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Conventional and Nano-Based Therapy against Chronic Inflammatory Autoimmune Diseases

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Authors' contributions

This work was carried out in collaboration between all authors. Authors RGK and SMS collected literature and wrote the manuscript. Authors GD and JKP revised and edited the manuscript. All the authors read and approved the final manuscript.

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ABSTRACT

Structural or functional damage to cells, tissues, organs, or organ systems emerging from immunologically competent cells or antibodies against a normal component of the host body may lead to autoimmune disorder or diseases. There are about 152 autoimmune diseases classified till now by American Autoimmune Related Disease Association. Current research investigators are more focused on certain autoimmune disorders such as rheumatoid arthritis, lupus, celiac disease, Sjögren's syndrome, polymyalgia rheumatica, multiple sclerosis, ankylosing spondylitis, type-1 diabetes, alopecia areata, vasculitis and temporal arteritis. Chronic inflammation is a common link among most of the autoimmune disorder, but the exact link is not clear. Therefore an effective cure for the disease could not be developed. The conventional therapeutics available is steadily getting constrained because of the development resistance. Present therapeutic shows some limitations such as unidirectional, unspecific and resistance with specific side-effect. With the present

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advancement in science and technology, it is now possible to alienate the present constraints offered by the present conventional therapeutics by the application of biocompatible, biodegradable nano-formulated drug delivery system. Therefore the intention of this mini-review is to provide a base knowledge about the relationship of autoimmune diseases with inflammation as well as the efficiency of the conventional and nanotechnology-based therapy.

Keywords: Autoimmunity; inflammation; nanotechnology; nanoformulation; drug delivery; biodegradable; biocompatible.

1. INTRODUCTION

Host's existing intricate networks of cellular and humoral immunity in unity have proven to be a unique protective barrier against a vast majority of diseases. Despite the fact that chronic inflammation is generally considered as one of the significant co-conspirators of diseases leading to deregulation of homeostasis but still then, the basis of conspiracy behind this is passably understood [1]. Basically overproduction of cytokines and chemokines in autoimmune disease triggers the inflammatory response resulting in recursion of immunologically competent cells to aggravate further the situation resulting in the intensification of the inflammatory response [2]. In short it is assumable that conditions when the protective system of the host starts ambushing and damaging the self-tissue, organs and organ-system then the resulting deregulation of homeostasis can be regarded as autoimmune diseases. Out of 152 autoimmune diseases classified by American Autoimmune Related Disease Association (AARDA) up to present rheumatoid arthritis, lupus, celiac disease, Sjögren's syndrome, polymyalgia rheumatica, multiple sclerosis, ankylosing spondylitis, type-1 diabetes and vasculitis are the most common inflammatory autoimmune diseases currently being widely explored [3-5]. In these conditions, the intricate immune regulators could be exogenously modulated within the host by a number of synthetic or natural therapeutics. Though presently there are a number of diverse biological therapy against these inflammatory autoimmune diseases but still than the associated limitations withholds their use as a first-line medication. Some of the common limitations include inefficient intravenous administration, high cost and lastly side effects [4]. Considering the drawbacks of the present conventional unidirectional therapeutics it could be assumed that, the nano-based therapeutics could just be a fruitful alternative. Nanoparticulate drug delivery systems (NDDSs) are among the spectacular applications of nanotechnology in pharmaceutical science. And they can also the silver lining at the interface of conventional therapy and the next generation advanced medication.

There are number of inflammatory target molecules associated with specific autoimmune diseases. For example, in rheumatoid arthritis CD40L, C-Reactive Protein, ELAM-1, GM-CSF, IL-1, IL-6, IL-15 etc. could be specifically targeted [6]. Likewise, there are heterogeneous inflammatory targets for different autoimmune diseases are evaluated more and more. Therefore the present paper is utterly concentrated on molecular mechanism and different inflammatory target molecules associated with specific autoimmune diseases pathogenesis as well as the conventional and advanced therapeutic.

2. AUTOIMMUNE DISEASE PATHOGENESIS

In a simplified form, the disturbance in the process of specific antigenic recognition and elimination may be regarded as autoimmunity. This is mostly, due to physical, chemical or due to biological influence, the cells undergo antigenic alternation (neo-antigens) which may activate a verity immunological response [7]. As previously known autoimmune disorder or diseases are the destruction of self components by immunologically competent cells or antibodies which is an output of a number of specific mechanisms. Further, almost every mechanistic phenomenon giving rise to autoimmune diseases revolves around three basic interactions involving genetic, environmental and endocrine factors within the host [8,9]. Currently the suggested mechanisms involved in various autoimmune diseases are described here [10]. Targeted cell cytolysis via compliment system, activated by tissue-specific autoantibodies released by the immune cells, plays the initial role [11]. Later on, autoantibody-antigen (soluble mediators)

