by TNF targeting through an IL-10/STAT3 mechanism, Front. Immunol. 10 (2019) 3, https://doi.org/10.3389/fimmu.2019.00003.

[25] E.K. Kim, J.E. Kwon, S.Y. Lee, et al., IL-17-mediated mitochondrial dysfunction impairs apoptosis in rheumatoid arthritis synovial fibroblasts through activation of autophagy, Cell Death Dis. 8 (1) (2017) e2565, https://doi.org/10.1038/cddis.2016.490.
[26] J. Angelini, R. Talotta, R. Roncato, et al., JAK-inhibitors for the treatment of rheumatoid arthritis: a focus on the present and an outlook on the future, Biomolecules 10 (7) (2020) 1002, https://doi.org/10.3390/biom10071002.
[27] Z. Xie, H. Hou, D. Luo, R. An, Y. Zhao, C. Qiu, ROS-dependent lipid peroxidation and reliant antioxidant ferroptosis-suppressor-protein 1 in rheumatoid arthritis: a covert clue for potential therapy, Inflammation 44 (1) (2021) 35–47, https://doi.org/10.1007/s10753-020-01338-2.
[28] R.B. Özgül Özdemir, Soysal Gündüz Ö, A.T. Özdemir, Ö. Akgül, Low levels of pro-resolving lipid mediators lipoxin-A4, resolvin-D1 and resolvin-E1 in patients with rheumatoid arthritis, Immunol. Lett. 227 (2020) 34–40, https://doi.org/10.1016/j.imlet.2020.08.006.
[29] M. Dimik, P. Abeysinghe, J. Logan, M. Mitchell, The exosome: a review of current therapeutic roles and capabilities in human reproduction, Drug Deliv Transl Res 13 (2) (2023) 473–502, https://doi.org/10.1007/s13346-022-01225-3.
[30] Z. Ni, S. Zhou, S. Li, et al., Exosomes: roles and therapeutic potential in osteoarthritis, Bone Res 8 (2020) 25, https://doi.org/10.1038/s41413-020-0100-9.
[31] L. Luo, X. Jian, H. Sun, et al., Cartilage endplate stem cells inhibit intervertebral disc degeneration by releasing exosomes to nucleus pulposus cells to activate Akt/autophagy [published correction appears in Stem Cells, 2021 Dec;39(12):E6], Stem Cell. 39 (4) (2021) 467–481, https://doi.org/10.1002/stem.3322.
[32] C. Castaño, A. Novials, M. Párrizas, Exosomes and diabetes, Diabetes Metab Res Rev 35 (3) (2019) e3107, https://doi.org/10.1002/dmrr.3107.
[33] R.J. Henning, Cardiovascular exosomes and MicroRNAs in cardiovascular physiology and pathophysiology, J Cardiovasc Transl Res 14 (2) (2021) 195–212, https://doi.org/10.1007/s12265-020-10040-5.
[34] J. Chen, C. Li, R. Li, H. Chen, D. Chen, W. Li, Exosomes in HIV infection, Curr. Opin. HIV AIDS 16 (5) (2021) 262–270, https://doi.org/10.1097/COH.0000000000000694.
[35] W.M. Wang, C. Wu, H.Z. Jin, Exosomes in chronic inflammatory skin diseases and skin tumors, Exp. Dermatol. 28 (3) (2019) 213–218, https://doi.org/10.1111/exd.13857.
[36] L. Zhang, D. Yu, Exosomes in cancer development, metastasis, and immunity, Biochim. Biophys. Acta Rev. Canc 1871 (2) (2019) 455–468, https://doi.org/10.1016/j.bbcan.2019.04.004.
[37] G.S. Firestein, I.B. McInnes, Immunopathogenesis of rheumatoid arthritis, Immunity 46 (2) (2017) 183–196, https://doi.org/10.1016/j.immuni.2017.02.006.
[38] A.M. Curran, P. Naik, J.T. Giles, E. Darrah, PAD enzymes in rheumatoid arthritis: pathogenic effectors and autoimmune targets, Nat. Rev. Rheumatol. 16 (6) (2020) 301–315, https://doi.org/10.1038/s41584-020-0409-1.
[39] C.Y. Wu, H.Y. Yang, J.H. Lai, Anti-citrullinated protein antibodies in patients with rheumatoid arthritis: biological effects and mechanisms of immunopathogenesis, Int. J. Mol. Sci. 21 (11) (2020) 4015, https://doi.org/10.3390/ijms21114015.
[40] E. Darrah, F. Andrade, Rheumatoid arthritis and citrullination, Curr. Opin. Rheumatol. 30 (1) (2018) 72–78, https://doi.org/10.1097/BOR.0000000000000452.
[41] Y. Takeuchi, K. Hirota, S. Sakaguchi, Impaired T cell receptor signaling and development of T cell-mediated autoimmune arthritis, Immunol. Rev. 294 (1) (2020) 164–176, https://doi.org/10.1111/imr.12841.
[42] G. Adami, O. Viapiana, M. Rossini, et al., Association between environmental air pollution and rheumatoid arthritis flares, Rheumatology 60 (10) (2021) 4591–4597, https://doi.org/10.1093/rheumatology/keab049.
[43] J. Sigaux, J. Biton, E. André, L. Semerano, M.C. Boissier, Air pollution as a determinant of rheumatoid arthritis, Joint Bone Spine 86 (1) (2019) 37–42, https://doi.org/10.1016/j.jbspin.2018.03.001.
[44] M. Jing, J. Yang, L. Zhang, et al., Celastrol inhibits rheumatoid arthritis through the ROS-NF-κB-NLRP3 inflammasome axis, Int. Immunopharm. 98 (2021) 107879, https://doi.org/10.1016/j.intimp.2021.107879.
[45] G. Nygaard, G.S. Firestein, Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes, Nat. Rev. Rheumatol. 16 (6) (2020) 316–333, https://doi.org/10.1038/s41584-020-0413-5.
[46] S. Singh, T.G. Singh, K. Mahajan, S. Dhiman, Medicinal plants used against various inflammatory biomarkers for the management of rheumatoid arthritis, J. Pharm. Pharmacol. 72 (10) (2020) 1306–1327, https://doi.org/10.1111/jphp.13326.
[47] Z. Hong, X. Zhang, T. Zhang, et al., The ROS/GRK2/HIF-1α/NLRP3 pathway mediates pyroptosis of fibroblast-like synoviocytes and the regulation of monomer derivatives of paeoniflorin, Oxid. Med. Cell. Longev. 2022 (2022) 4566851, https://doi.org/10.1155/2022/4566851.
[48] H.W. Fan, G.Y. Liu, C.F. Zhao, X.F. Li, X.Y. Yang, Differential expression of COX-2 in osteoarthritis and rheumatoid arthritis, Genet. Mol. Res. 14 (4) (2015) 12872–12879, https://doi.org/10.4238/2015.October.21.7.
[49] H.C. Lin, T.H. Lin, M.Y. Wu, et al., 5-Lipoxygenase inhibitors attenuate TNF-α-induced inflammation in human synovial fibroblasts, PLoS One 9 (9) (2014) e107890, https://doi.org/10.1371/journal.pone.0107890.
[50] P. Rzodkiewicz, E. Gąsińska, M. Gajewski, M. Bujalska-Zadrożny, D. Szukiewicz, S. Maśliński, Esculetin reduces leukotriene B4 level in plasma of rats with adjuvant-induced arthritis, Reumatologia 54 (4) (2016) 161–164, https://doi.org/10.5114/reum.2016.62469.
[51] F. De Luca, Y. Shoenfeld, The microbiome in autoimmune diseases, Clin. Exp. Immunol. 195 (1) (2019) 74–85, https://doi.org/10.1111/cei.13158.
[52] G.L.V. de Oliveira, A.Z. Leite, B.S. Higuchi, M.I. Gonzaga, V.S. Mariano, Intestinal dysbiosis and probiotic applications in autoimmune diseases, Immunology 152 (1) (2017) 1–12, https://doi.org/10.1111/imm.12765.
[53] G. Horta-Baas, M.D.S. Romero-Figueroa, A.J. Montiel-Jarquín, M.L. Pizano-Zárate, J. García-Mena, N. Ramírez-Durán, Intestinal dysbiosis and rheumatoid arthritis: a link between gut microbiota and the pathogenesis of rheumatoid arthritis, J Immunol Res 2017 (2017) 4835189, https://doi.org/10.1155/2017/4835189.
[54] M. Attur, J.U. Scher, S.B. Abramson, M. Attur, Role of intestinal dysbiosis and nutrition in rheumatoid arthritis, Cells 11 (15) (2022) 2436, https://doi.org/10.3390/cells11152436.
[55] D. Yu, J. Du, X. Pu, et al., The gut microbiome and metabolites are altered and interrelated in patients with rheumatoid arthritis, Front. Cell. Infect. Microbiol. 11 (2022) 763507, https://doi.org/10.3389/fcimb.2021.763507.
[56] Z. Wu, D. Ma, H. Yang, et al., Fibroblast-like synoviocytes in rheumatoid arthritis: surface markers and phenotypes, Int. Immunopharm. 93 (2021) 107392, https://doi.org/10.1016/j.intimp.2021.107392.
[57] N. Komatsu, H. Takayanagi, Mechanisms of joint destruction in rheumatoid arthritis - immune cell-fibroblast-bone interactions, Nat. Rev. Rheumatol. 18 (7) (2022) 415–429, https://doi.org/10.1038/s41584-022-00793-5.
[58] Alamgeer, U.H. Hasan, A.M. Uttra, et al., Phytochemicals targeting matrix metalloproteinases regulating tissue degradation in inflammation and rheumatoid arthritis, Phytomedicine 66 (2020) 153134, https://doi.org/10.1016/j.phymed.2019.153134.
[59] K. Maeda, K. Yoshida, T. Nishizawa, et al., Inflammation and bone metabolism in rheumatoid arthritis: molecular mechanisms of joint destruction and pharmacological treatments, Int. J. Mol. Sci. 23 (5) (2022) 2871, https://doi.org/10.3390/ijms23052871.
[60] S. anaka, Y. Tanaka, RANKL as a therapeutic target of rheumatoid arthritis [published correction appears in J Bone Miner Metab, 2020 Dec 17;:], J. Bone Miner. Metabol. 39 (1) (2021) 106–112, https://doi.org/10.1007/s00774-020-01159-1.
[61] M.F. Bakker, J.W. Jacobs, P.M. Welsing, et al., Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial, Ann. Intern. Med. 156 (5) (2012) 329–339, https://doi.org/10.7326/0003-4819-156-5-201203060-00004.
[62] T. Pincus, I. Castrejon, Y. Yazici, Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis, Ann. Intern. Med. 157 (4) (2012) 299–300, https://doi.org/10.7326/0003-4819-157-4-201208210-00018.
[63] H. Radner, D. Aletaha, Anti-TNF in rheumatoid arthritis: an overview, Wien Med. Wochenschr. 165 (1–2) (2015) 3–9, https://doi.org/10.1007/s10354-015-0344-y.
[64] O. Pala, A. Diaz, B.B. Blomberg, D. Frasca, B lymphocytes in rheumatoid arthritis and the effects of anti-TNF-α agents on B lymphocytes: a review of the literature, Clin. Therapeut. 40 (6) (2018) 1034–1045, https://doi.org/10.1016/j.clinthera.2018.04.016.
[65] Y. Wang, W. Gao, Effects of TNF-α on autophagy of rheumatoid arthritis fibroblast-like synoviocytes and regulation of the NF-κB signaling pathway, Immunobiology 226 (2) (2021) 152059, https://doi.org/10.1016/j.imbio.2021.152059.

