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REVIEW

Exploring the role of exosomes in rheumatoid arthritis

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Abstract
In prosperous countries, autoimmune illnesses affect minimum 7% of the community. Rheumatoid Arthritis (RA) as an autoimmune illness is thought to be induced through a variety of genomic, physiological, and biological factors. Many experts in the field of nanomedicine have looked to stem cells as a viable strategy to repair human tissue; however, exosomes have demonstrated greater potential in recent years. Exosomes, produced from stem cells in particular, have exhibited a high propensity to give therapeutic effects. To resist local cellular stress, they are secreted in a paracrine manner from cells. As a result, exosomes produced from stem cells can provide enormous health uses. If treatment is not given, autoantibodies produce synovial inflammation and arthritis, which can lead to chronic inflammation, and impairment. Exosomes could be administered for the treatment of RA, by acting as therapeutic vectors. Exosomes are murine extracellular vesicles that influence biological mechanisms and signal transduction by transporting genetic and protein components. Diseases like RA and bone fractures could be treated using cell-free therapeutic strategies if exosomes could be isolated from stem cells efficiently and packaged with specific restorative substances. To get to this position, many breakthroughs must be achieved, and the following review summarises the most recent developments in stem cell-derived exosomes, with a focus on the important literature on exosome dynamics in RA.

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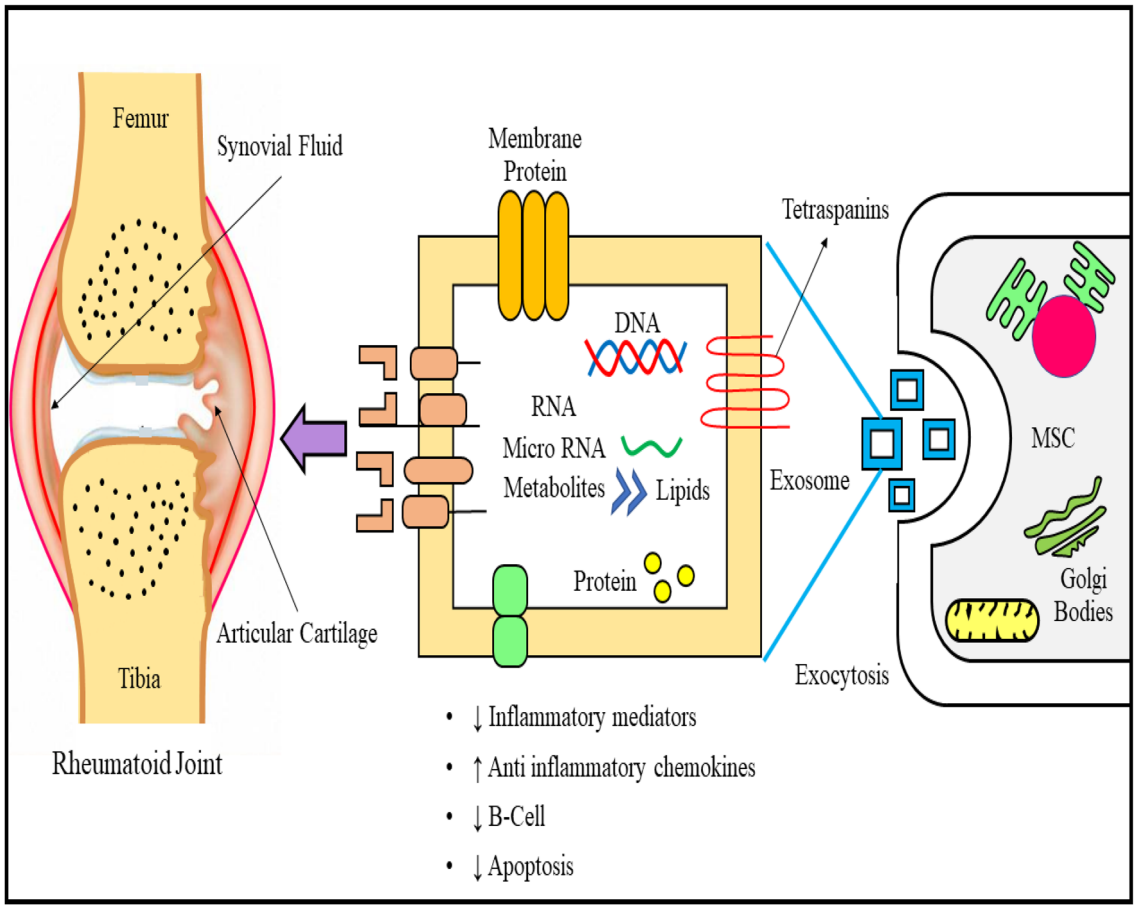
Graphical abstract



