Review
The Extracellular MicroRNAs on Inflammation: A Literature Review of Rodent Studies

Seri Lee 1,2, Jade Heejae Ko 1 and Seung-Nam Kim 1,*

1 College of Korean Medicine, Dongguk University, Goyang 10326, Korea; serilee99@gmail.com (S.L.); jadeko@dongguk.edu (J.H.K.)
2 Graduate School, Dongguk University, Seoul 04620, Korea
* Correspondence: snkim@dongguk.edu; Tel.: +82-31-961-5830

Abstract: Inflammation is an indispensable biological process stimulated by infection and injuries. Inflammatory mechanisms related to extracellular vesicles (EVs), which are small membrane structures carrying various molecules, were summarized in this review. Emerging evidence from animal studies has highlighted the role of EVs in modulating inflammatory responses, by transporting various molecules involved in host defense. In this review, we have discussed the role of EV miRNAs in inflammation. Rodent studies associated with extracellular miRNAs in inflammatory diseases, published from 2012 to 2022, were explored from PUBMED, EMBASE, and MEDLINE. A total of 95 studies were reviewed. In summary, EV-associated miRNAs play a key role in various diseases, including organ injury, immune dysfunction, neurological disease, metabolic syndrome, vesicular disease, arthritis, cancer, and other inflammatory diseases. Diverse EV-associated miRNAs regulate inflammasome activation and pro- and anti-inflammatory cytokine levels by targeting genes.

Keywords: extracellular vesicle; inflammation; organ injury; immune dysfunction; metabolic syndrome; neurological disease; arthritis; cancer

1. Introduction

The inflammatory response is a rapid and complex physiological process that involves defense mechanisms acting against infections and injuries [1,2]. Inflammation is often regarded as a failure of homeostasis between the host and immune cells. Dysregulation of the inflammatory response underlie various pathological conditions, including chronic inflammation [3], autoimmunity [4], neurodegenerative diseases [5], and cancer [6]. Previous discoveries in inflammatory processes have highlighted the physiological and cellular basis of inflammation under experimental conditions using bacterial lipopolysaccharide (LPS), peptidoglycan, and viral double-stranded RNA [7]. Intracellular signals sent to immune cell nuclei are followed by initial inflammatory cues, which stimulate various transcriptional changes [8]. In addition to the discovery of molecular mechanisms of regulation and initiation of inflammatory responses, a new perspective on inflammatory processes was revealed in recent decades, with the emerging interest in the discovery of mammalian microRNAs (miRNAs) and extracellular vesicles (EVs) [9,10].

EVs are small vesicles (30–10,000 nm in diameter) that can be categorized into the following three types according to their size and biogenesis: exosomes, microvesicles, and apoptotic bodies [11]. EVs are evident in almost all living cells and have been gaining attention as a novel mediator of communication between cells and numerous biological processes and regenerative properties [12,13]. EVs carry various molecules, such as proteins, mRNA [14], long non-coding RNA, circular RNAs, RNA, and miRNAs [10]. miRNAs are endogenous non-coding RNA molecules that use exosomes as carriers to achieve intercellular communication and regulation of protein biosynthesis, while being protected from degradation in the harsh extracellular environment [15]. Extracellular miRNAs have numerous functions in inflammatory processes [16,17], cell migration [18], apoptosis [19],
and proliferation [20]. From the perspective of inflammatory responses, various extracellular miRNAs have recently been reported to be expressed in immune cells, affecting the magnitude of their responses [21]. Moreover, the structural stability of extracellular miRNAs has been widely recognized; extracellular miRNAs are now considered potential noninvasive biomarkers for inflammatory disease monitoring and prognosis [22].

This report presents an overview of the recent studies on extracellular miRNAs, with a focus on their role in inflammatory diseases in animals.

2. Study Methods

2.1. Literature Search

All relevant studies were initially searched on EMBASE, MEDLINE and PUBMED database using the following search keywords: “extracellular vesicles”, “exosome”, “inflammatory diseases”, and “microRNA”. We included rodent studies published from November 2012 to April 2022 and overlapping studies were excluded. Eventually, we identified 320 potentially relevant literatures for further eligibility assessments.

2.2. Study Selection

Three authors (S.L., J.H.K. and S.-N.K.) independently assessed the 320 literatures and a total of 208 studies were excluded based on the following exclusion criteria: (1) review article (n = 100); (2) full text not available (n = 1); (3) not English (n = 1), (4) virus or infection-induced experiment model (n = 14), (5) not a rodent study (n = 92). Title and abstract screening were performed and six studies with no specific microRNA target (n = 12) and five studies with no mention of microRNA mechanism were excluded. As shown in Figure 1, this study ultimately included a total of 95 articles for further analyses.

3. Main Text

3.1. Organ Injuries

Among the 95 articles, 35 articles were related to organ-injury-associated miRNAs in exosomes. The uncontrolled inflammatory response is one of the major factors among various causes of organ injuries. The miRNAs are known to target mRNAs and modulate the level of protein expression encoded by these mRNAs. We attempted to determine

Figure 1. Flowchart of study selection.
how miRNAs in exosomes influence organ injury-related diseases, including myocardial infarction, liver failure, ulcerative colitis, and acute lung injury (Table 1).

