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Erythrocyte Mediated Drug Delivery System for Inflammatory Diseases and Disorders: A Review

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A B S T R A C T

Inflammation serves as a crucial defence mechanism, helping the body maintain internal balance and repair damaged tissues following injury or infection. While acute inflammation is beneficial and necessary, its prolossnged or uncontrolled presence can contribute to a range of chronic conditions affecting multiple organ systems. These inflammatory diseases and disorder are thus generally treated with anti-inflammatory drug with common drug delivery system, that produces side effect over the period of time in patient. Thus in several decade different kind of novel drug delivery systems come into existence proving their therapeutic beneficence over conventional drug delivery that includes Nanoparticle, nanocarriers such as liposomes, dendrimers, polymeric nanoparticles (micelles, spheres, capsules), nanobars, nanoemulsions, vesicles, nanosuspension, cell based drug delivery, thermoresponsive nanogel, etc. In that cell based drug delivery primarily erythrocyte based drug delivery system is getting more focus in treatment in the treatments of inflammation and other disease and disorder. Due to the unique structural and physiological nature of RBC they improve pharmacokinetic and pharmacodynamics efficiency of drugs. Hence, in this review the several erythrocytes based drug delivery system and their application in different inflammatory disease and disorder is highlighted for future therapeutic approaches.

Keywords: Red Blood cell, Inflammation, Drug Delivery System

1. Introduction

Inflammation is a vital immune response that is triggered in response to various harmful aggressions, such as pathogens, tissue lesions, toxic substances,or radiation. Its main purpose is to neutralize or remove harmful substances and promote tissue repair. Therefore, inflammation plays a vital role in maintaining health by promoting internal body stability and healing [1]. During an acute inflammation, a well-coordinated game of cellular and molecular interactions aims to reduce tissue lesions and eradicate infectious agents, promoting homeostasis restoration and the resolution of the inflammatory response. However, if this process remains unresolved or inadequately managed, the inflammation can persist and transition into a chronic state, which is associated with the development of various long-term inflammatory diseases and disorder linked to several organ system [2]. The same has been illustrated in fig. 1.

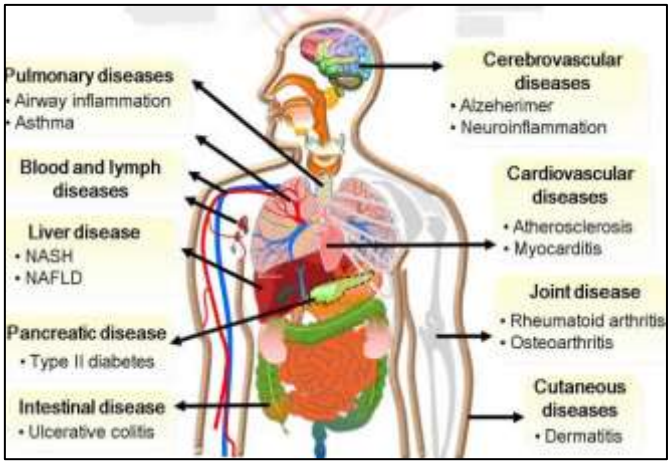

Fig. 1: Inflammatory diseases linked to different organ system [3]

Conventional treatments for inflammation focus on reducing symptoms and suppressing inflammation through long-term NSAID's, corticosteroid, and immunosuppressive treatments. The advancements in treatment now include monoclonal antibodies that specifically target important pro-inflammatory cytokines like TNF-α and IL-1β, allowing for a more precise modulation of the inflammatory response [4]. But, these conventional anti-inflammatory

agents have their own side effects too. Such as NSAIDs, they have the common adverse effects including gastrointestinal issues—from mild discomfort to serious bleeding—and kidney complications such as nephropathy. Their widespread availability and easy access without prescription can frequently lead to improper use, disregard for dosage instructions, and dangerous drug interactions, which is a major obstacle to their safe and responsible use in clinical practice [5].

In addition to NSAID's, glucocorticoids are very effective at treating chronic inflammation, primarily because of their strong ability to modulate immune responses through intracellular glucocorticoid receptors linked to membranes. Despite their therapeutic benefits, prolonged use often leads to a variety of side effects, such as reduced bone density, increased blood pressure, lipid imbalances, psychological disturbances, skin thinning, and metabolic disorders like insulin resistance and diabetes, all of which constrain their suitability for long-term treatment [6]. DMARDs, which are small-molecule drugs primarily used to manage arthritis and other chronic autoimmune conditions, exert strong immunomodulatory effects. Despite being widely accepted, these substances can cause serious but uncommon adverse reactions, such as allergic reactions that endanger life, the destruction of red blood cells, respiratory problems, and renal insufficiency [7].

By utilizing the biological functions of cells for a specific therapeutic delivery, cell-based drug delivery systems (CB-DDSs) offer an enticing solution to the issues raised by traditional drug delivery. These systems can be divided into three main categories: passive transporters that use native blood cells or their membranes, active bio-hybrid micro robots that are created by modifying the chemistry or genetics of blood cells, and platforms that are modelled after synthetic cells. Among these, blood-derived carriers—especially erythrocytes, leukocytes, and platelets—stand out for their feasibility, with early designs focusing on embedding drugs within these cells to create intracellular reservoirs for targeted release [8]. Among these, the platforms mediated by red blood cells (RBCs) stand out due to the abundance and distinctive features of erythrocytes [9]. Red blood cells, which are essential for carrying oxygen and carbon dioxide and supporting metabolic processes, have been shown to be effective delivery systems for therapeutic agents such as enzymes, nucleic acids, peptides, proteins, and nanoparticles, shown in fig. 2 [10], [11], [12]. Their unique biological characteristics, such as their biconcave shape, semi-permeable membrane, enable effective drug encapsulation and protection within their cellular space. The delivery of targeted medications is further enhanced by the addition of ligands to the red blood cell membrane. Over the years, a variety of drug delivery systems based on red blood cells have been developed using these characteristics. This includes intact red blood cells for prolonged circulation, nanoparticles that mimic red blood cells for targeted treatment, and extracellular vesicles derived from red blood cells for various biomedical applications [13]. Each strategy offers unique benefits in tissue targeting and therapeutic modulation, expanding the field of disease treatment and biological intervention at the same time [14].