[66] D. Arcuri, M. Kaouache, F. Lagacé, D. Sasseville, I. Litvinov, A case-control pharmacovigilance study of TNF-alpha inhibitors and interleukin inhibitors on tuberculosis, Candida, lymphoma and suicidality using the FAERS database (2014-2020), J. Am. Acad. Dermatol. 89 (3) (2023) 619–621, https://doi.org/10.1016/j.jaad.2023.05.041.

[67] P. Ruscitti, P. Cipriani, V. Liakouli, et al., The emerging role of IL-1 inhibition in patients affected by rheumatoid arthritis and diabetes, Rev. Recent Clin. Trials 13 (3) (2018) 210–214, https://doi.org/10.2174/1574887113666180314102651.

[68] M. Narazaki, T. Tanaka, T. Kishimoto, The role and therapeutic targeting of IL-6 in rheumatoid arthritis, Expet Rev. Clin. Immunol. 13 (6) (2017) 535–551, https://doi.org/10.1080/1744666X.2017.1295850.

[69] L.S. Taams, Interleukin-17 in rheumatoid arthritis: trials and tribulations, J. Exp. Med. 217 (3) (2020) e20192048, https://doi.org/10.1084/jem.20192048.

[70] A. Shetty, R. Hanson, P. Korsten, et al., Tocilizumab in the treatment of rheumatoid arthritis and beyond, Drug Des. Dev. Ther. 8 (2014) 349–364, https://doi.org/10.2147/DDDT.S41437.

[71] Y.K. Sung, Y.H. Lee, Comparative efficacy and safety of biologic agents in patients with active rheumatoid arthritis and inadequate response to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled trials, Int. J. Clin. Pharm. Ther. 60 (1) (2022) 13–23, https://doi.org/10.5414/CP204036.

[72] I. Serio, F. Tovoli, Rheumatoid arthritis: new monoclonal antibodies, Drugs Today 54 (3) (2018) 219–230, https://doi.org/10.1358/dot.2018.54.3.2788019.

[73] K. Hofmann, A.K. Clauder, R.A. Manz, Targeting B cells and plasma cells in autoimmune diseases, Front. Immunol. 9 (2018) 835, https://doi.org/10.3389/fimmu.2018.00835.

[74] C.A. Bounia, S.C. Liossis, B cell depletion treatment decreases Th17 cells in patients with rheumatoid arthritis, Clin. Immunol. 233 (2021) 108877, https://doi.org/10.1016/j.clim.2021.108877.

[75] A. Kerschbaumer, A. Sepriano, S.A. Bergstra, et al., Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis, Ann. Rheum. Dis. 82 (1) (2023) 95–106, https://doi.org/10.1136/ard-2022-223365.

