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CELL MEMBRANE COATED POLYMERIC NANOCARRIERS: A NOVEL DRUG DELIVERY APPROACH FOR THE TARGETED THERAPY OF RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis is a chronic inflammatory disorder that affects the joints and can lead to significant disability. RA may affect other parts of the body, leading to various issues including damage to the joints, deformity, disability, and reduced mobility. The pathogenesis of RA involves a complex interplay between genetic, environmental and immunological factors. The treatment of rheumatoid arthritis typically reduces inflammation, manages pain, stiffness and prevents joint damage. However, these medications have several side effects no single therapeutic remedy directly targets the disease. Researchers in the field are focused on developing new treatments that are more effective and have fewer side effects as well as understanding the underlying mechanisms of the disease. Some areas of current research include the use of nanotechnology such as cell membrane-coated nanoparticles for the treatment of RA as well as the development of new biologic drugs that target specific molecules involved in inflammation. The use of cell membrane-coated nanoparticles for the treatment of rheumatoid arthritis has several potential benefits including targeted drug delivery, reduced inflammation, improved safety and biocompatibility, and reduced frequency of administration. However, more research is needed to fully understand the potential benefits and limitations of this approach to develop effective cell membrane coated nanoparticle-based therapies for RA. In this review cell membrane-coated nanoparticles may become valuable for numerous biomedical problems.

***Keywords*:** Cell membrane; Nanoparticles; Rheumatoid arthritis; Targeted therapy; Inflammation; Drug delivery; Nanocarriers

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1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that affects roughly 5 out of every 1,000 persons globally (Otón and Carmona 2019). The disease affects women two to three times more than men and can attack at any age of life (Smith and Berman 2022). The sixth decade has the highest incidence (Myasoedova et al. 2010). RA was formerly linked to disability, inability to work, and an increased risk of death. Because of a better understanding of the etiology of RA and the introduction of better outcome markers and treatments, outcomes have lately improved (Lin et al. 2022). RA etiology involves chronic inflammation of the synovial membrane, which can cause damage to articular cartilage and para-articular bone (Vis et al. 2006). New discoveries of biological pathways have expanded our understanding of the processes connected with rheumatoid inflammation and its repercussions (Chen et al. 2019). As therapeutic targets, new substances and cells have been discovered in biological processes. This review focuses on the most recent findings in the pathophysiology, diagnosis, and management of RA (Aletaha and Smolen 2018). Joint problems have a serious and incapacitating impact on global health security. Joint illnesses have become a big problem with far-reaching effects on people's health of the social healthcare system (Prasad and Sengupta 2019). One of the most common arthritic conditions is rheumatoid arthritis.

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RA is a long-lasting inflammatory condition that causes synovitis and cartilage degradation. Approximately 5 to 10 individuals per 1000 people worldwide have RA (Aletaha and Smolen 2018).

2. RHEUMATOID ARTHRITIS

2.1. RA Etiology

Both emerging and developed nations have experienced significant socioeconomic costs as a result of this illness. According to various etiologic and pathological causes, at least a dozen more forms of disorders affecting the joints in addition to RA have been discovered (Rohr et al. 2019). Most joint illnesses are incurable in terms of their etiology. Modern therapy use strategies that include surgery to reinstate a patient's function and medication to treat symptoms and manage illness. In the pathophysiology of this condition, no efficient therapy has yet been discovered (Han et al. 2021). Pannus is caused by RA pathology, which involves aberrant neovascularization and hyperplastic synovial membranes. In the hyperplastic synovial membrane, T cells, B cells, endothelial cells, fibroblasts, monocytes, and macrophages proliferate. The faulty synovial membrane invades the periarticular bone in the presence of infiltrating cells and cytokines, producing bone erosion and cartilage degeneration (Wang et al. 2022). The inflammatory process is exacerbated by hypervascularization of the synovial membrane. Imaging revisions have also highlighted corroborated inflammatory processes in causing bone damage. Outside of synovitis, inflammation of neighboring tissues is linked to bone degradation in RA (Haavardsholm et al. 2008). According to new studies, both innate and adaptive immunity have a role in the development of RA. This process is aided by a variety of cells and inflammatory chemicals. Osteoimmunology studies in RA may thus provide an essential feature for future study. Modifications in RA lesions enable newborn CD4 T cells to differentiate into proinflammatory helper T cells capable of entering tissue and triggering inflammation via immunogenic cell death (Han et al. 2021). In a mouse model containing IL-17 and IFN splenic CD4+ T cell subsets, T cell activation and differentiation into Th1 and Th17 cells contribute to collagen-induced arthritis (Li et al. 2018). Cartilage damage rather than bone damage, is more strongly connected to permanent physical problems. The two major compact components type II collagen and aggrecan make up the bulk of cartilage. Active and passive nanotherapeutic technology initiatives targeting cartilage are focused on enhancing tissue penetration and extending cartilage retention (DiDomenico et al. 2018). Molecular size, charge, and shape are the most important elements influencing intrachondral molecular transit. To improve tissue adhesion, penetration, and retention duration, nanocarriers often use reversible electrostatic interactions with anionic cartilage tissue (Brown et al. 2020).