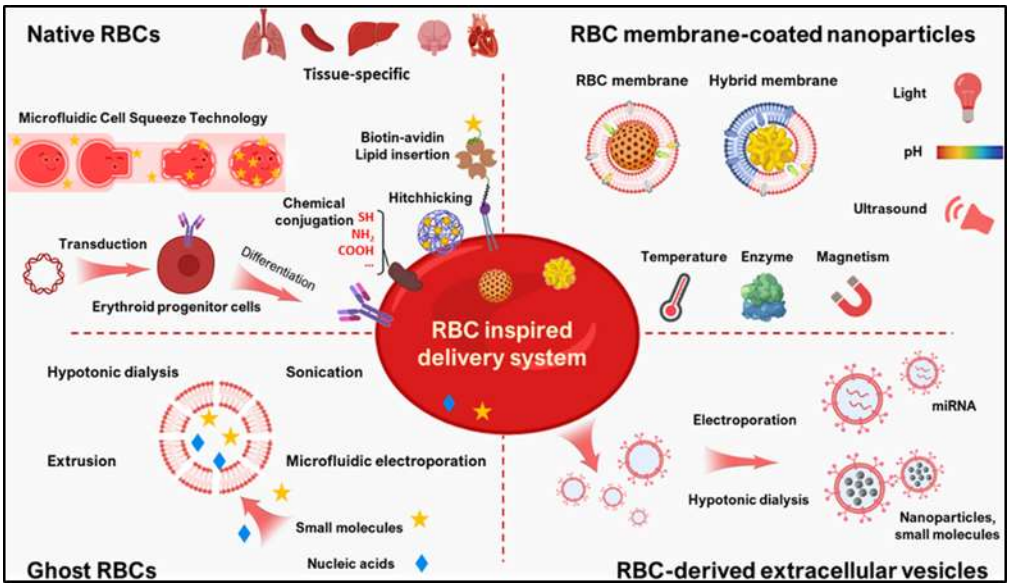

Fig.2: Different type of RBC mediated drug delivery system. [14]

2. RBC Based drug delivery system

Red blood cells exhibit specialized morphological and mechanical adaptations that are optimized for oxygen transport, despite the fact that they share fundamental cellular characteristics with other human cells. Their biconcave-disc shape and phospholipid bilayer—characterized by minimal cytoskeletal bending rigidity—grant them exceptional deformability and extensibility under fluid stress, allowing passage through narrow micro vessels such as the splenic sinusoids represented in fig. 3. With a lifespan of about 120 days, RBCs act as thin, high–surface-area biofilms, and their membrane dynamics closely resemble those of phospholipid vesicles. These distinctive biomechanical properties make RBCs highly attractive candidates for use as drug delivery vehicles, offering significant therapeutic potential [15].

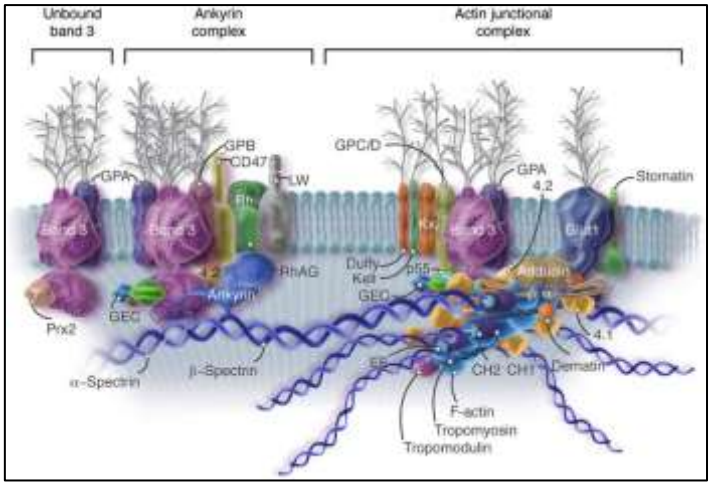

Fig. 3: The cytoskeletal framework and spatial distribution of proteins within the RBC membrane [16].

The red blood cells naturally extended circulation time makes them interesting vectors for extending the in vivo activity of treatments. They have the ability to either bind the medications to membrane proteins or sequester them in their cytosol, allowing for controlled release and a meaningful extension of their lives [17]. Recent studies have demonstrated the successful integration of various agents, including interferons, various antibiotics, peptide and steroidal hormones, and various synthetic drogues, into red blood cell carriers, highlighting their versatility for prolonged medication administration. [18],[19], [20], [21].

A hybrid delivery approach dubbed red blood cell (RBC) hitchhiking merges the biocompatibility and longevity of erythrocytes with the prolong release and solubility enhancements of engineered nanoparticles (NPs). In this method, NPs are non-covalently adsorbed onto RBC membranes in vitro to form RBC–NP complexes; upon intravenous administration, shear forces in the narrow capillaries strip the particles from the cell surface, driving their preferential accumulation in the lung microvasculature. This method enables the parenteral administration of agents that are poorly soluble in water and significantly extends their systemic duration of action by linking the long-term solubilization and prolonged release properties of nanoparticles (NPs) with the extended circulation of red blood cells (RBCs) [22].

Recently new therapeutic approach has been introduced i.e. RBC derived nanovaccine. A current research shown combining the tumour-associated peptide $hgp100_{25–33}$, the immune-boosting agent monophosphoryl lipid (MPLA), and a delivery platform consisting of PLGA nanoparticles enveloped in mannose-modified red blood cell membranes. This innovative design goes beyond traditional vaccinations in terms of preventing tumors, limiting their growth, and lowering metastases. The core polymer ensures effective antigen encapsulation and controlled release, while the red blood cell membrane preserves native proteins that promote antigen presentation and immune activation [23].

Many comprehensive study has been aims to utilize the functional characteristics of red blood cell (RBC) membranes to create membrane-redesigned nanoparticles with enhanced biological activity. A variety of nanoparticles have been created using red blood cell membranes to inherit their innate immune evasion capabilities, allowing for a longer blood flow. However, these changes may compromise the integrity of vital membrane proteins like CD47, a key marker for cellular recognition, and may lessen the immune evasion capacity of the membrane of the original red blood cell. [24].

Recent research has shown that nanoparticles disguised by the red blood cell membrane may promote the circulation of their respective treatments, thereby improving their distribution to the targeted tissues in a variety of diseases, including cancer and inflammatory diseases. In contrast to PEGylated nanoparticles, in red blood cell membranes may evade macrophage elimination and result in a noticeably longer circulation. [25].