[76] A. Kerschbaumer, A. Sepriano, J.S. Smolen, et al., Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis, Ann. Rheum. Dis. 79 (6) (2020) 744–759, https://doi.org/10.1136/annrheumdis-2019-216656.

[77] A. Suda, S. Nagaoka, S. Ohono, H. Ideguchi, T. Soga, Y. Ishigatsubo, The efficacy and safety of bucillamine as a second-line DMARD in the treatment of rheumatoid arthritis: a retrospective cohort study, Mod. Rheumatol. 18 (6) (2008) 609–614, https://doi.org/10.1007/s10165-008-0103-7.

[78] M. Aso, Y. Tanaka, K. Saito, et al., Additive combination of actarit and methotrexate in the treatment of refractory rheumatoid arthritis, Mod. Rheumatol. 10 (2) (2000) 103–109, https://doi.org/10.3109/s101650050007.

[79] F. Behrens, M. Koehm, H. Burkhardt, Update 2011: leflunomide in rheumatoid arthritis - strengths and weaknesses, Curr. Opin. Rheumatol. 23 (3) (2011) 282–287, https://doi.org/10.1097/BOR.0b013e328344fddb.

[80] Y. Kaneko, Y. Kawahito, M. Kojima, et al., Efficacy and safety of tacrolimus in patients with rheumatoid arthritis - a systematic review and meta-analysis, Mod. Rheumatol. 31 (1) (2021) 61–69, https://doi.org/10.1080/14397595.2020.1719607.

[81] S. Xie, S. Li, J. Tian, F. Li, Iguratimod as a new drug for rheumatoid arthritis: current landscape [published correction appears in front pharmacol. 2020 apr 08; 11:488], Front. Pharmacol. 11 (2020) 73, https://doi.org/10.3389/fphar.2020.00073.

[82] J. Wollenhaupt, E.B. Lee, J.R. Curtis, et al., Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study, Published 2019 Apr 5, Arthritis Res. Ther. 21 (1) (2019) 89, https://doi.org/10.1186/s13075-019-1866-2.

[83] S. Assadiasl, Y. Fatahi, B. Mosharmovahed, B. Mohebbi, M.H. Nicknam, Baricitinib: from rheumatoid arthritis to COVID-19, J. Clin. Pharmacol. 61 (10) (2021) 1274–1285, https://doi.org/10.1002/jcph.1874.

[84] S. Zhao, L. Chadwick, E. Mysler, R.J. Moots, Review of biosimilar trials and data on adalimumab in rheumatoid arthritis, Curr. Rheumatol. Rep. 20 (10) (2018) 57, https://doi.org/10.1007/s11926-018-0769-6.

[85] S. Zhao, E. Mysler, R.J. Moots, Etanercept for the treatment of rheumatoid arthritis, Immunotherapy 10 (6) (2018) 433–445, https://doi.org/10.2217/imt-2017-0155.

[86] H. Kameda, K. Nishida, T. Nanki, A. Watanabe, Y. Oshima, S. Momohara, Safety and effectiveness of certolizumab pegol in Japanese patients with rheumatoid arthritis: results from a 24-week post-marketing surveillance study [published online ahead of print, 2022 jul 12], Mod. Rheumatol. (2022), https://doi.org/10.1093/mr/roac073 roac073.

[87] Y.K. Sung, S.K. Cho, D. Kim, et al., Characteristics and outcomes of rheumatoid arthritis patients who started biosimilar infliximab, Rheumatol. Int. 37 (6) (2017) 1007–1014, https://doi.org/10.1007/s00296-017-3663-z.

[88] J.A. Singh, S. Noorbaloochi, G. Singh, Golimumab for rheumatoid arthritis, Cochrane Database Syst. Rev. 1 (2010) CD008341, https://doi.org/10.1002/14651858.CD008341.

[89] L.J. Scott, Tocilizumab: a review in rheumatoid arthritis [published correction appears in drugs, 2017 Dec 19;, Drugs 77 (17) (2017) 1865–1879, https://doi.org/10.1007/s40265-017-0829-7.

[90] M.G. Raimondo, M. Biggioggero, C. Crotti, A. Becciolini, E.G. Favalli, Profile of sarilumab and its potential in the treatment of rheumatoid arthritis, Drug Des. Dev. Ther. 11 (2017) 1593–1603, https://doi.org/10.2147/DDDT.S100302.

[91] K. Kastrati, D. Aletaha, G.R. Burmester, et al., A systematic literature review informing the consensus statement on efficacy and safety of pharmacological treatment with interleukin-6 pathway inhibition with biological DMARDs in immune-mediated inflammatory diseases, RMD Open 8 (2) (2022) e002359, https://doi.org/10.1136/rmdopen-2022-002359.

[92] J. Ramírez, J.D. Cañete, Anakinra for the treatment of rheumatoid arthritis: a safety evaluation, Expet Opin. Drug Saf. 17 (7) (2018) 727–732, https://doi.org/10.1080/14740338.2018.1486819.

[93] P. Sfriso, S. Bindoli, A. Doria, E. Feist, P. Galozzi, Canakinumab for the treatment of adult-onset Still's disease, Expet Rev. Clin. Immunol. 16 (2) (2020) 129–138, https://doi.org/10.1080/1744666X.2019.1707664.

[94] M.I. Koenders, W.B. van den Berg, Secukinumab for rheumatology: development and its potential place in therapy, Drug Des. Dev. Ther. 10 (2016) 2069–2080, https://doi.org/10.2147/DDDT.S105263.

[95] I. Serio, F. Tovoli, Rheumatoid arthritis: new monoclonal antibodies, Drugs Today 54 (3) (2018) 219–230, https://doi.org/10.1358/dot.2018.54.3.2788019.

[96] M. Montepaone, E. Lubrano, A. Carboni, A. Spadaro, Profile of ustekinumab and its potential in the treatment of active psoriatic arthritis, Open Access Rheumatol 6 (2014) 7–13, https://doi.org/10.2147/OARRR.S56048.

[97] H.A. Blair, E.D. Deeks, Abatacept: a review in rheumatoid arthritis, Drugs 77 (11) (2017) 1221–1233, https://doi.org/10.1007/s40265-017-0775-4.

[98] S. Tavakolpour, S. Alesaeidi, M. Darvishi, et al., A comprehensive review of rituximab therapy in rheumatoid arthritis patients, Clin. Rheumatol. 38 (11) (2019) 2977–2994, https://doi.org/10.1007/s10067-019-04699-8.

[99] Y. Wu, G. Zhang, X. Wang, et al., Early detection of rheumatoid arthritis in rats and humans with 99mTc-3PRGD2 scintigraphy: imaging synovial neoangiogenesis, Oncotarget 8 (4) (2017) 5753–5760, https://doi.org/10.18632/oncotarget.13953.

[100] Y. Matsuzaka, R. Yashiro, Extracellular vesicles as novel drug-delivery systems through intracellular communications, Membranes 12 (6) (2022) 550, https://doi.org/10.3390/membranes12060550.

[101] S. Gay, R.E. Gay, Cellular basis and oncogene expression of rheumatoid joint destruction, Rheumatol. Int. 9 (3–5) (1989) 105–113, https://doi.org/10.1007/BF00271866.

