Dendritic Cells and Their Role in Immunotherapy

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Abstract

Dendritic cells (DCs) serve as critical orchestrators in the immune system, bridging the innate and adaptive responses. This review explores the role of DCs in immunotherapy, particularly in cancer treatment. The article starts by discussing existing DC-based treatments, categorizing them into ex vivo and in vivo methodologies, with a particular emphasis on vaccine creation and the use of nanovaccines. Moreover, innovative approaches like blocking inhibitory pathways to enhance DC functionality are explored. Despite significant advancements, challenges such as DC migration inefficiencies and dosing concerns remain. Finally, future prospects in DC-based therapies, including combination therapies with traditional cancer treatments, are highlighted. This review paper underscores the transformative potential of dendritic cell interactions in reshaping cancer immunotherapy paradigms.

Keywords: Dendritic Cells, Innate Immune System, Immunotherapy, Cancer, Toll-like receptors, Major Histocompatibility Complex, T cell, Antigen Presentation.

1. Introduction

1.1 Innate immune system

The innate immune system allows the human body to thrive by protecting it from pathogens. It consists of Leukocytes, Natural Killer cells, platelets and protein groups which consist of Antimicrobial peptides (AMPS), Cytokines, and Complements. The innate immune system, which is nonspecific (meaning it attacks all pathogens without differentiating between them), allows the body to react quicker to pathogens such as bacteria that duplicate quickly. This article focuses on a specific type of cell within the innate immune system that helps activate the adaptive immune system (the active branch of the immune system that targets specific pathogens): dendritic cells. [76]

1.2 Dendritic cells

Dendritic cells are key regulators of the immune system, and they orchestrate immune responses by processing and presenting antigens to T cells of the adaptive immune system [100]. They are produced by CD34+ hematopoietic stem cells in the bone marrow, which create dendritic cells through the use of lymphoid progenitors and myeloid progenitors. Dendritic cells (DCs) are generally spread out as much as possible in most organs to maximize antigen capture and presentation to T cells [100]. Thus, they are found in both lymphoid and non-lymphoid organs. One of the most important kinds of receptors that DCs use are toll-like receptors (TLRs) which are type I integral membrane receptors [100]. These receptors

recognize and capture the antigens that are unique to the invading pathogen and bring it back to the lymph nodes to communicate to the right T cells and B cells for that specific antigen.

Dendritic cells are being explored for their potential in immunotherapy, especially in the context of certain cancers. Researchers are investigating ways to exploit the unique properties of dendritic cells to enhance the body's immune response against cancer cells. Additionally, there is ongoing research into the use of dendritic cells to induce tolerance in organ transplantation, aiming to minimize the risk of rejection.

