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Review Article
Published: 30 Apr, 2018

Journal of Bacteriology and Vaccine Research

Therapeutic Spectrum of Dendritic Cells

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Abstract

Professional antigen presenting cells (Dendritic cells) have distinctive potential to process and present any foreign antigen to naïve T cells resulting in initiation of immune response. This property of dendritic cells has instigated many researchers to use these cells as new therapeutic strategy. Dendritic Cells based Immunotherapeutic approaches have been shown to be feasible, secure and effective in treating different diseases (Cancer, Autoimmune, and infectious), which are otherwise difficult to manage. The results of the clinical trials have provided evidences for the potential applications of dendritic cells as a cell-based adjuvant for the development of therapeutic vaccines. In this review we have discussed the current state of knowledge regarding how the DCs have been exploited and being used as therapeutic tools to improve treatment modalities focusing on autoimmune diseases, different types of cancers and chronic viral hepatitis.

Keywords: Dendritic cells; Autoimmune diseases; Cancer; Hepatitis; Vaccine; Immunotherapy

Introduction

Dendritic cells (DCs) are the professional antigen presenting cells having a unique capability to process any foreign organisms entering our body and present them to T-cells (via MHC -peptide-TCR complex) to initiate an adaptive immune response [1]. Properties of dendritic cells such as antigen uptake, antigen processing and presentation, activation of immune cells leading to generation of an immune response and linking innate & adaptive immune system have made these cells as propitious candidates to be used as vaccines [2]. Dendritic cell based immunotherapy has been focused as a therapeutic approach for treating many diseases which are otherwise not curable. Dendritic cells, discovered in 1973 by Ralph Steinmann and Zanvil A. Cohn, reside in peripheral tissues and circulate in an immature state in the human body [3]. These immature dendritic cells have lower expression of co-stimulatory molecules such as CD80, CD86 and CD40; express fewer major histocompatibilty complex (MHC) - Class II molecules, secrete lower amounts of inflammatory cytokines such as IL-12 but show high phagocytic capacity. When these immature dendritic cells encounter any foreign particle or antigen, these antigens are endocytosed and degraded in endosomes by acid dependent proteases (exogenous pathway) [4]. During this process, DCs migrate to T-cells rich areas of lymph nodes and the processed peptide is then presented to naïve T-cells on the MHC-Class II molecules forming Peptide-Class II MHC complex. At this stage, DCs become phenotypically mature as they express higher co-stimulatory molecules, higher MHC Class II molecules and even become functionally mature as they secrete higher levels of inflammatory cytokines like IL-12, TNFα etc. These peptide-MHC complexes are recognized by T-lymphocytes which results in their activation. The activated T-lymphocytes express surface markers such as CD25, CD71 and other co-stimulatory molecules such as CD40L, CD26, CD27, CD28 and CD134. These cells then interact with other cells such as B-lymphocytes and thus an immune response is generated.

Apart from their function in inducing a primary immune response, dendritic cells are found to play an important role in pathogenesis of various diseases such as infectious diseases, autoimmune diseases, and cancer. Till date no vaccine for the prevention of many of these diseases is available. Also, the medicines which are available are not 100% effective. Many trials using dendritic cells as vaccines have been carried out but the success rate is not so high due to lack of optimization. In this review we have tried to focus on how the DCs have been exploited in different trials using different routes of administration and in different diseased conditions.

Autoimmune Diseases

Autoimmune diseases (AD) are a major health problem. It refers to the pathological state where

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Received Date: 23 Mar 2018
Accepted Date: 26 Apr 2018
Published Date: 30 Apr 2018

Citation: Tomer S, Arora SK. Therapeutic Spectrum of Dendritic Cells. J Bacteriol Vaccin Res. 2018; 1(1): 1003.

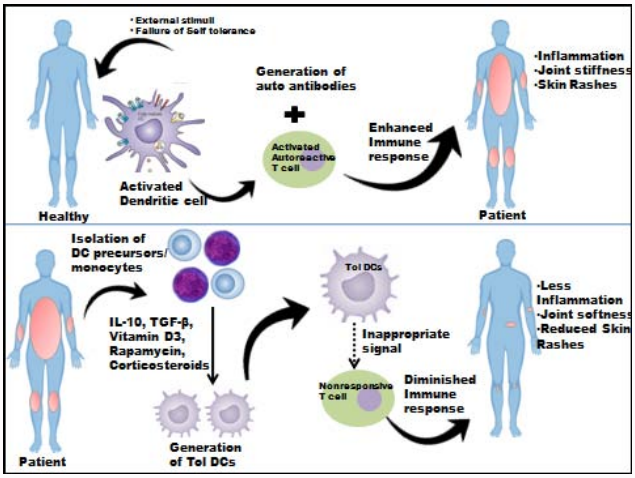

Figure 1: Schematic representation of dendritic cell therapy in patients' suffering from autoimmunity.

