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Review Article

Dendritic Cells: Crucial Regulators of Immune Responses on Cancer Cells

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ABSTRACT

Dendritic Cells (DCs) play a pivotal role in the immune system, acting as sentinels that capture, process and present antigens to T cells, thus initiating and regulating immune responses. Activation of DCs stands at the forefront as they work as coordinators of the immune system, spotting and presenting microbe fragments to T cells, thereby commencing Cell-Mediated Immunity (CMI). This review aims to trace the origin of DCs and find out what makes them stand out among other antigen-presenting cells. The research takes us into the DC mechanisms of activation that affect T-cell proliferation, especially in cancer pathologies. Participants are also outlined the possible effects of DC study related to the oncological treatments' development. Briefly, discrimination based on the complex participation of DCs and T cells should pave the way for more potential interventions for improving immunotherapy and other diseases. In summary, dendritic cells are central players in orchestrating immune responses, including those against cancer cells. Understanding their biology and interactions with cancer cells is crucial for developing effective immunotherapies for cancer treatment.

Keywords: Dendritic cells, Immune system, Cancer cells, T-cells.

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INTRODUCTION

DCs are specialized Antigen-Presenting Cells (APCs) that capture antigens from their surroundings, process them into smaller fragments and present them on their surface using Major Histocompatibility Complex (MHC) molecules. Hematological Stem Cells (HSCs) with pluripotency identified in bone marrow were the precursors of Dendritic Cells (DCs). They keep on a particular cluster of APCs, or antigen-presenting cells that additionally comprises macrophages and B-cells.[1] When compared to other cells dendritic cells are scientifically proven to serve as the most potent T-Lymphocytes immune system generator. The discovery of monoclonal antibodies that were specific to DCs made possible the ability to quickly isolate and analyze DCs. An extensive system of antigen presentation, transport and capture is created by DCs.[2]

It is believed that DC develops in discrete stages. Under unidentified circumstances, hematopoietic pluripotent stem cells continuously produce DC generators within the myeloid tissue and fatty tissue, which additionally results in blood-circulating precursors.[3] These types of cells are distinct from neutrophilic leukocytes (macrophages), Plasmacytoid Cells (PCs), or islet cells which are known to be the DCs in different contexts. These cells very much mimic the ones that were initially discovered by Steinman and Cohn.[4]

A large number of juvenile DCs dwell on mucosal surfaces, where solid organs and skin serve as protectors to detect antigens. Human Leukocyte Antigen (HLA), binding molecules and T lymphocyte factor of mutual stimulation have all been generated at lower concentrations in these DCs.[5] Inflammatory cytokines are not secreted by immature DCs. They can migrate, though. After absorbing antigens, immature DCs move towards the secondary lymphatic gland, in which they disclose antigenic substances towards plasma cells or CD4-positive T-lymphocytes (white blood cells) cells to provoke specific responses from Cytotoxic Lymphocytes, or T Lymphocytes (CTLs).[6]

Additionally, they progressively increase their flexibility and express more of the CC-chemokine transporters 7 and 8 (CCR7, 8).[7] fully developed Dendritic cells, however, possess large capacity for migration but less capacity for the processing and the digestion of antibodies.

Additionally, it's been shown that fully developed antigen-presenting cells produce more chemokines and cytokines that promote inflammation and express more substances that are stimulatory, such as CD40, CD70 and CD80, in addition to CD86.[8,9]

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DCs have been a crucial objective throughout both avoidance and intervention of disease due to their application in investigation and treatments, for example, the creation of vaccines and the spread of viruses, along with its crucial use in several DC-based immunotherapies including malignancy treatment, in which a few days ago these are being applied as surveillance and therapy. Still, in spite of several research experiments on DCs, there has been a shortage of data among individuals with DCs as well as different kinds of animals, so they need to be further investigated.[10]

As a result, this study clarifies the general information on dendritic cells, including their mechanism, process and relationship with immunology. The defense mechanism's role within the origins of cancer development and its ability to reduce tumor peptides through dendritic cells, are potential for future uses.