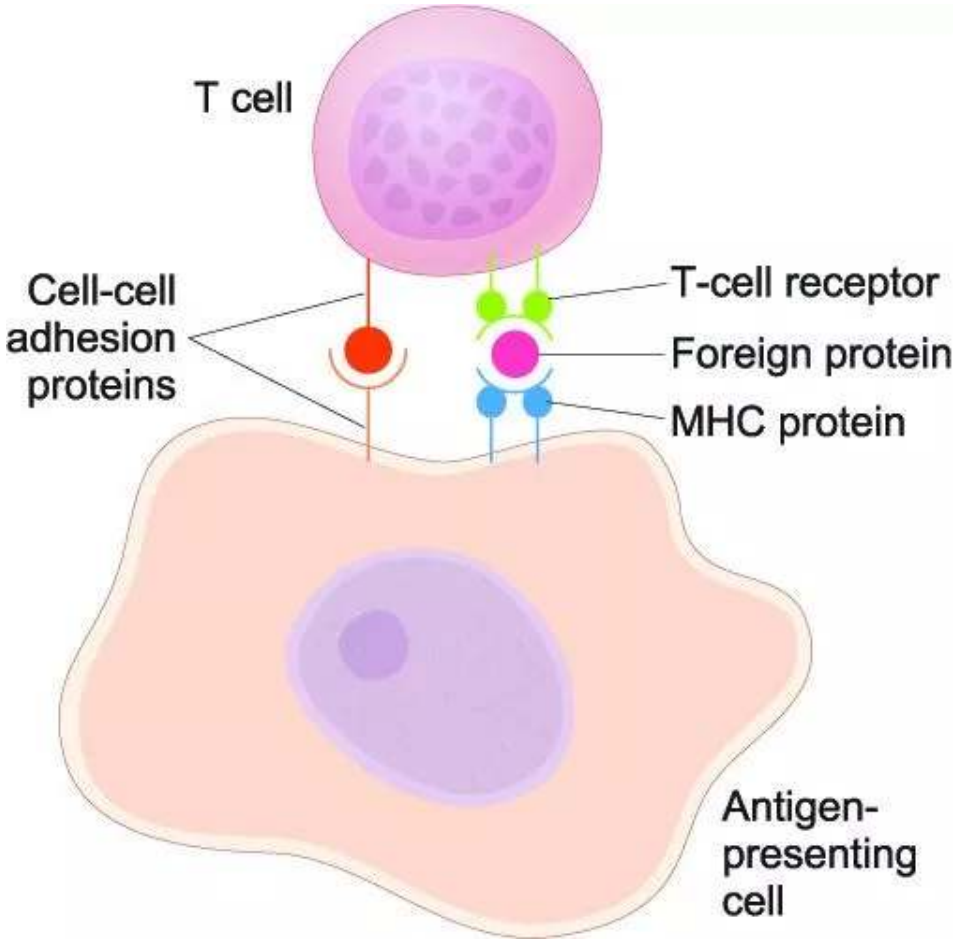

Figure 1. Adapted from [105]. This figure shows the surface protein interaction between DCs and T cells.

Hematopoietic stem cells differentiate into most immune cells and originate from the bone marrow [108]. Many environmental cues such as cytokines, transcription factors, bone marrow microenvironments, growth factors, cell surface markers and the Notch signaling pathway cause hematopoietic stem cells to differentiate to the Lymphoid and Myeloid progenitors. These progenitors differentiate into immature dendritic cells through cytokines such as IL-4, other notable factors including: Flt3 Ligands, Granulocyte-macrophage colony-stimulating factor and the Notch signaling pathway [104,94]. These immature dendritic cells mature through activations from cytokines such as IL-1, TNF-α and IFN-γ and TLR activation through pathogens, PAMPs &

DAMPs [110,111]. A large factor is also the activation of the NF-κB pathway [109]. Once mature they start to express more MHC Class II expressions .[85,86]. They also express more adaptive immune system ideals such as decreasing phagocytic activity and the expression of more chemokines and their receptors.

Myeloid progenitors differentiate into pre-cDC1 and pre-cDC2 which then differentiate into conventional dendritic cells 1 (cDC1) and conventional dendritic cells 2 (cDC2) These cells are known to be cancer specific because they are dominant in T cell based immunotherapies and stopping immunogenic cancers. They help initiate natural killer cells and Cytotoxic T cells/CD8+ T cells, through the use of chemokines and cytokines. They also help in uptake of antigens from cancer cells and activating the T cells in the tumor microenvironments or the tumor infected lymph nodes[101]. On the other hand, cDC2 mainly provides antigens to helper T cells ,CD4+ T cells, which causes differentiation [88].

