DENDRITIC CELLS AS AN IMMUNOTHERAPY TOOL

AS CÉLULAS DENDRÍTICAS COMO FERRAMENTA DE IMUNOTERAPIA

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ABSTRACT

Dendritic cells (DCs) are antigen-presenting cells that orchestrate the innate and adaptive immune response. These cells in their mature state have the characteristic of binding to T lymphocyte receptors through the specificities present in DC histocompatibility molecules that are attracted to T receptors (TCR). The interaction between DCs and T lymphocytes guarantees the immunological synapse, which results in clonal expansion of T lymphocytes, production of cytokines and chemokines, a diagram that configures the effectiveness of immunological responses in the face of recognized homeostasis disorders. Recently, the role of DCs in pathologies associated with the immune system was células dendríticas discovered, as it is associated with the induction or suppression of autoreactive T cell responses. The capacity of immunotherapies with DCs for therapeutic interventions in cancers, HIV, autoimmune diseases and adaptations improved physiological characteristics in transplants contributes to a new perspective on the disparate functionalities of these cells. The study of the applications of DCs in the management of clinical conditions is totally relevant not only for their application as monotherapies, but also for their association with other therapeutic alternatives with the prospect of finding promising treatments and cures. In this sense, it is important to understand the applicability of DCs in therapeutic interventions in different scenarios, in order to improve existing treatments and also discover new approaches related to these cells, a set that guarantees positive results in public health.

KEYWORDS: oncology, cancer, T lymphocytes.

RESUMO

As células dendríticas (DCs) são células apresentadoras de antígeno que orquestram a resposta imune inata e adaptativa. Essas células em seu estado maduro possuem a característica de expressar moléculas de histocompatibilidade principal (MHC) que apresentam antígenos de forma específica aos receptores de linfócitos T (TCR). A interação entre DCs e linfócitos T garante a sinapse imunológica, que resulta em expansão clonal de linfócitos T, produção de citocinas e quimiocinas, diagrama que configura a efetividade de respostas imunológicas frente aos distúrbios de homeostase reconhecidos. Recentemente, foi descoberto o papel das DCs frente às patologias associadas ao sistema imunológico, uma vez que está associada a indução ou supressão de respostas autorreativas das células T. A capacidade de imunoterapias com DCs para intervenções terapêuticas em cânceres, HIV, doenças autoimunes e adaptações fisiológicas melhoradas em transplantes contribui para uma nova ótica sobre as díspares funcionalidades deste

tipo celular. O estudo sobre as aplicações das DCs no manejo de quadros clínicos é totalmente relevante não só para a aplicação em monoterapias, mas também para associação com outras alternativas terapêuticas com perspectivas de encontrar tratamentos e curas promissoras. Nesse sentido, é importante compreender a aplicabilidade das DCs nas intervenções terapêuticas em diferentes cenários, a fim de aprimorar tratamentos já existentes e, ainda, descobrir novas abordagens relacionadas a essas células, conjunto que garante resultados positivos na saúde pública.
PALAVRAS-CHAVE: oncologia, câncer, linfócitos T.

INTRODUCTION

The conventional treatment of certain diseases associated with immune system suppression is linked to significant adverse effects, along with a high recurrence rate and patient rejection. Immunotherapy has an important anti-tumor use due to low collateral responses and specificity to the tumor, suggesting a strategy for diseases other than cancer[1].

The purpose of immunotherapy is to stimulate the patient's immune system to induce a passive or active immune response capable of combating the disease. The passive response involves using agents formed outside the patient's body, which do not rely on the body's machinery to be immunologically active. On the other hand, the active response relies on the normal functioning of the immune system and its ability to contain the development of the disease. This is associated with vaccination using immunomodulatory cells that induce a specific cytotoxic response to the target[1].