Identifying Markers and Transport Functions in Dendritic Cell Subsets

Two distinct methodologies were employed in the identification of markers exhibiting varying expression levels in DC2s.[11] Initially, the expression profiling of Conventional dendritic cells 1, 2 and antigen-presenting cells subgroups, derived via a type of immune cell made in the bone marrow of six individual contributors, were juxtaposed. This was facilitated through the utilization of a DNA chip or bio-chip encompassing 50,684 DNA sequences.

Conventional Dendritic Cells 1 (myeloid dendritic cell)

Myeloid dendritic cells are prevalent in the proximal bloodstream and tissue of both humans as well as mice. However, the abundance in mouse blood is notably low. Mouse cDC1s exhibit a high degree of uniformity in the expression of CD8 and/or CD103.[12]

Conventional Dendritic Cells 2 (cDC2s)

Conventional DC2s exhibit a remarkable degree of heterogeneity and are recognized for their bifunctional role in orchestrating immune activation and regulation. Upon activation within the peripheral blood, cDC2s elicit an intricate cytokine milieu, featuring the release of Interlukin-1-beta, Interlukin-6 and Interlukin-23, consequently instigating the T helper 17 cells (subsets of pro-inflammatory T helper cells) mediated immune response.[13]

Interferon Producing Cells (IPC)

Natural interferon-producing cells were initially identified in an individual's lymphatic vessels. Phenotypically, individuals' plasmacytoid dendritic cells tend to be analogous towards their murine counterparts characterized by PDCA-1C+ expression. Their differentiation hinges upon the transcription factors E2.2 and IRF7, while they exhibit a distinctive repertoire of surface markers encompassing transmembrane glycoproteins and the immunomodulatory compound ILT2.[14-16]

Dendritic Cell's Transporter Mechanisms

The SLC7 transporter family consists of Cationic Amino acid Transporters (CATs) and L-type amino Acid Transporters (LATs), among which cationic amino transporters primarily facilitate the transport of arginine. Notably, CAT2 (also known as SLC7A2) emerges as an essential player in controlling Dendritic Cell (DC) activation as well as anti-inflammatory responses.[17]

Glutamine transport in tumor cell biology

Specific transporters, such as Solute Carrier family 1 member 5 (SLC1A5), additionally referred to as an Alanine, Serine and Cysteine-preferring Transporter 2 (ASCT2), facilitate glutamine intake by tumor cells. Subsequent enzymatic conversion mediated by Glutaminase (GLS) transforms glutamine into glutamate, a crucial metabolite. Further downstream, glutamate undergoes conversion into α-Ketoglutarate (α-KG), integrating into the Krebs cycle. This metabolic axis is intricately linked to the initiation, progression and dissemination of tumors.[18]

Cysteine Transporters: Guardians of Intracellular Redox Equilibrium

The cellular uptake of Cysteine (Cys) predominantly relies on the complimentary amino acid transporters ASCT1 and ASCT2, while cystine (Cys2) is just carried via the xc 2 cystine/glutamate antiporter. While cystine (Cys2) utilizes the exclusive xc- antiporter system for cystine/glutamate exchange. Intracellular reduction rapidly converts imported Cys2 into Cys within the cytosol. Previous studies indirectly suggested T cell expression of ASCT1 along with ASCT2 transporters, although nevertheless the xc- antiporter, based on Cys and Cys2 uptake measurements. The results gave rise to the hypothesis; therefore, activated Antigen-Presenting Cells (APCs) provide a sufficiently high concentration of extracellular Cys for T cells, with this APC-derived Cys being essential for T cell activation.[19]

Exploring SLC15A4: A Lysosomal Transporter in Cellular Homeostasis Histidine Transporter

SLC15A4, a lysosome-localized transporter, has an essential function in the movement concerning histidine and oligo peptides across cellular compartments. Through its proton-coupled mechanism, SLC15A4 orchestrates the transport of these molecules from the lysosomal interior to the cytosol within eukaryotic cells. Notably, its involvement in Toll-Like Receptor 7 (TLR7), as well as TLR9-mediated type I Interferon (IFN-I) production inside plasmacytoid Dendritic Cells (pDCs), underscores its significance in immune responses. Furthermore, studies have implicated SLC15A4 in the etiology of autoimmunity-related illnesses that include lupus-like autoimmunity, suggesting its potential as a therapeutic target.