3. Application of Different Erythrocyte-based Drug Delivery in the Treatment of Inflammatory Diseases and Disorder

3.1 In Autoimmune Disorder

Zywot, E.M. et al, introduces a light-activated drug delivery system in which dexamethasone (Dex) is carried by red blood cells (RBCs) and released at inflamed sites upon exposure to red light (650 nm) in arthritis study. The responsiveness of the system was confirmed using tissue phantoms that simulate the light absorption characteristics of different skin types. Since its activation, the released Dex has produced cellular effects that are comparable to those of the conventional medication. The modified red blood cells have maintained a circulation pattern akin to that of the red blood cells marked by fluorescence, indicating a stable systemic performance. It should be noted that a single light-triggered dose of Dex has been shown to be five times more effective at reducing inflammation than multiple doses of the medication without any changes. These findings support the idea that the circulatory system can be used as a controlled drug reservoir, enabling targeted and effective treatment of localized inflammation [26]. A gel-based hydrocolloid system based on red blood cells was presented by Chen, H. et al. to deliver localized Bulleyaconitine A (BLA) in the treatment of arthritis rheumatoid arthritis (RA). There in vitro findings demonstrated the BLA treatment on activated RAW264.7 macrophages that is a mouse monocyte macrophage (responsible to IL-6 cytokines, TNF-α, and IL-1β like inflammatory agents on their activation) found to reduce the inflammatory signal by modulating the NF-κB pathway. In vivo studies by using collagen-induced arthritis murine mouse model have shown that intra-articular administration of red blood

cells loaded with BLA (BLA@RBCs) results in a prolonged preservation of the medication at inflammatory sites, improving therapeutic outcomes and reducing systemic toxicity. This delivery method mediated by erythrocytes is a promising approach to the treatment of rheumatoid arthritis and merits further investigation in the hopes of a clinical application. [27]

Hao et al. used a method of emulsification by nanodrop to demonstrate a system of PLGA nanoparticles remodelled from a red blood cell membrane (RBCm) for the administration of cyclosporine A (CsA-RNPs) in treatment of systemic lupus erythematosus shown in fig. 4. The prepared CsA-RNPs showed the drug loading capacity of 5.93% and encapsulation efficiency of 63.05%. The core shell produced was found to satisfactory with Transmission Electron Microscope, resembling good coating RBCm. Hence, RBCm coating has made it possible to prolong the medication's presence in the body, prevent an overly rapid release, make it more compatible with the body, and protect it from immune system attacks. These changes have made it possible for the CsA to function better within the organization. Studies conducted in vivo on MRL/lpr mouse have demonstrated remarkable therapeutic effect of CsA-RNPs (contain 1mg/g dose of CsA) against systemic lupus by reducing l infiltration and mesangial proliferation, reduced infiltration of lymphocytes in renal arteries and also showed reduced level of TNF-α and IL-6 inflammatory factor in serum. Highlighting the formulation's potential for clinical use in the treatment of autoimmune diseases [28].

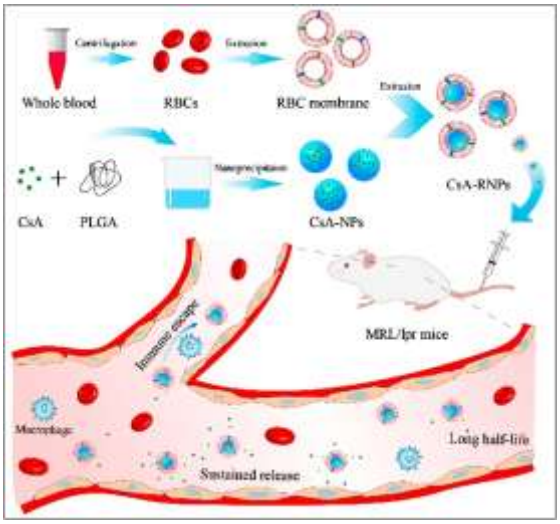

Fig. 4: CsA-RNPs method of preparation and role in systemic lupus erythematous [28].

Hao, X. et al. have presented a new biomimetic liposomal system (R-Lipo) by combining natural erythrocyte membrane vesicles with synthetic liposomes in an innovative way. They intended to use it to target dendritic cells (DC) in order to treat systemic lupus erythematosus (LES). The resulting molecular hybrids i.e. MPA-R-Lipo showed drug loading capacity of 3.085 and encapsulation efficiency of around 79.35%. MPA-R-Lipo hence shown good biocompatibility in animal and cell models, which suggests that dendritic cells will incorporate them. It had controlled the progression of lupus nephritis while also preventing the lengthening of dendritic cells without causing any significant side effects. The hybrid vesicular system has succeeded in directing MPA to the dendritic cells in the MRL/lpr murine model of systemic lupus erythematosus (LES), which impairs their maturation and increases immunological tolerance. This biomimicry platform has great potential for treating SLE and other conditions related to immune responses in dendritic cells because of its safety, effectiveness, and ease of production. The results show that R-Lipo is a promising, safe, and easily adjustable method for treating lupus erythematosus other effects caused by immune responses mediated by DC represented in fig. 5. [29].

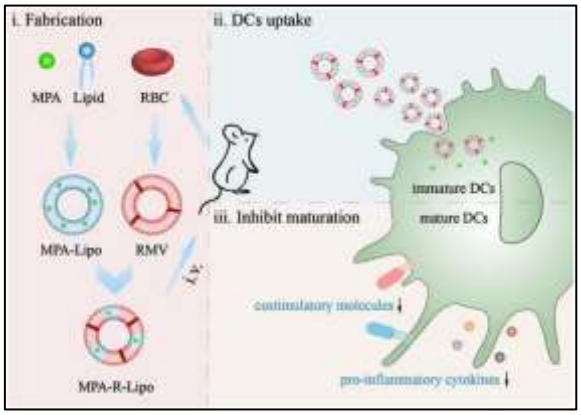

Fig. 5: Design of hybrid biomimetic liposome (MPA-R-Lipo) [29]

3.2 In Gastrointestinal Disorder

Annese, V. et al. conducted an uncontrolled study in which they investigated a novel drug delivery method using autologous erythrocytes as vectors for dexamethasone 21-phosphate (Dex 21-P) in patients with inflammatory bowel disease (IBD) dependent on steroids. Five patients with Crohn's disease and five with ulcerative colitis underwent three perfusions of their own red blood cells charged in Dex 21-P at four-week intervals. The majority also received immunosuppressant's, but two had been stopped due to intolerance. The procedure was to withdraw 50 mL of blood, encapsulate Dex 21-P (10 mM concentration corresponding to 0.5 g of drug) with specialized equipment, and then re-inject the modified cells into the original donor. It is noteworthy that plasmatic dexamethasone was detected up to 28 days after infusion and that all patients were able to stop corticosteroids by the second month. During a follow-up of eight months, four patients lost their remission while six experienced a relapse, and secondary effects related to steroids were noted. These findings show that administering Dex 21-P via erythrocytes is both safe and effective, offering an alternate approach that reduces the risks for managing IBD [30]. Also Castro, M. et al, reported in their case report, the red blood cells as a valuable vector for the targeted administration of medications. They reported the patient where diagnosed with Crohn's disease (CD) at age of 10 and for further 6 years subjected for different kind of therapeutic strategies. Also the patient was treated with infliximab but showed the side effect with the course of time. Afterword when patient started with periodic infusions of autologous erythrocytes loaded with Dex 21P for continue 4 week shown to reduced pathological sign of CD. Also over period of 3 year patient paediatric Crohnactivity index (pCDAI) also get decreased indicating therapeutic safety and efficacy of autologous erythrocytes loaded with Dex 21P infusion [31].

