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# Modulation of Immune Responses by Exosomes Derived from Antigen-Presenting Cells

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**ABSTRACT:**

The mediating role of exosome-mediated signalling in the inflammatory response is significant. Exosomes transport a wide variety of biomacromolecules, such as proteins, lipids, coding and non-coding RNAs, and a variety of lengths of RNA, to the cells they infect in order to carry out their biological or pathological activities. Therapeutic effects may be conferred by attenuating or boosting the immune response via exosomes released by antigen-presenting cells. In order to modify T cell responses specific to antigens, exosomes are essential for transporting and displaying functional major histocompatibility peptide complexes. Dendritic cell (DC) exosomes have immunostimulatory capabilities and have been investigated for use in cancer treatment due to their ability to stimulate T and B cells. In animal models of several inflammatory diseases, exosomes produced by macrophages and DCs have immunosuppressive characteristics that alleviate inflammation. Research on exosomes produced by dendritic cells (DCs) and macrophages (macrophages) is the primary emphasis of this review, which aims to shed light on the protective function of exosomes in reducing inflammation and enhancing the immune response.
Inflammation, exosomes, dendritic cells, and macrophages are relevant terms.

## Introduction

The inflammatory response is a tightly controlled process that involves a complex network of cells communicating with each other. Biomolecules like as cytokines, chemokines, and even metabolites are secreted and then detected by receptors, allowing for several channels of information transmission. Inflammation is initiated, maintained, and resolved by uni- and bidirectional communication between immune and non-immune cells.1 Cytokines are molecules that mediate most interactions between immune cells. These molecules are produced in response to various stimuli. A new way whereby exosomes, a kind of extracellular vesicles (EVs), regulate inflammation has recently come to light in the scientific literature.
You can categorise the extracellular vesicles (EVs) secreted by cells according to their size and where they originated inside the cell. Ectosomes and microvesicles are the names given to extracellular vesicles (EVs) that are produced when a cell's plasma membrane bursts. In contrast to ectosomes, exosomes are formed when the inner endosomal membrane undergoes inward budding, resulting in multivesicular structures. Thereafter, the plasma membrane is fused with multivesicular bodies.2 Sizes of these vesicles vary between 30 and 150 nanometers. Enclosing messenger RNAs (mRNAs) and microRNAs (miRNAs), these lipid bilayers include proteins both transmembrane and cytosolic.3–8 To help identify whatever biological cargo or activities are associated with EVs, the International Society for Extracellular Vesicles has published an editorial outlining a basic set of biochemical, biophysical, and functional criteria.9 Once exosomes have been isolated, their purity may be assessed by using techniques such as western blotting and electron microscopy. Exosome processing, such as centrifugation, dehydration, and fixation for transmission electron microscopy, may change the shape and size of the vesicles, according to reports. It has been suggested that variations in sample processing would explain why some investigations have found exosomes with a cup-shaped form.10,11 One way to detect exosomes is by looking for proteins that are abundant in them. Hsp70, CD63, CD81, and CD914 are exosomal markers often utilised in tet-raspanin family glycoprotein research. Cells are able to interact with nearby and faraway cells via these vesicles. The chemicals found on electric vehicle surfaceS

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let them zero in on recipient cells. By interacting with their receptors and ligands, these EVs may trigger signalling. They can also be taken in by the cell by endocytosis and phagocytosis, or they can fuse with the target cell's membrane and release their contents into the cell's cytoplasm.8 The secretion of exosomes by donor cells is crucial for the biological effects that exosome absorption mediates in recipient cells.12, 13 The origin and physiological state of the cells secreting the exosomes determine their specific composition. Infection, inflammation, or tumour cell transformation may cause changes that impact and change the exosome composition. This tightly controlled process is dynamically changed by signalling signals, however, since not all components of the parent cell make it into the exosomes. Their biomarker value and biological effects upon absorption are both rooted in the diversity of biomolecules inside exosomes. We know that exosomes may be either protective or harmful, and their involvement in pathogenesis is well-established, but their significance in normal cellular homeostasis is still being figured out.14 Researchers have shown that exosomes produced by dendritic cells (DCs) and macrophages may reduce inflammation and boost the immune response; here, we will mainly discuss these effects.