Further investigations into the regulatory mechanisms and functional implications of SLC15A4 promise to deepen our understanding of cellular dynamics and disease pathogenesis.[20]

Dendritic cell's multifaceted functions

Stimulation of antigen-presenting cells via bacterial infection and warning signs

Developing dendritic cells have integral components of tissue surveillance, capable of detecting both the identification of pattern receptors for antibodies, molecular patterns associated with pathogenic organisms and molecular patterns related to damage.[21,22] PAMPs, deriving mainly from pathogens, encompass a spectrum of molecular motifs including bacterial Lipopolysaccharide (LPS) and nucleic acids.[23] Toll-Like Receptors (TLRs), a diverse group consisting of twelve receptors based upon leukocytes and stromal cells, play a vital role in recognizing both DAMPs and PAMPs.[21,24]

Upon TLR activation, a signaling cascade ensues, ultimately resulting in the replication factors induction, notably NF-κB.[25] NF-κB, in response, modulates the manifestation of pro-inflammatory cytokines, thereby initiating an immunological reaction.[26]

The movement of dendritic cell populations in surrounding cells

Dynamic Behavior of Developing Dendritic Cells Towards Tissue Surveillance Immature Dendritic Cells (DCs) pervade all tissues of the body, actively engaged in antigen surveillance and sampling.[27,28] This process primarily involves the uptake of antigens through receptor-mediated phagocytosis or non-specific micropinocytosis. Among them, developing islet cells nestled through the layers of epithelium, comprise a pivotal component within the early therapeutical defense in contrary to infectious disease.[29] Their immobile nature fosters the formation of an extensive network bridging tissue interfaces with the external milieu, facilitating efficient antigen surveillance.[30,31] While some subsets of immature DCs exhibit limited migratory behavior until maturation, others undergo a transition in response to potential threats, shifting from endocytosis to migration. This migratory shift is facilitated by dynamic cellular processes involving actin-rich protrusions at the slicing end, associated towards the leading end by inactive transpiration, enabling cellular movement, often referred to as "flowing".[32]

Dendritic cells' motility within the flow of lymphatics

The motility of dendritic cells within the flow of lymphatics is a highly orchestrated process that facilitates immune surveillance, antigen transport and the initiation of adaptive immune responses. Understanding the mechanisms underlying DC motility in lymphatics is essential for elucidating immune system function and developing strategies for modulating immune responses in health and disease. DCs suppress functions connected to their sentinel activity as they mature. Lowering Cdc42 and diminishing Arp2/3 levels throughout the cell inhibit macropinocytosis.[33] DCs exhibit barotaxis to compensate for their greater susceptibility to hydrodynamic resistance, which leads to a reduction in macropinocytosis. Furthermore, it was previously observed that when subjected to confinement, neutrophils exhibited barotaxis, preferring the shortest possible path.[34] Both CCL19 and CCL21 are chemical messengers that adhere to CCR7.

However, it has been proposed that CCL21 is the chemokine that serves as necessary for DC migration.[35,36] On the contrary, CCL19 shows less effect.[37] In a state of equilibrium, DC chemotaxis becomes possible through the constitutive release of CCL21 via Lymphatic Epithelial Cells (LECs).[35,38]

Entry of dendritic cells into lymphatic's: A regulated process

DCs have to pass through a process called infiltration when they enter to access the lymph nodes and use sympathetic lymphatic veins. DCs typically penetrate the bloodstream's lymph capillaries, which are located in the initial, blind-ended lymphatics.[39] surpassing the basement membrane's cellular matrix barrier, which conceals the lymphatic canal, represents the first phase in the passage of blood. The molecular makeup of this underlying membrane is non-linear, and infiltration DCs seek gaps through which they might enter the lymphatics. DCs compress through the matrix of cell barriers by initially expanding a cell extension into the channel, followed by constricting the cell again.[40] They proceed to penetrate via the LEC monolayer. A button-like circulation of compounds that adhere has been observed at particular junctions situated within maple-structured LECs which coincide with the blood vessels of lymph.[41]