3.3 In the treatment of Respiratory Disease

Intestinal microbiota plays a crucial role in regulating arginine metabolism and reducing respiratory inflammation in people with Obese Asthma (OA). Luu, Q. et al., reported people with OA have higher bacterial counts, lower levels of arginine in the blood, and decreased pulmonary function when compared to non-obsessive and healthy individuals. While a direct arginine or citrulline supplement not increased level of arginine and also not able to reduce the respiratory obstruction. In order to address this issue, they have created nanovesicles derived from red blood cell containing arginine (NV^{Arg}), illustrated in fig. 6. They have the ability to deliver arginine to epithelial cells through the respiratory system and trigger AMPK and eNOS pathways in OA induced 6-week-old BALB/c mice. The produced nanovesicles NV^{Arg} size ranges from 70 to 90nm and contain 0.8 μg/mL arginine per 1 μg/mL total protein of $NV^{Arg.}$ This has led to a decrease in inflammation mainly IL-8 and resistance in the respiratory channels. These findings suggest that NV^{Arg} may be a promising treatment for OA by blocking the metabolic changes brought on by the microbiota. [32].

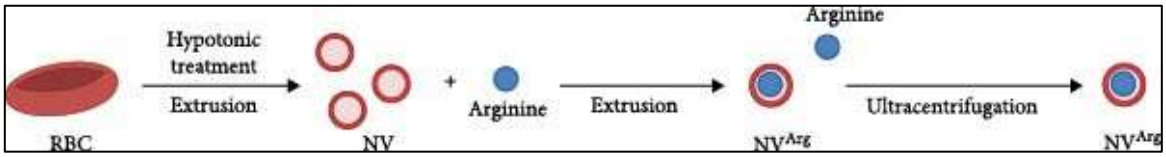

Fig. 6: Method of preparation of NV^{Arg} [32]

Ding, Y. et al. propose a novel method for pulmonary medication diffusion that uses chitosan nanoparticles (CSNP) loaded with methylprednisolone sodium acetate (MPSS) that bind to red blood cell through non-covalent interactions called RBC-hitchhiking chitosan nanoparticles. The obtained RBC-MPSS-CSNPs demonstrated improved pharmacokinetics in vivo male F344 rats, model reducing systemic exposure to the drug and prolonging circulation time, as suggested by the increase in mean residence time and surface area under the curve compared to standard MPSS formulations. Imaging and tissue distribution analyses in in BALB/c mice have revealed a preferential build-up of nanoparticles in pulmonary tissue and a decrease in hepatic captation. From a therapeutic perspective, this red blood cell-hitchhiking system significantly lowers inflammatory cytokines like TNF-α and IL-6, effectively preventing the pulmonary lesion caused by lipopolysaccharide in F344 rats, represented in fig. 7. These findings support "RCB-hitchhiking" as a promising strategy for the targeted administration of anti-inflammatory agents in conditions like acute pulmonary lesions and acute respiratory distress syndrome. [33].

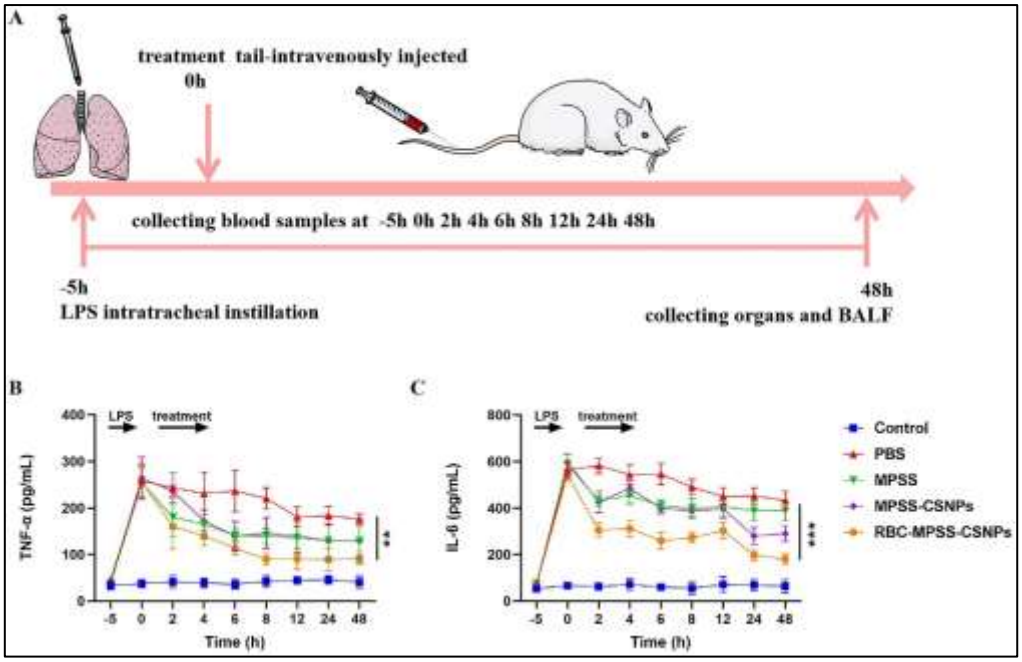

Fig. 7: (A) Illustrate the treatment regimen; (B) and (C) respectively represent the blood level of TNF-α and IL-6 in Control, PBS, MPSS, MPSS-CSNPs and RBC-MPSS-CSNPs treated Male F344 rats [33].