immune complex deposition within the tissue again contributes to the pathogenesis [7,12]. Furthermore, phagocytosis, cytotoxicity and antibody-mediated cellular immunity results when the immune system is attacked by the autoantibodies [13]. Molecular mimicry is another phenomenon where the destruction of self-tissue occurs by the autoantibodies directed against epitopes of autoantigens mimicking the foreign antigens [14]. Targeted cell surface structure could also be modulated by the action of autoantibodies which also up to certain extent involved in the progression of autoimmune diseases [15]. Lastly, autoantibody-mediated induction of inflammation at the site of binding further contributes to the pathogenesis of autoimmune diseases [16].

Out the above-mentioned mechanisms for autoimmune disease pathogenesis, the role of inflammation or more specifically inflammatory mediators are vividly explored [1]. The evolving knowledge and understanding of these vast arrays of inflammatory mediators were efficient in backing up the present investigators with a tool to target pathways right from the primary phase and control of the severity/ pathogenicity towards the later phase of the disease [2,8]. In following up these inflammatory mediators right from the primary phase, it would be possible to act quickly in order to prevent or ameliorate the ultimate progression of the disease towards damaging the organ [17].

3. THE ROLE OF INFLAMMATION IN VARIOUS AUTOIMMUNE DISEASES

Such condition where host' homeostasis compromised, inflammatory response acts as a protective barrier by recruiting cytokines, chemokines, biogenic amines etc. starting from the local vascular response to a more diverse modulated temperature of the host [1]. The diverse, crucial and obscure obligations of associated inflammatory signal transduction cascade to furnish the adequate requirements could be direct a manifestation of their impact on homeostatic circuit [18]. For instance, the cascade of diverse homeostatic regulation can uninterruptedly be stimulated or inhibited by inflammatory signals [19]. Along with it, the inflammatory signals may also reduce the sensitivity of various therapeutics of either natural or synthetic origin to diverse homeostatic signals [20]. Furthermore, inflammatory modulators could also influence a key molecules or controlling receptors in a particular pathway by decreasing their expression, which results in reduced sensitivity of that particular ligand [1]. Overall it could be assumed that the inflammatory regulators could overrule the homeostatic signals and also to which they are antagonist [1,21].

In the current decade, the role of inflammatory molecules as an antagonist to homeostatic circuit is widely investigated by the investigators. In a number of autoimmune diseases such as rheumatoid arthritis, lupus, celiac disease, Sjögren's syndrome etc. inflammation may orchestrates a central role in disease but the exact link is not properly understood. For example in rheumatoid arthritis both innate and adaptive immune systems simultaneously contribute towards inflammation and tissue damage [22]. The autoimmune response and activation of T lymphocytes by the concordant interaction among the immunological competent cells at lymphoid node, mediates the differentiation of activated B lymphocytes into memory B lymphocytes and plasma cells. Auto antibodies such as rheumatoid factor and anti-citrullinated protein antibodies are secreted by plasma cell and B lymphocytes secrets tumour necrosis factors, interlucin-6 (IL-6) and lymphotoxin-α, which further boosts inflammation and synovial lymphoneogenesis. A positive feedback loop is generated during the interaction of synovial membrane with T cells, synovial fibroblast, natural killer (NK) cells, osteoclasts and macrophages mediated by cytokines, chemokines, cathepsins and matrix metalloproteases which further contributes immensely to the unceasing phase of diseases pathogenesis [6].

Lupus, otherwise known as systemic lupus erythematosus categorized as a systemic autoimmune disease with multiple organ inflammation and is characterized by autoantibody secretion against nucleic acid and the binding protein leading to the loss of self-tolerance [23]. Patients with lupus it has been observed that number of T lymphocytes, B lymphocytes and natural killer cells decreased but there is a swift increased IgG and IgM production. The reason behind it might be reduced along with malformed production of transforming growth factor beta (TGFβ). Further, malformed production of cytokines might also up to certain extent contribute to the pathogenesis of lupus. For example reduced production of IL-2 with decreased response, increased expression of interferon gama (INF-γ), increased production

of IL-10, IL-4. Compliment factors such as C1q, C1r, C1s, C2 and the decreased binding efficiency of CR1 with C3b and C4b fragment additionally increases the susceptibility of the disease pathogenesis [24]. Together, the cytokines and different immune cells directly or indirectly activate the adaptive immune system which boosts the chronic inflammation resulting in tissue damage [23].