Keywords Exosomes · Rheumatoid arthritis · Inflammation · Nanoparticles

Introduction

Inflammatory disorders, such as RA, are persistent joint conditions that affect many people. Systemic inflammation, reactive arthritis, and the emergence of numerous joint deformities are all symptoms, which result in long-term illness and increased mortality. The immune system's inability to distinguish self-cells from non-self-cells is thought to be the culmination of auto-immune disorders (Rose et al. 2006). There are more than 80 systemic and organ-specific autoimmune illnesses, which are thought to impact at least 7% of the world's population and cause substantial illness and mortality (Mario et al. 2014). Such diseases most commonly occur in adults between the ages of 20 and 40. Autoimmune illnesses are often chronic, immobilizing conditions that impose a major financial and health burden (Mikael et al. 2009). The pathophysiology of RA is uncertain. As the disease advances, cartilage and bones are damaged, leading to disability (Alexander et al. 2012; Stefania et al. 2015). Glucocorticoids (GCs) are the primary medication for RA, they relieve irritation and discomfort immediately by lowering pro-inflammatory chemokine discharge and activating the anti-inflammatory protein interleukin-10, that additionally lowers the release of inflammatory mediators (Bobrie et al. 2011). Anti-RA medicines delivered on the nanoscale may help target treatments to damaged areas, enhancing restoration power while lowering negative impacts (Colombo et al. 2014; Thanh-Huyen et al. 2015).

Nanoparticles may concentrate in inflamed areas via a procedure termed “extravasation via leaky vasculature and subsequent inflammatory cell-mediated sequestration” (ELVIS), which is similar to the “improved permeability and retention” effect, which could cause nanoparticles to aggregate in tumours (Pan et al. 1983). Because they are diluted in circulation, physically encapsulated micelles are unstable and can react with biomolecules and other plasma constituents (Ela et al. 2013). Although polymer nanoparticles are more stable than liposomes and physically enclosed