[102] S. Li, D. Lv, H. Yang, Y. Lu, Y. Jia, A review on the current literature regarding the value of exosome miRNAs in various diseases, Ann. Med. 55 (1) (2023) 2232993, https://doi.org/10.1080/07853890.2023.2232993.

[103] W. Whitford, P. Guterstam, Exosome manufacturing status, Future Med. Chem. 11 (10) (2019) 1225–1236, https://doi.org/10.4155/fmc-2018-0417.

[104] C. Noonin, V. Thongboonkerd, Exosome-inflammasome crosstalk and their roles in inflammatory responses, Theranostics 11 (9) (2021) 4436–4451, https://doi.org/10.7150/thno.54004.

[105] Y. Ju, H. Bai, L. Ren, L. Zhang, The role of exosome and the ESCRT pathway on enveloped virus infection, Int. J. Mol. Sci. 22 (16) (2021) 9060, https://doi.org/10.3390/ijms22169060.
[106] D. Wei, W. Zhan, Y. Gao, et al., RAB31 marks and controls an ESCRT-independent exosome pathway, Cell Res. 31 (2) (2021) 157–177, https://doi.org/10.1038/s41422-020-00409-1.
[107] S.P. Li, Z.X. Lin, X.Y. Jiang, X.Y. Yu, Exosomal cargo-loading and synthetic exosome-mimics as potential therapeutic tools, Acta Pharmacol. Sin. 39 (4) (2018) 542–551, https://doi.org/10.1038/aps.2017.178.
[108] D.M. Pegtel, S.J. Gould, Exosomes. Annu Rev Biochem. 88 (2019) 487–514, https://doi.org/10.1146/annurev-biochem-013118-111902.
[109] G.O. Skryabin, A.V. Komelkov, E.E. Savelyeva, E.M. Tchevkina, Lipid rafts in exosome biogenesis, Biochemistry (Mosc.) 85 (2) (2020) 177–191, https://doi.org/10.1134/S0006297920020054.
[110] R.N. Hamzah, K.M. Alghazali, A.S. Biris, R.J. Griffin, Exosome traceability and cell source dependence on composition and cell-cell cross talk, Int. J. Mol. Sci. 22 (10) (2021) 5346, https://doi.org/10.3390/ijms22105346.
[111] L. Xu, L.F. Wu, F.Y. Deng, Exosome: an emerging source of biomarkers for human diseases, Curr. Mol. Med. 19 (6) (2019) 387–394, https://doi.org/10.2174/1566524019666190429144310.
[112] M. Mathieu, N. Névo, M. Jouve, et al., Specificities of exosome versus small ectosome secretion revealed by live intracellular tracking of CD63 and CD9, Nat. Commun. 12 (1) (2021) 4389, https://doi.org/10.1038/s41467-021-24384-2.
[113] L. Yang, A. Salai, X. Sun, et al., Proteomic profiling of plasma exosomes reveals CD82 involvement in the development of esophageal squamous cell carcinoma, J. Proteonomics 265 (2022) 104662, https://doi.org/10.1016/j.jprot.2022.104662.
[114] C. Caruso Bavisotto, F. Cappello, A.J.L. Macario, et al., Exosomal HSP60: a potentially useful biomarker for diagnosis, assessing prognosis, and monitoring response to treatment, Expert Rev. Mol. Diagn 17 (9) (2017) 815–822, https://doi.org/10.1080/14737159.2017.1356230.
[115] J. Larios, V. Mercier, A. Roux, J. Gruenberg, ALIX- and ESCRT-III-dependent sorting of tetraspanins to exosomes, J. Cell Biol. 219 (3) (2020) e201904113, https://doi.org/10.1083/jcb.201904113.
[116] Q. Lin, C.R. Zhou, M.J. Bai, et al., Exosome-mediated miRNA delivery promotes liver cancer EMT and metastasis, Am J Transl Res 12 (3) (2020) 1080–1095.
[117] I. Wortzel, S. Dror, C.M. Kenific, D. Lyden, Exosome-mediated metastasis: communication from a distance, Dev. Cell 49 (3) (2019) 347–360, https://doi.org/10.1016/j.devcel.2019.04.011.
[118] J. Meldolesi, Exosomes and ectosomes in intercellular communication, Curr. Biol. 28 (8) (2018) R435–R444, https://doi.org/10.1016/j.cub.2018.01.059.
[119] M. Chivet, C. Javalet, F. Hemming, et al., Exosomes as a novel way of interneuronal communication, Biochem. Soc. Trans. 41 (1) (2013) 241–244, https://doi.org/10.1042/BST20120266.
[120] M.F.S. Lindenbergh, W. Stoorvogel, Antigen presentation by extracellular vesicles from professional antigen-presenting cells, Annu. Rev. Immunol. 36 (2018) 435–459, https://doi.org/10.1146/annurev-immunol-041015-055700.
[121] S. Wang, F. Li, T. Ye, et al., Macrophage-tumor chimeric exosomes accumulate in lymph node and tumor to activate the immune response and the tumor microenvironment, Sci. Transl. Med. 13 (615) (2021) eabb6981, https://doi.org/10.1126/scitranslmed.abb6981.
[122] B. Yue, H. Yang, J. Wang, et al., Exosome biogenesis, secretion and function of exosomal miRNAs in skeletal muscle myogenesis, Cell Prolif. 53 (7) (2020) e12857, https://doi.org/10.1111/cpr.12857.
[123] L. Zhang, D. Yu, Exosomes in cancer development, metastasis, and immunity, Biochim. Biophys. Acta Rev. Canc 1871 (2) (2019) 455–468, https://doi.org/10.1016/j.bbcan.2019.04.004.
[124] R.J. Henning, Cardiovascular exosomes and MicroRNAs in cardiovascular physiology and pathophysiology, J Cardiovasc Transl Res 14 (2) (2021) 195–212, https://doi.org/10.1007/s12265-020-10040-5.
[125] Y. Hu, Y. Wang, T. Chen, Z. Hao, L. Cai, J. Li, Exosome: function and application in inflammatory bone diseases, Oxid. Med. Cell. Longev. 2021 (2021) 6324912, https://doi.org/10.1155/2021/6324912.
[126] D. Jafari, S. Malih, M. Eini, et al., Improvement, scaling-up, and downstream analysis of exosome production, Crit. Rev. Biotechnol. 40 (8) (2020) 1098–1112, https://doi.org/10.1080/07388551.2020.1805406.
[127] W.M. Xu, A. Li, J.J. Chen, E.J. Sun, Research development on exosome separation technology, J. Membr. Biol. 256 (1) (2023) 25–34, https://doi.org/10.1007/s00232-022-00260-y.
[128] M. Barzin, A.M. Bagheri, M. Ohadi, A.M. Abhaji, S. Salarpour, G. Dehghannoudeh, Application of plant-derived exosome-like nanoparticles in drug delivery, Pharmaceut. Dev. Technol. 28 (5) (2023) 383–402, https://doi.org/10.1080/10837450.2023.2202242.
[129] M.D. Hade, C.N. Suire, Z. Suo, Mesenchymal stem cell-derived exosomes: applications in regenerative medicine, Cells 10 (8) (2021) 1959, https://doi.org/10.3390/cells10081959.
[130] H. Valadi, K. Ekström, A. Bossios, M. Sjöstrand, J.J. Lee, J.O. Lötvall, Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells, Nat. Cell Biol. 9 (6) (2007) 654–659, https://doi.org/10.1038/ncb1596.
[131] M.A. Mori, R.G. Ludwig, R. Garcia-Martin, B.B. Brandão, C.R. Kahn, Extracellular miRNAs: from biomarkers to mediators of physiology and disease, Cell Metabol. 30 (4) (2019) 656–673, https://doi.org/10.1016/j.cmet.2019.07.011.
[132] S. Wani, I.K. Man Law, C. Pothoulakis, Role and mechanisms of exosomal miRNAs in IBD pathophysiology, Am. J. Physiol. Gastrointest. Liver Physiol. 319 (6) (2020) G646–G654, https://doi.org/10.1152/ajpgi.00295.2020.
[133] J.Y. ang, Y.T. Chuang, J.P. Shiau, et al., Connection between radiation-regulating functions of natural products and miRNAs targeting radiomodulation and exosome biogenesis, Int. J. Mol. Sci. 24 (15) (2023) 12449, https://doi.org/10.3390/ijms241512449.
[134] S.V. Krylova, D. Feng, The machinery of exosomes: biogenesis, release, and uptake, Int. J. Mol. Sci. 24 (2) (2023) 1337, https://doi.org/10.3390/ijms24021337.
[135] K. Saliminejad, H.R. Khorram Khorshid, S. Soleymani Fard, S.H. Ghaffari, An overview of microRNAs: biology, functions, therapeutics, and analysis methods, J. Cell. Physiol. 234 (5) (2019) 5451–5465, https://doi.org/10.1002/jcp.27486.
[136] C. Diener, A. Keller, E. Meese, Emerging concepts of miRNA therapeutics: from cells to clinic, Trends Genet. 38 (6) (2022) 613–626, https://doi.org/10.1016/j.tig.2022.02.006.
[137] M. Correia de Sousa, M. Gjorgjieva, D. Dolicka, C. Sobolewski, M. Foti, Deciphering miRNAs' action through miRNA editing, Int. J. Mol. Sci. 20 (24) (2019) 6249.
[138] J. Jie, D. Liu, Y. Wang, Q. Wu, T. Wu, R. Fang, Generation of MiRNA sponge constructs targeting multiple MiRNAs, J. Clin. Lab. Anal. 36 (7) (2022) e24527, https://doi.org/10.1002/jcla.24527.
[139] M. Hill, N. Tran, miRNA:miRNA interactions: a novel mode of miRNA regulation and its effect on disease, Adv. Exp. Med. Biol. 1385 (2022) 241–257, https://doi.org/10.1007/978-3-031-08356-3_9.
[140] J. Withrow, C. Murphy, Y. Liu, M. Hunter, S. Fulzele, M.W. Hamrick, Extracellular vesicles in the pathogenesis of rheumatoid arthritis and osteoarthritis, Arthritis Res. Ther. 18 (1) (2016) 286, https://doi.org/10.1186/s13075-016-1178-8.
[141] H. Liu, R. Li, T. Liu, L. Yang, G. Yin, Q. Xie, Immunomodulatory effects of mesenchymal stem cells and mesenchymal stem cell-derived extracellular vesicles in rheumatoid arthritis, Front. Immunol. 11 (2020) 1912, https://doi.org/10.3389/fimmu.2020.01912.
[142] R. Mirzaei, F. Zamani, M. Hajibaba, et al., The pathogenic, therapeutic and diagnostic role of exosomal microRNA in the autoimmune diseases, J. Neuroimmunol. 358 (2021) 577640, https://doi.org/10.1016/j.jneuroim.2021.577640.
[143] C. Chang, L. Xu, R. Zhang, et al., MicroRNA-mediated epigenetic regulation of rheumatoid arthritis susceptibility and pathogenesis, Front. Immunol. 13 (2022) 838884, https://doi.org/10.3389/fimmu.2022.838884.
[144] Z. Bagheri-Hosseinabadi, M.R. Mirzaei, M.R. Hajizadeh, F. Asadi, M. Rezaeian, M. Abbasifard, Plasma MicroRNAs (miR-146a, miR-103a, and miR-155) as potential biomarkers for rheumatoid arthritis (RA) and disease activity in Iranian patients, Mediterr J Rheumatol 32 (4) (2021) 324–330, https://doi.org/10.31138/mjr.32.4.324.