Immune sensitive reaction resulting in chronic inflammation in small intestine arising from ingestion of gluten is another autoimmune diseases celiac disease also known as celiac sprue [25]. The complex interplay of genetic, environmental and stochastic events encompassing innate and adaptive immunity, hormonal regulations and nervous system, together with an independent form of inflammation contributes in the pathogenesis of Sjögren's syndrome [26]. Chronic inflammation resulting in central nervous system lesions in multiple sclerosis, on the other hand, is another autoimmune disease, which may further progress into physical or cognitive disability and other neurological defects [27]. Type-1 diabetes results when T cells selectively recognize glutamic acid decarboxylase and p2C peptides and react with each using different restriction elements, which later results in inflammation, tissue damage and release of islet autoantigens [28]. Vasculitis or systemic vasculitis may result secondary to autoimmune disease, where the blood vessel walls undergo inflammatory necrotization [29].

4. CONVENTIONAL AND NANOTECHNOLOGY-BASED ADVANCED THERAPEUTIC STRATEGIES

Though there has been a tremendous development in the field of pharmaceutical sciences still then there is a number of biomedical problems that need additional consideration. Among them, the development of a stable and novel therapeutics to ameliorate the severity of autoimmune disease may be considered as one of the primary concern. Lerner et al. [30] have estimated that the net percentage increase in autoimmune disease incidence globally per year and the prevalence show a mean standard deviation of 19.1±43.1 and 12.5±7.9 respectively. They also stated over last 30 years (till 2015) both incidences and prevalence have dramatically increased [30]. The conventional mainstay treatment is anti-TNF and non-steroidal anti-inflammatory drugs (NSAIDs) against a number of autoimmune diseases are gradually depicting in their efficiency [31,32]. It has been documented that these NSAIDs have shown some detrimental side-effects such as kidney injury, ulcer, intestinal bleeding [32]. Though certain first-line drugs such as abatacept, belimumab, certolizumab, epratuzumab, golimumab, ofatumumab, rituximab, sifalimumab and tocilizumab majorly targeting anti-IL-1, anti-IL-6 molecules have proven to be beneficial but are unidirectional with some adverse effect [4]. And other therapeutics such as anti-TNF biologics which includes TNF receptor 2 fusion proteins and anti-TNF antibodies are losing their sensitiveness in about 40% of patients and also have been found to elicit *de novo* autoimmune disease development [32].

The limitations brought about by the conventional therapeutics could only be mitigated by alternative biocompatible, biodegradable, non-toxic, targeted and tunable therapeutic formulations. Formulations that could specifically target TNF receptors and other biological markers related to the particular diseases [32]. Demand for such an alternative therapy with advanced serviceability could be easily accomplished nano-formulated drug delivery system (Fig. 1) [33]. For example, Dianzani et al. developed a dexamethasone (Dx) cholesteryl butyrate (Cb) encapsulated solid lipid nanoparticle (SLN) by worm microemulsion method and both *in vitro* and *in vivo* models evaluated its anti-inflammatory activity. They concluded that lower concentration of DxCb-nanoformulations were more effective in comparison to free DxCb by significant *in vitro* inhibition of cell adhesion molecule and both *in vitro* and *in vivo* decrease of pro-inflammatory cytokines such as IL-1β and TNF-α [34].

Drug resistance and side-effect are significant challenges to present pharmaceutical researchers could be swiftly overthrown by the application of NDDSs of which polymeric nanoparticles (PNPs) is one example [35]. These PNPs could be either nano-capsules or nanospheres, depending on the preparation method. Morphologically a nano-capsules possesses an aqueous or oily cavity consisting of the active ingredient encapsulated by an outer biodegradable polymer and a nano-spehers are spherical matrix like structure of uniformly dispersed polymer consisting of active