### Immunomodulatory Function of exosomes

The immune response is a combination of innate and adaptive reactions. All multicellular creatures possess an innate immune system that has been maintained via evolution, however only vertebrates have an adaptive immune response.15 A few number of receptors mediate the innate immune system's activation by identifying molecular patterns associated with pathogens or damage.the number of An example that has been extensively studied in mammals is Toll-Like Receptors (TLRs). These germline-encoded receptors are often known as pattern recognition receptors. Antigen receptors in adaptive immune systems are produced by somatic hypermutations rather than being germline encoded.18 The adaptive immune system's large repertoire of antigen receptors is a direct contrast to the innate immune system's small repertoire of receptors for molecular patterns associated with pathogens or damage.19 The adaptive immune system primarily consists of two cell types: T cells and B cells. T lymphocytes identify antigens via the process of antigen presentation, while B cells are capable of directly recognising antigens. APCs include dendritic cells and macrophages. These APCs take in foreign antigens and attach them to molecules of major histocompatibility complexes I and II (MHCI and MHCII), respectively, so that naïve CD8 and CD4+ T cells may be presented with them. The T cells are then taught to remember the antigen.20

To modify antigen-specific CD8+ and CD4+ responses, exosomes transport and display functional MHC-peptide complexes.6,21 The talk at hand

both direct and cross-presentational forms are possible. When antigen-specific T cells contact MHC-peptide complexes on exosomes in direct presentation, it activates the T cells. In cross-presentation, APCs take in antigens in exosomes, digest them further, and then offer the resulting peptides to T lymphocytes. When antigenic peptide-MHC complexes are deposited onto DCs and then pre-sent to T lymphocytes, this process is called cross-dressing. It may also lead to cross-presentation.6 The therapeutic or protective advantages imparted by exosomes are therefore based on these characteristics.

### Immunomodulatory Role of exosomal RNA

Exosomes isolated from human plasma samples were subjected to RNA-sequencing analysis, which revealed the existence of many RNA species inside these circulating vesicles.22 Long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) are examples of these types of noncoding regulatory RNAs.23, 24-27 It has been shown that RNA, upon absorption, may operate in the receiving cell4,28. According to research using RNA sequencing in both inactive and activated macrophages, inflammation changes the gene expression pattern. Regulating the

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transcriptionome alterations caused by inflammation is a process that depends on the time of transcription factor activation and the location of nascent transcripts, which may be either chromatin-associated, nucleoplasmic, or cytoplasmic.29,30 dollars A different research sequenced exosomal RNA from naïve and lipopolysaccharide (LPS)-stimulated macrophages to find out whether inflammation-induced changes are mirrored in the exosomal transcriptome. Exosomal mRNAs from naïve cells and those from LPS-stimulated cells varied in pathways associated to NF-κB activation and TLR cascades, according to pathway analysis, which demonstrated significant alterations in both the adaptive and innate immunological processes.31 Inflammatory cytokines are produced and NF-κB is activated when tumour cells release exosomal miRNAs miR-21 and miR-29a, which may bind to TLR8 and TLR7 in immune cells.32 Research including RNA profiling and sequencing has shown that exosomes contain a high concentration of miRNAs.2,4 Additionally, it is well-known that exosomal miRNA repertoires vary from donor cell repertoires.33 New research on the processes that decide which cellular miRNAs make it into exosomes suggests that there may be active regulation of which miRNA species make it into exosomes. Endogenous messenger RNAs regulate messenger RNA sorting to exosomes and transmission to acceptor cells, according to one research.34 The results of this work suggest that cells modify miRNA:mRNA balance by exosomal miRNA release, a process by which miRNAs are quickly disposed of outside their targets. Four possible methods for miRNA sorting into exosomes have been identified based on current research. The following procedures comprise the sorting process for miRNAs found in exosomes: (1) The pathway depends on neural sphingomyelinase 2 (nSMase2): an increase in exosome secretion and exosomal miRNAs was seen with overexpression of nSMase2. On the other hand, suppression