Dendritic cells Migration to Lymphatic Vessels

About 24 to 72 hr are required for DCs to get to the lymphatic vessels, especially the draining ones via blood vessels. Antigen-presenting cells called dendritic cells proceed passively down the vessel wall into the lymphatics. While either lymph flow or passive movement may be involved, it is believed that within the capillaries, the hydrodynamic forces are low for slow-moving fluid.[42] During all DC migration inside lymphatics, their cells and fronts are actively moved ahead, similarly as it happens with interstitial movement. Bone marrow DCs go via the lymph sinus floor in the direction of the paracortex, the space in a place where T-cells and cells that contain fibroblast are mixed.[43]

These specialized fibroblasts which will be referred to as FRCs, produce and cover the reticular fibers composed of collagen fibers as well as different kinds of matrix elements. Collectively, these fibers constitute the piping system that lymphatic fluid uses. This network of FRCs situated inside the lymphatic system

serves as a structural platform when it comes to the migration of immunological cells.[44-46]

Functions of DCs in Tumour

Dendritic Cells (DCs) or their precursors have the capability to be recruited into the Tumor Microenvironment (TME), where they may undergo differentiation into mature DCs. Within this environment, DCs are capable of sensing various molecular cues that influence their fate, which can include processes such as cell death, incomplete activation, or successful maturation. Immature DCs typically lack the ability to effectively initiate T cell responses against tumors and may even promote immune tolerance. Conversely, mature DCs possess the capacity to migrate to lymph nodes draining the tumor, where they can prime T cell responses, recruit T cells into the TME and produce immunostimulatory cytokines that modify the TME (Figure 1).

Dendritic Cell Migration in Tumor microenvironment

It is the tumor microenvironment, especially the cellular components, that are the main determining factor for the tumor growth and the changes of the tumor to the treatments.[47] Besides cancer cells, other stromal cells (fibroblasts and indigenous as well as cells of the reactive immune system also reside inside the modest surroundings that are the niche of the tumor.[48] Unlike various immune cells like fibroblast or dendritic cells, which promote tumorigenesis, pDCs are mostly involved in immunity and protect the system against various cancer mechanisms.[49]

On the other hand, pDCs can yield results because they induce T lymphocytes that regulate within the cancerous miniature surroundings and inhibit malignant immunity. Thus, most of the time, dendritic cell migration and their presence in cancer have an adverse outcome in diagnosis.[50,51] Conversely, however, the CD8+ T lymphocytes which were directed against the tumors in an immunogenic context, either as a result of *in vivo*[52-53] or *ex vivo*[54] antigen-activated pDCs, produce strong and lethal responses. CD9- CD81+ pDCs activate the generation of functional T lymphocytes and decrease the body's immune response, while CD9+ CD81- pDCs generate Interferon type I (IFNα) and additionally stimulate cytotoxic CD8+ T cells which encourage immunity against tumors.[55, 56]

While injecting therapeutic DC vaccines, the scientific name of both of those tetraspanins can be utilized to identify and concentrate for pDC subgroups that possess the capacity to boost immunization beneath the malignant microenvironment.[57] CDCs especially cDC1s have been shown to contribute to the immunological system's suppression of tumors.[58,59] The propensity of cDC1s to ingest and deliver antigens from tumors to naïve CD8+ T lymphocytes that are located in the lymph node that drains the cancerous tissue through molecules of the MHC class I has been attributed to their anti-cancer properties.[60]

The cytotoxic CD8+ T lymphocytes possess the capability to relocate toward malignancies as well as destroy cancer cells after they have been activated. In generating substantial quantities of Interleukin-12 (IL-12), a kind of inflammatory mediator has taken place in promoting CD8+ T cell's cytotoxic activation activity, cDC1 cells are additionally able to promote CD8+ T cells.[61]