2.2. Current Research about RA

The current study demonstrated that neutrophils can induce the development of modified autoantigens, which can affect antigen-specific T-cell and autoantibody responses and epitope dissemination (Curran et al. 2020). Macrophages and B cells are immune cells that have a role in the pathophysiology of RA. As a result, targeting the inflammatory process's molecular and cellular components during RA is a significant therapeutic strategy (Smolen et al. 2020). Further, people don't respond to therapy well enough. Numerous research studies have been conducted on the exact pathophysiological processes of RA and numerous of the findings point to prospective therapeutic targets. However, it can be challenging to act in these potential processes using traditional therapy (Cortes Rivera et al. 2019). The express residence period in the lesion partial absorption rate and reduced tissue specificity no single therapy can achieve the targeted therapeutic objective, regardless of molecular bulk or delivery technique (Frey et al. 2013). Nanocarriers such as dendrimers, micelles, nano-emulsions, liposomes, and nanogels have been employed in preclinical research to treat RA. However, a recent clinical trial found that curcumin nano-micelles had minimal impact in RA patients (Javadi et al. 2019). According to the results of this study, neutrophil nanoparticles have a unique affinity for inflammatory cells and cartilage matrix, which is thought to be beneficial. Neutrophil nanoparticles reduced synovial immune infiltration more than anticytokine therapy in a RA animal model. The rheumatoid synovium, in particular, is made up of a diverse population of cells produced from monocytes, macrophages, dendritic cells, and T cells, all of which contribute to the advancement of rheumatoid arthritis phases. These cells' membranes can be coated with nontherapeutic substances and combined to produce individualized and synergistic RA therapies (Zhang et al. 2018). Many studies have established that abnormal T-cell activation and a lack of immunological resistance play an important role in the pathophysiology of RA from initiation to progression. Although the precise pathophysiological activities of T cells in RA are unknown, it is widely acknowledged that the balance of regulatory and effector T cells plays a crucial role in regulating the inflammatory process in RA (Wu et al. 2022). In recent preclinical and clinical research, regulatory T cells and helper T cells 17 have emerged as two important therapeutic targets for T cell treatment. Histological staining revealed that CoQ10-loaded NPs dramatically reduced the number of Th17 cells and IL-17 expression. IL-23 is a pro-inflammatory cytokine that stimulates Th17 cell and development of many anti-IL-23 antibody medicines have been authorized

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for clinical use or are being researched for the treatment of RA (Smolen et al. 2020). In recent years, there has been a significant interest in cell-mediated biological drug delivery strategies that are inspired by natural biological systems.

By covering the biological endogenous cell membranes as functional materials on the surface of the nanoparticles (Fig. 1, this method decreases the immunogenicity of the nanoparticles and increases blood circulation time (Li et al. 2018). The researchers used nanoparticles encapsulated in macrovesicles produced from macrophages to treat RA. The researchers utilized cytochalasin B to break the connection between the macrophage cytoskeleton and the cell membrane, resulting in an increase in the production of macrophage-derived vesicles (Hussein et al. 2021). When macrophage-derived bleb membrane proteins are comparable to macrophage membrane proteins, they have the same ability to combat inflammation as macrophages. The nanoparticles were then coated with macrophage-derived blebs and tacrolimus was encapsulated in the biomimetic nanomaterial (Takito and Nakamura 2020). Biomimetic nanomaterials show increased anti-inflammatory and targeting characteristics than erythrocyte membrane-coated nanoparticles, according to in vitro and in vivo investigations. The findings suggest that macrophage-derived blebs could be promising target biomimetic vehicles for arthritis treatment (Headland et al. 2015).