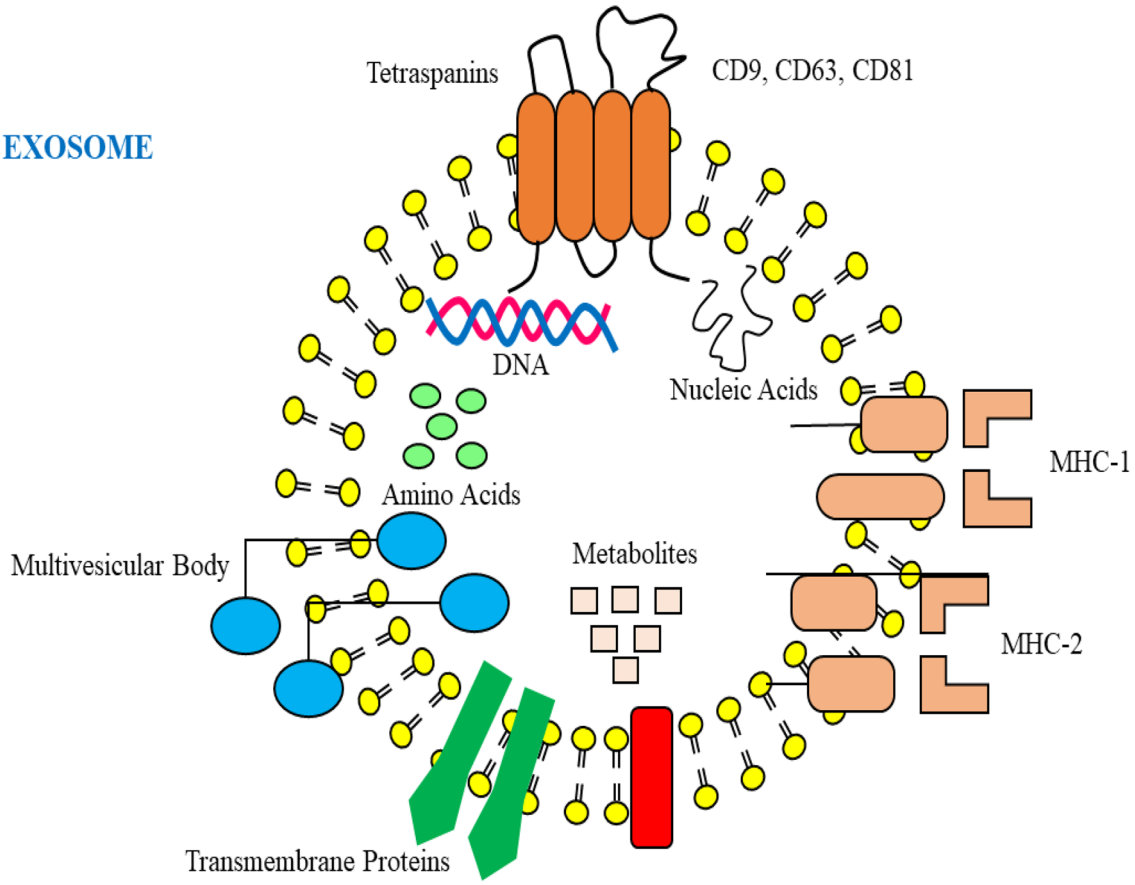


Fig. 1 Structure of exosome

micelles, they have problems in terms of long-term biocompatibility and safety. As a result, producing more dependable and stronger nanocarriers is a top priority (Wang et al. 2017a, b, c).

Exosome formation and origin

Exosomes are microscopic, membrane-bound extracellular vehicles (EVs) that have a size of 30 to 100 nm (Tkach et al. 2016). Pan and Johnstone first characterized them around 1980, and it was a method by which cellular waste could be removed at the time of maturation of sheep reticulocytes (Hessvik and Llorente 2018). Scientists started to notice that the study of exosomes was complicated as it was neglected for several years and they became prominent research topics (Huang et al. 2017). Over 1800 papers on exosomes have been published in the last decade, and the number is growing every year (Skotland et al. 2017). Exosomes have shown presence in plasma, synovial fluids (SF), nasal secretions, and malignant ascites.

Along with that, they are also visible in cellular culture media, particularly stem cells, in vitro. During endocytic internalization, exosomes emerge from the cell membrane. Endosomes, multivesicular bodies (MVBs), and exosomes are the three phases of exosome synthesis, according to the most well-established mechanism (Valadi et al. 2007). Young endosomes give rise to mature endosomes, which are circular and proximal to the nucleus. MVBs are mature endosomes that transport intraluminal vesicles containing a range of data (Kolhe et al. 2017) (Fig. 1).

Exosomes are absorbed in the extracellular space by recipient cells in three ways: paracrine (exosomal fusion), juxtacrine, and endocytosis (Williams et al. 2018). Immunologically active exosomes are produced by B lymphocytes, monocytes, dendritic cells, and pathogenic organisms. They carry out activities such as antigen exposition, inflammatory stimulation, immune inhibition, and immunological monitoring (Domenis et al. 2017; Yu et al. 2017). Cell-to-cell contact is mediated by exosomes containing cargo. Exosome cargo includes proteins, plasmid DNA, RNA molecules, and lipids, that are incorporated into exosomes during the MVB stage (Lobb et al. 2015). These can be secreted in

the external environment and transferred to targeted cells in homeostasis and illness for vasculature and cell–cell communication, and they reflect the physiological condition of parent organisms (Tian et al. 2014). Johnstone found and named the now characterized exosomes in sheep reticulocytes in 1983. However, the low yield of the manufacturing technology used and unanticipated therapeutic effects prevented its widespread clinical usage (Kato et al. 2014). A thorough understanding of exosome formation, origins, and contents are essential to optimize the application. Exosome biogenesis is the process through which exosomes are formed. The process of exosome cellular cell growth commences with a twofold engulfment of the cell membrane (Zhang et al. 2006).