the immune system attacks the body's own healthy cells and damages them resulting from an abnormal immune response. More than 100 million people are affected worldwide by different autoimmune diseases [5]. Prevalence (2017) of autoimmune conditions in some Asian countries such as China and Japan are 8% and 3% respectively (https://www.statista.com/statistics/418328/diagnosed-autoimmune-conditions-prevalence-in-selected-countries/). The incidence and prevalence of autoimmune diseases is increasing at a rapid pace over the last decades. The net percent increase per year incidence was 19.1± 43.1 whereas prevalence of these diseases is 12.5 ± 7.9 worldwide. AD can be either systemic {involving auto antibodies not specific to antigens or are found generally as multi-organ diseases such as Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE)} or localized (specific to a particular tissue or organ such as Psoriasis, Type 1 diabetes mellitus, multiple sclerosis etc.).

There are many obstacles in the diagnosis and treatment of these diseases. No specific treatment for many of these diseases is yet known. The main goal of treatment is to reduce the symptoms especially during flare ups, control the progression of diseases and maintain the body in such a state that it can help fight against the disease.

We discuss the role of DCs in these diseases and how these DC- based vaccines are becoming a potentially powerful tool for the treatment of autoimmune diseases.

Rheumatoid Arthritis

Rheumatoid arthritis (RA), also called as atrophic arthritis, is a chronic inflammatory disorder primarily affecting the joints thus resulting in painful and swollen joints. The global prevalence of RA was reported to be 0.24% during 1990-2010 [6]. The Centers for Disease Control and Prevention (CDC) estimated that 52.5 million U.S. adults were suffering from arthritis in 2013, which accounts for around 23 percent of the population (https://www.cdc.gov/arthritis/data_statistics/arthritis-related-stats.htm). In India, the estimated prevalence was 0.7% [7]. There is no cure for this disease till date and the treatment involves combination of drugs that ease the symptoms and slows down the disease activity. Studies have shown that app. 30% of patients treated with anti-TNF biological agents fail to respond to therapy [8]. In another study, 40% patients failed to achieve remission [9].

Dendritic cells seem to play an important role in the pathogenesis of this disease. It has been reported that immature and mature dendritic cells are present in rheumatoid synovium [10]. Increased number of Myeloid and plasmacytoid DCs are found to be present in the synovial fluid of RA patients with active disease, suggesting a significant role of dendritic cells in the progression of disease [11]. The infiltrating dendritic cells activate the T-cells which drives organ inflammation. In patients with RA, synovial tissue is enriched with differentiated DC. These DC present arthritogenic antigens to autoreactive T- lymphocytes resulting in the initiation and perpetuation of the disease.

Dendritic cells play an important role in maintaining immune tolerance (peripheral tolerance) and this function of dendritic cells have been exploited in generating tolerogenic dendritic cells (tolDCs), which are being used as an immunotherapeutic tool to treat various autoimmune diseases resulting from abnormal immune response [12]. Tolerogenic DCs are semi-mature dendritic cells, which do not result in immunogenic response but induce tolerance, resulting in non-responsiveness of immune system towards any antigen. The effect of tolerogenic DCs in the maintenance of peripheral tolerance are mediated by different mechanisms. It can be either through T-cell clonal deletion, T-cell apoptosis, T-cell anergy induction and/or the expansion of T-regulatory cells (Tregs; both natural and induced Foxp3+ Treg) where in T-cells do not get activated and fail to generate an active immune response. This tolerance can also be achieved by deviating cytokine response towards Th2 response.