Table 1. Extracellular miRNAs in organ injury.

| Author | Disease                  | Subject | EV Type | Targeted miRNAs          |
|--------|--------------------------|---------|---------|--------------------------|
| Bala et al. (2012) [23] | Alcoholic liver disease | Mouse   | Exo     | miR-122, miR-155, miR-223 |
| Chen et al. (2018) [24] | Autoimmune hepatitis    | Mouse   | Exo     | miR-34c, miR-151, miR-483, miR-532, miR-687 |
| Chen et al. (2018) [25] | Liver fibrosis          | Mouse   | EV      | miR-17                   |
| Liu et al. (2018) [26]  | Acute liver failure     | Mouse   | Exo     | miR-223                  |
| Liu et al. (2020) [27]  | Nonalcoholic fatty liver disease | Rat | Exo     | miR-192                  |
| Lu et al. (2019) [28]   | Autoimmune hepatitis    | Mouse   | Exo     | miR-223                  |
| Shao et al. (2020) [29] | Acute liver injury      | Mouse   | Exo     | miR-455                  |
| Jiang et al. (2021) [30] | Acute lung injury       | Mouse   | Exo     | miR-125b                 |
| Liu et al. (2021) [31]  | Acute lung injury       | Mouse   | Exo     | miR-384                  |
| Shen et al. (2022) [32] | Septic lung injury      | Mouse   | Exo     | miR-490                  |
| Tian et al. (2021) [33] | Septic lung injury      | Mouse   | Exo     | miR-16                   |
| Wei et al. (2020) [34]  | Acute lung injury       | Mouse   | Exo     | miR-377                  |
| Zhang et al. (2019) [35] | Lung inflammation       | Mouse   | MV      | miR-223, miR-142         |
| Zheng et al. (2021) [36] | Acute lung injury       | Rat     | Exo     | miR-22                    |
| Chen et al. (2017) [37] | Myocardial infarction   | Rat     | Exo     | miR-133                  |
| Kwon et al. (2021) [38] | Myocardial infarction   | Rat     | EV      | miR-7004, miR-7b         |
| Luo et al. (2017) [39]  | Acute myocardial infarction | Rat | Exo     | miR-126                  |
| Milano et al. (2020) [40] | Cardiotoxicity         | Rat     | Exo     | miR-146a                 |
| Pan et al. (2019) [41]  | Myocardial infarction   | Rat     | Exo     | miR-146a                 |
| Peng et al. (2020) [42] | Myocardial infarction   | Mouse   | Exo     | miR-25                   |
| Sun et al. (2022) [43]  | Sepsis induced myocardial infarction | Mouse | Exo     | miR-24                   |
| Wang et al. (2015) [44] | Sepsis induced myocardial dysfunction | Mouse | Exo     | miR-223                  |
| Wang et al. (2022) [45] | Myocardial infarction   | Mouse   | Exo     | miR-129                  |
| Yu et al. (2021) [46]   | Cardiac hypertrophy     | Rat     | Exo     | miR-155                  |
| Cai et al. (2021) [47]  | Colitis                 | Mouse   | Exo     | miR-378a                 |
| Deng et al. (2021) [48] | Ulcerative colitis      | Mouse   | Exo     | miR-590                  |
| Lu et al. (2021) [49]   | Ulcerative colitis      | Mouse   | Exo     | miR-21a                  |
| Sun et al. (2020) [50]  | Inflammation-injured IEC | Rat | Exo     | miR-200b                 |
| Li et al. (2019) [51]   | Tubulointerstitial inflammation | Mouse | Exo     | miR-23a                  |
| Li et al. (2020) [52]   | Ischemia/reperfusion injury | Rat | Exo     | miR-146a                 |
| Li et al. (2020) [53]   | Diabetic kidney diseases | Mouse   | Exo     | miR-26a                  |
| Pan et al. (2019) [54]  | Sepsis, Acute kidney injury | Mouse | Exo     | miR-21                   |
| Jimenez-Alesanco et al. (2019) [55] | Acute pancreatitis | Rat | Exo     | miR-155                  |
| Liang et al. (2019) [56] | Urethral stricture      | Rat     | Exo     | miR-146a                 |
| Liu et al. (2021) [57]  | Intrauterine adhesion   | Mouse   | Exo     | miR-223                  |

Exo: exosome; EV: extracellular vesicle; MV: micro vesicle.

3.1.1. Liver Injury

In alcoholic and inflammatory liver diseases, serum/plasma miR-122 and miR-155 increased during drug-induced liver injury, and these miRNAs were present in the protein-rich fraction [23]. In a mouse model with autoimmune hepatitis (AIH) induced by hepatic injection of S100 protein, miR-223 in the exosomes derived from bone marrow mesenchymal stem cells (BMSCs) protected the liver from injury and inhibited NLRP3 activation that causes hepatic damage and liver dysfunction [24]. In hepatic fibrogenesis or fibrosis in a carbon tetrachloride-or thiacetic acid-induced liver injury mouse model, EVs of
normal mice suppressed hepatocyte death and circulating pro-inflammatory cytokine levels. miR-34c, -151, -483, -532, and -687, which are highly expressed in EVs, have therapeutic effects in injured hepatocytes [25]. In acute liver failure induced in mice by LPS and D-GalN, miR-17 in AMSC-derived exosomes suppressed NLRP3 inflammasome activation by targeting TXNIP [26]. In a high-fat high-cholesterol diet-fed-induced NAFLD rat model, more exosomes were released, contained more miR-192, and the levels of M1-specific cytokines, such as iNOS, IL-6, and TNF-α, increased. miR-192 in exosomes from hepatocytes activated pro-inflammatory macrophages via Rictor/Akt/FoxO1 signaling [27]. In another experimental AIH mouse model, miR-223 carried in MSC exosomes attenuated liver injury and inflammatory responses [28]. In an endotoxemia and chemical liver injury induced by LPS, miR-455 in exosomes from hUC-MSCs attenuated macrophage infiltration and cured liver damage via PI3K signaling [29].