Dendritic cells (DCs) are innate immune cells with the ability to present antigens to adaptive immune cells, serving as a bridge between innate and adaptive immune responses. DCs are classically divided based on their origin and/or function into conventional dendritic cells (cDCs), plasmacytoid (pDCs), or follicular (fDCs)[2,3].

cDCs originate from myeloid precursor cells in the bone marrow and are skilled at presenting protein antigens derived from microorganisms to T lymphocytes. pDCs. On the other hand, They originate from lymphoid precursor cells in the bone marrow and play a significant role in antiviral responses by producing IFN-I[2,3].

Follicular dendritic cells (fDCs) are non-hematopoietic stromal cells located in the B cell areas of secondary lymphoid organs. They play a crucial role in humoral immunity as they have the ability to retain antigens with immunogenic characteristics and induce antibody production through the maturation of B lymphocytes[3].

The activation of cDCs occurs due to disturbances in tissue homeostasis, either through the recognition of pathogen-associated molecular patterns (PAMPs) or damage-

associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs) expressed on the plasma membrane, cytoplasm, or endosomal membranes. Once antigens are recognized and processed, cDCs migrate to lymphoid organs, where they present the antigens via the major histocompatibility complex (MHC) to helper T lymphocytes (CD4+) and cytotoxic T cells (CD8+), inducing adaptive immune responses. [2,3]Upon recognition by DCs, antigens are processed into peptides that bind to MHC molecules, allowing interaction with lymphocyte receptors (TCR), directing DCs toward their terminal maturation. This results in further differentiation of T lymphocytes into effector T cells associated with cytokine production, providing a specific and appropriate immune response. When DCs are not activated, they may present self-antigens, leading to the formation of regulatory T lymphocytes (Tregs) and the induction of immune tolerance[2,5,6].

The ability of DCs to modulate adaptive immune responses has formed the basis for the development of therapeutic strategies based on DCs in various contexts, such as autoimmune diseases and tumors. DCs can be used to effectively activate T lymphocytes due to their high expression of co-stimulatory molecules, and they also express high levels of inhibitory molecules, enabling them to inhibit immune responses. This makes DCs a potent therapeutic tool (Figure 1)[3,5].

COMBINATION WITH OTHER THERAPIES

Dendritic cells (DCs) are widely employed in vaccines due to their ability to induce immune responses, although their efficacy may vary. The primary goal of these vaccines is to create adaptive immune memory. Their preventive strategy is to produce neutralizing antibodies that can block the virus before it infects cells. The interaction between the antigen and the receptors of cognate B cells is crucial for activation, clonal expansion, and differentiation into plasma cells that produce antigen-specific immunoglobulin. Additionally, in the lymph node, follicular dendritic cells (fDCs) facilitate interaction with cognate B cells to select antibodies with high affinity and avidity, thus optimizing pathogen neutralization[7].

An innovative approach to vaccination, potentially more effective as a therapeutic vaccine against chronic viral infections, is the use of personalized vaccines, when the antigen is incubated ex vivo with autologous DCs (Figure 1). After this incubation, DCs phagocytize and process the antigens to present them to other cells of the immune system. This approach involves DCs on two levels: first, antigen-loaded DCs are injected ex vivo and can migrate to lymph nodes, and second, local cutaneous and Langerhans DCs

respond to the injected DCs .Strategies using these cells may be preferable for generating cytotoxic T cells capable of destroying infected cells. Additionally, DCs facilitate immune responses from B cells. Ex vivo incubation of dendritic cell vaccines (DCV) with viral antigens has demonstrated efficacy in preventing Herpes simplex and influenza in animal models. In a model of antigen-presenting cell-specific immunosuppression and influenza infection, DCV injections induced high levels of specific antibodies, while vaccination with proteins did not achieve the same result[8].

Vaccination with modified dendritic cells resulted in specific cellular immune responses to the antigen, indicating that the patients' immune systems were developing specific defenses against the COVID-19 virus. These findings suggest that the personalized dendritic cell vaccination approach could be a promising strategy for the development of highly specific vaccines against COVID-19, capable of boosting more effective and targeted immune responses. However, despite these promising results, additional large-scale studies are needed to confirm the effectiveness and safety of this approach and to consider its possible implementation in the fight against the COVID-19 pandemic[9].

