

Nanomedicine in rheumatology: A new field in the diagnosis and therapy of rheumatic diseases

Editorial

Nanomedicine is a prolific and vastly expanding field of medicine rendering important new avenues to improve diagnosis and treatment of human maladies [1]. Although it has raised exciting expectations for many medical problems, scientific challenges have arisen as well, mainly due to the lack of knowledge about the behavior of nanomaterials inside living organisms [2]. Hopefully, autoimmune diseases could one day be treated by systemic administration of nanoparticles coated with disease-relevant peptides bound to major histocompatibility complex class 2 molecules [3].

Drug-loaded liposomes, nanoparticles, polymeric micelles, nano-ointments, nanocapsules and polymer–drug or protein conjugates and antibodies are all considered nanomedicines [4]. They are developed to shield the drug from elimination, stay in the circulation longer, be customized for macrophage-uptake or target specific receptors and to pervade through explicit diseased tissues as inter-endothelial cell spaces, normally 1–2 nm, reach 600 nm in synovitis [2,5].

Among the strategies to minimize drug removal is by taking benefit of the red blood cells ability to avoid their clearance by elements of the innate immune system. Inclusion of CD47 on the drug-carrier surface prevents connection to neutrophils and macrophages, thus increasing their half-lives and reducing inflammation [6]. Effective diagnosis and therapy should cover the ability to target macrophages which play a central part in the features and progress of rheumatoid arthritis (RA) [7].

On top of managing the solubility, half-life, and immune-system identification, nanocarriers may enhance the drug effectiveness on release when administrated locally. Restricted implantation

of bioactive drugs set in porous matrices and/or hydrogels able to resist surrounding micro-environmental characteristics can offer guided release and actions. Encapsulation within these formulations can also provide sustained release [8]. Nano-scale manipulation of the drug and its carrier is crucial to achieve controlled diffusion, limiting immune response while supporting sustained release of the therapeutic molecules [9]. Interestingly, the reduced access to the nanoparticles by elements of the immune system may also provide an avenue to preserve transplanted tissues [10,11]. However, there are concerns over the potential side effects which may limit their translation to patients. When nanocarriers and nanomedicine are injected in the blood, they can quickly adsorb blood proteins, a condition known as the ‘protein corona’. The physicochemical properties including size, configuration, water affinity, elimination and catalytic capability all may influence their fate and subsequent biological responses [12,13]. The quick uptake of nanomedicine by reticuloendothelial system (RES) cells results in their high accumulation in the liver and spleen [12]. Improving the drug delivery carrier’s bio-distribution may be attained by including immune-evading moieties and/or affinity molecules that support attachment to biomarkers according to the level of needed selectivity [14]. The emergence of PEGylation techniques –involving polyethylene glycol–significantly improved the targeting efficiency of colloidal delivery systems by reducing the RES uptake [15]. Using nanocarriers permits an enhanced site-specific drug delivery to areas of inflammation by boosting the penetration or changing the pH of inflamed tissues and by making use of monocytes as active targets for drug delivery [2]. However, when treating ulcerative colitis and Crohn’s disease, the nanoparticles

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dosage may be adapted orally as the intestine is the drug target [2].

Conditions that promote chronic systemic inflammation, such as obesity, cancer, and autoimmune and infectious diseases, are now known to play key roles in the development of cardiovascular disease (CVD). In response to this new understanding, new-generation therapies based on endogenous molecules with anti-inflammatory properties are in progress. This target-to-treat approach that leverages the phenotypic differences between non-inflamed and inflamed endothelia have the potential to selectively deliver therapeutics and reduce the morbidity and mortality of CVD patients [16].

Using nanomedicines in targeting diseased cells may be appropriate in more than 80 autoimmune diseases. It would be considered a rheumatology breakthrough to not only control the course of inflammation but also reset and normalize the immune response to its non-diseased situation. Moreover, having disease specific medications for RA and other autoimmune diseases is superior [17]. Current progress in understanding inflammation has led to an enhanced interest in using nanomedicine in the management of RA. Unfortunately, RA inflammatory process continues to be puzzling and detecting potentially effective drugs novel procedures for its early diagnosis have been overwhelming missions. In RA synovial hyperplasia results from the accumulation of fibroblast and macrophage-like synoviocytes [18].

Indeed, the synovial intimal lining in RA is usually up to five-fold deeper than normal. Accordingly, more macrophages, lymphocytes, and fibroblasts are triggered and inflammation persists [18]. Nanodelivery systems are able to reduce the drug dose and administration frequency by prolonging circulation time and increasing the metabolic stability of small molecules. Also, as a result of the enhanced vascular permeability in inflammation sites, nanocarriers can preferentially accumulate in arthritic joints [15]. The destructive nature of the disease with irreversible cartilage and bone damage, demonstrates the pressing need for a very early RA diagnosis. Promising candidates are the nanoparticles which are already in use as contrast enhancers for magnetic resonance imaging due to their favorable physicochemical properties and biocompatibility [19]. In RA, nanomedicine passively accumulates into chronic inflammatory

tissues through the increased permeability and retention phenomenon, or be surface-connected with a ligand and attach to receptors overexpressed by cells, leading to an improved effectiveness and diminished side-effects [2].

Nanoparticles containing a much smaller dosage of methotrexate (MTX) for treatment of RA have been developed [2]. Nanomedicine has flourished and is currently providing new avenues for using nanomaterials in drug delivery and tissue regeneration of medical purpose. It may also provide an innovative chance to merge diagnosis and therapy in one mode. In RA, using nanocarriers capable of acting as a diagnostic imaging agent and targeted drug delivery system concurrently, also known as nanotheranostics may permit an advanced efficacy and safety pharmacologic profile, a timely diagnosis, and tracking of the disease. Progress in the theranostics approaches may help build up up-to-the-minute modes to diagnose, fight and follow the disease. The release and action of anti-rheumatic medications may thus be augmented and managed effectively without causing harm to healthy tissues and organs, yet presenting a non-invasive and precise imaging tool for RA [7].