3.1.2. Lung Injury

In an acute lung injury (ALI) mouse model established by cecal ligation puncture (CLP), miR-125 in exosomes derived from endothelial cells promoted VEGF expression, inflammatory response, improved pathological changes, restrained lung water content, protein content in bronchoalveolar lavage fluid, and cell apoptosis by targeting TOP2A [30]. In an LPS-induced ALI rat model, miR-384 in exosomes derived from BMSC alleviated pathological changes in lung, pulmonary vascular permeability, and attenuated the inflammatory response by targeting Beclin-1 [31]. In a sepsis-induced lung injury mouse model and an LPS-induced AEC damage model, ADSCs exosomes promoted autophagy activation through the delivery of circ-Fryl and the regulation of the miR-490/SIRT3 pathway [32]. In a mouse model of CLP-induced septic lung injury, miR-16 in exosomes developed from ADSCs relieved lung injury and promoted macrophage polarization by suppressing TLR4 [33]. In another study on an LPS-induced ALI mouse model, miR-377 in exosomes from hucMSCs suppressed bronchoalveolar lavage, inflammatory factors, and ameliorated lung injury by targeting RPTOR [34]. In a hyperoxia-induced ALI model established using LPS or K. pneumoniae, microvesicles containing miR-223/142 targeted lung macrophages and suppressed inflammatory lung responses by blocking N1rp3 and Asc [35]. In another LPS-induced ALI rat model, miR-22 in exosomes derived from UCB-MSCs suppressed pathological changes, apoptosis, NF-κB expression, and oxidative stress response by reducing FZD6 levels [36].

3.1.3. Heart Injury

miR-133-MSC transplantation improved cardiac function, and miR-133-overexpressing MSCs repressed cardiac expression of snail-1 and reduced inflammation and fibrosis in the infarcted heart in a rat myocardial infarction model [37]. βARKct EVs altered pro- and anti-inflammatory cytokine levels and prevented heart failure in a myocardial infarction or catecholamine toxicity mouse model. The miRNA profiling revealed that miR-7004 and mi7-7b were upregulated in βARKct present in EVs [38]. In a rat model of hypoxia-induced H9c2 myocardial cell injury, miR-126-enhanced ADSC-derived exosomes decreased the myocardial injury area of infarction, cardiac fibrosis, and inflammatory cytokine expression [39]. In a doxorubicin/trastuzumab-induced cardiac toxicity rat model, cardiac progenitor cell-derived exosomes were highly enriched in miR-146a that prevented myocardial fibrosis, CD68+ inflammatory cell infiltration, inducible nitric oxide synthase expression, and left ventricular dysfunction [40]. In an acute myocardial infarction rat model produced by surgical ligation of the left anterior descending coronary artery, exosomes from miR-146a-ADSCs promoted myocardial cell apoptosis, inflammatory response, and fibrosis, and attenuated myocardial infarction by downregulating EGR1 [41]. Using the same rat model, cardioprotection was observed by exosomes from miR-25-MSCs, and exosomes attenuated myocardial infarction by targeting EZH2 and pro-apoptotic proteins [42]. In a sepsis-induced mouse with myocardial infarction, miR-24 in exosomes derived from M2 macrophages had cardioprotective effects and alleviated myocardial injury by suppressing
miR-223 targeted SEMA3A and STAT3, and this miRNA in mice exosomes, had cardioprotective effects in CLP-induced sepsis [44]. In a mouse model of myocardial infarction caused by coronary artery ligation, exosomes overexpressing miR-129 showed enhanced cardiac function and production of inflammatory cytokines, and inhibited apoptosis and fibrosis by targeting HMGB1 [45]. In angiotensin II-induced hypertrophy in rat cardiomyocytes, hypertrophic cardiomyocyte-derived exosomes regulated macrophage activation and induced phosphorylation of ERK, JNK, and p38 through the miR-155-mediated MAPK pathway [46].

3.1.4. Bowel Disease

In a dextran sulfate sodium (DSS)-induced colitis mouse model, miR-378 carried by hucMSC exosomes attenuated colitis by regulating macrophage pyroptosis and inhibiting NLRP3 inflammasome activation [47]. Moreover, miR-590 carried by M2 macrophage exosomes suppressed inflammatory signals and promoted epithelial repair via the LAT51/YAP/β-catenin signaling axis [48]. Another study on the same model showed that miR-21a in M1 exosomes attenuated DSS-induced enteritis by decreasing the expression of E-cadherin and subsequent activation of ILC2s via KLRG1/GATA-3 [49]. In a rat small bowel transplantation model of allograft rejection, miR-200b in exosomes derived from heme oxygen-1 (HO-1)-modified BMSCs alleviated inflammatory injury of intestinal epithelial cells (IECs) by targeting Hmgb3 [50].