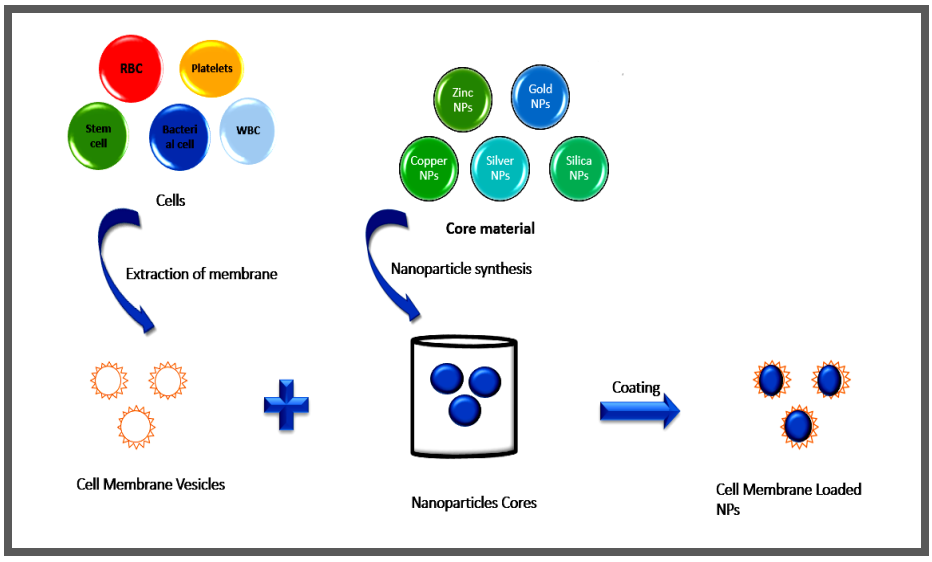

Fig. 1: Scheme of study related to cell membrane coated nanoparticles.

2.3. Treatment of Rheumatoid Arthritis by Cell Membrane Coated Nanoparticles

There is not a treatment for RA, contemporary therapeutic strategies can provide effective disease control. Disease-modifying antirheumatic medications can be used to treat RA. These can assist in alleviating RA symptoms and effects. They boost athletic performance while slowing the progression of joint deterioration (Aletaha and Smolen 2018). The analgesics, corticosteroids, and nonsteroidal anti-inflammatory drugs in addition to disease-modifying antirheumatic pharmaceuticals play an important role in supplemental treatment. Methotrexate monotherapy as an essential disease-modifying antirheumatic medication produces considerable clinical relief in almost 40% of RA patients (Hazlewood et al. 2016). Methotrexate in conjunction with conventional and biologic disease-modifying antirheumatic medications improves disease control in a greater proportion of RA patients. For newly diagnosed patients, the European League against Rheumatism recommends short-term methotrexate and corticosteroids (Rastogi 2014). Despite limited efficacy or bad side effects, more than half of patients who got newer disease-modifying antirheumatic medications had to discontinue them within 12 to 18 months. As a result, medication efficacy and safety are hurdles to RA treatment (Friedman et al. 2021). A growing body of research suggests that the interaction between the immune system and bone has a role in the pathogenesis of RA and its potential targets (Smolen et al. 2020). Recent advancements in nanomedicine have been made to cure a variety of ailments, avoiding severe shortcomings in existing therapies. Passive nanoparticle accumulation is encouraged by the increased permeability and retention effects in RA lesions, such as cancer. This is because of the defective vasculature and inflammatory response (Ren et al. 2019). Therapies that target the inflammatory markers that macrophages contain have also had encouraging outcomes. Small interfering RNAs (siRNAs) that target IL-1 and TNF, two significant macrophage-produced proinflammatory cytokines, show promise therapeutic benefits in the treatment of RA (Kim et al. 2019).

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2.4. Advantages of Cell Membrane Coated Nanoparticles Treatment of Rheumatoid Arthritis

The advantages of nanotechnology include accurate and specific dose administration of drugs and therapeutic response to particular disease conditions (Mitchell et al. 2021). As a result, major efforts have been concentrated on nanotechnology as a technique for discovering advanced treatments for arthritis. Considering biomimetic nanoparticles have the potential to combine the benefits of synthetic and natural nanomaterials, enabling accurate molecular imaging and drug delivery through biomimetic approaches, researchers have recently been interested in them (Choi et al. 2020; Jan et al. 2023).