nSMase2 expression decreased the quantity of miRNAs found in exosomes.35 (2) A mechanism relying on sumoylated heterogeneous nuclear ribonucleoproteins (hnRNPs) and the miRNA motif: sumoylated hnRNPA2B1 identified the GGAG motif (EXOmotif) in miRNA sequences and triggered the packing of certain miRNAs into exosomes.36 A transport protein called hnRNPA2B1 is able to precisely recognise and bind to miRNAs that are often found in exosomes because of its short EXO-motif sequence. The loading of these microRNAs into exosomes is controlled by this motif.36 The miRNAs that were abundant in the exosomes produced by T cells have this particular 4-nucleotide sequence (GGAG) repeated many times. (3) The 3□miRNA sequence-dependent pathway: direct miRNA sorting into exosomes may be aided by adenylation and uridylation of miRNA at its 3□end, suggesting that the 3□end may include a crucial sorting signal.37(4) The miRNA-induced silencing complex (miRISC) pathway: mature miRNAs may engage in the formation of the miRISC complex via interactions with the assembly proteins GW182 and AGO2. Multi vesicular bodies and miRISC components were shown to be co-localized, and AGO2 was found to be correlated with exosomal miRNA sorting. Reduced kinds or quantity of selectively exported miRNAs may be seen in AGO2 knockout mice.38 In conclusion, exosomal miRNA sorting may be regulated by certain sequences in miRNAs, which in turn may be guided into exosomes. Other factors, such as the mRNA targets of miRNAs that are being sorted, may also contribute to this process.34 Endogenous microRNAs (miRNAs) are known to have a role in the inflammatory response via their transfer between immune cells and their functionalization in recipient cells. A functioning immunological synapse improves the exosome-mediated transport of miRNAs from T cells to APCs. The definition has expanded to include interactions with innate immune cells like Natural Killer (NK) cells, while it was first defined in terms of cells of the adaptive immune system, such as T and B cells.40 T cells and their related APCs are able to exchange miRNA-loaded exosomes across the immunological synapse.3

The transforming growth factor-beta (TGF-β) pathway, chemokine signalling, and the LPS-responsive miRNAs found in exosomes have all been linked to verified mRNA targets.41 The exosomal biomolecular signature will vary across cell types and between species, as shown by a comparison of the miRNA profile in exosomes

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extracted from THP-1 cells (a human-derived monocytic cell line) and RAW 264.7 murine macrophages, both with and without LPS stimulation. Therefore, the chemicals in the vesicles will be affected by the species and physiological condition of the cells that secrete the exosomes.31 After LPS stimulation of RAW 264.7 cells, the most abundant noncoding RNA populations underwent a dramatic change, as seen in the same research. Since exosomes include pre-miRNAs and snoRNAs, it's reasonable to assume that they transport molecules with the potential to regulate the recipient cells' temporal epigenetics.

the progression of genes involved in inflammation.30 Instead of relying on nuclear control, the fast release of inflammatory-relevant pre-miRNAs into LPS-stimulated cells suggests a requirement for an immediate response to inflammation. By rapidly modifying inflammatory protein mRNA levels, mature miRNAs may fine-tune inflammation control, while pre-miRNAs provide a subsequent wave of regulation. The benefit of exosomes is that they may transport easily-translated messenger RNAs (mRNAs) and proteins and microRNAs (miRNAs) that are ready to operate instantly.31
Exosomes contain mRNA fragments that are abundant in the 3□ untranslated regions (UTR), according to a recent research.42 The 3' untranslated regions (UTRs) of messenger RNAs (mRNAs) play an important regulatory function and include the coding regions of several RNA-binding proteins that control how well mRNAs are translated and how stable they are. The RNA-induced silencing complex (RISC) is guided by its various miRNA target-binding sites, which in turn cause miRNA binding via seed sequence complementarity, leading to destruction or translational suppression. Some have hypothesised that exosome-transported mRNA fragments could compete with other RNAs for target-cell mRNA stability, localization, and translational activity.42