Exosomes in rheumatoid arthritis

Exosomes have been labelled "trash cans", because they can be utilized for the removal of undesirable proteins from cells. Later, they were employed in cytosol gulps to transport bioactive molecules like peptides and micro RNAs in cellular interactions (Zhang et al. 2017). Exosomes serve a variety of functions regardless of cell type. The transmission of bioactive chemicals between cells has been identified as the most essential of these tasks (Rhodes et al. 2010). Immune cells, such as mast cells, mesenchymal stem cells (MSCs), dendritic cells, lymphocytes, and pathogenic cells have been found to release exosomes (Song et al. 2015). Furthermore, MSCs release exosomes containing anti-inflammatory chemicals, which are required for polarising macrophages into the M2 phenotype in the presence of hypoxia (Zhu et al. 2016). Exosomes have been thought to use two separate techniques to influence surrounding cells: dependent fusion and independent fusion (Han et al. 2016). The basic function of fusion is the delivery of MHC-peptide with a connection to the T cell receptor on T cells via exosomes (Jiang et al. 2017). Different features, like cell types, exosome-specific membrane proteins, and RNA, can be used to identify exosomes (Mehrotra and Tripathi 2015). While further research is needed to develop a consensus on the usage of exosome-derived HOTAIR (HOX transcript antisense RNA, HOTAIR is a long noncoding RNA that promotes tumor growth and metastasis), in various patients, it can be considered a useful biomarker for diagnosing RA (Linero and Chaparro 2014). Exosomes are thought to be carriers for transporting suppressive substances generated by the dendritic cells (DCs), despite the underlying structural process of immunosuppressive DC-derived exosomes is unknown. MHC II and B7-1/2 molecules are the best examples of inhibitory molecules since they act only when specific exosome and target model components are present. As a result, immunosuppressive DC exosomes have the ability to alter the activity of endogenous lymphocytes such as APCs, resulting in an anti-inflammatory impact (Cosenza et al. 2017).

Exosome formation in inflammatory cells

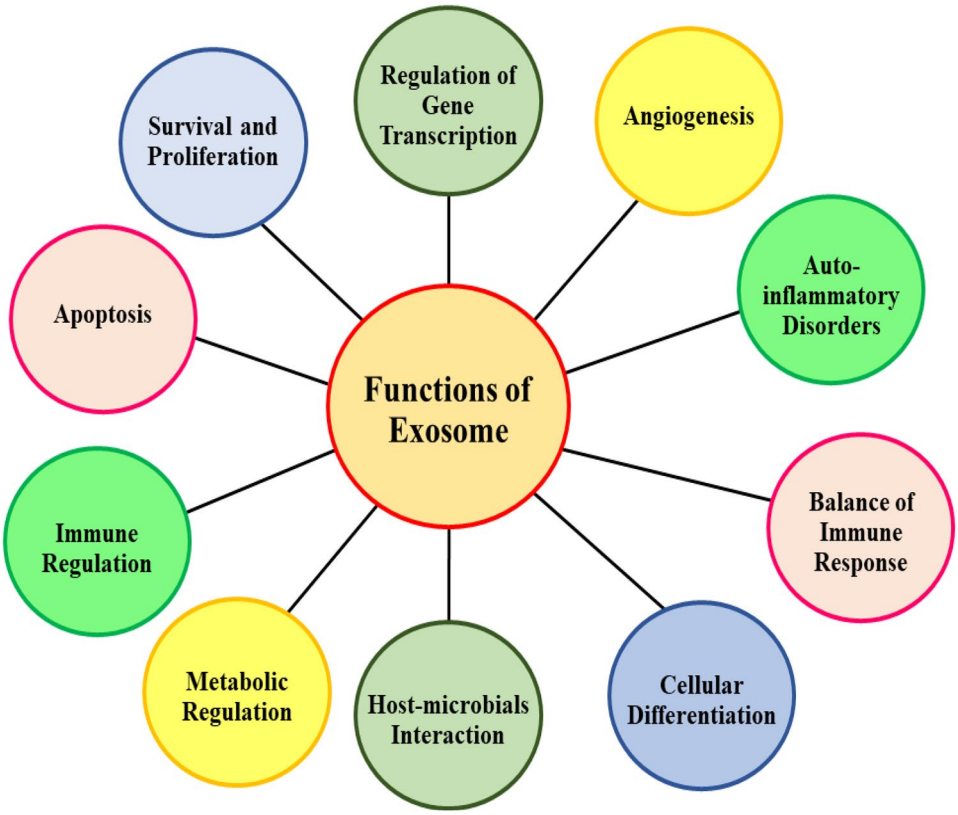
Exosomes appear to play diverse functions in intra-cellular communication in vitro and in vivo, according to multiple studies. Immune modulation, antigen presentation, signaling chemical transmission, and genetic information are all aided by exosomes (Zhu et al. 2017). Exosomes are important in immune response modulation, because they carry ligands and receptors, also antigenic material, and peptide-MHC complexes. Exosomes are produced by adipocytes, chondrocytes synovium-derived MSCs, macrophages, synovial fibroblasts (SFBs), adipose-derived stem cells, lymphocytes and DCs (Zhang et al. 2016; Wang et al. 2017a, b, c). Exosomes perform functions in joint homeostasis, along with the progression of arthritis as shown in Fig. 2. Intricate signalling compounds like triglycerides, peptides, enzymes, nucleotides, and cytoplasmic and cell-surface proteins can be transported as cell-specific payloads by these external membrane-bound vesicles (Guo et al. 2016). Exosomes use in clinical therapeutics and diagnosis has increased significantly in recent years, and this is mostly due to their potential (Liu et al. 2017a, b, c). Engineered exosomes can carry a variety of therapeutic payloads to a target, including DNA, RNA, metabolites, chemo drugs, cytokines, antisense oligonucleotides, and immunological modulators (Casado et al. 2017).