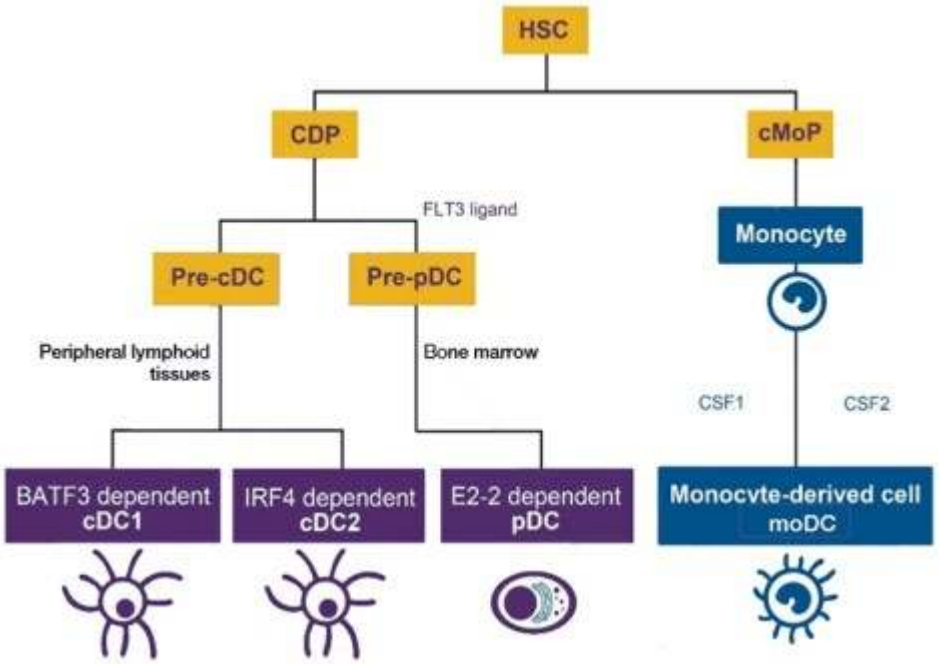

Figure 2. Adapted from [106]. Diagram showing the differentiation of DCs.

1.3 Cancer

Cancer is caused by genetic mutations in the cell cycle which causes abnormal cell growth and behavior. Mutations can activate oncogenes (genes that promote the cell division) or inactivate tumor suppressor genes (genes that inhibit cell division). Typically, an accumulation of multiple mutations causes cancer. Mutations can be caused by either environmental factors such as carcinogens or genetic causes. Either one of these can cause DNA damage that affects these protooncogenes and tumor suppressor genes which causes excessive cell proliferation. This causes a tumor, which has to be malignant to be considered cancer. Malignant cells have to

invade nearby tissue and metastasize to blood vessels or lymph vessels that help its growth. Once the invasive tumor implants near vital organs, it can threaten the life of the patient.[92]

2. Molecular Mechanisms of Dendritic Cells

2.1 Interactions

Dendritic cells carry out their roles in the immune response by utilizing various kinds of interactions. In the adaptive immune response, dendritic cells capture, process, and present antigens as well as induce T cell responses. They capture the antigens specific to a pathogen through the use of toll-like receptors (TLRs); this constitutes an interaction between the DC and pathogen because the dendritic cell phagocytizes the pathogen. There are two main groups of TLRs: one group is expressed within the cell membrane and recognizes microbial membrane components (TLR1, TLR2, TLR4, TLR5, TLR6 and TLR11), while the other recognizes microbial nucleic acids strictly within the cell (TLR3, TLR7, TLR8 and TLR9). [89]

After dendritic cells capture the antigens, they process them into proteolytic peptides. They then move to the nearest lymph node to present the antigens to T cells. The presentation itself is done through the use of a major histocompatibility complex (MHC), which is where the antigen is loaded. The dendritic cell will display the antigen to different T cells until the specific and correct ones are found. This interaction between the dendritic cell, the MHC, and T cells is what connects the innate immune system with the adaptive immune system, because the phagocytic cell that initially broke down the pathogen is now presenting the resultant peptides to the specific lymphocytes that will attack the infection later on. [90]

2.2 Receptors

Between the innate immune response and the formation of the adaptive immune response, dendritic cells take advantage of many receptors in order to make possible the different actions they take. Already mentioned earlier were the toll-like receptors which aided in the “capture” portion of the innate immune response.

Many other receptors aid in the entire journey of the immune response. For example, dendritic cells utilize MHC Class I in order to present antigens to CD4+ and CD8+ T cells within the lymph nodes [4]. MHC Class I receptors themselves are glycoproteins on the cell surface of dendritic cells, and allow them to present the broken down antigens from the “processing” phase much more effectively and efficiently. The ability to present these antigens on MHC Class I molecules comes from the unique feature of dendritic cells known as cross presentation. However, this ability was also deemed to be somewhat less efficient than direct presentation [3].