Biomimetic nanoparticles can mimic a number of immune-related targets involved in RA, which are frequently ignored in conventional nanomedicine designs. Several AR targets that can be used in the experimental stage for biomimetic nanocarriers in nanomedicine will be covered in this review, as well as elements that make it easier to investigate nanotherapeutics for arthritis (Hazlewood et al. 2016). A growing body of research indicates that neutrophils contribute significantly to the onset of RA and the subsequent loss of immunological tolerance to synovial joint inflammation, both directly in the synovium and via response regulation (O'Neil and Kaplan 2019). Regarding RA lesions, nanomedicine has a significantly longer clearance time than free medications extending drug residence length and biodistribution. Furthermore, nanoparticles can enter tissues more easily (Chen et al. 2021).By encapsulating these drugs in nanocarriers, which allows for more precise dosing to the intended site of action, avoids repeated or large doses, increases drug solubility and pharmacokinetics, and achieves optimal drug concentration, adverse effects related to currently available non-selective RA treatments can be reduced (Qamar et al. 2019). Cell membrane coated NPs in the treatment of rheumatoid arthritis are enlisted in Table 1.

Table 1: Cell membrane coated NPs in the treatment of rheumatoid arthritis

Cell Membrane	Nanoparticles	Characterization	Pharmacological Characteristics	References
RBC	Gold NPs	15-70nm	RBC membrane coating successfully protects AuNP surfaces from synthesized probes and greatly lowers particle phagocytic absorption	Wang et al. (2019)
WBC	Copper NPs	12nm	White blood cells are coated with copper nanoparticles that great effect on the treatment of rheumatoid arthritis disorders	Wang et al. (2022)
Platelets	Silver NPs	20nm	Platelet cell membranes coated on silver nanoparticles that influence the treatment of Rheumatoid arthritis	Yang et al. (2021)
Stem cell	Metal NPs	10-30nm	Metal nanoparticle-coated stem cell membrane vesicle affects arthritis	Zou et al. (2020)
Neutrophil	Silica NPs	70nm	Neutrophil cell membrane-modified nanoparticles have been tested for high-efficiency medication delivery	Zhou et al. (2021)
Basophil	Zinc NPs	25-200nm	As different systems and their affected pathways repair the removal of these NPs from the body, the better for the treatment of rheumatoid arthritis. Zinc nanoparticles have the potential to cross the intestinal barrier and cause a variety of toxic effects that can be reversed and restore normal physiological responses	Mir et al. (2020)
Eosinophil	Iron oxide NPs	536nm	Iron oxide nanoparticles are a promising possibility for the treatment of rheumatoid arthritis due to their tiny size and magnetic sensitivity	Easo and Mohanan (2016)
T cell	Titanium oxide NPs	13nm	T cells activating the autoimmune system can efficiently prevent cell lining development with low toxicity and high efficacy in the case of Rheumatoid arthritis	Guo et al. (2018)
B cell	Nickel oxide	12nm	The discovery of effective treatments for RA is considerably aided by a deeper comprehension of the etiology of rheumatoid arthritis	Brzustewicz and Bryl (2015)
Macrophage	Silver NPs	5.7 to 20.4	Macrophages coated with silver nanoparticles are among the most popular nanotechnology products today due to their superior pharmacological properties.	Paladini and Pollini (2019)
Bacterial cell	zinc gluconate-loaded chitosan NPs	10-40nm	Pro-inflammatory cytokine expression is decreased in bacterial cells coated with zinc gluconate and chitosan nanoparticles	Han et al. (2021)
Dendritic Cell	Copper NPs	3mm in diameter	Treatment of rheumatoid arthritis using dendritic cells coated in copper nanoparticles	Zhao et al. (2021)

2.5. Limitation

Several disadvantages of conventional nanoparticles have been reported in vivo as an unanticipated effect. When nanomaterials are administered systemically the immune system quickly recognizes foreign components which may possibly aggravate the inflammatory reaction (Wilczewska et al. 2012). Numerous initiatives to increase the biocompatibility and biotoxicity of nanomedicines have been made over the past ten years. Recent times have seen the emergence of biomimetic methods as potential alternatives for upcoming clinical nanomedicine applications (Barani et al. 2020). Complex pathogenic variable biomimetic technology can decrease

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immunogenicity, promote biocompatibility, and reduce cytotoxicity of nanomedicine because RA is a chronic disease (Park 2013).