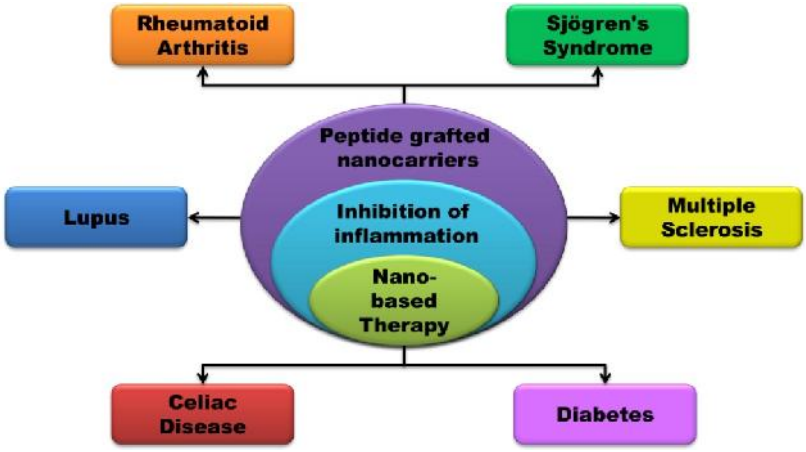

Fig. 1. Application of nano-based therapy against various diseases

compounds [36]. Mitigation of the side-effect and increase in the sensitivity of conventional drugs on the other hand, are being immensely influenced by utilization of these polymers such as polymeric micelles, PEGylated liposomes, polymeric-drug conjugates, inorganic scaffolds and other hybrid nanoparticles. For example glucocorticoids a strong anti-inflammatory and immunosuppressive in nature which could be used to treat a number of diseases including some autoimmune diseases, but its high dose and long-term intake arises serious side-effects. Later with the advancement of nanotechnology, bioactive, biocompatible, and biodegradable polymer encapsulated glucocorticoids could be effectively used for various therapeutic purposes [35]. With the gradual upraise of new branches of applied science and technology the grip of nanoscience in the development of advanced smart drugs is in gradual progress. Discovery of versatile inorganic, organic and hybrid-NDDS have significantly enhanced the understanding of mankind like never before. The progress made is considerably less but could be enhanced if the current research focus would drift towards exploring the Pandora's Box of all naturally available phytocompounds instead of developing the new synthetic drugs.

5. NANO-BASED MARKETED PRODUCTS AGAINST AUTOIMMUNE DISEASES

It took time for the nanotechnology-based products to reach the market with its unique potentials. But since then the research made in the advancement of the nano-based product is remarkable. A PEGylated nano-formulation, Certolizumab Pegol with a tread name CIMZIA® used for the treatment of Crohn's disease and rheumatoid arthritis [36]. It is actually Poly Ethylene Gylated (PEGylation) antibody superficially Fab' fragment of a rumanized anti-TNF-α antibody [36]. This nano-based drug might also be regarded as one of the pioneering nano-based therapy against autoimmune diseases. Prolonged circulation, retention time, increased hydrodynamic radius, decreased proteolysis decreased renal excretion and non-immunogenic targeted interaction with the substrate are some of the highlighted attribution of PEGylated nano-formulations [37]. Another polymer-based nano-formulation Glatiramer Acetate with a tread name Copaxone® an immunomodulatory medicine approved for the treatment of multiple sclerosis [38]. The medicine is a 6.4 kDa polypeptide composed 4 amino acid (glatiramer) [36]. Pujol-Autonell et al. [39] developed a liposome based immunotherapy against multiple sclerosis. The nano-formulation basically consists of phosphatidylserine-rich liposomes loaded with a disease specific autoantigen specifically Myelin Oligodendrocyte Glycoprotein Peptide. The efficiency of liposome nano-formulation against multiple sclerosis was evaluated both by *in vitro* and *in vivo*. The evaluation resulted in, re-establishing tolerance in dendritic cells, autoimmunity detention which further decreased the progression of the phenomenon by delaying the onset and ameliorating the sternness of the experimental diseases [39]. Singha et al. [40] developed a hybridised inorganic nano-formulation of gold (Au) against type-1 diabetes (T1D). They functionalized Au nanoparticles with multiple copies of T1D-relevant NRP-V7/Kd peptide-major histocompatibility complex and evaluated its biological activity. In their work, they showed

that the nano-particulate system was effective autoimmunity function as T-cell receptor micro-clustering devices and also had no off-targeted toxicity in *Danio rerio* embryos [40]. Overall, the nano-carriers have been proven to be a prospective tool used in the improvement of the safety and healing proficiency of the currently available drugs or techniques for the treatment of autoimmune diseases, mainly for those with powerful but deadly compounds [41]. Though there are many nano-based therapeutics already been approved for other diseases such as cancer, microbial and fungal infections but the approved nano-therapeutics in relation to autoimmune diseases is scanty.

6. CONCLUSION

Globally autoimmune diseases may be considered as one of the major causes of mortalities, and the severity is growing day by day. Development of an effective therapy against autoimmune diseases is possible if associated inflammatory molecular pattern in the pathogenesis of the disease is understood correctly. The conventional and the present and the available therapy have certain limitations such as unidirectional, unspecific and resistance with a certain side-effect. The nullification of these obstructions is possible by the application of nanotechnology. Exploitation of NDDSs is an effective and advanced therapeutics against autoimmune diseases in the present decade. The amalgamated science and technology involved are simply mesmerizing. Thus, it may be acknowledged that therapeutics with negligible side-effect such as natural bioactive compounds with anti-inflammatory activity could be a beneficiary approach to treat autoimmune diseases. But the effectiveness of these nontoxic natural bioactive compounds might be further enhanced either by their encapsulation within or surface immobilization on these NDDSs is carried out. The focus of the present generation researchers should be to engineer bioactive conjugated NDDS against autoimmune diseases.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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