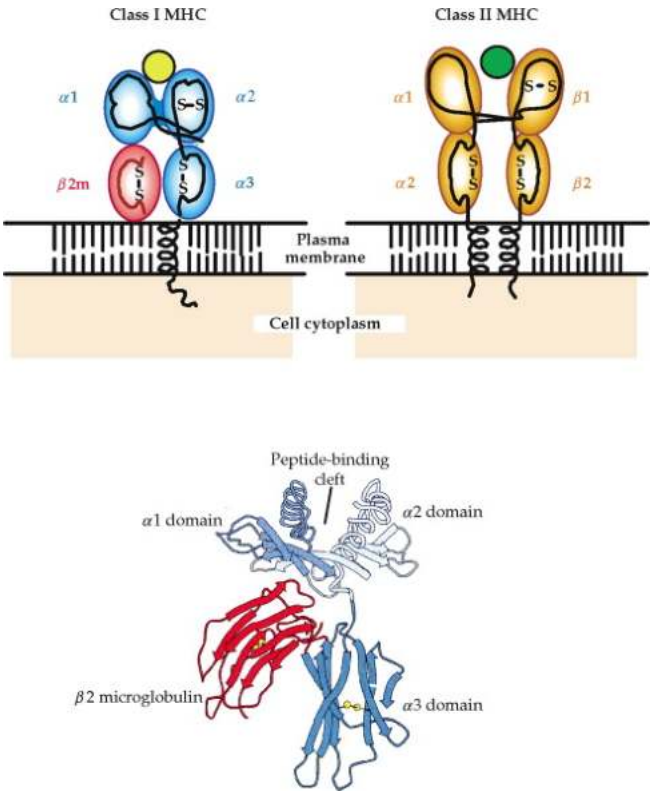

Figure 3. Adapted from [107]. MHC Receptors

Another crucial receptor is the CD40 receptor, which is a co-stimulatory molecule and belongs to the tumor necrosis factor receptor family. In other words, they are involved in activating cell death pathways and survival [34]. They are found on B cells, however they may even be found on non-immune cells as well as tumors [34]. The ligand for this receptor is known as CD40L, which is found on T cells and others during the inflammatory response. The main role of this receptor on dendritic cells is that it increases the generation of cytokines, co-stimulatory molecules which are located on the cell surface, and enable the cross presentation of antigens. It can enhance anti-tumor immune responses and plays a key role in adaptive immunity [34].

2.3 Pathways

Dendritic cells utilize many pathways within their role in the immune response. For example, their use of the cell to cell communication pathways within the innate immune response to the “bridge” between innate and adaptive immune response [5]. Dendritic cells, as mentioned before, use their TLRs to bind to and recognize the unique antigens to the foreign pathogen. However, what makes it a pathway is how the dendritic cell migrates to the lymph nodes and makes the use of MHC Class 1 receptors to present the antigens. When either the

correct CD4+ or CD8+ T cells recognize the antigens and bind to it themselves, that is a cell to cell communication from pathogen to lymphocyte.

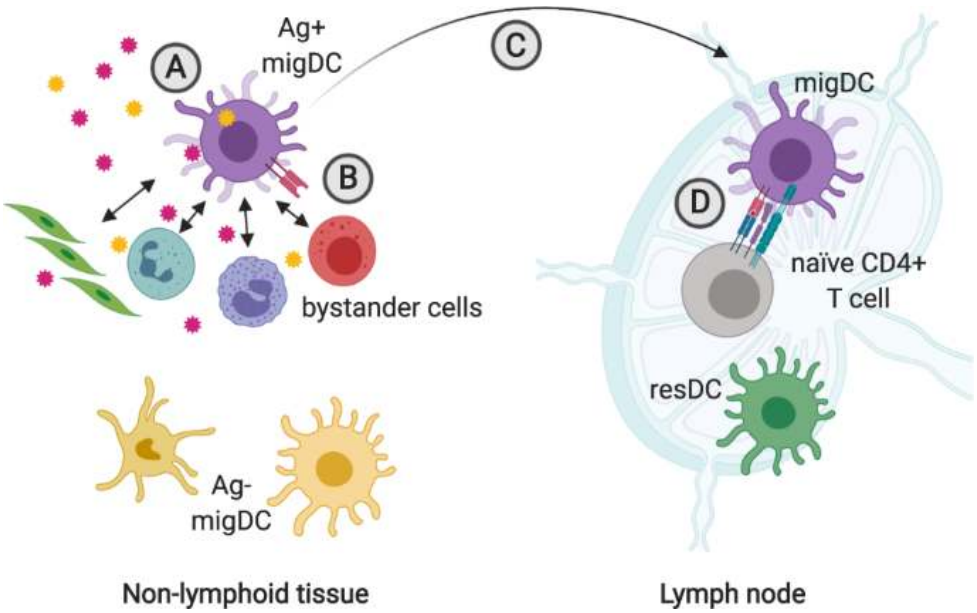

Figure 4. Adapted from [102].