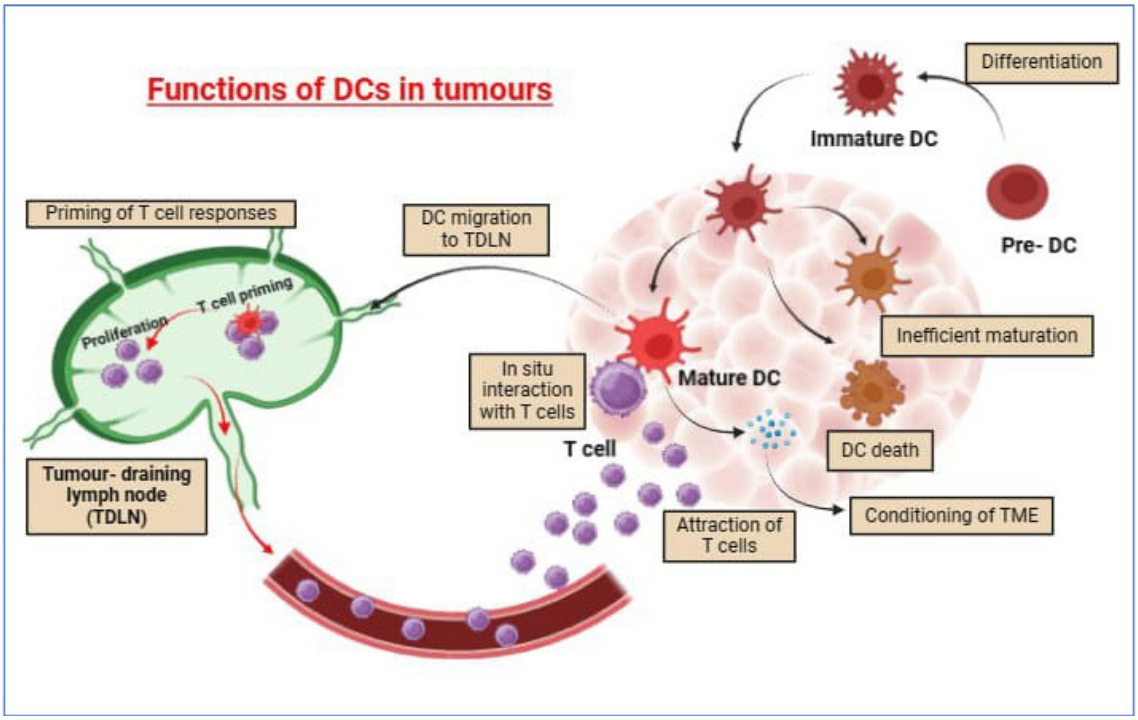

Figure 1: Functions of DCs in Tumour. Source: Created with BioRender.com

Dendritic cells relationship with immunology and its critical initiation

Regulation of immune responses

Dendritic Cells (DCs) have significance both for activating tolerance of the immune system to harmless antigens also for initiating a defense against invading infections. The effective migration of DCs to one specific region is a requirement for their organized roles in inflammation and immunology.[62] DCs comprise an intricate, variable number of cells presenting antigens which shows an extensive amount of behavioral and physiological variation.[63] The bone marrow is the origin of the progenitors for standard dendritic cells (pre-cDCs), plasmacytoid DCs (pDCs), as well as leukocytes. These stem cells are carried through the blood vessels to lymph nodes like the spleen along with lymphatic vessels in addition to nonlymphoid tissues including the outer layer of the skin, pulmonary and stomach.[64]

Pre-cDCs and neutrophils in surrounding tissues, such as the epidermis, specialize in juvenile cDCs and monocyte-derived DCs (moDCs), which then migrate within the epidermis. Evolving from developmental embryonic cells, islet cells consist of a specific bunch of hybridized DCs and neutrophils that can be identified in the epidermis.[65]

Impact across the Immunology on Tumor Cell Maturation

Emerging field during immune-modulation therapy highlights the preventive significance of the autoimmune system in cancer. After initially getting platinum-based radiation therapy to combat their tumors in the lungs, people who have continued treatment reported a longer overall survival percentage while receiving a PD-1 immune checkpoint inhibitor antibody.[66] Within the past two decades, findings revealed that proinflammatory immunological components have an important role in inflammation linked to cancer. The investigation is currently focusing on comprehending whether malignant growth is influenced by cells from the immune system at multiple phases during the illness, especially malignancies and the initial tumor development that have already been clinically recognized the spread of metastatic disease and therapeutic intervention.[67]