3. THERAPEUTIC TARGETING STRATEGY - CELL MEMBRANE COATED NANOPARTICLES

3.1. Passive Targeting

Controlling nanomaterial zeta potential has been shown to be an active passive cartilage targeting approach. Conjugating polyethylene glycol to the end of polyamidations dendrimers, researchers were able to boost the drug's absorption into cartilage tissue by around 70% (Geiger et al. 2018). A single dose of dexamethasone is easily absorbed and delivered over a long period of time into cartilage thanks to a positively charged molecule known as the main antibody. The interaction with the synovial fluid, however, modifies the nanocarriers' surface characteristics and colloidal stability (Barani et al. 2020). The effectiveness of designed nanocarriers will therefore almost probably rely on pathological circumstances and synovial fluid, and cartilage nanocarrier techniques cannot be focused exclusively on a single attribute, such as zeta potential, shape, or size (Bajpayee et al. 2016).

3.2. Active Targeting

Active targeting nanocarriers promote cartilage formation in the knees but not passive ones (Brown et al. 2020). The majority of these active targeting strategies rely on interactions with collagen and chondrocyte networks for binding. Type II collagen and trace levels of collagen make up the majority of the collagen fibers in articular cartilage. By a special peptide-collagen interaction, the peptide-bound dexamethasone prodrug was demonstrated in an ex vivo model to penetrate and hold deep regions of cartilage (Hayes and Melrose 2019). Non-human primates, animal models of CIA and synovial fluid from RA patients have all been reported to include antibodies against type II collagen. Use of post - translationally altered type II collagen neoepitope reactive oxygen species for the diagnosis of RA autoantibodies. Neutrophil-derived extracellular vesicles have recently had their surfaces coated with anti-ROS-CII antibodies (Topping et al. 2020).

4. SYNOVIUM AND INFILTRATED CELLS

The articular surface and the inside of the joint capsule are lined by synovium, a thin layer of tissue. It is necessary for drug delivery because it regulates the molecular exchange between the joint fluid and the circulation fluid (Scanzello 2022). Inflammation of the synovium also contributes to the development of RA. As a result, synovial tissue is a key area of focus for RA treatment. Type A monocytes/macrophages and type B FLS fibroblast-like synoviocytes are the two different types of synoviocytes (Asif Amin et al. 2017).

4.1. Macrophages

In addition to being an indication of active RA, increased macrophage infiltration of the synovial membrane is also related to how severely bone deterioration is progressing. Macrophages divide into many phenotypes to carry out a variety of tasks (McGarry et al. 2021). Due to the prevalence of the TNF family and IL-1 in RA lesions, M1 macrophages are thought to be the primary driver of RA pathogenesis. Additionally, macrophages are mostly biased to the M1 subtype because of the unique inflammatory milieu present in RA, which includes hypoxia and ROS macrophages (Alivernini et al. 2020). The two major methods for targeting macrophages in RA therapy are physical harm to M1 macrophages and converting M1 macrophages to M2 macrophages that can release anti-inflammatory cytokines (Li et al. 2022). Methotrexate has been administered to M1 macrophages via a number of nanocarriers. Recently, it was discovered that bovine serum albumin treated with palmitic acid had improved SR-A targeting properties both in vitro and in vivo. We describe a customizable method to identify and selectively target active proinflammatory M1 macrophages in RA lesions (Shi et al. 2020). PEGylated FA-AgNPs are activated by intracellular glutathione and disintegrate to release AgFe. M1 macrophages with Ag iron accumulation are slowly reduced by apoptosis, but M2 polarization is boosted by ROS knockdown (Hosseinikhah et al. 2021). These anti-inflammatory reactions make it possible to treat RA successfully. By ROS scavenging and synergistic oxygen generation, synthetic ceria-manganese ferrite nanoparticles anchored in mesoporous silica nanoparticles improve M2 polarization of macrophages in RA lesions (Kim et al. 2019; Li et al. 2020).

4.2. Fibroblast-Like Synoviocytes

FLS interacts with other immune cells in RA lesions and is crucial for the progression of RA. As a result, several nanodrugs can act on these cells concurrently to fulfil therapeutic objectives. If more investigations of several FLS in RA lesions are conducted, nanomedicine research may incorporate more precise treatment targets (Park et al. 2020). Fig. 2 shows the cell membrane coated nanoparticles for the treatment of rheumatoid arthritis.