3. Existing treatments

There are two main classes in existing treatments centered around Dendritic Cells (DCs): *ex vivo* and *in vivo* treatment. *Ex vivo* is defined as modification of the DCs outside the body and then subsequent introduction/reintroduction into the body [1]. *In vivo* is defined as modification or stimulation of DCs inside the body [1].

3.1- Vaccines

The current major method of immunotherapy combines *ex vivo* and *in vivo* in the creation of vaccines by loading DCs *ex vivo* and after reinjection, *in vivo* T-cell activation [7]. The cells derived from the patient are typically monocyte-derived DCs or hematopoietic precursors such as CD34+ cells [4]. The specific type of DC used in the process is not shown to produce significant variance in results [2]. Vaccination works by isolating DCs from the patient's bloodstream, and then activating (maturing) them using tumor antigens, a tumor lysis compound, and various cytokines [1]. They are then reinjected into a patient where they present antigens to helper T-cells, which produce an immune response. One key thing to note is that the efficacy of vaccines drastically increases when the antigens and immunopotentiators present are delivered directly to DCs [22].

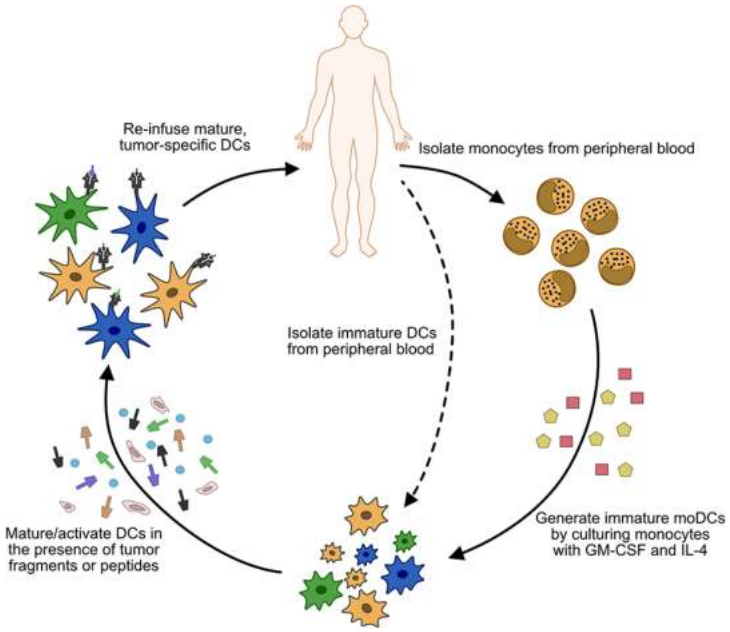

Figure 5. Adapted from [1].

3.1.1 *Ex vivo* maturation of DCs

The maturation process of DCs when they are taken out from the body is critical. Cytokines and growth factors are used to activate dendritic cells in ex vivo to aid in cancer immunotherapy. This starts by isolating monocytes from the blood and using factors to differentiate them into immature dendritic cells. Subsequently, they are exposed to Granulocyte-Macrophage Colony-Stimulating Factors and the cytokine IL-4, turning them into mature dendritic cells which are reinjected into the patient [91]. Conventional DCs (cDCs) are usually injected with IL-2 and IL-4; IL-2 helps activate T cells, specifically cytotoxic T cells, and IL-4 promotes dendritic maturation and an immune response that affects tolerogenic characteristics and regulator pathways [91]. Granulocyte-macrophage colony stimulating factors also promote maturation of dendritic cells, but they also promote more inflammatory characteristics which helps the activation of T cells, causing other cytokines to start being produced by matured cDCs. The final stage of maturation includes the addition IL-12 which is produced by dendritic cells to support NK cells and the production of interferon gamma. These cytokine and growth factor treatments have shown to be very effective [104].