Since T lymphocytes have been fairly functional upon eradicating cancerous mutated fibroblasts, however, could certain malignant tissues escape these effector T cell attacks? According to experimental studies conducted on both humans and mice, cancer cells make use of T cells' suppressing features to inhibit antitumor T cells' capacity to carry out their effector duties, including penetrating tumors and improving their capacity for survival, growth and mortality.[68] The capacity of effector T lymphocytes to depend on antigens indicates that the anti-tumor T-cell immunized reactions effectiveness has become dependent on the antigenic material for cancer's ability to trigger an immunological reaction (immune-stimulating response) in addition to the presence or absence of vascular and malignant cells. That may lead to decreased levels of antigen-presenting cell adhesion, so it hinders the chemotherapeutic interventions of

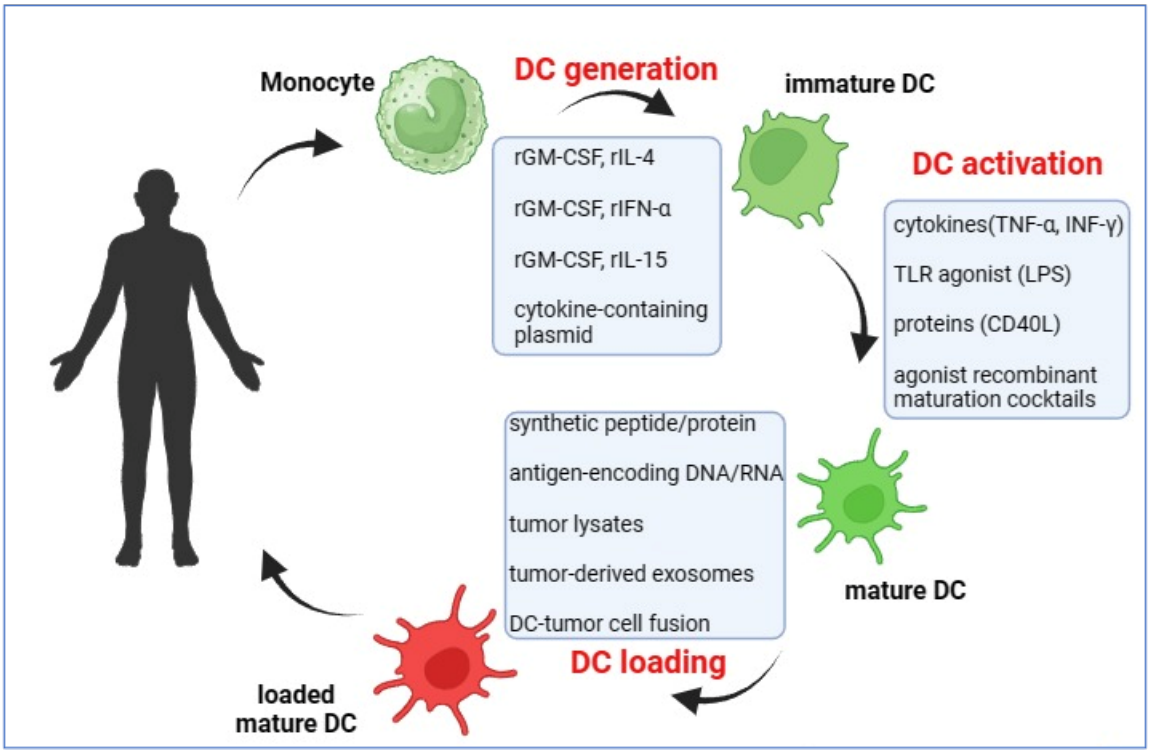

Figure 2: The process of Dendritic cells vaccine loading. Source: Created with BioRender.com

T-cells; this includes relocation, growth and apoptotic intervenor, additionally exclusion in destroying cell membranes.[69]

It is widely recognized that a vast majority of cancerous cells presenting highly immunological antigens will eventually be identified and destroyed in the initial phases of cancer development via a T-cell-dependent mechanism.[70] A mechanism termed "cancer immunological editing" permits the less immune-stimulating malignant cells to avoid T cells' immunology control and live.[71] As an outcome, the malignant cells that endure take on a phenotype, resulting in becoming immune-resistant. Meanwhile, as the tumor grows, cancer cells generate responses to defense that mimic tolerance in the peripheral region and are capable of preventing regulatory T cells from executing a targeted cytotoxic approach.[72]