### Immunomodulatory Role of exosomal Proteins

Different types of vesicles, ranging in size and origin, are secreted by cells. It is common practice to distinguish EVs using protein markers. In a recent work, the protein content of all EVs recovered using the several phases of the differential ultracentrifugation protocol—the conventional method for isolating exosomes—was carefully analysed.43 The capacity of DCs produced from human primary monocytes to enhance immunological responses led to their selection as source cells. The results of quantitative proteomic analysis showed that although certain protein markers are general, others are exclusive to exosomes. Exosome specific protein markers were found to be one of three tetraspanins: CD63, CD81, or CD9.43
Unlike cell waste, which contains a random assortment of proteins, exosomes have an enriched proteome that comprises membrane, cytosolic, nuclear, and endosomal proteins.44 Protein composition of exosomes from different research is compiled in databases like as Exocarta, Vescilepedia, and EVpedia.47 Exosomes include a variety of proteins, including those linked with endosomes (Rab GTPase, SNAREs, Annexins, and flotillin), proteins involved in the formation of exosomes (ESCRT complex, ALIX, TSG101), the aforementioned tetraspanins, heat shock proteins (HSP70, HSP90), and MHC.48 Important soluble mediators, including cytokines, are transported by exosomes. Cytokines without an N-terminal signal peptide are secreted in a leaderless fashion by exosomal release.49 There is a known inventory of cytokines released by EVs.48 LPS-induced RAW 264 activation.Seven mouse macrophage cells have the ability to stimulate the release of cytokines into culture medium after a 24-hour period. Endosomes isolated from RAW 264.7 macrophages in an LPS-stimulated mouse

had elevated levels of cytokines, most of which were chemokines. When stimulated with LPS, RAW 264.7 cells released 16 cytokines, whereas only 10 of them were found in RAW 264.7. Exosomes produced by cells.31 The whole range of cytokines linked with EVs has not been determined by systematic investigations. Furthermore, it is still unclear how much vesicular localization of cytokines impacts standard cytokine assays.49

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### Therapeutic Benefits of exosomes

By reducing or enhancing the immune response, exosomes may provide therapeutic advantages.5 Exosomes produced by dendritic cells (DCs) have the ability to enhance immunological responses in living organisms. This is achieved by passing peptide-MHC complexes from DCs that have come into contact with an antigen to another DC that has not (Fig. 1).5 The maturation status of the DCs secreting the exosomes determines their capacity to activate immunological responses. As they mature, dendritic cells (DCs) increase their capacity to stimulate T cells by carrying additional costimulatory molecules, intercellular adhesion molecule-1 (ICAM-1), and MHCII.50,51 It is also known that the miRNA profile of exosomes generated from DCs is affected by their maturation status.52

By using Dex, immunotherapy has been made possible, overcoming some of the obstacles that have previously been encountered with using DCs in clinical settings. In addition to being able to be manufactured in a controlled environment and stored for an extended period of time, exosome administration removes the dangers of in vivo replication.

and microvasculature cell lodging.15 A single intradermal injection inhibited tumour development or completely eradicated existing tumours in mice, suggesting that Dex generated from tumour peptide-stimulated DCs may drive tumor-specific cytotoxic T lymphocyte responses in vivo.53 Strategies that use DCs or their roles in eliciting T-cell responses specific to tumor-associated antigen (TAA) have shown promise in cancer immunotherapy.7 The ability of DCs to display TAA and trigger responses specific to TAA is maintained by exosomes.54,55 The in vivo effectiveness of exosomes is enhanced by the presence of antigen-presenting MHC I and II molecules, the ICAM for adherence, and integrins for docking. Two trials validated the safety profile of Dex and shown its viability for large-scale production in patients.56; 57 Patients with advanced-stage melanomas56 or non-small cell lung cancer (NSCLC)57 expressing melanoma-associated antigen were included in the clinical studies. Researchers found that patients with advanced disease who took the first generation of Dex saw NK-cell effector functions, but they saw very few or no T-cell responses specific to antigens linked with melanoma.56; 57 The development of second-generation Dex was spurred by the limited immunogenic capabilities of the first, with the goal of enhancing NK and T-cell immune responses. Dex released by DCs treated with interferon-α (IFN-γ) has increased immunogenicity compared to Dex released by immature DCs because it expresses larger quantities of CD40, CD80, CD86, and ICAM-1 molecules.58