Exosomes from a variety of sources in the joint have been detected and demonstrated to vary as RA progresses, including MSCs, chondrocytes, and SFBs. Pharmacological therapy, including the use of NSAIDs, and other techniques are currently available to give symptomatic relief (Tao et al. 2017a, b). These methods, on the other hand, are inefficient at healing cartilage damage and are limited by small therapeutic effects (Barter et al. 2015). These restrictions limit their therapeutic potential. The significance of exosome joint disorders is becoming well understood (Li et al. 2017b). The majority of exosome-joint disease research has focused on diseases like RA and osteoarthritis (OA). These diseases are all extremely common around the world, have a profound impact on the health of patients, and place a significant societal cost (Liu et al. 2017a, b, c).

Exosomes/EVs: inflammatory joint disorder modulators

The EV membrane is mostly made up of phospholipids, with glycolipids, cell adhesion molecules, sphingomyelin, cholesterol, integrins, prostaglandins, and growth factor receptors interspersed throughout (Tao et al. 2017a, b). These

Fig. 2 Functions of exosomes



molecules aid recipient cell adhesion and/or fusion and may play a role in ligand-receptor signaling. Membrane transport proteins and ion channels can also be found in the EV membrane (Sari et al. 2012). Because of these qualities, EVs can operate as active processing sites for signaling molecules as well as shuttling vehicles for the passive movement of physiologically active components (Liu et al. 2017a, b, c). EVs can be produced by any cell type that has been tested so far (Perez-Hernandez et al. 2015).

Production and release are highly regulated processes that differ depending on physiological and pathologic circumstances (Chen et al. 2016). Furthermore, external stimuli can dramatically alter the pace of EV creation as well as the content or composition of EVs (Hon et al. 2017). EVs are present at significant levels in the synovial fluid of people suffering from RA or OA, in addition to the high concentrations of cytokines, which could be detected in the synovial fluid (Ha et al. 2016; Luo et al. 2017). Up to now, EVs from SFBs, erythrocytes, platelets, and T cells have been found in these samples. EVs in the synovium are obtained from blood plasma, in addition to being formed by activated synoviocytes or invading immune cells, which are hallmarks of joint disorders (Zhou et al. 2016). Lastly, chondrocytes could be a source of EVs, but no chondrocyte-derived EVs have been found in SF as far as we know. Although the precise mechanism of action of EVs in inflammatory joint illnesses is yet unknown, numerous general processes linked to inflammation have been proposed (Li et al. 2016). These include immune cells recognizing pathogen-derived EVs, inflammatory cytokines, and receptors to carry proteolytic enzymes that promote damage to the tissues and inflammation. EVs are also thought to play a function in autoimmune illnesses like RA (Gilligan and Dwyer 2017). The most intriguing and pressing subject right now is what role EVs play in various kinds of inflammatory disorders and at various stages of the disease pathology (Li et al. 2017c). These discoveries will also pave the way for the use of EVs as possible biomarkers for initial classification and detection of joint inflammation, but they will also drive continued prospects of EV therapies aimed at blocking inflammation-inducing EV pathways or lowering inflammation at the systemic level (Prasad et al. 2015).