3.1.2- Coated Vaccines

An alternative method used is coating the vaccine with lipids or peptides to facilitate the *in vivo* component of vaccines [22]. Typically, coating of DCs with lipids are taken up more than uncoated DCs or antigens. Liposomes carrying antigens with TLR5 ligand-related peptides on their surface are taken up significantly more by mouse DCs and induce tumor inhibitory responses (Faham and Altin, Targeting Nanoparticles to DC for Vaccine Therapy 151 2010). DC specific targeting can also be increasing by using specific antibodies that recognize certain antigens on the target.

One drawback to using liposomes is that they are much larger than the typical strategy for vaccination. Liposomes are usually 50-250 nm in size, which while allowing more molecules to be within the capsule, may be less effective in penetrating helper Ts and other targets [22].

Another type of coating used is Poly(lactic-co-glycolic acid) (PLGA). PLGA is a biodegradable polymer known for its slow-release properties. It has been used extensively for drug delivery and vaccination due to its stability and controlled release features [22].

3.1.3- Nanovaccines

Nanovaccines are defined as compounds injected into the body that are directly able to present tumor antigens directly to T cells, or indirectly to DCs. By presenting them directly to helper Ts, they bypass DCs entirely [7].

When presenting nanovaccines to DCs indirectly, there are two methods to do so: active and passive targeting strategies. Passive targeting includes using the natural phagocytosis that DCs use to facilitate uptake of the encapsulated antigens, while active targeting includes putting specific receptors on nanovaccines that bind to complementary receptors specific on the surface of DCs [7]. Specifically, targeting of CD40 or MHC class II antigen containing complexes on DCs increased survival of mice.[85,86].

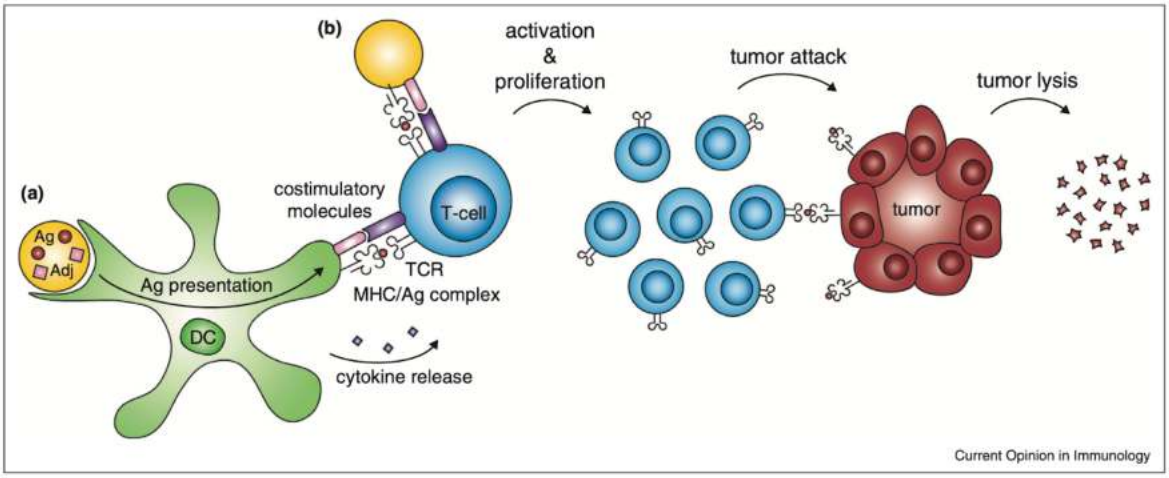

Figure 6. Adapted from [7]. Simplified diagram how a nanovaccine works.

This method trumps the traditional method of making DC based vaccines outlined in section 3.1 by skipping the use of autologous stem cells, which saves money and labor [7].