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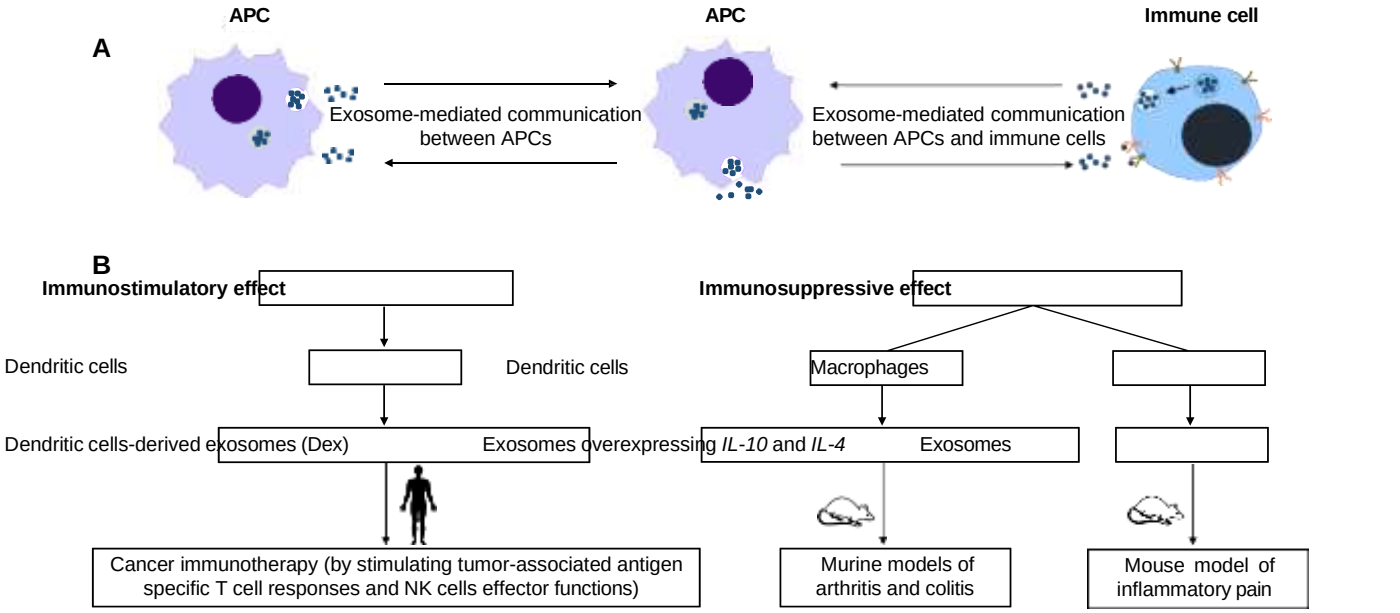


**Figure 1.** Immunomodulatory effects of exosomes derived from APCs.
**Notes:** (**A**) Exosomes released from APCs including Dendritic Cells (DCs) and macrophages can play a role in carrying and presenting functional MHC–peptide complexes. This presentation can be direct or occur as a cross-presentation. Exosomes can thus establish a bi-directional mode of communication between APCs and immune cells. (**B**) Exosomes secreted by APCs can have both immunostimulatory and immunosuppressive effects. Dex augment anticancer immune response by enhancing NK and T-cell effector functions. Immunosuppressive effects have been demonstrated for exosomes secreted by DCs and macrophages. Exosomes produced by DCs engineered to over express certain genes including *IL-10* and *IL-4* reduced inflammation in murine models of arthritis. Exosomes from LPS-stimulated macrophages can reduce thermal hyperalgesia and edema in a mouse model of inflammatory pain.