Therapeutic efficacy of exosomes in joint disorders

Exosomes are a prospective treatment due to their stability, physiologically active content, and specificity. Exosomes, in contrast to traditional delivery techniques like liposomes or polymeric nanoparticles, may be able to resist degradation, pass through obstacles, and carry payload straight to the cytoplasm (Quan et al. 2014). Exosome transfer into recipient cells is a major topic of clinical translation research. The majority

of cooperative research focuses on the benefits of exosomes generated from stem cells, particularly MSCs (Wang and Sun 2017).

Clinical and animal investigations have shown that MSC therapies are effective and that MSC paracrine secretion is important in a variety of illnesses (Leblond et al. 2017). When compared to contralateral nontreated defects, exosome-treated defects had better gross appearance and histology scores. However, only a little amount of study has been done on the joint aspects of these disorders (Wang and Sun 2017; Jiang et al. 2017). Exosomes produced from MSCs can reduce pro-inflammatory factor release while increasing anti-inflammatory factors (Barnes 1998).

Exosomes may also have an impact on T cell function (Wang et al. 2016). These findings imply that exosomes produced from MSCs have immunomodulatory characteristics. Scientific investigations should concentrate on the immunological function of exosomes in these illnesses. Biomarkers can aid in the diagnosis, prognosis, and treatment response evaluation. The identification and biomarker development for joint illnesses, particularly the ones difficult to detect in the initial stages, should be continued (Vandwalle et al. 2017). Exosomes were recovered from blood or synovial fluid in only around 30% of all exosome studies. As a result, collecting exosomes from samples more effectively and efficiently remains a challenge. The therapeutic efficacy of stem cells appears to be substantially dependent on their paracrine effects, according to studies (Wang et al. 2019).

Exosomes, which are released by stem cells, contain vital biologically active substances that can treat disease (Li et al. 2017a). Furthermore, stem cells produce more exosomes than normal cells, which are easy to cultivate and collect in in vitro (Zhou et al. 2018). Exosomes that have been genetically modified are another prominent treatment option (Yoo et al. 2017). Exosome functions and biological impacts are influenced by the status and functions of parental cells, which influences the components of exosome cargos transferred to recipient or target cells to a great extent (Li et al. 2019). Exosomes derived from parental cells containing bioactive material, such as miRNA and small compounds, are presently being investigated for therapeutic applications, benefiting from their extremely effective delivery mechanism. The enrichment of exosomes with genetic elements like potent bioactive miRNA has received considerable attention. Exosomes with genetic modifications were utilized in some systems, such as cancer therapy (Wu et al. 2020).

Exosome-based nanoparticles that target inflammatory joints

Exosomes have proven to be a feasible replacement for exogenous nanoparticles (Bunggulawa et al. 2018). These membrane-enclosed vesicles are organically released by a variety of cell categories, endowing these with remarkable natural qualities such as non-immunogenicity, minimal cytotoxicity, favorable cytocompatibility, and extended systemic circulating ability (Koenders and VandenBerg 2015). Because of their unique properties, they are ideal pharmaceutical delivery nano-carriers. Furthermore, whereas exosome-based nanoparticle delivery of drugs has been utilized successfully in the therapy of a range of disorders such as renal inflammation and cancer, it is rarely used in RA (Qu et al. 2018). Exosome-based drug delivery, on the other hand, has a limitation in terms of specific aggregation to target locations in vivo (Haney et al. 2015). Inflamed areas have a high number of activated macrophages with folic acid receptors (FRs) on their surface, according to a report on the inflammatory microenvironment of RA (Yuan et al. 2017). As a result, researchers hypothesized that encapsulating exosome-based nanoparticles with folic acid (FA) to increase aggregating capability via proactive targeted impact on FR in vivo could be beneficial (Lin et al. 2019).