The modification of DCs to silence specific intracellular immune checkpoint points has also been studied (Figure 1). Intracellular immune checkpoint proteins can suppress the immune response, limiting the effectiveness of conventional DC-based vaccines. These modified DCs have been tested in animal models or patients with cancer or other immune-related diseases. This approach has resulted in increased activation of cytotoxic T cells, potentially enhancing the immune system's ability to combat cancer cells or viral infections. However, as this is an early-stage study, further research and clinical trials in humans are necessary to confirm the safety and efficacy of this approach before potential widespread clinical implementation[10].

CANCER

The immune system should be able to act as a tumor suppressor to eliminate and/or control developing tumors. [11]However, many malignancies lack an obvious etiology and, therefore, do not present abundant antigens to stimulate innate immune responses. Some studies indicate the release of certain endogenous adjuvants by tumor cells that can activate DCs for antigen presentation. Nevertheless, the immune response induced by these signals is not potent enough to effectively control cell proliferation. [12]Immunotherapy in cancer emerged with William Coley, who, after treating patients with

bacterial extracts to activate immunity, opened opportunities for immunotherapy vaccination in cancer treatment[13].

To understand the composition and diversity of T lymphocytes, specific neoantigens, and their effect on vaccination, short-term expanded neoantigen-specific T cells were utilized, generating libraries of complementary-determining region 3 (CDR3) sequences. During pre-vaccination for melanoma, one to ten unique TCRβ clonotypes per neoantigen in CD8+ T cell populations were identified. With vaccination, existing TCRβ showed an increase, along with new clonotypes for antigens. This suggests that vaccination with mature DCs leads to the expansion of neoantigens and TCRs (Figure 1)[14].

Personalized vaccines with pulsed DCs with neoantigens, inducing specific T cell immunity, show safe results for advanced lung cancer. These vaccines cause antitumor effects without toxic and collateral effects, with adverse events only occurring at low levels or being transient. Objective response rates were 25%, and disease control rates were 75% in pre-treated patients (Figure 1)[15].

Another possibility is the use of a DC-based vaccine using allogeneic tumor lysate (MesoPhers), which shows reactivity in patients with malignant mesothelioma. This reactivity can be observed through delayed-type hypersensitivity (DTH) skin reactions mediated by Th1 profile CD4+ T lymphocytes. Shared clones between activated T cells from infiltration and CD4+PD-1+ activated circulating T cells can also be detected after vaccination. This indicates that MesoPhers induces changes in circulating activated CD4+ T cells, leading to a response to specific T cells (Figure 1)[16].

In patients with castration-resistant prostate cancer, the immune response after dendritic cell immunotherapy is qualitatively evaluated as responders and non-responders and quantitatively by considering prostate-specific antigen (PSA) concentration and INF-gamma cytokine. Seventy-two percent of cases showed clinical improvement, and 50% demonstrated a tumor-specific response with a decrease in PSA concentration independent of INF-gamma-mediated response. [17]The use of this therapeutic tool against ovarian cancer was tested and showed minimal or almost no emerging adverse effects. There was a significant improvement in patients treated with the combination of chemotherapy and dendritic cell vaccination, resulting in a 60% reduction in mortality compared to chemotherapy alone (Figure 1)[18].

The methodology was tested for breast cancer in Balb/C mice. The use of DCs revealed the dynamics of the immune response in these animals. Fourteen days after the

first vaccine dose, a significant presence of CD8+ T cell infiltrate was observed, along with a decrease in CTLA-4, an immunosuppressive co-stimulatory molecule. Considering the association of CD8+ T cells with a favorable cancer prognosis and the presence of CTLA-4 with a poor prognosis, the findings suggest a relatively short time interval for cellular activation and an immune response against the tumor. In addition to tumor control, immunotherapy was tested as prophylaxis against hepatic metastases in Balb/C mice, showing a reduction in metastatic foci in those treated with dendritic cells compared to untreated mice[20].