Participants in a phase-II clinical study lacked tumour progression and had incurable NSCLC. After induction chemotherapy, maintenance immunotherapy was performed using IFN-η-Dex loaded with cancer antigens that were limited to MHC class I and class II. The major aim of this 22-patient trial was not achieved; that is, to have at least half of the patients still alive four months after treatment stopped. But this research shown that these Dex may strengthen the anti-tumor immunity of NK cells in those with advanced NSCLC.59 Multiple disease models, including rheumatoid arthritis (RA), have shown that APC-derived exosomes impart immunosuppressive effects.Inflammation and hypertrophy of the synovium are hallmarks of rheumatoid arthritis (RA), a systemic autoimmune disease. Murine collagen-induced arthritis was delayed by DCs treated with recombinant murine IL-10 or DCs transduced with an adenovirus expressing the IL-10 gene.61 plus 62 Evidence from many trials shows promise for the use of exosomes produced by DCs modified to overexpress certain genes, such as IL-10, IL-4, FasL, and indoleamine 2,3 dioxygenase (IDO). Direct injection of recombinant murine IL-10 had no impact on the course of carrageenan-induced arthritis in mice, however systemically delivering a single dose of these exosomes significantly improved the condition.In a study on inflammation in murine arthritis, 63 DCs altered to express IL-4 were shown to be beneficial. Systemically administered exosomes produced from these DCs proved to be more efficient than repeated injections of recombinant IL-4 in lowering the severity and occurrence of established arthritis.61 Exosomes produced by DCs that express FasL had an impact that was comparable to that of the parent cells; they may downregulate collagen-reactive T cells and halt the advancement of carrageenan-induced arthritis in mice after systemic injection.62 Upon local injection, FasL-expressing DCs exhibited an anti-inflammatory impact in a delayed hypersensitivity paradigm in mice.64 By reducing inflammation, inhibiting T cell activation, and suppressing T-cell responses to auto- and alloantigens by tryptophan deprivation and/or generation of toxic metabolites, exosomes from DCs expressing IDO were shown to be effective.65 Exosomes produced by IL-10-treated dendritic cells (DCs) reduced TNBS-induced colitis.66 Exosomes produced from modified DCs have immunosuppressive effects, according to these findings, which suggests they may have therapeutic potential (Fig. 1).
A single intraplantar injection of complete Freund's adjuvant (CFA) significantly decreased paw edoema in mice when administered via exosomes from LPS-stimulated macrophages. In a mouse model of inflammatory pain, a single injection of exosomes reduced heat hyperalgesia, indicating that exosomes produced from macrophages may have an immunoprotective function (Fig. 1). Animals treated with CFA showed a transitory increase in thermal hypersensitivity

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when injected with exosomes purified from LPS-stimulated macrophages, but animals treated with saline did not exhibit this effect. Injections of exosomes from LPS-stimulated RAW 264.7 cells into CFA-treated mice resulted in decreased heat hyperalgesia and enhanced paw withdrawal latency by 24 hours compared to PBS-treated animals. In response to exosome administration from both LPS-stimulated and naïve macrophages, animals treated with CFA showed less thermal hyperalgesia at 48 hours. This suggests that the reduction in thermal hypersensitivity after 48 hours was unrelated to the inflammatory status of the macrophages.