3.1.5. Kidney Injury

In the ischemia/reperfusion-injured mouse kidney, miR-23a-enriched exosomes from hypoxic tubular epithelial cells promoted tubulointerstitial inflammation in mice by inhibiting A20; hence, miR-23a inhibition suppressed renal tubulointerstitial inflammation [51]. In a lethal renal ischemia/reperfusion injury rat model, miR-146a, in exosomes derived from USC, inhibited injury via IRAKI and inhibited the activation of NF-κB signaling [52]. A mouse model that was administered a high-fat diet and streptozotocin injection showed that inhibiting Rab27a attenuated inflammation through the miR-26a/CHAC1/NF-κB pathway in renal proximal tubular epithelial cells [53]. In a kidney injury mouse model induced by CLP, miR-21 expression in exosomes extracted from the serum of mice with limb remote ischemic preconditioning in remote organs attenuated sepsis-induced renal injury and regulated the PDCD4/NF-κB and PTEN/AKT pathways [54].

3.1.6. Other Organs

In a taurocholate-induced acute pancreatitis rat model, pro-inflammatory miR-155 was increased in plasma exosomes, and miR-122 and miR-21 were decreased compared to that in plasma control exosomes. The levels of miRNAs in pancreatitis-associated ascitic fluid exosomes were similar to those in plasma control exosomes. Plasma exosomes had higher pro-inflammatory activity in macrophages [55]. In a rat model of urethral stricture generated with TGFβ1 injection, miR-146a in exosomes derived from TNF-α-treated MSCs inhibited fibroblast activation and suppressed the inflammatory response, TRAF6, IRAK1, and NF-κB signaling [56]. In an acute uterine injury mouse model induced by LPS, miR-223 enriched BMSC-Exos degraded NLRP3 via interaction with endothelial progenitor cells and suppressed LPS-induced cell pyroptosis [57].

3.2. Immune Dysfunction

Ten articles that we explored were related to the immune dysfunction of miRNAs in exosomes. Immune dysfunction is a disorder of the immune system that includes sepsis and asthma. Recent studies have investigated the roles of miRNAs in immune dysfunction and the associated diseases. We have now organized each miRNA that was introduced as the target of different immune dysfunction studies (Table 2).
Table 2. Extracellular miRNAs in immune dysfunction.

| Author                      | Disease                  | Subject | EV Type | Targeted miRNAs                  |
|-----------------------------|--------------------------|---------|---------|----------------------------------|
| Alexander et al. (2017) [58] | Chronic inflammation    | Mouse   | Exo     | miR-155                          |
| Appiah et al. (2021) [59]   | Sepsis                   | Mouse   | EV      | miR-146a, miR-9, and miR-155     |
| Balusu et al. (2016) [60]    | Systemic inflammatory diseases | Mouse | EV     | miR-1a, miR-9, miR-146a, miR-155 |
| Fernández-Messina et al. (2020) [61] | Immune diseases | Mouse | EV     | miR-20a, miR-25, miR-155         |
| Gao et al. (2021) [62]       | Sepsis                   | Rat     | Exo     | miR-1                            |
| Li et al. (2021) [63]        | Asthma                   | Mouse   | Exo     | miR-370                          |
| Okoye et al. (2014) [64]     | Systemic disease         | Mouse   | Exo     | let-7d                           |
| Shan et al. (2022) [65]      | Asthma                   | Mouse   | Exo     | miR-188                          |
| Song et al. (2017) [66]      | Sepsis                   | Mouse   | Exo     | miR-146a                         |
| Yue et al. (2017) [67]       | Systemic inflammation    | Mouse   | Exo     | miR-375                          |

Exo: exosome; EV: extracellular vesicle.

For a Rab27KO mouse model that displays a chronic, low-grade inflammatory condition, exosomes carrying miR-155 can rescue LPS responsiveness, and the reduction in miR-155 targeting SHIP1 and IRAK-M is involved in this rescue [58]. In an intestinal lavage of a septic mouse model, pro-inflammatory cytokines TNF-α and IL-17A were suppressed by septic-EV injection, and pro-inflammatory cytokines were targeted by multiple miRNAs upregulated by sepsis-induced exosomes. IEC-derived luminal EVs carry miRNAs that can alleviate pro-inflammatory responses [59]. In a CLP mouse model with severe sepsis, miR-146a, miR-9, and miR-155 functioned as pro-inflammatory messengers. Choroid plexus-derived EVs into CSF transferred pro-inflammatory messages to recipient brain cells, and blockage of EV secretion inhibited brain inflammation [60]. Using mouse chimeras with Rab27KO EV-deficient T cells, miR-20a, miR-25, and miR-155, which are carried in T-cell EV-modulated key mRNA in B cells, promote proliferation, survival, and transfer of EV-miRNA-controlled germinal center reaction and antibody production [61]. In a CLP rat model of sepsis, miR-1 increased in exosomes, and it inhibited proliferation, and promoted apoptosis and cytoskeleton contraction via SERP1 [62]. A mouse model of asthma induced by ovalbumin and miR-370 carried by M2 macrophage-derived exosomes alleviated asthma progression by inhibiting the FGF1 and MAPK/STAT1 signaling pathways [63]. In a mouse model of colitis and systemic inflammation, exosomes transferring let-7d from Treg cells to Th1 cells contributed to the inhibition and suppression of systemic disease [64]. In another ovalbumin-induced asthma mouse model, miR-188 in exosomes derived from hBM-MSCs suppressed the proliferation of BSMCs and lung injury through the JARID2/Wnt/β-catenin axis [65]. In CLP-induced sepsis, miR-146a in exosomes derived from MSCs with IL-1β promoted macrophage polarization to the M2 phenotype, reduced inflammation, and increased the survival of mice [66]. Using an IL-10 KO mouse model of systemic inflammation, endothelial progenitor cell exosomes improved endothelial cell proliferation and tube formation, and inhibited apoptosis. With IL-10 deficiency, impaired function was observed. Modulation of enriched miR-375 rescued IL-10KO-EPC-Exo dysfunction [67].