Patients newly diagnosed with neoglioblastoma, aged 19 to 73, who had previously undergone surgical resection, recovery, leukapheresis, and 6 weeks of radiochemotherapy, experienced disease recurrence and were then subjected to DC immunotherapy. The observed results showed a relative 20% reduction in the risk of death, along with favorable prognostic characteristics. This rate increased over time with continued treatment (Figure 1)[21].

The strategy of using immunotherapy based solely on DCs, in many cases, does not show sufficient reversal of tumor progression. This underscores the need to develop strategies for combining with conventional therapies to achieve a reduction in tumor mass accompanied by robust immunomodulation, providing a lasting and massive antitumor response[18].

HIV

Infection with HIV-1 is treated with antiretroviral therapy (ART), although a cure is not achieved due to the persistence of a reservoir of HIV-1-infected T CD4+ cells that remain latent. [22-26]These reservoirs lead to rapid viral rebound when ART is interrupted[22,25,26]. Viral latency prevents the expression of surface proteins, favoring a form of immune surveillance escape[23].

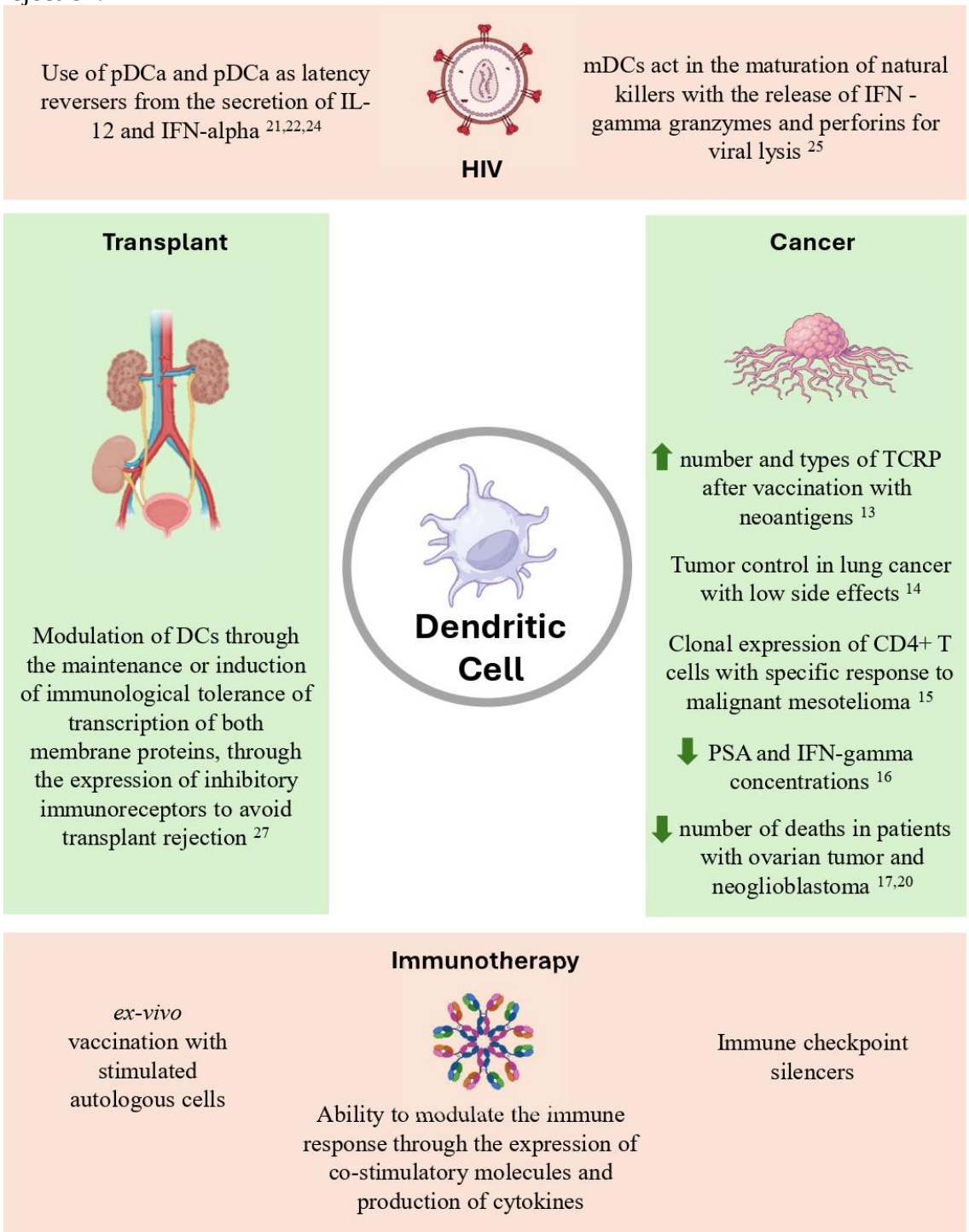
One potential therapeutic approach is to strengthen the immune response by HIV-specific T CD8+ cells, thus the use of DCs that can be divided into two subgroups. Monocyte-derived DCs (MD-DCs) and plasmacytoid DCs (pDCs) provide a link between the innate and adaptive immune responses through T CD4+ and T CD8+ lymphocytes, inducing an increase in antigen-specific T cell responses in animal models and patients with chronic infections and cancer[22,25,26].