Exosomes, containing dexamethasone sodium phosphate (Dex), are often utilized GCs in clinical arthritis treatment, were used by the researchers to create Exo/Dex nanoparticles (Tang et al. 2019). Biodistribution research in mice found that Exo/Dex were persistent in joint tissues for more length of time than Exo (Thomas et al. 2011). These results support the "FPC" alteration of Dex exosomes, which enabled proactive targeting of immune-mediated areas in RA (Chiba 2012). Dex and other GCs have been utilized to cure arthritis because they prevent activated macrophages from secreting inflammatory cytokines like IL-1, TNF-α, and IL-6 at inflammation sites while enhancing the secretion of the anti-inflammatory cytokine IL-10 (Siafaka et al. 2015). According to some findings, the modification with FA-polyethylene glycol (PEG)-cholesterol (Chol) compound (FPC) to prepare FPC-Exo/Dex active targeting drug delivery, the FPC-Exo/Dex induced various beneficial properties in murine mice to a higher extent than Dex formulations (Yang et al. 2013). These effects were linked to considerably reduced cartilage and articular bone damage, as well as lower H&E staining analysis histopathology scores (Quan et al. 2016; Wu et al. 2018).

Exosome: separation, recognition, and preservation

Exosomes are commonly collected from a conditioned cell culture medium. To maximize the extraction, many methods based on the various physiochemical features of exosomes have been devised, but no standard operating procedures have been created (Reumson et al. 2015). Exosome extraction techniques include charge neutralization-based polymer precipitation, immunoaffinity capture, ultracentrifugation, size-exclusion chromatography, ultrafiltration, and microfluidics (Crielaard et al. 2012). Exosome separation kits based

on precipitation and columns have also been produced (Zhao et al. 2020). The sample qualities and research aims will determine whether a single approach or a combination of procedures should be used. Regardless of the method used, the goal of extraction remains the same: maximize productivity and quality while limiting changes in peptide content, size variation, and surface charge (Beez et al. 2019; Singh et al. 2012). Several papers have examined the advantages and disadvantages of various strategies for extracting, characterizing, and purifying exosomes, and the best method depends on the origin of the exosomes. External characterization and inclusion characterization are the main types of exosome characterization procedures (Zhang et al. 2014). Nanoparticle tracking analysis technique is used to quantify exosome concentration and size. Inclusion analysis is frequently used to detect transmembrane molecules, lipids, and phospholipids in the lipid bilayer, which could also be detected via flow cytometry, and western blot analysis (Lai et al. 2012).

Cryopreservation, freeze-drying, and spray-drying are the most common methods for preserving exosomes (Johnsen et al. 2016). Low temperatures aid in the preservation of exosome quantity and content (Hood et al. 2014; Kooijmans et al. 2016). Exosomes are protected from ice crystal formation inside vesicles and unbalanced osmosis during the freezing process by adding permeable and non-permeable antifreeze (Ju 2013). Exosomes can be dehydrated and dried at low temperatures under vacuum circumstances using freeze-drying, which is a process for conserving temperature-dependent materials. Lyophilized exosomes can be incubated at normal temperature and reheated quickly (Pathak et al. 2014). Spray drying is a one-step procedure, unlike lyophilization, which needs three continuous phases. It is less expensive, but it increases the chance of exosomal morphological changes (Son et al. 2020). Exosome storage conditions are often less stringent than those for cell-based therapies. Furthermore, unlike exosomes, cryogenic cells need restoration and functional recovery before being used in therapeutic conditions, making them less practical (Yang et al. 2015).

Conclusion

RA is a progressive, widespread inflammatory disease wherein cells damage endogenous synovium as well as other tissues. Inflammatory cell infiltration and joint enlargement commonly occur in the gradual loss of cartilage. Even though several treatments exist to cure ailments, no known medication has been successful in arresting the disease process. Biotechnologies and computational methods have made it possible to understand mitochondrial dysfunction in diseases such as RA, obesity, cardiac problems, etc. The current treatments for RA, which include biological therapy such as proteins and antibodies linked to inflammatory factors, are mostly aimed at alleviating symptoms rather than reversing the illness. Although novel gene therapy methods have been judged to offer potential in treating such conditions, the question of whether such procedures are safe has remained a source of contention. Exosomes generated from immunosuppressive DCs, blood plasma, and serum have shown to improve treatment processes of inflammation and disorders such as RA, according to multiple studies. These include antifibrotic, anti-apoptotic, and immune-modulatory actions that prevent cartilage from degrading and instead promote its regeneration. Overall, the utilization of exosomes in the medication of arthritis can be considered a successful, innovative, and safe therapeutic technique.

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Data availability Not applicable.

Declarations

Conflict of interest The authors declared that they have no conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent to publish All authors have given consent for publication of the current article.

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