3.3. Neurological Disease

Only 13 articles included in this study were related to neurological diseases of miRNA in exosomes. Neurological diseases are associated with nervous system disorders. Here, we have discussed the roles or attenuation of miRNAs in exosomes in neurological diseases (Table 3).
Table 3. Extracellular miRNAs in neurological disease.

| Author                | Disease                      | Subject | EV Type | Targeted miRNAs               |
|-----------------------|------------------------------|---------|---------|------------------------------|
| Cai et al. (2021) [68]| Ischemic stroke              | Mouse   | Exo     | miR-542                      |
| Fang et al. (2020) [69]| Depression                   | Rat     | Exo     | miR-455, miR-126a, miR-122, miR-1b |
| Giunti et al. (2021) [70]| Neuroinflammation           | Mouse   | Exo     | miR-467f, miR-466q           |
| Huang et al. (2018) [71]| Traumatic brain injury—neuronal inflammation | Mouse   | Exo     | miR-124                      |
| Li et al. (2018) [72]  | Neuroinflammation            | Mouse   | Exo     | miR-21, miR-125a, miR-146a, miR-155 |
| Li et al. (2020) [73]  | Depression                   | Mouse   | Exo     | miR-207                      |
| Li et al. (2020) [74]  | Spinal cord injury           | Rat     | Exo     | miR-544                      |
| Ma et al. (2019) [75]  | Spinal cord injury           | Rat     | Exo     | miR-219a-2                   |
| Simeoli et al. (2017) [76] | Neuropathic pain           | Mouse   | Exo     | miR-21-5p, miR-21           |
| Song et al. (2019) [77] | Ischemic brain injury        | Rat     | Exo     | miR-181c                     |
| Xiaoying et al. (2020) [78] | Epilepsy                     | Mouse   | Exo     | miR-181a                     |
| Yang et al. (2021) [79] | Alzheimer’s disease          | Mouse   | Exo     | miR-146a                     |
| Zhai et al. (2021) [80] | Alzheimer’s disease          | Mouse   | Exo     | miR-22                      |

Exo: exosome; EV: extracellular vesicle.

In a mouse with middle cerebral artery occlusion used for cerebral infarction model, exosome-miR-542 derived from MSCs suppressed cerebral injury and inflammation by inhibiting TLR4 [68]. In a stress-induced depression mouse model, levels of BDNF, TrkB, and synaptotagmin 1 were decreased in the hippocampus, PFC, and serum exosomes. The miRNA profiling revealed that differentially expressed miRNAs were possibly involved in the pathogenesis of depression through the MAPK, Wnt, and mTOR pathways [69]. In an amyotrophic lateral sclerosis mouse model, miR-467f and miR-466q associated with MSC-derived s-EV reduced neuroinflammation. Furthermore, miR-467f and miR-466q reduce the activation of p38 MAPK signaling by inhibiting Map3k8 and Mk2 [70]. Using a repetitive traumatic brain injury mouse model, a study showed that miR-124 in exosomes improved neurologic outcomes and inhibited neuroinflammation by targeting PDE4B, thus suppressing mTOR signaling [71]. A study on a mouse model of endotoxemia induced by LPS that stimulated neuroinflammation revealed that the inflammatory cytokine mRNA, miR-155, and systemic inflammatory cytokine production increased. The serum-derived exosomes elevated inflammation-related miRNAs, such as miR-21, miR-125a, miR-146a, and miR-155. These miRNAs were engaged in modulating TLR signaling [72]. Using a chronic mild stress mouse model of depression, NK cell-derived exosomes carrying miR-207 alleviated symptoms such as depression and decreased pro-inflammatory cytokines, targeted TLR4, and hence an inhibited NF-kB signaling in astrocytes [73]. In a rat model of spinal cord injury, miR-544 in exosomes derived from BMSC attenuated histological deficits and neuronal loss, and inhibited inflammation induced by spinal cord injury [74]. Another study used a rat model of spinal cord injury and revealed that exosomes improved neuroprotective effects through the miR-219a-2/YY1 axis [75]. In a mouse model of spared nerve injury, miR-21 antagonir in the dorsal root ganglia reduced pro-inflammatory macrophage infiltration, and miR-21 deletion in sensory neurons reduced neuropathic hypersensitivity [76]. For an ischemic brain injury rat model established by middle cerebral artery occlusion, miR-181c in the cortical neuron released exosomes that inhibited neuroinflammation by suppressing CXCL1 [77]. In a mouse model with KA-induced epileptic seizures, circHivep2 exosomes prevented microglial cell activation and inflammatory factors through the miR-181a/SOCS2 mechanism [78]. In a mouse model of Alzheimer’s disease induced by LPS, miR-146a was enriched in EVs under inflammatory conditions, and EVs can induce inflammation and LPS tolerance [79]. Using the APP/PS1 mouse model of Alzheimer’s disease, miR-22 in exosomes from ADMSC enhanced neurological function, inhibited PC12 apoptosis, and decreased inflammatory factors by inhibiting proptosis [80].
3.4. Metabolic Syndrome