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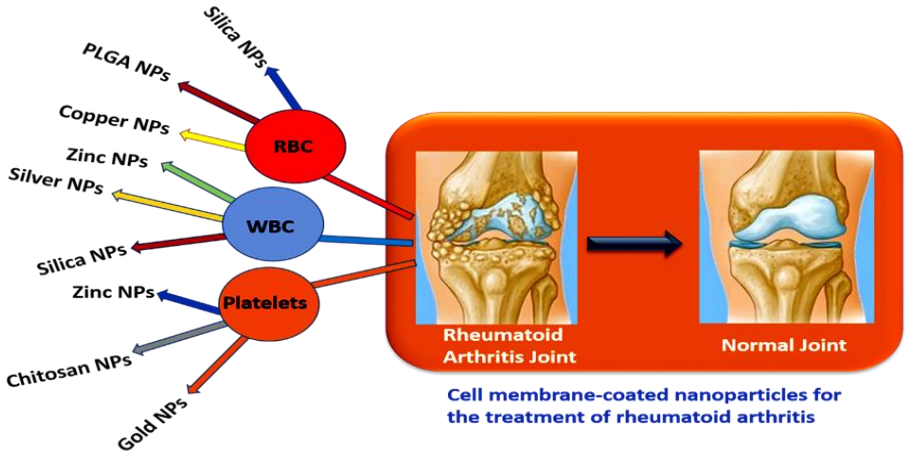

Fig. 2: Cell membrane coated nanoparticles for the treatment of rheumatoid arthritis.

4.3. Endothelial Cells

A common pathologic alteration in RA is aberrant neovascularization, in addition to synovial hyperplasia and bone degradation. New blood vessels allow a significant amount of inflammatory cells and cytokines to enter the lesion, making RA more damaging and aggressive (Leblond et al. 2017). A potentially effective treatment approach for RA is endothelial cell-directed therapy. Several drug delivery techniques use compounds with high endothelial cell affinities to deliver drugs directly to vascular locations (Cevaal et al. 2021). The scientists discovered ART-1, a 9-amino acid peptide ligand that binds to the vascular endothelium of inflammatory joints in vitro and in vivo, by screening a phage peptide display library (Meka et al. 2018).

4.4. Immune Cells

A chronic immune-mediated condition called RA is characterized by a number of immune-related dysfunctions that impair the body's natural healing processes and cause tissue damage, especially in the joints. Immune cells, including neutrophils, T cells, and B cells, have a significant pathogenic role in all stages of RA (Zheng et al. 2020).

4.5. Neutrophils

The most prevalent form of cell in joint fluid, neutrophils, is a RA lesion. Because of cytokine reuptake and neutrophil extracellular traps, inflammation and bone degradation are brought on by neutrophils in RA (Kanashiro et al. 2020). Neutrophil cytokine production and neutrophil extracellular trap creation are thus newly discovered therapeutic targets in RA. A crucial protein in the creation of neutrophil extracellular traps, DEK is a nuclear autoantigen (Fousert et al. 2020). In animal investigations, neutrophil extracellular trap formation and joint inflammation were demonstrated to be inhibited by DEK-targeted DNA aptamers (Mor-Vaknin et al. 2017). Researchers have used several protein nanocarriers to carry popular medications like doxorubicin, methotrexate, and neutrophils for therapeutic purposes. Also, to restrict the recruitment of neutrophils for therapeutic reasons, anti-inflammatory medications including the Ac2-26 peptide nerol and tannic acid were encapsulated in nanoparticles (Yeo et al. 2020). It is important to note that nanoparticles of the correct size can activate granulocytes and cause neutrophil extracellular traps to form. For 20 minutes, neutrophil extracellular traps occur as a result of the interactions between the 10–40 nm nanoparticles and various types of cells and tissues that damage the plasma membrane and destabilize the lysosomal compartment. For enhanced safety, use medium nanoparticles between 100 and 1000 nm in size (Muñoz et al. 2016).