Dey, P. et al. investigated the possibility of using erythrocyte from Wister Albino Rats as vehicles to administer anti-inflammatory agent i.e. ambroxal hydrochloride (AH) to the lungs using a preswell dilution technique with help of cross linking agent i.e. glutaraldehyde (GA). The erythrocyte encapsulated with AH have been systematically characterized using in vitro evaluations that include the drug's encapsulation efficiency (DEE), morphology, release kinetics, osmotic stability properties, and hematopathological parameters. These AH loaded RES have biconcave disks, spherical shape. In hypotonic solution the Ambroxal loaded RBC had diameter of 4.11–4.45 μm with the maximum entrapment efficiency was found to 61.50%. They demonstrated a controlled release of the medication at zero order. The localization in the lungs has been confirmed by in vivo distribution studies, and fluorescence imaging shows that the carrier is widely distributed in the pulmonary epitheliums following intravenous administration. It has been noted that in a rat model of pulmonary lesion caused by albumin of eggs, treatment with erythrocytes charged in AH reduced IL-6 levels in Bronchoalveolar Lavage (BAL) fluid, prevented pulmonary fibrosis, and enhanced pulmonary architecture in less than 72 hours. These findings support the use of GA-treated erythrocytes as a promising distribution system for localized pulmonary therapy, which enhances recovery by modifying inflammatory responses [4].

3.4 In Cardiovascular Disease

Despite its uncertain bioavailability, probucol (PU), known for its anti-inflammatory, anti-oxidant, and hypolipidemic properties, shows promise in the treatment of Atherosclerosis. To solve this issue, Liang, X. et al. encapsulated PU in biomimetic nanoparticles (RP-PU) using ethylene polymers and red blood cell membranes of C57BL/6J mice, shown in fig. 8. Compared to linear polymers, this has allowed for a better drug loading, decreased viscosity, and improved long-term release behaviour. The particle size of RP-PU was found to be 239.2 ± 5.40 nm and polydispersity index (PDI) was 0.162 ± 0.033. Thus RP-PU has demonstrated exceptional cellular absorption and biocompatibility, improving the bio-distribution and therapeutic efficacy in $ApoE^{-/-}$ mice. The RP-PU treatment significantly decreased the levels of lipids, the activity of metabolic enzymes, and the accumulation of collagen in aortic tissues. Also decreased the expression of MCP-1 and ICAM-1. The RBC membrane's has extended the drug's half-life and made it easier for it to interact with macrophages, which has improved vascular outcomes and decreased lesion formation. These findings suggest that RP-PU nanoparticles may be a promising therapeutic approach at the nanoscale for the targeted and efficient management of atherosclerosis. [35].

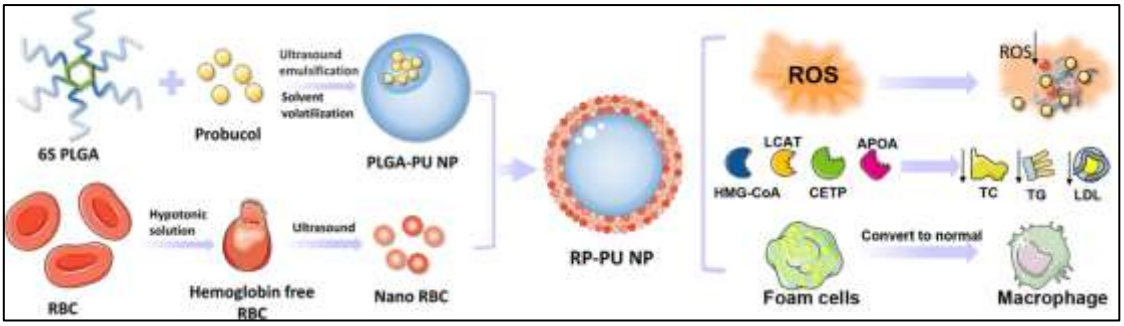

Fig. 8 : method of preparation of RP-PU [35]

Wang, Y. et al., In their study, offers a biomimetic Nano transport system for the treatment of atherosclerosis. It is based on rapamycin (RAP), a potent mTOR pathway inhibitor with anti-inflammatory, antiproliferative, and autophagic properties. This latter is encapsulated in PLGA nanoparticles and reoriented from red blood cell membranes nanocomplexes (RBC/RAP@PLGA) by co-extrusion method. This idea significantly extended the RAP's circulation life, encouraged its accumulation within atherosclerotic plaques, and effectively inhibited the disease's progression in ApoE$^{-/-}$ mice that were fed a High fat diet. The nanoparticles showed hydrodynamic diameter of 97.4 ± 2.4 nm with the PDI of 0.184, a negative surface charge, a prolonged release of the drug through a dissolution-diffusion mechanism, and an inhibition of macrophage proliferation in vitro. These findings highlight RAP nanoparticles that recover red blood cells as a promising and safe platform for the targeted treatment of chronic inflammatory diseases like atherosclerosis. [36].

Karami, Z., et al. present a novel biomimetic approach for treating atherosclerosis by employing PLGA nanoparticles known as nanoghosts that are remodelled membranes of red blood cells (RBCs) and contain glibenclamide (Glyburide), represented in fig. 9. These extruded nanoghosts have demonstrated hydrodynamic properties and a modified surface charge. With a membrane thickness of 8.3 nm, electronic transmission microscopy has provided confirmation of their structure in the heart and in a 125 nm-diameter core-shell. These nanoghosts shown the drug loading capacity of 0.202 % and encapsulation efficiency of 17 % for Glyburide. The formulation has demonstrated excellent hemocompatibility and biocompatibility with negligible apoptotic effects. The genetic expression analysis revealed a significant suppression of inflammatory markers, including NLRP3, IL-1β, IL-18, and caspases 1, 8, and 9. In a rabbit model, nanoghosts treatment resulted in decreased foam cell accumulation, decreased intimal thickness, decreased CD14+ cell count. These findings highlight the potential therapeutic use of Glyburide-loaded RBC nanoghosts as a precise and safe method to lower inflammation and slow the progression of atherosclerotic plaques. [37].

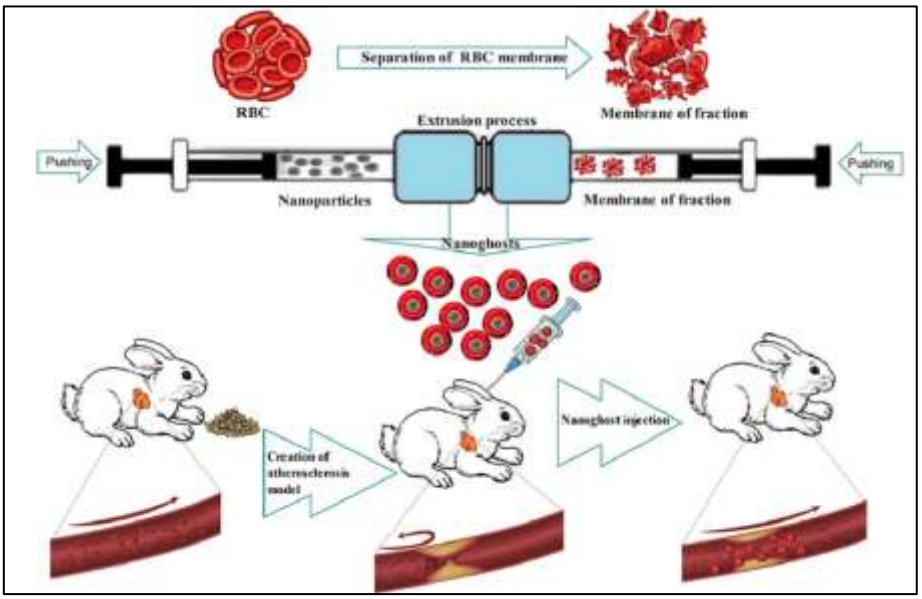

Fig. 9: Method of preparation of RBC mediated nanoghosts and its evaluation for inflammation based therapy of atherosclerosis [37]