Only seven of the ninety-five articles explored were related to metabolic syndromes involving miRNAs of exosomes. Metabolic syndrome increases the risk of heart disease, diabetes, and other health problems. Here, we determined how miRNAs in exosomes play a role in metabolic syndrome (Table 4).

| Author                  | Disease                                      | Subject   | EV Type | miRNAs                                      |
|-------------------------|----------------------------------------------|-----------|---------|---------------------------------------------|
| Huang et al. (2021)     | Ischemic disease—diabetic foot               | Rat       | Exo     | miR-21                                      |
| Lakhter et al. (2018)   | Type 1 diabetes                              | Mouse     | EV      | miR-21                                      |
| Li et al. (2021)        | Diabetic retinopathy                         | Mouse     | Exo     | miR-17                                      |
| Pan et al. (2019)       | Obesity-induced metabolic inflammation       | Mouse     | Exo     | miR-34a(let-7d, miR-142, let-7i, miR-145a, miR-190, miR-15b, miR-192, miR-21a, miR-29a, miR-342, miR-345, miR-409, miR-486a, miR-744) |
| Resaz et al. (2020)     | Glycogen storage disease type 1a             | Mouse     | Exo     | miR-34a                                     |
| Sun et al. (2021)       | Type 2 diabetes mellitus                     | Mouse     | Exo     | miR-29                                      |
| Ying et al. (2021)      | Obesity                                      | Mouse     | Exo     | miR-690                                     |

Exo: exosome; EV: extracellular vesicle.

In a streptozotocin (STZ)-induced diabetic rat model, miR-21 exosomes from MSCs promoted ulceration repair, ischemic hindlimb blood perfusion, ischemic repair, and angiogenesis [81]. Using a non-diabetic NOD mouse model of type 1 diabetes, the increase in serum EV miR-21 preceded hyperglycemia and circulating EV miR-21 could be a biomarker of developing type 1 diabetes [82]. In a mouse model, miR-17 containing hucMSCs-derived exosomes alleviated oxidative injury by inhibiting STAT1 [83]. In a mouse model of dietary obesity induced by STC nutrition and a high-fat diet (HFD), miR-34a of adipocyte-secreted exosomal vesicles led to obesity-induced metabolic dysfunction and M2 macrophage proliferation by inhibiting KLF4 [84]. Using the plasma exosomes from a glycogen storage disease type 1a mouse model, differentially expressed miRNAs were correlated with various pathologic liver states and circulating miRNAs could be a biomarker of glycogen storage disease type 1a [85]. In the case of a type 2 diabetic mouse, miR-29 promoted inflammation and diabetes via TRAF3 [86]. In an obese mouse model established by feeding a HFD, miR-690 in exosomes from M2-polarized bone marrow-derived macrophages improved insulin sensitivity via NADK [87].

3.5. Vesicular Disease

Among the 95 articles, only 8 articles were associated with miRNAs exosomes in vesicular disease. Vesicular disease is a kind of blood vessel disorder, which can occur in the location of different types of artery and veins. We organized the relations between miRNA exosomes and vesicular diseases (Table 5).

In a mouse model of atherosclerotic diabetes, EPC-derived exosomes and its miRNAs ameliorated diabetic atherosclerotic plaques, endothelial dysfunction, and inflammatory factors [88]. In an atherosclerosis mouse model established by feeding a HFD, IRES-II-10 mRNA carried in exosomes can be activated by miR-155 and alleviate local inflammation [89]. miR-512 enriched by MSC-derived exosomes had a protective effect on EC cells against oxidized low-density lipoprotein via targeting KEAP1 [90]. In the same HFD-induced atherosclerosis mouse model, hUCMSC-derived exosomes carrying miR-100 decreased the atherosclerotic plaque area and inflammation via FZD5/WNT/β-catenin pathway [91]. In a mouse model of hypoxic pulmonary hypertension, MSC-derived exosomes inhibited STAT3 and increased the miR-17 microRNA superfamily [92]. In another HFD-induced atherosclerosis mouse model, MSCs-exosomes suppressed the atherosclerotic plaque area and macrophage infiltration via let-7/HMGA2/NF-kB pathway [93]. In an
atherosclerosis mouse model established by feeding a HFD, miR-146a derived from oxidized low-density lipoprotein treated THP-1 cells exosomes enhanced the atherosclerotic plaque area and led to atherosclerosis deterioration via targeting SOD2 [94]. In the rat myocardial ischemia-reperfusion injury model, miR-98 in exosomes from hypoxic BMSCs promoted cardiac function and suppressed the inflammation response by targeting TLR4, and thus activating the PI3K/Akt signaling pathway [95].