4.6. T-cells

Admittedly, the use and usefulness of antibody treatments are constrained by their brief half-life and serious side effects. In vitro, IL-23 antibody shortage was successfully made up for and Th17 cell growth was reduced through the use of nanoparticle delivery techniques (Gehin 2012). SiRNA targeting inflammatory pathways has shown to be a successful strategy to control Th17 cells responses in addition to encapsulating cytokines in nanoparticles. An essential part of the inflammatory response in RA patients' synovial fluid is an increase in regulatory T cells (Chemin et al. 2019). In RA lesions, regulatory T cell dysfunction causes an immune system imbalance. Hence, reactivating regulatory T cells is one of the potential anti-inflammatory treatment approaches for RA. Anti-CD2/CD4 antibodies are coated on IL-2 and TGF, which are then enclosed in poly (lactic-co-glycolic

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acid) nanoparticles (Campa-Carranza et al. 2022). The body's number of regulatory T cells grew thanks to the nanomedicine, which also stopped nephritis from getting worse. In a recent clinical trial, turmeric-containing biodegradable polymer nanoparticles for ankylosing spondylitis showed a promising therapeutic benefit via altering regulatory T cells (Ahmadi et al. 2020).

4.7. B-cells

The development of RA pathology involves B lymphocytes. One of the most popular B cell-targeting medications is rituximab, a human CD20 monoclonal antibody. While having long-term effectiveness, rituximab can temporarily reduce B cells after therapy, which raises the risk of infection (Guo et al. 2018). According to certain research, reducing specific B cell populations with targeted nanotechnology may be a more effective therapy method. In order to assault autoreactive B cells, autoantibodies against citrullinated proteins are frequently used as a ruse. The idea is that ex vivo therapy using magnetic nanoparticles that bind to particular antigens might eliminate autoreactive B cells, such as hemodialysis (Bollmann 2012). Recently, it was discovered that autoreactive B cells target disease-associated B cells by identifying citrulline-containing peptides' epitopes. Using self-epitope peptides and complement-dependent cleavage, we made functional nanoparticles. Functional nanoparticles were shown to trigger lysis in RA patients whose B cells were preferential for citrullinated peptides in an ex vivo research (Szarka et al. 2018). The rising trend is B cell-specific gene therapy. Numerous research looked into the possibility of treating RA with siRNA-encapsulated NPs that target the B-cell activating receptor. In a preclinical model, scientists developed a 3DNA nanocarrier coated with an anti-CD19 antibody, and they looked into the possibility of using this special anti-B cell siRNA-loaded nanocarrier to treat autoimmune arthritis (Dagenais-Lussier et al. 2021).

5. CELLULAR BIOMIMETIC STRATEGIES

Nanodrug clinical use is currently under threat from a number of angles. The immune system quickly clears the nanoparticles after the plasma proteins immunodirect them. Second, there is less overall nanoparticle aggregation because nanoparticles frequently fail to fully sensitize and travel to the site of infection. The most recent statistical analysis indicates that the objective accumulation efficiency is barely 0.7% (Bourzac 2016). An effective targeting approach might be the efficient dispersion and aggregation of a substance in a given region. As a result, the use of biomimetic nanoparticles for active transmission has appeared as a novel option for directed treatment (Ren et al. 2021). Drug delivery methods can gain some endogenous camouflage by incorporating nanoparticles with cell membranes or proteins. These innovative biomimetic drug delivery technologies drastically reduce nanoparticle removal and prolong medication efficacy (Bourzac 2016). Some cell membrane receptors not only greatly improve biocompatibility but also provide nanoparticles "additional capabilities." Given the notable cytokine release and cellular infiltration in RA lesions, biomimetic nanoparticle formulations utilizing immune cell proteins and membranes may be a suitable and efficient method to maximize nanoparticle targeting and therapy efficacy and the RA. Longer lifespans, better binding specificity, and minimal immunogenicity are further benefits of biomimetic medicinal vectors. Also, this section will go through them (Pantulap et al. 2022).

5.1. WBC Cell Membrane Cloaking Nanoparticles

White blood cells which are a crucial part of the immune system and circulate to RA lesions to promote inflammatory activity, include neutrophils, lymphocytes, monocytes, eosinophils, and basophils (Abdulkhaleq et al. 2018). This makes it possible to create leukocyte-like nanoparticles that can interface with the inflamed synovium at the RA site and lead to a high concentration of therapy. Nanoparticles with cell membrane coatings have recently gained attention as potential treatments (Han et al. 2021).These nanoparticles are produced by joining the native cell membrane to a synthetic core; as a result, they take on the donor cell's antigenic signature and can act as decoys that can absorb and neutralize a number of complex disease-causing substances, regardless of specificity. Impact on the structure (Chen and Bothun 2013). The most prevalent leukocytes that infiltrate RA lesions are macrophages. Current research on inflammatory and cancerous illnesses indicates that macrophage membranes may be exploited as biomimetic, customized medication delivery systems (Sun et al. 2020). For the treatment of RA lesions, intravenously given MMV-tacrolimus nanoparticles were superior to tacrolimus-only and erythrocyte membrane-coated nanoparticles. The researchers also postulated that inflammatory cytokines might lessen the development of osteoclasts, decreasing RA-related bone deterioration (Geiger et al. 2018).