In mouse models, when tolerogenic DCs pulsed with type II collagen were injected in arthritic mice, disease severity and progression was significantly inhibited [13]. In another study, it was shown that when allogenic tolerogenic dendritic cells were given to collagen induced arthritis (CIA) mice, severity of the disease was reduced [14]. Also, when tolDCs modified by tacrolimus (an immunosuppressive drug) were injected into CIA mice, it was observed that CD4+ T-cell proliferation was suppressed inhibiting arthritis in mice [15]. Clinical trials with tolDCs have been done in patients with RA to check the safety and efficacy of these cells. In the first phase I trial, dendritic cells were taken from a patient, modified using NF-κB inhibitor (Bay11-7082), exposed to citrullinated peptides and were injected back into the same patient. It was observed that the modified DCs were well tolerated with a reduction in effector T-cells, Treg:T-effector ratio was increased, serum cytokine (IL-15, IL-29, CX3CL1, and CXCL11) levels were decreased, there was no flare induction and also Disease Activity Score (DAS) of 28 joints was decreased in patients with active disease [16]. In other trial named Autologous tolerogenic dendritic cells for RA (AUTODECRA) trial, tolDCs were generated from monocytes and were injected intra-articularly into the knee joint of respective patient to check the safety, tolerability, feasibility of tolDCs [17]. So, overall the literature reports suggest that use of these modified autologous tolDCs was safe, feasible and acceptable as observed in RA patients. Further research and large-scale clinical trials are warranted to validate the efficacy of these modified DCs for management of debilitating auto-immune disorders (Figure 1).

Type1 Diabetes

Type1 diabetes (T1D) is a T-cell mediated autoimmune disease, in which little or no insulin is produced due to destruction of beta cells in islets of langerhans by body's own immune system [18]. Globally, 422 million (estimated value) are living with diabetes

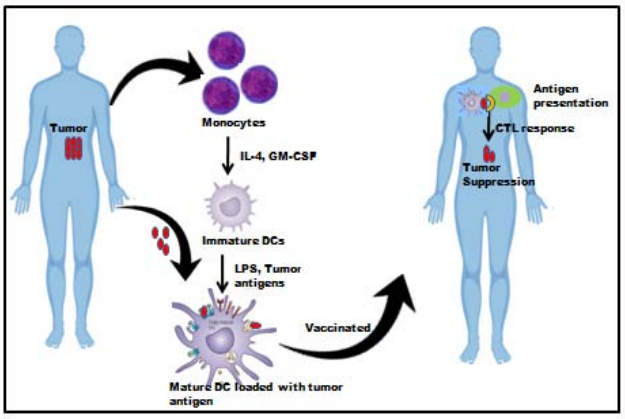

Figure 2: Representative diagram of Dendritic cell vaccine therapy in cancer patients.

according to World health Organization (2016) (http://www.who.int/mediacentre/factsheets/fs312/en/). Approximately 62 million people are affected by diabetes in India [19]. Currently it is treated with insulin, but insulin has many side effects such as hypoglycemia, low potassium level in blood and blurred vision.

Many studies have reported that DCs contribute to the onset and development of T1D, thus playing an important role in the pathogenesis of the disease [20]. DCs capture the β-islet cell derived antigens and present them to auto reactive T cells, thereby initiating T1D development [21]. Many reports have shown that DC in NOD mice shows alterations in numbers as well as development, highlighting the role of DCs in pathogenesis of T1D [22]. Plasmacytoid DCs have also been suggested to elicit the immune response responsible for initiation of this disease by secreting IFN-α, as reported in NOD mice [23].

In experimental model of NOD mice, when bone-marrow derived dendritic cells were cultured with antisense oligonucleotides targeting genes for co-stimulatory markers such as CD40, CD80 and CD86 and injected in syngeneic mice, the protection against diabetes was conferred to the mice [24]. Also, the incidence of T1D was significantly delayed by injecting engineered NOD DCs. Based on the above data, Giannoukakis et al., carried out a similar study in human subjects [25]. Phase 1 clinical trial was carried out for checking the safety of autologous tolerogenic (engineered) dendritic cells in patients inflicted with T1D. When injected into patients, it was observed that these cells were safe and well tolerated. Also, the frequency of B220+ CD 11c- B cell population was upregulated and this population is potentially beneficial in T1D autoimmune disease. In another phase 2 clinical trial, DCs were incubated with antisense DNA oligonucleotides targeting co-stimulatory molecules such as CD40, CD80 and CD86 to check whether these cells modulate the immune responses that destroys pancreatic beta cells which is responsible for T1D development. The efficacy and safety of antisense DNA-treated co-stimulation-impaired immunoregulatory dendritic cells were assessed and was found to be safe and well tolerated. Thus, DC-based vaccine may serve as future therapy for treating T1D and increasing B cell mass, thus resulting in the improvement of blood glucose levels.