3.1.4- The Future of Vaccine Therapy

Many great strides have been made in cancer immunotherapy, and going forward, it will certainly be an important part of immunotherapy. Many studies have been already conducted that prove the effectiveness of vaccines at combating cancer. One study done by J. Rosenblatt et al. developed a vaccine by fusing patient-derived myeloma cells with autologous DCs, and

this vaccine was generated successfully in 17 out of 18 patients [26]. In another study conducted by M. Morse et al., autologous DCs were loaded with MAGE tumor antigens in non-small cell lung cancer, and the survival time after the first DEX dose ranged from 52 to 665+ days [27]. Studies like these and a plethora of others, have demonstrated the viability of DC vaccines, and ensure continued research and development in the field.

3.2 Blocking Inhibitory Pathways

An alternative approach is to block inhibitory pathways that reduce cDC functionality. By "inhibiting the inhibitor", there is an increase in DCs that kill tumors, enhancing the activation state of tumor cDCs [1]. Healthy cells typically express MHC class I molecules that inhibit NK (a cell of the innate immune system similar to DCs) cell activity. This is because the NK cells recognize MHC Class I molecules as belonging to healthy body cells [103]. In contrast, dangerous or stressed cells display activating ligands that stimulate NK cell responses. Blocking inhibitory pathways in DC cells aims to achieve a similar result by stimulating DCs [16].

3.2.1 Blocking inhibitory pathways in conjunction with vaccines

When used in conjunction with vaccines, inhibiting certain pathways and cells can increase efficiency of vaccines. Administration of an CTLA-4 antibody, which inhibits Tr cells, can result in antitumor immunity [33]. More specific proteins that can be targeted when blocking inhibitory pathways in cells which help vaccines include IL-2 (a cytokine) coupled to cytotoxic molecules, which is shown to improve immune responses [33]. In mice, inhibition of CD4+ Tr cells (a specific type of regulatory T cell) by using anti-CD25 antibodies resulted in slowed tumor growth.

4. Future Treatments

4.1- Current problems

Many great strides have been made in the use of DCs to aid immunotherapy and cancer treatment. Most notably, recently, scientists have discovered that myeloid DCs can be easily procured from monocytes or stem cell precursors, which for the first time allowed mass production of these rare DCs [47]. However, due to the complexity of the immune system, and the sheer number of factors involved in immunotherapy, there still is a lot of work that had to be done to push immunotherapy forward [47]