Table 5. Extracellular miRNAs in vesicular disease.

| Author             | Disease               | Subject | EV Type | miRNAs             |
|--------------------|-----------------------|---------|---------|---------------------|
| Bai et al. (2020)  | Atherosclerosis       | Mouse   | Exo     | miR-21a, miR-222, miR-221, miR-155, miR-29a, miR-199a, miR-146a |
| Bu et al. (2021)   | Atherosclerosis       | Mouse   | Exo     | miR-155            |
| Chen et al. (2021) | Atherosclerosis       | Mouse   | Exo     | miR-512            |
| Gao et al. (2021)  | Atherosclerosis       | Mouse   | Exo     | miR-100            |
| Lee et al. (2012)  | Pulmonary hypertension| Mouse   | Exo     | miR-204            |
| Li et al. (2019)   | Atherosclerosis       | Mouse   | Exo     | let-7              |
| Zhang et al. (2019)| Atherosclerosis       | Rat     | Exo     | miR-146a           |
| Zhang et al. (2021)| Coronary artery disease| Rat     | Exo     | miR-98             |

Exo: exosome; EV: extracellular vesicle.

3.6. Arthritis

Six of the ninety-five articles studied were related to miRNA exosomes involved in arthritis. Arthritis is a disorder that commonly affects joints. This usually makes it difficult for them to be active. We examined how exosomal miRNAs influence arthritis (Table 6).

Table 6. Extracellular miRNAs in arthritis.

| Author              | Disease              | Subject | EV Type | miRNAs     |
|---------------------|----------------------|---------|---------|------------|
| Donate et al. (2021)| Rheumatoid arthritis| Mouse   | EV      | miR-132    |
| Huang et al. (2021) | Osteoarthritis       | Mouse   | Exo     | miR-206    |
| Huang et al. (2022) | Rheumatoid arthritis | Rat     | Exo     | miR-223    |
| Tao et al. (2021)   | Osteoarthritis       | Rat     | Exo     | miR-361    |
| Tavasolian et al. (2020)| Rheumatoid arthritis| Mouse   | Exo     | miR-146a, miR-155 |
| Zheng et al. (2020) | Rheumatoid arthritis | Rat     | Exo     | miR-192    |

Exo: exosome; EV: extracellular vesicle.

In a mouse model of mBSA-induced arthritis, the injection of anti-miR-132 attenuated inflammatory arthritis [96]. In a mouse model of osteoarthritis, miR-206 in exosomes from BMSC promoted proliferation and osteoblast differentiation by inhibiting ELF3 [97]. In another rat model of arthritis, miR-223 in exosomes from BMSCs regulated inflammation by inhibiting NLRP3 [98]. Using an osteoarthritis rat model established by surgery, researchers found that miR-361 from hBMSC-derived exosomes alleviated chondrocyte damage by inhibiting DDX20; thus, the NF-κB signaling pathway was inactivated [99]. In a collagen-induced arthritis (CIA) mouse model, miR-146a in MSC-derived exosomes increased FOXP3, TGFβ, IL-10, and miR-155 levels that increased RORγt, IL-17, and IL-6 levels. Such modulations altered Treg cell levels and possibly improved the recovery of appropriate T-cell responses in RA [100]. In a CIA rat model, miR-192 in exosomes developed from BMSCs reduced the inflammatory response by targeting RAC2 [101].

3.7. Cancer

Only five of the ninety-five articles we studied were associated with roles of miRNA exosomes in cancer. Cancer is a type of disease with abnormally increased growth of cells that spreads easily, commonly leading to low survival rates. We discussed the relationships between the different types of cancer and miRNAs in exosomes and determined the underlying mechanism (Table 7).
Table 7. Extracellular miRNAs in cancer.

| Author                      | Disease          | Subject | EV Type | miRNAs            |
|-----------------------------|------------------|---------|---------|-------------------|
| Gorczynski et al. (2017)    | Breast cancer    | Mouse   | Exo     | miR-155, miR-205  |
| Guo et al. (2020)           | Breast cancer    | Mouse   | Exo     | miR-183           |
| Li et al. (2021)            | Lung cancer      | Mouse   | Exo     | miR-101           |
| Van der Vos et al. (2016)   | Glioblastoma     | Mouse   | EV      | miR-21            |
| Wang et al. (2022)          | Colorectal cancer| Mouse   | Exo     | miR-146a          |

Exo: exosome; EV: extracellular vesicle.

In a mouse model, tumor growth was decreased by miR-155, whereas miR-205 increased tumor growth. miR-155 and miR-205 play important roles in tumor growth of breast cancer cells in mice [102]. In a breast tumor mouse model, miR-183 in exosomes derived from tumor cells decreased tumor growth and promoted pro-inflammatory cytokines by targeting PPI2CA [103]. In a tumor initiated by xenographs of lung tumor cells of mice, the injection of miR-101 suppressed lung tumor growth, macrophage tumor infiltration, and inflammation and inhibited CDK8 and Ki-67 expression [104]. In an intracranial mouse glioma model induced by injections of GL261 glioma cells, uptake of glioma cell-released EVs by microglia/macrophages in the brain increased miR-21, decreased c-Myc mRNA, and increased the proliferation of mouse microglia [105]. In an azoxymethane/DSS-induced colitis-associated colorectal cancer model, miR-146a transfected into human MSC-derived exosomes alleviated cancer progression by inhibition of SUMO1 [106].