The control of regulatory T lymphocyte responses by resistant-mediated points within cytotoxic lymphocytes as well as triggered T helper cells that work to safeguard organs from injury caused by inflammation is a fundamental external tolerance mechanism during immune homeostasis. Checkpoint components CTLA-4 and PD-1, which are receiving greater emphasis, were recently shown to adversely impact T-cell exertion and are frequently linked with antibody tolerance in tumors.[73]

Immune tolerance and suppression of anti-tumor immune responses

The concept of "suppressor of tumor peptides through dendritic cells" highlights the role of DCs in promoting immune tolerance and suppression of anti-tumor immune responses, thereby contributing to tumor immune evasion and progression. Understanding the underlying mechanisms involved in DC-mediated immune suppression is essential for developing strategies to overcome immune tolerance and enhance anti-tumor immunity in cancer therapy. Cytotoxic lymphocytes, also known as T Lymphocytes (CTLs), are essential in facilitating immunological therapy-induced cancer eradication; however, structural peptide-based tumor immunotherapy wasn't very effective.[74]Among those events is tolerance to immunology generated by particular types of immune-related cells, which include phagocytes, Tumor-Associated Dendritic Cells (TADCs), suppressor cells derived from Myeloid Cells (MDSCs) and Tregs. TADCs diminish resistance by expressing molecules onto the cell's surface, which includes the destruction of cell 1 receptor 1 (PD-L1), enzymatic substances such as Indoleamine-2,3-Dioxygenase (IDO1) and Arginase (ARG) and cytokines which lead to cancer known as Transforming growth factor beta and Interleukins-10. Abnormal regulation of channels of signaling constitutes one of the cellular processes that control TADCs that block antitumor immunity. The JAK/STAT families of enzymes are necessary for the survival of cells, their proliferation and their transformation. Amplification of STAT3 is being linked to autoimmune inhibition in malignancy, as demonstrated by several studies.[75] Suppressor of tumor peptides through dendritic cells likely refers to a mechanism by which Dendritic Cells (DCs) promote immune tolerance or suppression of anti-tumor immune responses. This concept encompasses several aspects:

Immune Tolerance Induction

DCs can induce immune tolerance to tumor antigens through various mechanisms. For example, immature or tolerogenic DCs may present tumor antigens to T cells in the absence of co-stimulatory signals or in the presence of inhibitory signals, leading to T cell anergy or deletion.

Regulatory T Cell Induction

DCs can promote the differentiation and expansion of regulatory T cells (Tregs), a subset of T cells with immunosuppressive functions. Tregs can suppress anti-tumor immune responses and promote tumor immune evasion by inhibiting the activation and effector functions of other immune cells.

Immunosuppressive Cytokine Production

DCs can secrete immunosuppressive cytokines such as Interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF-β), which inhibit the function of effector T cells and promote immune tolerance.

Expression of Immune Checkpoints

DCs may express immune checkpoint molecules such as Programmed cell Death ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4), which interact with corresponding receptors on T cells to inhibit their activation and effector functions.

Induction of Exhaustion

Prolonged exposure to tumor antigens presented by DCs can lead to T cell exhaustion, characterized by progressive loss of effector functions and increased expression of inhibitory receptors. This exhaustion state impairs anti-tumor immune responses and facilitates tumor immune evasion.

Inhibition of Dendritic cell mechanisms inside cancerous microenvironment

Many types of cancer are associated with an inflammatory element, so when multiple leukocytes, which include myeloid MDSCs and TAMs, permeate the tumor as a consequence, an immunosuppressive environment develops that inhibits the immune system's responses of DC-instructed effector CD4+ and CD8+ T cells as well as triggers T-cells to multiply.[76,77] These cytokines generated by the tumor, carcinoma-infiltrating MDSCs, TAMs, or DCs in the draining lymphatic system that carry tumor-related antigens are mainly accountable for causing this immunosuppression.[78]