[145] R.S. Abdul-Maksoud, A.M. Sediq, A. Kattaia, et al., Serum miR-210 and miR-155 expression levels as novel biomarkers for rheumatoid arthritis diagnosis, Br. J. Biomed. Sci. 74 (4) (2017) 209–213, https://doi.org/10.1080/09674845.2017.1343545.
[146] M. Filková, B. Aradi, L. Senolt, et al., Association of circulating miR-223 and miR-16 with disease activity in patients with early rheumatoid arthritis, Ann. Rheum. Dis. 73 (10) (2014) 1898–1904, https://doi.org/10.1136/annrheumdis-2012-202815.
[147] S.C. Bae, Y.H. Lee, MiR-146a levels in rheumatoid arthritis and their correlation with disease activity: a meta-analysis, Int J Rheum Dis 21 (7) (2018) 1335–1342, https://doi.org/10.1111/1756-185X.13338.
[148] J. Stanczyk, C. Ospelt, E. Karouzakis, et al., Altered expression of microRNA-203 in rheumatoid arthritis synovial fibroblasts and its role in fibroblast activation, Arthritis Rheum. 63 (2) (2011) 373–381, https://doi.org/10.1002/art.30115.
[149] J. Ogando, M. Tardáguila, A. Díaz-Alderete, et al., Notch-regulated miR-223 targets the aryl hydrocarbon receptor pathway and increases cytokine production in macrophages from rheumatoid arthritis patients, Sci. Rep. 6 (2016) 20223, https://doi.org/10.1038/srep20223.
[150] Z. Chen, H. Wang, Y. Xia, F. Yan, Y. Lu, Therapeutic potential of mesenchymal cell-derived miRNA-150-5p-expressing exosomes in rheumatoid arthritis mediated by the modulation of MMP14 and VEGF, J. Immunol. 201 (8) (2018) 2472–2482, https://doi.org/10.4049/jimmunol.1800304.
[151] L.F. Wu, Q. Zhang, X.B. Mo, et al., Identification of novel rheumatoid arthritis-associated MiRNA-204-5p from plasma exosomes, Exp. Mol. Med. 54 (3) (2022) 334–345, https://doi.org/10.1038/s12276-022-00751-x.
[152] H.Y. Meng, L.Q. Chen, L.H. Chen, The inhibition by human MSCs-derived miRNA-124a overexpression exosomes in the proliferation and migration of rheumatoid arthritis-related fibroblast-like synoviocyte cell, BMC Muscoskel. Disord. 21 (1) (2020) 150, https://doi.org/10.1186/s12891-020-3159-y.
[153] Y. Xing, B. Li, J. He, H. Hua, Labial gland mesenchymal stem cell derived exosomes-mediated miRNA-125b attenuates experimental sjogren's syndrome by targeting PRDM1 and suppressing plasma cells, Front. Immunol. 13 (2022) 871096, https://doi.org/10.3389/fimmu.2022.871096.
[154] D. Xu, M. Song, C. Chai, et al., Exosome-encapsulated miR-6089 regulates inflammatory response via targeting TLR4, J. Cell. Physiol. 234 (2) (2019) 1502–1511, https://doi.org/10.1002/jcp.27014.
[155] Y. Huang, D. Lu, W. Ma, et al., miR-223 in exosomes from bone marrow mesenchymal stem cells ameliorates rheumatoid arthritis via downregulation of NLRP3 expression in macrophages, Mol. Immunol. 143 (2022) 68–76, https://doi.org/10.1016/j.molimm.2022.01.002.
[156] W. Ma, F. Tang, L. Xiao, et al., miR-205-5p in exosomes divided from chondrogenic mesenchymal stem cells alleviated rheumatoid arthritis via regulating MDM2 in fibroblast-like synoviocytes, J. Musculoskelet. Neuronal Interact. 22 (1) (2022) 132–141.
[157] Y. Huang, L. Chen, D. Chen, P. Fan, H. Yu, Exosomal microRNA-140-3p from human umbilical cord mesenchymal stem cells attenuates joint injury of rats with rheumatoid arthritis by silencing SGK1, Mol. Med. 28 (1) (2022) 36, https://doi.org/10.1186/s10020-022-00451-2.
[158] J. Chen, M. Liu, X. Luo, et al., Exosomal miRNA-486-5p derived from rheumatoid arthritis fibroblast-like synoviocytes induces osteoblast differentiation through the Tob1/BMP/Smad pathway, Biomater. Sci. 8 (12) (2020) 3430–3442, https://doi.org/10.1039/c9bm01761e.
[159] M. Chen, M.H. Li, N. Zhang, et al., Pro-angiogenic effect of exosomal microRNA-103a in mice with rheumatoid arthritis via the downregulation of hepatocyte nuclear factor 4 alpha and activation of the JAK/STAT3 signaling pathway, J. Biol. Regul. Homeost. Agents 35 (2) (2021) 629–640, https://doi.org/10.23812/20-537-A.
[160] D. Liu, Y. Fang, Y. Rao, et al., Synovial fibroblast-derived exosomal microRNA-106b suppresses chondrocyte proliferation and migration in rheumatoid arthritis via down-regulation of PDK4, J. Mol. Med. (Berl.) 98 (3) (2020) 409–423, https://doi.org/10.1007/s00109-020-01882-2.
[161] Y. Ding, L. Wang, H. Wu, Q. Zhao, S. Wu, Exosomes derived from synovial fibroblasts under hypoxia aggravate rheumatoid arthritis by regulating Treg/Th17 balance, Exp. Biol. Med. 245 (14) (2020) 1177–1186, https://doi.org/10.1177/1535370220934736.
[162] J. Zheng, L. Zhu, I. Iok In, Y. Chen, N. Jia, W. Zhu, Bone marrow-derived mesenchymal stem cells-secreted exosomal microRNA-192-5p delays inflammatory response in rheumatoid arthritis, Int. Immunopharm. 78 (2020) 105985, https://doi.org/10.1016/j.intimp.2019.105985.