For cytotoxic T CD8+ lymphocytes to be able to eliminate virus-infected cells, the reversal of latency is necessary, exposing epitopes to be recognized by antigen-

presenting cells that will induce the elimination of these targets. This can be achieved by using different subgroups of DCs associated with immunological cofactors. [22,23,25]MD-DCs associated with HIV-1 antigens, serving as inducers of interleukin-12 (IL-12) secretion, were necessary to maximize CD8+ T cell responses. Additionally, RNA from CD40L (CD40 ligand) was used to enhance responses and the immunological synapse interaction during antigen presentation, modulating IL-12 immunopotency (Figure 1). The methodology used shows that MD-DCs can induce latency reversal and promote an effective response via CD8+ T lymphocytes, but this depends on CD40/CD40L signaling or the presence of an antigen facilitating antigen presentation. [22,23]When considering the use of pDCs, the association with Toll-like receptor (TLR) agonists indicates latency reversal through a significant increase in IFN-α production in HIV-infected patients who previously showed no immune response to the virus (Figure 1)[25].

Chronic HIV infection shows an abnormal distribution of Natural Killer (NK) cell subsets and a decreased proportion of cytotoxic NK cells. [26]Additionally, there are high levels of inflammatory biomarkers and T cell exhaustion, even in patients on antiretroviral therapy, resulting in chronic cellular dysfunction characterized by impaired T cell proliferation and reduced anti-HIV cytokines, directly contributing to the maintenance of a latent reservoir of infected CD4+ T cells. In ex vivo experiments with pDCs, the expression of cell exhaustion markers such as LAG3, PD1, and TIGIT is associated with the CCR7 homing marker, supporting the hypothesis that HIV-1 can directly induce pDC maturation and positive regulation of CCR7, leading to effector cell production and thus being associated with the phenomenon of cellular exhaustion. However, the use of pDCs modulated with GS-9620 (TLR-7 agonists) in immune responder and elite controller patients shows normalization of PD1 levels in CD4 T cells after TLR stimulation in different HIV disease progression phenotypes[25].