Hu, C. et. al, introduces a novel cross-linking strategy that integrates biomimetic drug-loaded nanoparticles with biological heart valves to address limitations in current clinical applications in anti-coagulation, anti-inflammation, anti-calcification, and Endothelialisation. By incorporating RBC membrane-coated RAPA- (Rapamycin) and AC- (Atorvastatin calcium) loaded PLGA nanoparticles (RBC/RAPA&AC@PLGA), the modified valves retained the structural and mechanical integrity of traditional GLU-treated valves while demonstrating superior biological performance. Where these RBC/RAPA&AC@PLGA nanoparticles are loaded with 3.04% of RAPA and 5.43% of AC and shown the drug loading efficiency of 3.04 ± 0.21% and 5.43 ± 0.65 for RAPA and AC respectively. The size this drug loaded RBC/RAPA&AC@PLGA was found to be increased from 99 to 103 nm and carries negative charge to surface. Notably, the engineered valves exhibited enhanced long-term anticoagulant properties, improved blood compatibility, and

promoted endothelialization. In vivo studies in rats revealed strong resistance to calcification for up to 120 days, attributed to rapid endothelial coverage and sustained anti-inflammatory drug release. Also these nanoparticles able to enhance the heart valve collagen stability. Both in vitro and in vivo data confirmed the efficacy of this approach in reducing inflammation and preventing valve degeneration. This innovative design offers a promising platform for advancing heart valve therapies and holds significant potential for clinical translation [38].

Further to target Ischemic cardiac disease Liu, X. et al., demonstrates a method for delivering pharmaceuticals using liposomes and red blood cell. Where liposomes (Coumarin-6 loaded conventional liposomes) prepared by thin-film hydration method and further modified to mixed with micelles of peptides TAT (1%) and PCM (3%). These modified liposomes and RCM subjected to sonication to coat RBCm by mechanical adsorption. Characterization showed that the shape, size, zeta potential, and RCM coupling were all good. In vitro studies on myocardial cells (MC) demonstrated that RCM-modified liposomes exhibited high uptake efficiency and low cytotoxicity. In vivo pharmacokinetic studies in Kunming mice showed that these liposomes had a long circulation time and better heart accumulation. Among different formulations, RCM-coated liposomes were better at targeting the heart muscle. This suggests that RCM combined with functional peptides could be a good way to deliver drugs to the heart. [39].

3.5 In Metabolic Disease

The silibinin is an active constituent of milk thistle plant. This active constituent is already known to have its therapeutic effect in variety of liver disease and disorder. Considering this Tayebi Khorrami, V. et al., prepared NC by modified Stöber method and further elucidated a sustained-release formulation of silibinin (SBN) by encapsulating SBN-loaded mesoporous silica nanoparticles (SBN-NC) with red blood cell ghost membranes (RBCG) which are prepared by RBC's lysis and sonication, thereby creating a biomimetic system (SBN-NC-RBCG) for improved liver-targeted therapy, illustrated in fig. 10. SBN-loaded silica NC showed small size and high surface area with typical sustained release of SBN i.e. 90% over 12 hours. The DLS study shown mean particle size of SBN-NC-RBCG was found to be 117 ± 2.3 nm with the polydispersity index of 0.34. these SBN-NC-RBCG shown to release almost 78% of drug over period of 72 hr. These traits show that the RBCG-coated SBN-NC system is a promising way to make SBN more effective at treating liver inflammation and fibrosis. [40].

Fig. 10 : Method preparation of coating of RBC-ghost on the surface of SBN loaded NC [40]

Liang, H. et al, created a new nanoparticle called MRIN that is made up of a mesenchymal cells (MSC) encased in poly (lactic-co-glycolic acid) (PLGA) and red blood cell membranes (RBC) to increase circulation stability and reduce immunological elimination in the treatment of Carbon Tetrachloride-Induced Acute Liver Failure. The pre-treated human bone marrow-derived MSC- loaded with PLGA by double emulsion process followed by membrane extrusion to produce the MSC-NP. The whole blood withdrawn from the C57BL/6 mice undergoes various treatments and the subjected to hypotonic solution to collect the RBC shells the shells then coated on MSC-NP to form the MSC/RBC-inspired nanoparticle MRIN, shown in fig. 11. These MRIN had size of around 200 nm. These MRIN have demonstrated improved hepatocyte proliferation in vitro and decreased macrophage absorption. In a mice model of hepatic failure caused by carbon tetrachloride, intravenous MRIN administration effectively decreased inflammation (IL-6, IL-1β, TNF-α) and apoptosis, stimulated hepatic regeneration, and significantly improved survival outcomes. Due to improved distribution and biocompatibility, this therapeutically available approach offers a promising approach for treating liver failure utilizing the potential for regeneration of factors. [41]

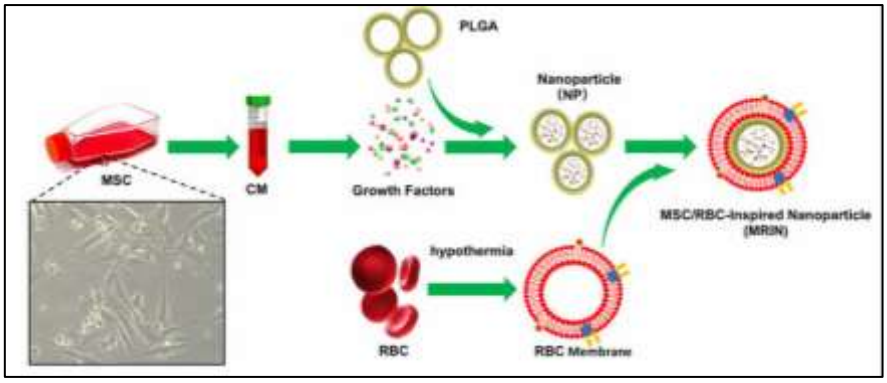

Fig. 11: Method of preparation of MRIN. [41]