[163] Y. Wang, F. Zheng, G. Gao, et al., MiR-548a-3p regulates inflammatory response via TLR4/NF-κB signaling pathway in rheumatoid arthritis, J. Cell. Biochem. 120 (2) (2019) 1133–1140, https://doi.org/10.1002/jcb.26659.
[164] L. Wang, C. Wang, X. Jia, J. Yu, Circulating exosomal miR-17 inhibits the induction of regulatory T cells via suppressing TGFBR II expression in rheumatoid arthritis, Cell. Physiol. Biochem. 50 (5) (2018) 1754–1763, https://doi.org/10.1159/000494793.
[165] L. Console, M. Scalise, C. Indiveri, Exosomes in inflammation and role as biomarkers, Clin. Chim. Acta 488 (2019) 165–171, https://doi.org/10.1016/j.cca.2018.11.009.
[166] J.E. Song, J.S. Kim, J.H. Shin, et al., Role of synovial exosomes in osteoclast differentiation in inflammatory arthritis, Cells 10 (1) (2021) 120, https://doi.org/10.3390/cells10010120.
[167] L. Zhang, Z. Qin, H. Sun, et al., Nanoenzyme engineered neutrophil-derived exosomes attenuate joint injury in advanced rheumatoid arthritis via regulating inflammatory environment [published correction appears in Bioact Mater, 2022 May 04;19:486], Bioact. Mater. 18 (2022) 1–14, https://doi.org/10.1016/j.bioactmat.2022.02.017.
[168] J.P. Mitchell, R.J. Carmody, NF-κB and the transcriptional control of inflammation, Int Rev Cell Mol Biol 335 (2018) 41–84, https://doi.org/10.1016/bs.ircmb.2017.07.007.
[169] L. An, Z. Li, L. Shi, et al., Inflammation-targeted celastrol nanodrug attenuates collagen-induced arthritis through NF-κB and Notch1 pathways, Nano Lett. 20 (10) (2020) 7728–7736, https://doi.org/10.1021/acs.nanolett.0c03279.
[170] J. Zhao, Y. Hu, J. Peng, Targeting programmed cell death in metabolic dysfunction-associated fatty liver disease (MAFLD): a promising new therapy, Cell. Mol. Biol. Lett. 26 (1) (2021) 17, https://doi.org/10.1186/s11658-021-00254-z.
[171] S. Wakisaka, N. Suzuki, Y. Takeba, et al., Modulation by proinflammatory cytokines of Fas/Fas ligand-mediated apoptotic cell death of synovial cells in patients with rheumatoid arthritis (RA), Clin. Exp. Immunol. 114 (1) (1998) 119–128, https://doi.org/10.1046/j.1365-2249.1998.00701.x.
[172] H. Hariharan, Y. Kesavan, N.S. Raja, Impact of native and external factors on exosome release: understanding reactive exosome secretion and its biogenesis, Mol. Biol. Rep. 48 (11) (2021) 7559–7573, https://doi.org/10.1007/s11033-021-06733-y.
[173] M. Ghisi, A. Corradin, K. Basso, et al., Modulation of microRNA expression in human T-cell development: targeting of NOTCH3 by miR-150, Blood 117 (26) (2011) 7053–7062, https://doi.org/10.1182/blood-2010-12-326629.
[174] N. Li, Z. Chen, W. Feng, et al., Triptolide improves chondrocyte proliferation and secretion via down-regulation of miR-221 in synovial cell exosomes, Phytomedicine 107 (2022) 154479, https://doi.org/10.1016/j.phymed.2022.154479.
[175] N. Mizushima, M. Komatsu, Autophagy: renovation of cells and tissues, Cell 147 (4) (2011) 728–741, https://doi.org/10.1016/j.cell.2011.10.026.
[176] K.R. Parzych, D.J. Klionsky, An overview of autophagy: morphology, mechanism, and regulation, Antioxidants Redox Signal. 20 (3) (2014) 460–473, https://doi.org/10.1089/ars.2013.5371.
[177] X.Q. Chen, L.L. Li, G.T. Fu, et al., Expression and regulatory mechanism of autophagy-related genes in synovial tissues of patients with rheumatoid arthritis, Zhongguo Yi Xue Ke Xue Yuan Xue Bao 44 (6) (2022 Dec) 950–960, https://doi.org/10.3881/j.issn.1000-503X.14779. Chinese.
[178] H. Zhou, L. Huang, K. Zhan, X. Liu, Wenhua juanbi recipe attenuates rheumatoid arthritis via inhibiting miRNA-146a-mediated autophagy, BioMed Res. Int. 2022 (2022) 1768052, https://doi.org/10.1155/2022/1768052.
[179] Y. Li, D. Zhou, Y. Ren, et al., Mir223 restrains autophagy and promotes CNS inflammation by targeting ATG16L1, Autophagy 15 (3) (2019) 478–492, https://doi.org/10.1080/15548627.2018.1522467.
[180] Y. Cai, C. Jiang, J. Zhu, et al., miR-449a inhibits cell proliferation, migration, and inflammation by regulating high-mobility group box protein 1 and forms a mutual inhibition loop with Yin Yang 1 in rheumatoid arthritis fibroblast-like synoviocytes, Arthritis Res. Ther. 21 (1) (2019) 134, https://doi.org/10.1186/s13075-019-1920-0.
[181] K. Xu, P. Xu, J.F. Yao, Y.G. Zhang, W.K. Hou, S.M. Lu, Reduced apoptosis correlates with enhanced autophagy in synovial tissues of rheumatoid arthritis, Inflamm. Res. 62 (2) (2013) 229–237, https://doi.org/10.1007/s00011-012-0572-1.
[182] S. Yang, W. Yin, Y. Ding, F. Liu, Lnc RNA ZFAS1 regulates the proliferation, apoptosis, inflammatory response and autophagy of fibroblast-like synoviocytes via miR-2682-5p/ADAMTS9 axis in rheumatoid arthritis, Biosci. Rep. 40 (8) (2020) BSR20201273, https://doi.org/10.1042/BSR20201273.