Figure 1. Role of dendritic cells in the treatment of cancer, HIV/AIDS, and transplant rejection.



mDCs have NK cell maturation activity that heavily depends on the interaction of inhibitory NK cell receptors (inhibitory KIRs) with MHC-I molecules. NK cells exhibit antibody-dependent cellular cytotoxicity (ADCC) activity, capable of specifically lysing viruses via immunoglobulins G, mainly IgG1 and IgG3, resulting in the production of IFN-γ, granzymes, and perforins (Figure 1). There is an increase in ADCC-mediated cell

death in patients analyzed two weeks after vaccination, as well as an increase in the T cell subgroup compared to HIV-positive patients before vaccination[26].

Results show that targeting DCs from HIV-1-infected patients induces and/or expands HIV-1-specific T CD4+ cells that secrete IFN-γ, IL-2, and IL-13, as well as T CD8+ cells producing IFN-γ, perforin, and granzymes. The production of cytokines indicating the presence of a response[23,24,25], along with an interesting NK-DC crosstalk, as NK cells can lyse immature DCs and induce the maturation of others, increasing the migration and maturation of new NK cells, thereby enhancing the production of IFN-γ and ADCC[26].

TRANSPLANTS

Organ, tissue, or cell transplantation involves the repair of a specific site that is genetically and immunologically compatible, in the face of a factor exposing it to some functional impairment or damage. Transplants can be categorized according to the donor and recipient as autologous, heterologous, syngeneic, allogeneic, xenogeneic, and orthotopic[27].

Autologous transplants involve the same individual as both donor and recipient, while heterologous transplants involve different individuals. Heterologous transplants can be further divided based on the donor's origin: syngeneic refers to genetically identical individuals, such as identical twins, while allogeneic or haploidentical refers to genetically similar individuals, such as siblings with at least one common parent. Xenogeneic transplants come from individuals of different species, such as an animal and a human. [27]Orthotopic and heterotopic ones refer only to the location of the transplants, with the former occurring in the same anatomical location and the latter in a different location than normal. Additionally, tissue transplants can be divided into different graft types: autograft, isograft, allograft, and xenograft, following the same classification mentioned earlier[27].

The adaptive response present in transplants is closely correlated with the modulation of DCs, through the maintenance or induction of immunological tolerance in the presence of transplants, regardless of their type. This process occurs through tolerogenic DCs responsible for regulating the immune response to avoid rejection of organ and tissue transplants. [28]In certain transplants, such as stem cell transplants for patients with hematological neoplasms, immune adaptation occurs not only through

donor T cells and natural killer cells but also through interferon-gamma 1 and 2, promoting dendritic cell licensing and, consequently, an local immune response[29,30].

DCs exhibit tolerogenic receptors that mediate this mechanism. These receptors can be expressed through membrane protein transcription containing cytoplasmic inhibitory tyrosine-based immunoreceptors or simply receptors functioning as biomarkers expressed in subsets of monocytes (Figure 1). There are studies suggesting that such DC subsets play an important role in reducing post-transplant infections through the release of damage-associated molecular patterns (DAMPs) expressed in dendritic cells. However, in general, the mechanisms by which this regulation of the immune adaptation process during transplantation occurs, either through immune response or vaccination, are not yet fully understood. [31]Therefore, understanding how DCs regulate the adaptive immune response to be favorable to the patient after transplantation is of utmost importance. The ultimate goal is not only to reduce the risk of rejection but also to inhibit the inflammatory response and the immunological alert state present in any transplants[28].

CONCLUSION

Studies related to the functionality of dendritic cells (DCs) as a means of therapeutic intervention are recent, although they have broad applications in different pathologies. The presentation of antigens through DCs enables the effectiveness of the adaptive immune response, either by inducing the differentiation of cytotoxic effector cells or by modulating cells of the immune system that allow disease control. In this context, comprehensive knowledge about intervention methods based on these cells and their actual function in the face of autoimmune diseases can contribute to complementing existing therapies with the aim of curing and extending life. Furthermore, their use as monotherapy in a less aggressive and more tolerable scope than conventional therapies is also a possibility. Understanding the use of DCs as a therapeutic method for pathologies with relevant clinical manifestations is of utmost importance for improving the quality of life and for public health management.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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