Cancer

Cancer is abnormal cell proliferation, dysregulated division, differentiation and apoptosis of cells resulting in formation of cell mass and destroying body tissues. Cancer leads to severe health consequences, and is a leading cause of death. According to WHO report, around 8.2 million people die each year from cancer (www.who.int/mediacentre/factsheets/fs297/en/). In India, 3, 95,400 cancer incidences were reported in 2017 (http://cancerindia.org.in/statistics/).

There are many studies which have reported the role of dendritic cells in the pathogenesis of cancer. Altered DC numbers are found in the blood of patients with cancer and also in tumors [26]. Also, DCs infiltrating tumors have immature phenotype expressing intermediate or low CD11c expression, having low co-stimulatory molecules (CD80, CD86), high levels of inhibitory molecules such as Programmed death-ligand 1 (PD-L1) whose expression is further up regulated by tumor micro environment, having impaired antigen presenting capacity [27]. These DCs also suppresse innate and adaptive immune responses. Studies have reported that many tumor derived factors such as IL10, IL6 and tumor-specific antigen result in suppression of dendritic cells by impairing differentiation and maturation of DCs [28,29]. Other factors in tumor microenvironment like gangliosides, nitric oxide and hyaluron induces apoptosis in vitro [14,30,31]; GM-CSF and VEGF results in accumulation and generation of immature antigen presenting cells displaying inhibitory function both *in vitro* and *in vivo* [32,33]; Prostanoids, tumor-derived mucin, *HER-2/neu* oncogene product results in impairment and alteration of maturation and function *in vitro* [34].

Prostate Cancer

Extensive research has been carried out on dendritic cells to be used as vaccine against many tumors. Many clinical trials have already been done and cell based cancer immunotherapy for prostate cancer namely Sipuleucel-T (White blood cells + prostate cancer proteins) has already been approved by FDA [35]. To make this therapy more effective, research and trials are being carried out using specifically modified autologous dendritic cells. In phase 1/2 clinical trial, patients with Non-metastatic Castrate Resistant prostate cancer were injected with tumor MUC1 bearing Tn glycopeptide isolated from rhesus monkey and homologous to human (Tn-rmMUC1), loaded on dendritic cells and it was observed that Tn-MUC1 DC vaccination was safe, well tolerated, biologically active (Prostate Specific Antigen doubling time improved significantly indicating lower risk of recurrence) and induced T-cell responses [36]. In another phase1/2 clinical trial, patients with metastatic, castration-resistant prostate cancer were injected with autologous mature dendritic cells, which were pulsed with killed LNCaP prostate cancer cells (DCVAC/PCa) [37]. No serious adverse events were reported. There was a decrease in Treg cells and PSA specific T cells were also induced in these patients. Overall survival of patients was also found to be increased. Another, phase 1 clinical trial was done using CD1c (BDCA-1)+ dendritic cells which were pulsed with HLA-A*0201 peptides in patients with metastatic hormone refractory prostate cancer, and it was observed that the vaccination was safe, feasible and well tolerated [38].

Breast Cancer

In patients with breast cancer (ER/PR double-ve), when autologous dendritic cells pulsed with autologous tumor lysate was injected, no adverse effect was observed [39]. Also, there was increased Th1 cytokine secretion, increased NK cells and increased CD8+ IFN- cells thus suggesting that there was an increased anti-

cancer immune response. In phase 1/2 clinical trial using dendritic cells and IL-2, it was reported that the vaccine was well tolerated and induced cellular immunity (antigen specific) [40]. In another phase 1 study carried out in HER2 +ve breast cancer, vaccination with autologous DCs activated with lapuleucel-T has shown that it is safe, feasible and well tolerated [41].

Melanoma

Many clinical trials have been done in patients with melanoma using DC as vaccine. In phase 1/II trial when patients with malignant melanoma were vaccinated with autologous dendritic cells pulsed with tumor antigens, it was observed that vaccination is safe and feasible along with prolonged survival [42]. In another multicenter phase II trial, when matured dendritic cells loaded with melanoma cell line lysate were injected in patients with advanced melanoma, immunogenic and antitumor response was generated [43]. In patients infected with metastatic melanoma (phase I/II trial), when dendritic cells transfected with DNA which encodes for melan A and gp100, it was observed that diverse T-lymphocyte responses were induced along with tumor regression [44]. Overall survival rate was also prolonged when metastatic melanoma patients were infected with peptide cocktail treated DCs (Phase II study) [45]. Autologous dendritic cell vaccine along with cyclophosphamide when infected in patients with cutaneous melanoma (stage III-IV), DC vaccine was well tolerated and also immunological and clinical responses were generated [46]. In another study, it was reported that monocyte-derived dendritic cells (MoDC) loaded with tumor antigens (gp100 and tyrosinase) generate tumor antigen specific responses in patients with stage III melanoma patients [47]. Thus, dendritic cell vaccination is safe, feasible and well tolerated in patients with melanoma along with generation of immunogenic response.