[183] H.Y. Meng, L.Q. Chen, L.H. Chen, The inhibition by human MSCs-derived miRNA-124a overexpression exosomes in the proliferation and migration of rheumatoid arthritis-related fibroblast-like synoviocyte cell, BMC Muscoskel. Disord. 21 (1) (2020) 150, https://doi.org/10.1186/s12891-020-3159-y.
[184] J. Zhao, P. Jiang, S. Guo, S.J. Schrodi, D. He, Apoptosis, autophagy, NETosis, necroptosis, and pyroptosis mediated programmed cell death as targets for innovative therapy in rheumatoid arthritis, Front. Immunol. 12 (2021) 809806, https://doi.org/10.3389/fimmu.2021.809806.
[185] K. Xu, Y.S. Cai, S.M. Lu, et al., Autophagy induction contributes to the resistance to methotrexate treatment in rheumatoid arthritis fibroblast-like synovial cells through high mobility group box chromosomal protein 1, Arthritis Res. Ther. 17 (2015) 374, https://doi.org/10.1186/s13075-015-0892-y.
[186] M.F. Bustamante, R. Garcia-Carbonell, K.D. Whisenant, M. Guma, Fibroblast-like synoviocyte metabolism in the pathogenesis of rheumatoid arthritis, Arthritis Res. Ther. 19 (1) (2017) 110, https://doi.org/10.1186/s13075-017-1303-3.
[187] W.X. Cheng, H. Huang, J.H. Chen, et al., Genistein inhibits angiogenesis developed during rheumatoid arthritis through the IL-6/JAK2/STAT3/VEGF signalling pathway, J Orthop Translat 22 (2019) 92–100, https://doi.org/10.1016/j.jot.2019.07.007.
[188] C.H. Wang, H. Yao, L.N. Chen, et al., CD147 induces angiogenesis through a vascular endothelial growth factor and hypoxia-inducible transcription factor 1α-mediated pathway in rheumatoid arthritis, Arthritis Rheum. 64 (6) (2012) 1818–1827, https://doi.org/10.1002/art.34341.
[189] Q. Chen, K. Fan, X. Chen, et al., Ezrin regulates synovial angiogenesis in rheumatoid arthritis through YAP and Akt signalling, J. Cell Mol. Med. 25 (19) (2021) 9378–9389, https://doi.org/10.1111/jcmm.16877.
[190] C.H. sai, C.J. Chen, C.L. Gong, et al., CXCL13/CXCR5 axis facilitates endothelial progenitor cell homing and angiogenesis during rheumatoid arthritis progression, Published 2021 Sep 13. Cell Death Dis. 12 (9) (2021) 846, https://doi.org/10.1038/s41419-021-04136-2.
[191] Y. Wang, H. Wu, R. Deng, Angiogenesis as a potential treatment strategy for rheumatoid arthritis, Eur. J. Pharmacol. 910 (2021) 174500, https://doi.org/10.1016/j.ejphar.2021.174500.
[192] Y.L. Hsu, J.Y. Hung, W.A. Chang, et al., Hypoxic lung-cancer-derived extracellular vesicle MicroRNA-103a increases the oncogenic effects of macrophages by targeting PTEN, Mol. Ther. 26 (2) (2018) 568–581, https://doi.org/10.1016/j.ymthe.2017.11.016.
[193] W. Wang, C. Li, Z. Zhang, Y. Zhang, Arsenic trioxide in synergy with vitamin D rescues the defective VDR-PPAR-γ functional module of autophagy in rheumatoid arthritis, PPAR Res. 2019 (2019) 6403504, https://doi.org/10.1155/2019/6403504.
[194] J. Zhang, Y. Zhang, Y. Ma, L. Luo, M. Chu, Z. Zhang, Therapeutic potential of exosomal circRNA derived from synovial mesenchymal cells via targeting circEDIL3/miR-485-3p/PIAS3/STAT3/VEGF functional module in rheumatoid arthritis, Int. J. Nanomed. 16 (2021) 7977–7994, https://doi.org/10.2147/IJN.S333465.
[195] L. Wang, Q. Zhao, N. Wang, Y. Ding, L. Kong, J. Wang, Circ_0000396 inhibits rheumatoid arthritis synovial fibroblast growth and inflammatory response via miR-203/HBP1 axis, J. Biol. Res. 28 (1) (2021) 1, https://doi.org/10.1186/s40709-020-00131-4.
[196] C. Fan, X. Cui, S. Chen, S. Huang, H. Jiang, LncRNA LOC100912373 modulates PDK1 expression by sponging miR-17-5p to promote the proliferation of fibroblast-like synoviocytes in rheumatoid arthritis, Am J Transl Res 12 (12) (2020) 7709–7723.
[197] Y. Zamudio-Cuevas, K. Martínez-Flores, G.A. Martínez-Nava, D. Clavijo-Cornejo, J. Fernández-Torres, R. Sánchez-Sánchez, Rheumatoid arthritis and oxidative stress, Cell. Mol. Biol. (Noisy-Le-Grand) 68 (6) (2022) 174–184, https://doi.org/10.14715/cmb/2022.68.6.28.
[198] N.T. Costa, T.M.V. Iriyoda, D.F. Alfieri, A.N.C. Simão, I. Dichi, Influence of disease-modifying antirheumatic drugs on oxidative and nitrosative stress in patients with rheumatoid arthritis, Inflammopharmacology 26 (5) (2018) 1151–1164, https://doi.org/10.1007/s10787-018-0514-9.
[199] A.R. Phull, B. Nasir, I.U. Haq, S.J. Kim, Oxidative stress, consequences and ROS mediated cellular signaling in rheumatoid arthritis, Chem. Biol. Interact. 281 (2018) 121–136, https://doi.org/10.1016/j.cbi.2017.12.024.
[200] L.J.S. da Fonseca, V. Nunes-Souza, M.O.F. Goulart, L.A. Rabelo, Oxidative stress in rheumatoid arthritis: what the future might hold regarding novel biomarkers and add-on therapies, Oxid. Med. Cell. Longev. 2019 (2019) 7536805, https://doi.org/10.1155/2019/7536805.
[201] A. Mihanfar, S.K. Shakouri, M.H. Khadem-Ansari, et al., Exosomal miRNAs in osteoarthritis, Mol. Biol. Rep. 47 (6) (2020) 4737–4748, https://doi.org/10.1007/s11033-020-05443-1.
[202] G. Sun, G. Li, D. Li, et al., hucMSC derived exosomes promote functional recovery in spinal cord injury mice via attenuating inflammation, Mater. Sci. Eng., C 89 (2018) 194–204, https://doi.org/10.1016/j.msec.2018.04.006.