**Table 1.** Exosomes as potential biomarkers for inflammatory disorders.

| DISEASE | MODEL | EXOSOME SOURCE | BIOMARKER | REFERENCE |
|---|---|---|---|---|
| Rheumatoid arthritis | Patients | Serum | Hotair, the HOX transcript antisense RNA | 82 |
| | Patients | Synovial | Citrullinated proteins | 75 |
| Systemic lupus | Patients | Urine | Lower levels of miR-26a, miR-29c, higher levels of miR-146a | 69–71 |
| Alcoholic hepatitis | Mouse model of alcoholic hepatitis and patients | Serum and plasma | miRNA-192 and miRNA-30a | 83 |
| Sjögren's syndrome | Patients | Saliva | miR-let7b, miR-let 7c, miR-128 hsa-miR-4524b-3p, hsa-miR-4524b-5p, hsa-miR-5571–3p, hsa-miR-5571–5p, hsa-miR-5100, and hsa-miR-5572 | 72,73 |
| Inflammatory bowel disease | Dextran sulfate sodium (DSS) induced colitis mouse model | Serum | 56 differentially expressed proteins identified by proteomics | 84 |
| | Patients | Serum | Annexin-A1 | 76 |
| Chronic hepatitis C | Patients | Plasma | HCV RNA level in the exosomes was 3–20-fold higher than that in exosome-free fractions | 85 |
| Complex regional pain syndrome | Patients | Serum | miRNA profiling showed differential expression of 127 miRNAs compared to control | 31 |
| Systemic sepsis | Mouse cecal ligation and puncture | Serum | Increase in exosomal expression of miR-16, miR-17, miR-20a, miR-20b, miR-26a, and miR-26b | 86 |

extracted exosomes. Exosomeal administration does not cause a proinflammatory response, as saline-treated paws upon injection do not experience discomfort or edoema. Exosomes derived from macrophages may have mitigated thermal hyperalgesia in CFA-treated animals. This could be because exosomes mediate temporal regulation by synergistically influencing multiple inflammatory pathways, delivering biomolecules like cytokines that act immediately and those that are translation dependent, which influence gene transcription and cause changes in recipient cells.31

Reportedly, anti-inflammatory medications may also cause changes in the composition of exosomes. Methotrexate and sulfasalazine are anti-inflammatory medications used to control rheumatoid arthritis.67 The exosome protein profiles were changed when the human synovial sarcoma cell line SW982 was treated with sulfasalazine and methotrexate. Part of the alterations in protein profile caused by IL-1β were reduced when the two medications were combined. The majority of the proteins that were shown to be involved in immunity or anti-oxidation were proteins with this function, and the authors imply that exosomes might play a role in mediating the effects of anti-inflammatory medications.

Biomarkers for inflammatory illnesses may also be found in exosomal contents. The biomolecular makeup of exosomes, which includes RNA, proteins, and lipids, makes them a promising biomarker for disease condition. What makes exosomes even more intriguing is their ability to adapt their content to different physiological stressors and pathological situations. Exosomes were studied as possible biomarkers for a number of inflammatory illnesses, as shown in Table 1. A number of inflammatory and auto-immune diseases, such as

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Sjögren's syndrome and systemic lupus69–71, may have miRNAs carried by exosomes as biomarkers.72,73 Exosomes may be a preferable source for biomarker research since they include 127 miRNAs, which are differently expressed, compared to 18 in whole blood (74 in whole blood vs. 127 in exosomes31) from individuals with complicated regional pain syndrome. Citrullinated proteins in RA75 and annexin-A1 in inflammatory bowel disorders are two key protein indicators that exosomes convey.76

## conclusions

Exosomes, and all EVs more generally, continue to pique a great deal of curiosity about their function in health and illness. Exosomes derived from DCs have immunomodulatory capabilities that have been investigated in cancer clinical trials and will provide direction when new treatment methods are sought for various inflammatory diseases. When it comes to therapeutic medication delivery, exosomes are quite promising. They provide many benefits compared to conventional delivery systems that rely on vectors or liposomes. For efficient delivery of the target substance, they function as natural, non-toxic, membrane-bound nanocarriers of bio-macromolecules. It is possible to load biological medications into exosomes using autologous exosomes, which are extracted from the recipient's own bodily fluids or cell culture.77 The make-up of exosomes

Additionally, it is being investigated for its use as biomarkers and a noninvasive method for the early detection of a range of diseases.78 Less is known about the function of exosomes in typical physiological processes. The validation of published findings depends on the standardised purification processes, which the EVs community is actively working to achieve.Pages 79–81 When it comes to developing plans to bring precision medicine to a variety of illnesses, exosome biology will surely play a significant role.

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