Hepatocellular Carcinoma

Patients with HCC were vaccinated (phase II study) with dendritic cells pulsed with tumor lysate and it was observed that vaccination is safe and well tolerated [48]. Also, the levels of serum alpha feto- protein were significantly reduced and antigen specific immune response was also generated in few patients. In study (Phase I/II) carried out by Tada et al., tumor-antigen pulsed dendritic cells when injected in patients were safe and well tolerated [49]. Study of Lee et al., also showed that when dendritic cells pulsed with tumor proteins were injected, there was no tumor recurrence up to 24 weeks, median time to progression was increased and stronger anti-tumor immune responses were generated in patients vaccinated with DC as compared to control group with no vaccination [50].

Non-small-cell Lung Cancer (NSCLC)

DC vaccines are well tolerated with no serious adverse effects and also showed biological activity in patients with NSCLC as evident from a study which reported that when DC pulsed with NSCLC cell line apoptotic bodies were injected in patients, antigenic specific responses were generated [51]. Also, overall survival rate was prolonged in patients injected with antigenic peptides loaded dendritic cells. Phase I study has also been carried out in which tumor lysate-loaded autologous dendritic cells were injected in patients [52]. The vaccination was safe with an increase in IFN-γ production by CD8+ T-cells (Figure 2).

Hepatitis C

Hepatitis C virus (HCV), a positive sense single stranded RNA virus, is becoming a significant global health problem. Transmitted through infected blood and body fluids, it is responsible for chronic hepatitis, which ultimately leads to life threatening liver diseases like fibrosis, cirrhosis, steatosis and finally causing Hepatocellular carcinoma (HCC), thus a need for liver transplant. According to the *WHO Global hepatitis report, 2017*, globally an estimated 71 million people had chronic hepatitis C infection in 2015, accounting for 1% of the population. Earlier the people infected with HCV were 130-170 million. There were 1.75 million new HCV infections globally and the deaths caused by viral hepatitis were 1.34 million in 2015. The global prevalence of HCV infection in 2015 was 1.0%. In India, the prevalence of HCV is approximately 1%. The highest prevalence was observed in the Eastern Mediterranean Region (2.3%) followed by the European Region (1.5%) (*Source*: WHO, work conducted by the Center for Disease Analysis).

There have been studies reported from our laboratory which showed that DCs are numerically, functionally and phenotypically dysfunctional in patients infected with CHC . The study also showed that functionally defective monocyte-derived dendritic cells (moDC) from CHC patients, who did not achieve SVR after receiving Peg IFN+Ribavirin based anti-viral treatment, failed to reconstitute the capacity to mature, indicating that the dysfunctional status of DC in CHC patients was directly associated with the persistence of the virus [53]. Plasmacytoid DCs (pDCs) and Myeloid DCs (mDCs) exhibit decrease in: cytokine production, cell-surface co-stimulatory molecule expression and/or allostimulatory activity, resulting in an inability to prime naïve Teff cells and, consequently, a reduction in anti-viral activity [54].

It has previously been shown that murine DCs pulsed with the lipopeptides showed no evidence of toxicity in mice [55]. Based on this, Phase I clinical trial was carried out in HCV-infected individuals using DCs loaded and activated with lipopeptides (presenting HCV-specific HLA A2.1-restricted cytotoxic T cell epitopes associated with clearance of acute HCV infection) and found that immunotherapy using autologous MoDCs pulsed with lipopeptides was safe, but was unable to generate sustained responses or alter the outcome of the infection [56]. In another trial, autologous DCs were transduced with a recombinant adenovirus encoding NS3 using the adapter protein CFh40L, facilitating DC transduction and maturation [57]. This trial was successful as DC was safe and no detectable virological effects were seen.

Conclusions

Dendritic cells' role in immune system is well established. Dendritic Cells based Immunotherapeutic approaches have been shown to be feasible, secure and effective in treating different diseases (Cancer, Autoimmune diseases, and infectious diseases). The results of the clinical trials have provided evidences for the potential applications of dendritic cells as a cell-based adjuvant for the development of therapeutic vaccines. But due to lack of optimization, further research and trials are needed, so that this therapy can be used as standard treatment for treating these diseases.

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