A promising collaborative project on nanoparticles for the diagnosis of RA (NanoDiaRA) funded by the European Union focused on the development of novel nanotechnology based diagnostic systems for RA and osteoarthritis (OA). Generation of superparamagnetic iron oxide nanoparticles was developed with promising effects on human immune cell survival, activity and as theranostics in rheumatic diseases [19]. Ongoing investigations on multifunctional mAb-modified nanoparticles for the delivery of MTX have been proposed with the advantage of providing a new theranostic route for RA treatment [18].

In systemic lupus erythematosus (SLE), corticosteroids and immunosuppressives are administered in high doses with increased side effects. Promising therapeutic methods involving nanostructures of immunomodulators are emerging with significant amelioration of manifestations and minimized side effects [20]. Re-establishing the loss of micro RNA polymorphism by nanotechnology was efficient in abolishing autoantibody production and reducing SLE advancement in lupus-prone mice [21]. Many of the drug delivery systems for lupus treatment have focused on lupus nephritis (LN);

clinically affecting up to 80% of SLE patients and is a leading cause of mortality. Glomerular mesangial cells are active targets and a novel immunoliposomal drug delivery system for LN is developed by surface modification with antibody against the alpha-8 subunit of integrin, which is expressed on the mesangial cell membrane [15].

The effects in systemic sclerosis (SSc) were more pronounced with nanoscale modulation of collagen stiffness providing future hope that this is clinically readily applied [22]. Moreover, nanostructured surfaces introduce a potentially revolutionary approach to the delivery of biologics and influence on fibrosis in SSc [12].

Precise targets in vasculitis are deficient and present therapeutics lead to broad immunosuppression. However, many immunosuppressives are widely distributed and frequently leading to many side-effects. Nano-vehicles hold the ability to overcome such limitations by allowing targeted delivery of their content [23].

In osteoarthritis (OA), nitric nanosensor allows the monitoring of the nitric oxide (NO) release in interleukin-1 β -stimulated chondrocytes, which may facilitate a noninvasive and real-time evaluation of the disease development [24]. Furthermore, Oligosaccharide nanomedicine of alginate sodium has shown better improvement in complications and therapeutic effects on degenerative lumbar disease by downregulating micro-RNA-155 [25]. Small-interfering RNA (siRNA) nanotherapy could reduce early inflammation and halt consequent joint injury making it a promising treatment option in idiopathic OA. Moreover, a major limitation to the production of an effective anti-osteoarthritic drug involves their impaired delivery to the chondrocytes in the avascular cartilage. Peptide-siRNA nanocomplex is not immunogenic and can easily penetrate OA cartilage presenting a platform offering potentially capable ways of drug delivery to the highly unreachable chondrocytes [26]. In juvenile patients, lipid nanoparticles in gene therapy are capable of conquering the prime barriers for approaching cells via degradation, internalization, intracellular trafficking and targeting certain cells. More importantly, they are safe, well tolerated and stable [27].

Treatment of rheumatic diseases stays a remarkable challenge. Nanomedicine-based delivery approaches offer promising avenues to enhance and maximize treatment options avoiding the common drawbacks of available

immunosuppressives and biologics. The clinical potential of original nanomedicine methods for induction of immunosuppression and immune tolerance in autoimmune diseases to rectify immune dysfunction is emerging [28].

Non-steroidal anti-inflammatory drugs are preferred treatments for symptomatic pain relief. However, they can cause serious dose-dependent side effects which prompted experts to recommend minimizing their dosage by implemented strategies including nano-formulation, encapsulation and topical delivery. However, there are challenges to developing these lower dose preparations and at the same time maximizing the clinical potential without impairing their safety and efficacy [29]. Nanoparticles also overcame the limited bioavailability and toxicity of selenium with enhanced anti-inflammatory and analgesic effects [30].

Corticosteroid nanoparticles reserve the capability to dampen proinflammatory cytokines at the least effective dose with the advantage of reducing the broad immunosuppression that occurs with many biologic TNF- α inhibitors [2]. More interestingly, a nanomedicine polymeric prodrug exhibited a superior and prolonged therapeutic efficacy in LN compared to free dexamethasone with reduction of the systemic side effects [15]. Excitingly, gold nanostructures have been successfully used in metastasis and pave the way for developing better strategies for rheumatic diseases [20].

The use of biologics for the treatment of rheumatic diseases is rapidly expanding and parental administration has been the mainstay route of their delivery because they are too large to permeate epithelial barriers [12]. In spite the effectiveness of biologics, major side effects occur [31] exposing patients to serious infections as tuberculosis [32]. The introduction of nanotechnology in many rheumatic diseases may help refine the management armamentarium by providing the least effective dose of biologics with minimum adverse effects.

Nanomedicine could potentially be used to treat any chronic inflammatory or rheumatic disease [3]. However, safety of the nanomaterials and therapeutic agents must be carefully considered. In the forthcoming future, more anti-inflammatory drugs targeting cytokines will hopefully be nanodeveloped to treat, making 'target-to-treat' as important as the emerging 'treat-to-target' strategy. Nanomedicines that

reduce the dosage, frequency and adverse-effects of the anti-inflammatory drugs used nowadays will possibly move to clinical practice.

Conflict of interest

The authors report no declarations for conflict of interest.

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