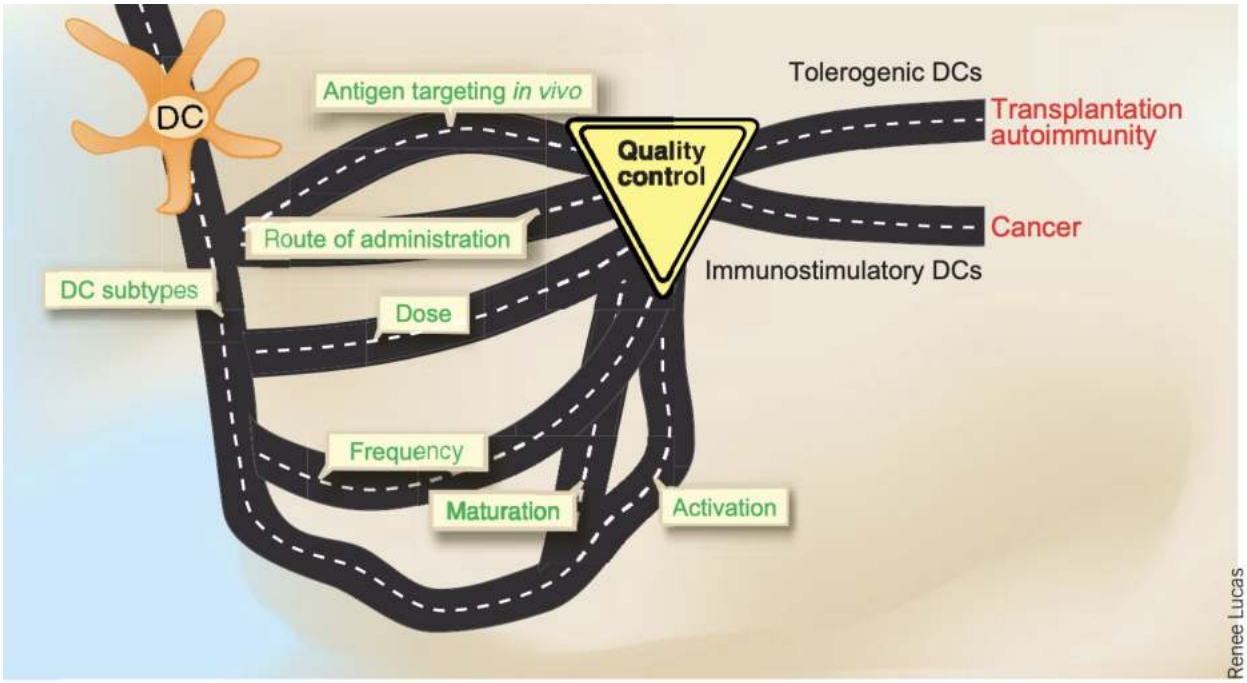

Figure 7. Adapted from [47].

Figure 7 outlines all the different factors that play a role when using DCs in the context of vaccines. This paper will outline the 2 most considered factors in therapy.

Activation: Many of the issues revolving around DC vaccines arise from the actual migration of DCs to lymph nodes before they can interact with T cells [87]. Studies have found that less than 5% of the mature DCs given to the patient actually reach the lymph nodes, which is ineffective. [87].

Dose: This is another problem, and one that specifically arises when the blocking inhibitor pathways technique is used. When too high concentrations of cytokines or antibodies are given, toxic autoimmune compounds that were potentially life-threatening were produced.

There are studies being conducted to try and understand these factors more deeply. A study by Rosenblatt et al. has injected patients with multiple myeloma with different dose levels (1 × 10^6, 2 × 10^6, and 4 × 10^6 fusion cells), and the vaccination was well received with no toxicity based on dose observed [26].

4.2 Future Treatments

There are many immunotherapies researchers are experimenting with. These treatments build on existing methods, introduce variations, or combine immunotherapy with other types of cancer treatment.

4.2.1- Combination Therapy

Combination therapy refers to the combination of immunotherapy with more traditional methods of treating cancer, such as chemotherapy. In some cases, combination therapy can be combining traditional DC therapy with T-cell therapy.

Often, vaccines are combined with strategies such as

- Suppression of pathways that interfere with the vaccine [23].
- Conventional treatments (eg. chemotherapy) [23].
- Inhibition of molecules such as CTLA-4 that can be costimulatory [33].

Combination therapy can also be used with T-cells to indirectly assist DCs. T-cells need a suitable environment in order to function at optimum capacity, so T-cell treatments are often used with DC vaccines [45]. Combinatorial therapy of CAR T cells and PD-1 blockade showed enhanced antitumor efficacy in a preclinical Her2 mouse model [45]. PD-1 blockade improved the proliferative and functional capacity of CAR T cells, leading to enhanced tumor regression [45].

However, one important thing to note is that many combination therapies are still being tested and not much is known about them, including potential toxicity and harmful effects to the body.

5. Conclusion

Dendritic cells are the center innovation in cancer immunotherapy, bridging the innate and adaptive immune responses. Their unique ability to process and present antigens makes them key players in activating T cells against pathogens and cancer cells. Interactions involving toll-like receptors (TLRs), major histocompatibility complexes (MHCs), and cytokines, DCs orchestrate immune responses that hold transformative potential for cancer treatment paradigms.

Current treatments using DCs combine both ex vivo and in vivo methodologies, including the creation of vaccines and the development of nanovaccines. While significant strides have been made, challenges such as DC migration inefficiencies and dosing concerns persist, but studies are being connected to solve those problems.

As research continues to reveal the complexities of DCs role in immunotherapy, it becomes clear that these cells offer a multifaceted approach to reshaping cancer treatment strategies. With ongoing advancements, a more complete understanding of DCs in the future will lead to greater knowledge of how we apply DCs in immunotherapy.

This review underscores the critical role of dendritic cells in immunotherapy, emphasizing the need for continued research, innovation, and collaboration to maximize their transformative impact on cancer treatment.

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