3.6 In Neurological Disorder

Alzheimer's disease is a progressive neurodegenerative disease. Its pathology includes beta-amyloid build up and chronic inflammation, which results in neuronal lesions, cerebral atrophy, and cell loss—all of which are crucial features of the disease's progression [42]. Taking this into consideration, Gao, C. et al, developed a system based on nanoparticles to deliver antioxidants directly to neuronal mitochondria. Human serum albumin (HAS) and curcumin (CUR) nanoparticle by modified ultra-sonication method. Which are the coated by RBC membrane of ICR rat collected by hypotonic method. Further these RBC-NP were added with functional conjugates (DSPE-PEG_{3400}-T807) which are prepared by NHS-amino coupling reaction to form the T807/TPP-RBC-NPs, shown in fig. 12. They were able to achieve a targeted delivery through the hemato-encephalic barrier. Using curcumin as an antioxidant test, the system has shown its effectiveness in reducing oxygen-related stress, inflammation related to the astrocytic and microglial activation and neuronal death associated with Alzheimer's disease in mice models [43].

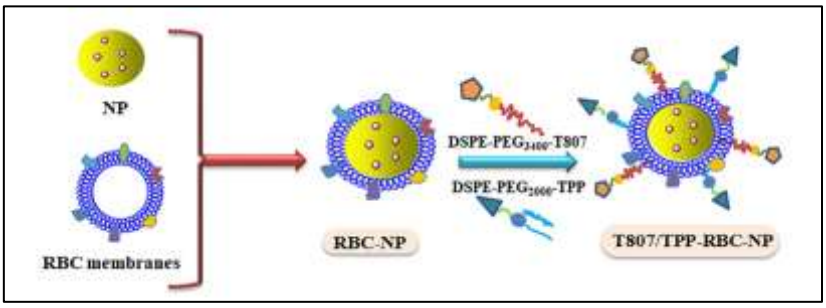

Fig. 12: Method of preparation of Curcumin T807/TPP-RBC-NPs [43]

Su et al. developed a red blood cell membrane-coated nanodrug system called TR-ZRA to treat Alzheimer's disease. The red blood cells collected from the mice were subjected to the centrifugation process to separate the red blood cell membrane which further centrifuged with the TFR-A aptameric to form TR. With this they prepared the Zn-CA nanoparticle by adding chlorogenic acid to $ZnNO_3$ solution. Further to the solution of Zn-CA nanoparticle, PEI polymer were added to form the ZC-PEI nanoparticles which then added with CD22 shRNA and AAP to form ZC/RNAi/AAP(ZRA). Finally, the TR and ZRA ultra sonicated to form the TR-ZRA. These prepared TR-ZRA showed the particle size of 93.3 nm. TR-ZRA were able to cross through the BBB and able to regulate the level of CD22 in surviving microglia, restoring their ability to eradicate beta-amyloid and reducing cerebral inflammation by reducing level of IL-1β, TNF-α, and IL-6. In APP/PS1 mice models, TR-ZRA has enhanced memory and learning, promising to be both a therapeutic and diagnostic tool for Alzheimer's disease, illustrated in fig. 13 [44].

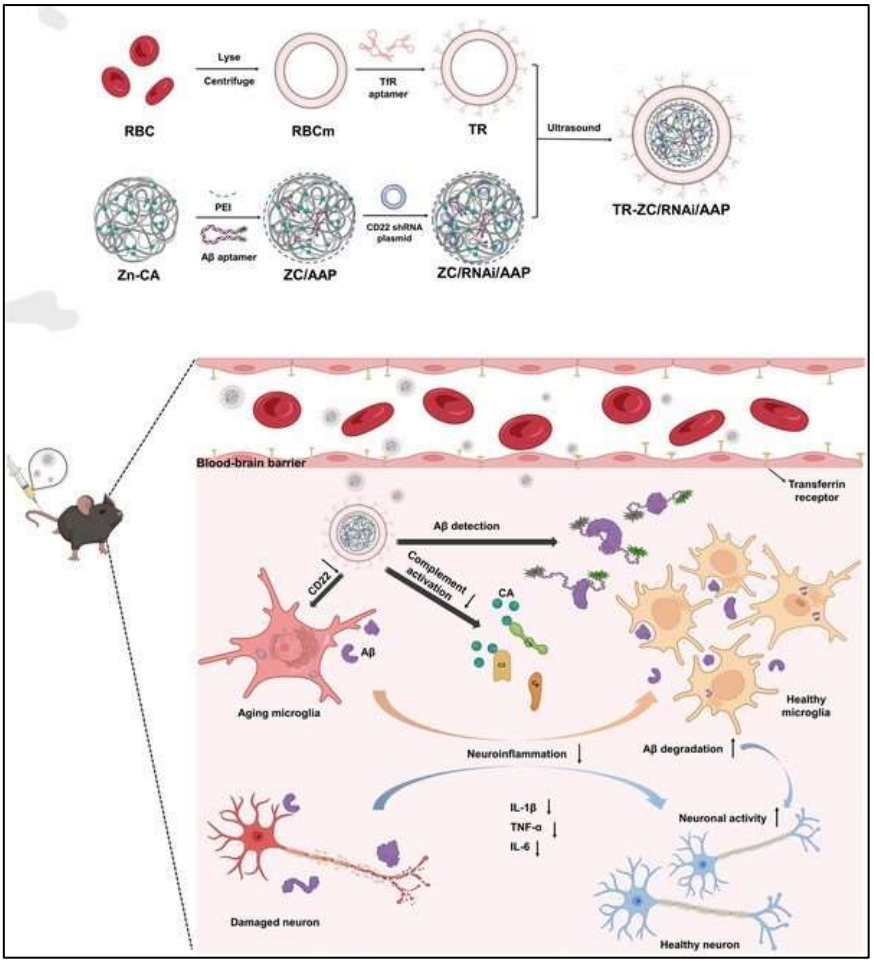

Fig. 13: Method of preparation of TF-ZRA and its application in Alzheimer disease [44]

To treat Parkinson's disease, Liu et al. have introduced a targeted nanodecoy system on the brain using red blood cell membranes altered with the peptide RVG29. They produced Curcumin nanoparticle (Cur-NP) by dissolving the Cur in solution of polyvinylpyrrolidone K90. Further they collected the RBCm form the derived RBC and those are incorporated with DSPE-PEG_{2000}-RVG29 to insert lipid on RBCm. These modified RBCm ultra sonicated with Cur-NP followed by coextrusion lead to coating of nanoparticle to form the RVG29-RBCm/Cur-NCs. These RVG29-RBCm/Cur-NCs have particle size of 84.3 nm with drug loading capacity of 5.13 ±0.31% and encapsulation efficiency of 99.47 ± 0.11%. In a mouse model of Parkinson's disease caused by MPTP/MPP^+, RVG29-RBCm/Cur-NCs has demonstrated significant neuroprotective effects. The animals that were showed improvements in their motor function, preservation of neurons that were positive for the tyrosine hydroxylase, suppression of the pathological accumulation of α-synucleine, restoration of dopamine levels, and reversal of mitochondrial dysfunction and it has shown similar level of inflammatory factor in treatment and control group. Additionally, the formulation has demonstrated exceptional biocompatibility [45].