5.2. Platelet Biomimetic Strategies

Platelets have a wide range of functions in RA and are an essential component of the immune and blood systems. Platelet activation in RA lesions intensifies the inflammatory response, encourages angiogenesis, and

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draws in different cells by producing inflammatory mediators like cytokines, chemokines, and growth factors (Olumuyiwa-Akeredolu et al. 2019). Additionally, because of the release of inflammatory chemicals and the expression of immune-related receptors, platelets have the capacity to influence a variety of immune cells. In addition, the specific affinity that platelets in RA lesions have for immune cells and tissues makes them excellent candidates for targeted drug delivery systems. To ensure the best possible drug delivery, platelets can be taken out of the circulation and altered in vitro, or they can be specifically conjugated with prodrugs and nanodrugs (Lu et al. 2019). Nanotechnology also allows for the production of synthetic platelets and the development of platelet membrane cloaking strategies, resulting in patterns that resemble platelets. Moreover, during platelet activation, morphological and functional changes might lead to drug release (Rahić et al. 2020). He created a platelet membrane-encapsulated PLGA nanoparticle as a biomimetic drug delivery method for FK506, a strong immunosuppressive medication for the treatment of RA that is resistant to methotrexate based on the biological role of platelets in RA lesions (Wei et al. 2016).

5.3. Nanoparticles Coated with different Cell Membranes for Treatment of Rheumatoid Arthritis

The antigenic exterior and associated membrane activities, including as chemotaxis in inflamed areas and cytokine neutralization are inherited by biological cell membrane-coated nanomaterials from the donor cell (Yaman et al. 2020). Neutrophils and macrophages are the two different types of innate immune cells found in the human body. By secreting a number of degrading enzymes that lead to cartilage deterioration and produce inflammatory factors, they help the body's inflammatory response (Gresnigt et al. 2012). Immune cells are therefore frequently utilized in the production of anti-inflammatory biomimetic nanodrugs (Geiger et al. 2018). They observed many neutrophil-derived blebs in the synovial fluid and mixed them with connexin A1, an anti-inflammatory, to produce a substance that shields the joint. In vitro tests showed that the complex can protect cartilage and create extracellular matrix by lowering prostaglandin E2 and IL-8 levels. AnxA1+ MV intra-articular injection lessens cartilage degradation brought on by inflammatory arthritis and encourages chondrocyte TGF-b production (Rao et al. 2018). Neutrophil membranes coated with nanoparticles can be directly applied to reduce joint pain. These nanoparticles can reduce synovial inflammation, prevent cartilage damage, and offer significant therapeutic advantages in CIA mice and transgenic animal models of human arthritis. Red blood cell membranes were used to encase polymer nanoparticles by RA Therapeutics researchers. For long-term drug delivery, polylactic-co-glycolic acid particles are extruded with erythrocyte vesicles to produce nanoparticles with a longer in vivo half-life (Crofford 2013).

6. CONCLUSION

Cell membrane coated nanoparticles have emerged as a promising approach for the treatment of rheumatoid arthritis. Their unique properties, including improved biocompatibility, targeting, and immune evasion, make them an attractive candidate for developing effective therapies for this complex disease. Preclinical studies have demonstrated the potential of cell membrane coated nanoparticles in reducing inflammation and disease progression in animal models of RA. However, more studies are needed to determine their safety and efficacy in humans. Furthermore, optimizing the design of these nanoparticles, identifying new targets for therapy, and developing new methods for evaluating their efficacy are important challenges that need to be addressed. Despite these challenges, the development of cell membrane coated nanoparticles for the treatment of RA holds great promise for improving patient outcomes and quality of life. Further research and development in this field are needed to advance this therapy to the clinic and provide new treatment options for patients with RA.

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