[203] R.N. Al-Modawi, J.E. Brinchmann, T.A. Karlsen, Multi-pathway protective effects of MicroRNAs on human chondrocytes in an in vitro model of osteoarthritis, Mol. Ther. Nucleic Acids 17 (2019) 776–790, https://doi.org/10.1016/j.omtn.2019.07.011.
[204] W. Liao, Z. Fu, Y. Zou, et al., MicroRNA-140-5p attenuated oxidative stress in Cisplatin induced acute kidney injury by activating Nrf2/ARE pathway through a Keap1-independent mechanism [published correction appears in Exp Cell Res. 2017 Dec 1;361(1):199], Exp. Cell Res. 360 (2) (2017) 292–302, https://doi.org/10.1016/j.yexcr.2017.09.019.
[205] W. Jiang, Y. Tan, M. Cai, et al., Human umbilical cord MSC-derived exosomes suppress the development of CCl4-induced liver injury through antioxidant effect, Stem Cell. Int. 2018 (2018) 6079642, https://doi.org/10.1155/2018/6079642.
[206] M. Liu, T. Ren, Z. Lin, M. Hua, Upregulated miR-146a expression in peripheral blood relates to Th17 and Treg imbalance in elder rheumatoid arthritis patients, Lifestyle Genom. 15 (3) (2022) 98–106, https://doi.org/10.1159/000525112.
[207] S.E. Walker, A. Senatore, R.L. Carlone, G.E. Spencer, Context-Dependent role of miR-124 in retinoic acid-induced growth cone attraction of regenerating motorneurons, Cell. Mol. Neurobiol. 42 (3) (2022) 847–869, https://doi.org/10.1007/s10571-020-00982-4.
[208] Y. Maeda, N.H. Farina, M.M. Matzelle, P.J. Fanning, J.B. Lian, E.M. Gravallese, Synovium-derived MicroRNAs regulate bone pathways in rheumatoid arthritis, J. Bone Miner. Res. 32 (3) (2017) 461–472, https://doi.org/10.1002/jbmr.3005.
[209] M.C. Miller, H.B. Manning, A. Jain, et al., Membrane type 1 matrix metalloproteinase is a crucial promoter of synovial invasion in human rheumatoid arthritis, Arthritis Rheum. 60 (3) (2009) 686–697, https://doi.org/10.1002/art.24331.
[210] Y. Takamura, W. Aoki, A. Satomura, S. Shibasaki, M. Ueda, Small RNAs detected in exosomes derived from the MH7A synovial fibroblast cell line with TNF-α stimulation, PLoS One 13 (8) (2018) e0201851, https://doi.org/10.1371/journal.pone.0201851.
[211] Y. Xin, Z. Yang, X. Fei, L. Ke, J. Juan, F. Ting, et al., THU0059 Plasma exosomal mir-92a are involved in the occurrence and development of bone destruction in ra patients by inhibiting apoptosis of fibroblast-like synoviocytes, in: Book THU0059 Plasma Exosomal Mir-92a Are Involved in the Occurrence and Development of Bone Destruction in Ra Patients by Inhibiting Apoptosis of Fibroblast-like Synoviocytes, BMJ Publishing Group Ltd, 2018.
[212] X. He, C. Zhang, S. Amirsaadat, et al., Curcumin-loaded mesenchymal stem cell-derived exosomes efficiently attenuate proliferation and inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes, Appl. Biochem. Biotechnol. 195 (1) (2023) 51–67, https://doi.org/10.1007/s12010-022-04090-5.
[213] S.H. Kim, N.R. Bianco, W.J. Shufesky, A.E. Morelli, P.D. Robbins, Effective treatment of inflammatory disease models with exosomes derived from dendritic cells genetically modified to express IL-4, J. Immunol. 179 (4) (2007) 2242–2249, https://doi.org/10.4049/jimmunol.179.4.2242.
[214] C. Yang, P.D. Robbins, Immunosuppressive exosomes: a new approach for treating arthritis, Internet J. Rheumatol. 2012 (2012) 573528, https://doi.org/10.1155/2012/573528.
[215] S.H. Kim, E.R. Lechman, N. Bianco, et al., Exosomes derived from IL-10-treated dendritic cells can suppress inflammation and collagen-induced arthritis, J. Immunol. 174 (10) (2005) 6440–6448, https://doi.org/10.4049/jimmunol.174.10.6440.
[216] Q. Zhang, Q. Li, J. Zhu, et al., Comparison of therapeutic effects of different mesenchymal stem cells on rheumatoid arthritis in mice, PeerJ 7 (2019) e7023, https://doi.org/10.7717/peerj.7023.
[217] Q. Jiang, G. Yang, Q. Liu, S. Wang, D. Cui, Function and role of regulatory T cells in rheumatoid arthritis, Front. Immunol. 12 (2021) 626193, https://doi.org/10.3389/fimmu.2021.626193.
[218] M. Maumus, C. Jorgensen, D. Noël, Mesenchymal stem cells in regenerative medicine applied to rheumatic diseases: role of secretome and exosomes, Biochimie 95 (12) (2013) 2229–2234, https://doi.org/10.1016/j.biochi.2013.04.017.

[219] Mi L, Gao J, Li N, et al. Human umbilical cord mesenchymal stem cell-derived exosomes loaded miR-451a targets ATF2 to improve rheumatoid arthritis. Int. Immunopharm.. doi:10.1016/j.intimp.2023.111365.
[220] B. Zhang, J. Gu, Y. Wang, L. Guo, J. Xie, M. Yang, TNF-α stimulated exosome derived from fibroblast-like synoviocytes isolated from rheumatoid arthritis patients promotes HUVEC migration, invasion and angiogenesis by targeting the miR-200a-3p/KLF6/VEGFA axis, Autoimmunity 56 (1) (2023) 2282939, https://doi.org/10.1080/08916934.2023.2282939.
[221] L. Ma, Y. Liu, F. Xu, et al., IL-27-induced, MSC-derived exosomes promote MMP3 expression through the miR-206/l3mbtl4 Axis in synovial fibroblasts, Alternative Ther. Health Med. 29 (8) (2023) 680–688.