3.7 In Cancer Condition

This study presents a novel red blood cell membrane-camouflaged nanoparticle system, RBC@BPQDs-DOX/KIR, designed for synergistic cancer therapy by combining chemotherapeutic and anti-inflammatory agents. The red blood cells were obtained from the male Balb/c-nu mice were subjected for centrifugation followed by hypotonic method to obtain the RBCm. Black phosphorus quantum dots (BPQDs), doxorubicin (DOX) and kirenol (KIR) were dissolved to load the BPQDs and these loaded BPDQs-DOX/KIR fused with previously obtained RBCm by ultra-sonication method to form the RBC@BPQDs-DOX/KIR. These nanoparticle having average size 63.0 ± 1.6 nm where 4.1% KIR and 10.2% DOX were encapsulated within this nanosystem. Further drug loading ability for the DOX and KIR in RBC@BPQDs-DOX/KIR was found to be 96.3% and 42.0% respectively. The outer red blood cell membrane shell enhances biocompatibility, immune evasion, and passive tumor targeting via the enhanced permeability and retention (EPR) effect. Upon reaching the acidic tumor microenvironment, the nanoparticles release their payload, where DOX and KIR act synergistically to suppress tumor cell survival by modulating apoptotic proteins (downregulating Bcl-2 and upregulating Bax) and reducing inflammatory cytokines such as TNF-α and IL-6. This dual-action approach remodels the tumor microenvironment, amplifies anti-tumor efficacy, and minimizes the side effects typically associated with DOX monotherapy, represented in fig. 14. With high drug-loading capacity, fluorescence properties, and selective tumor retention, RBC@BPQDs-DOX/KIR demonstrates strong potential as a safe and efficient platform for targeted cancer treatment. [46].

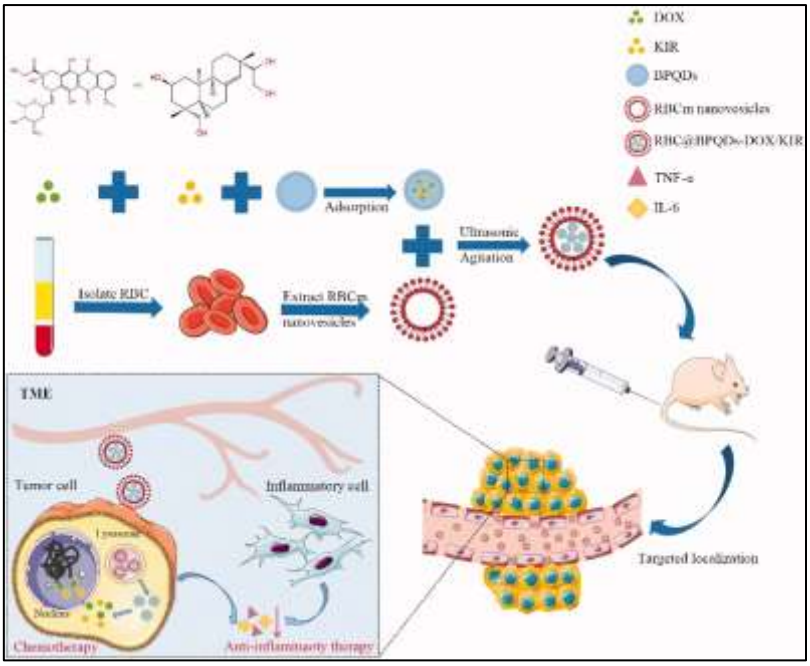

Fig. 14: Method of preparation of RBC@BPQDs-DOX/KIR and its application in cervical cancer-bearing mice [46]

Dai, J. et al, introduced a multifunctional nanoparticle system, RBC membrane-bound NPs (M@AP), designed for synergistic photodynamic and immunotherapy against tumours. The nanoparticles are constructed by self-assembling a positively charged aggregation-induced emission luminogen (P2-PPh3), which acts as a photosensitizer, with the negatively charged immune-stimulant Poly(I:C), and encapsulating the complex within a poly (lactic-co-glycolic acid) matrix and red blood cell (RBC) membrane. This M@AP nanoparticle have average particle size of about 120 nm showing good stability. The RBC shell enhances biocompatibility, immune evasion, and passive targeting to tumors via the enhanced permeability and retention (EPR) effect, while also directing some particles to the spleen through a homing mechanism. Upon light activation, P2-PPh3 generates reactive oxygen species (ROS), inducing tumor cell death and releasing tumor antigens, which, in combination with Poly(I:C), stimulates a robust immune response by activating IL-1α, IL-6, TNF-α and IFN-γ. In vivo experiments demonstrated that M@AP nanoparticles effectively suppress tumor growth, activate immune cells, and reduce metastasis in a lung cancer model, highlighting their potential as a powerful platform for preventing tumor recurrence and enhancing cancer treatment efficacy [46].

4. aSummary and conclusion

In this review, we have summarized the novel cell based drug delivery system i.e. erythrocyte based drug delivery system for the treatment of inflammation based diseases and disorders. These RBC based drug delivery system mainly includes (RBC) hitchhiking, RBC mediated carrier, RBC derived nanovaccine, RBC membrane redesigned nanoparticles, etc. With the recent developments this system showed controlled drug release over period of time and proved with several in vitro and in vivo trials. Also it is observed that, with the application of these delivery system it is possible employ alternate route of administration for the drug and reduce its dose to improve its bioavailability and the side effects. With the help of different animal study and some controlled and uncontrolled trials it has been proven that, an erythrocyte based drug delivery system is effective in carrying synthetic and natural drug to targeted organ with minimal drug-drug and immunological interaction. Although having such advantages, application of these delivery system is still minimal in the treatment of inflammation. Hence, these review support for more extensive research for erythrocyte based drug delivery inflammatory disease and disorder for the betterment of patient compliance and treatment.

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