3.8. Other Inflammatory Diseases

Eleven articles were discussed that dealt with other inflammatory diseases. We examined the mechanisms of action of miRNA exosomes in diverse diseases (Table 8).

Table 8. Extracellular miRNAs in other inflammatory disease model.

| Author                      | Disease                        | Subject | EV Type | miRNAs            |
|-----------------------------|--------------------------------|---------|---------|-------------------|
| Byun et al. (2022)          | Periodontitis                  | Mouse   | Exo     | miR-25            |
| Li et al. (2022)            | Traumatic bone defects         | Rat     | Exo     | miR-451a          |
| Liu et al. (2021)           | Aseptic loosening and poor osteointegration | Mouse/rat | Exo | miR-181b         |
| Liu et al. (2021)           | Acute graft-versus-host disease | Mouse   | Exo     | miR-223           |
| Song et al. (2022)          | Tendon pathologies             | Rat     | Exo     | miR-144           |
| Tsai et al. (2021)          | Ototoxicity-induced hearing loss| Mouse   | Exo     | miR-125a, miR-125b, miR-127 |
| Wang et al. (2019)          | OPMD                           | Hamster | EV      | miR-185           |
| Xu et al. (2021)            | Intervertebral disc degeneration | Mouse | Exo  | miR-141           |
| Yang et al. (2019)          | Placental oxidative stress, preterm birth | Mouse | Exo | miR-146a, miR-548e |
| Zhang et al. (2020)         | Periodontitis                  | Rat     | Exo     | miR-17            |
| Zhu et al. (2020)           | Intervertebral disc degeneration | Mouse | Exo  | miR-142           |

Exo: exosome; EV: extracellular vesicle.

In a ligature-induced periodontitis and diet-induced obesity mouse model, an miR-25 inhibitor suppressed local inflammation, and exosomes of miR-25 in saliva contributed to the advancement of diabetes-associated periodontitis [107]. Using a rat model of skull defects, a study found that exosomes from adipose-derived stem cells improved bone healing and regulated M1/M2 macrophage polarization via the miR-451a/MIF axis [108]. In a femoral defect model established by surgery, miR-181b in exosomes promoted osteointegration and suppressed the inflammatory response via the PRKCD/ AKT axis [109]. In an acute graft-versus-host disease mouse model, miR-223 in exosomes derived from MSCs inhibited inflammatory cytokines and attenuated disease progression by suppressing donor T-cell migration [110]. A study using a tendon defect model showed that miR-144 enriched in exosomes from tendon-derived stem cells improved the injured tendons. The performance of biomechanical testing was enhanced by targeting ARID1A [111]. In a
cisplatin-induced hearing loss mouse model, miRNAs such as miR-125a, miR-125b, and miR-127 were highly abundant in UCMSC exosomes that improved hearing loss through reduced cochlear hair cell loss [112]. In a dimethylbenzanthracene-induced oral potentially malignant disorder (OPMDs) hamster model, miR-185 in extracellular vesicles derived from MSCs alleviated the inflammatory response and suppressed the progression of OPMDs by targeting AKT [113]. In a mouse model of intervertebral disc degeneration, established using the puncture method and H2O2 exposure, platelet-rich plasma exosomes enriched with miR-141 suppressed IVD degeneration by activating the KEAP1/NRF2 pathway [114]. In a preterm birth induced by lipopolysaccharides (LPS), miR-146a levels were elevated. miR-146a and miR-548e from amniotic fluid-derived MSCs showed anti-inflammatory effects on human trophoblasts [115]. In a periodontitis rat model induced by LPS, miR-17 in periodontal ligament stem cells was suppressed by inflammation and alleviated its target VEGFA [116]. In an IL-1β-induced intervertebral disc degeneration model, miR-142 in exosomes derived from BMSCs alleviated NPC injury by targeting MLK3, thus inhibiting MAPK signaling [117].

4. Conclusions

Experimental studies of EVs and miRNAs are newly emerging and are in demand. We focused on diverse EV-associated miRNAs that play crucial roles in various inflammatory diseases. In this review, we have discussed the association of miRNAs in EVs with inflammatory diseases in rodent models. EVs have been recognized as the cargo of various molecules transported from origin cells to recipient cells mostly in all organisms. EVs also play complex and important roles in the pathophysiology of several diseases. Moreover, diverse EV-associated miRNAs play crucial roles in various inflammatory diseases. Given the previously suggested functions of EVs and increasing interest in clinical implications of EVs in various diseases, this study focused on miRNA in EVs in inflammatory diseases to further analyze their involvement in inflammatory responses. However, the studies included in this review are insufficient for comprehensive knowledge about the mode of action of extracellular miRNAs in inflammation. In addition, the included studies mostly reported changes in miRNA expression in different disease models, yet there was limited evidence of how the loss or gain of each miRNA function work in disease conditions. Further functional studies on each miRNA in inflammatory disease are needed to confirm the use of extracellular miRNAs as potential biomarkers or as a therapeutic method in which they can be safely and efficiently delivered to the target region. Nevertheless, our understanding suggests an opportunity for further study of extracellular miRNAs as biomarkers and the early diagnosis of inflammatory diseases and disorders. Moreover, the use of EVs might further offer the possibility of gene therapeutic approaches for inflammation.

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