The process of Dendritic cells vaccine loading

The figure outlines the various ways in which mature Dendritic Cells (DCs) can be loaded with antigens. These antigens can be proteins, peptides, or nucleic acids derived from pathogens or tumors. Once loaded, the mature DCs can stimulate T lymphocytes to initiate an immune response against the specific antigen. The different antigen sources for DC loading include; Synthetic peptides/proteins, Antigen-encoding DNA/RNA, Tumor lysates, Tumor-derived exosomes, DC-tumor cell fusion. The figure also shows different maturation cocktails, including cytokines (TNF-α, INF-γ) and TLR agonists (LPS) that can be used to activate DCs. These maturation cocktails help DCs to become more efficient at antigen presentation and T cell stimulation (Figure 2).

Potential mechanism for harnessing the immune system to eliminate cancer cells

"Danger commands," which include TLR ligands expressed by the bacteria, induce DC proliferation during microbial infection. It in turn stimulates powerful Th1 immune reactions, resulting in IFN-g and neurotoxic T Lymphocyte (CTL) reactions.[79] Even though several cancer cells, as well as the tissues that are linked to cancer, exhibit an inflammation that has been signed and even though so-called exogenous warning signs[80] including uric acid, thermal shock proteins, as well as elevated circulation group box 1 (HMGB1) protein may trigger antigen-presenting cell stimulation via perishable cancer cells, the level of DC development that results in tumor-antigen cross-representation in the context of malignancy tissue is typically far less powerful than that which is induced by highly pathogenic microorganisms.[81]

Treg cells' CTLA-4 stimulates T conv cells to produce antibodies erroneously and multiply, which may enable these types of cells to penetrate and potentially destroy nonlymphoid tissues and organisms.[82]

As a result, Treg cells' CTLA-4 is essential as well in preventing the proliferation of T lymphocytes which might threaten essential body parts. Regarding a hypothesis, according to the science of molecular biology, Treg cells expressing CTLA-4 might inhibit its volume of CD80/86 ligands that can be used for functional T cell positive mutual stimulation of CD28. The CTLA-4 could block the stimulation of T cells passively and cell-extrinsically by this kind of mechanism. Further, effector T lymphocytes bearing CTLA-4 are capable of trans-compete for CD80/86 ligands.[83]

Future Perspectives

Studies conducted so far have proved the efficacy of DC immunization in addition to controversy. The vast majority of dosage-reported adverse effects are mild and short-term and these generally involve fatigue, adenopathy, site of injection responses and illness.

A significant number of research studies have proven the immunologic value of DC vaccines, with many individuals exhibiting evidence of stimulating tumor-specific responses to T cells.[84]

Despite the unimpressive clinical findings, sufficient clinical trials are demonstrating the safety of DC-based immunization. However, we agree that immunization versus DCs has a promising future. With the FDA endorsement of the first therapeutic cell-based vaccination in 2010[85] and the drug therapy in 2011, chemotherapy may become a routine component of clinical treatment. To advance the subject matter of DC-related chemotherapy, it is important to look towards adjusting this strategy in light of current implications as well as expanding to cancer individuals along with lower tumor burdens. The number of laboratory tests employing equivalent development techniques for DC development seems accessible.[86]

CONCLUSION

In summary, here, the aim is to understand the interactions between DCs and T cells, as well as strategies to enhance DC function, which holds promise for the development of novel cancer treatments. By leveraging the immune-stimulating properties of DCs, researchers hope to develop more effective immunotherapies that can target a wide range of cancers and improve patient outcomes. Unlike innate immunity, which is characterized by a broad response to different antigens, adaptive immunity is specific and therefore, the APCs are in charge of presenting the antigens accordingly. DC cell development with its stages, which range from hematopoietic stem cells to fully mature ones, highlights the difficulty and variability in terms of these cells. Consequently, the rapidly changing scenery of DC-based immunotherapies including but not limited to cancer treatment gives us a glimpse into the future where DCs are used as therapeutic resources. With all the current achievements in understanding DC biology, yet, there is still the need for more research to enlighten the possibilities in the field of immunology and cancer treatment. As we solve the underlying networks of how DC acts, we can discover new terms that will help improve the body's immunity and fight diseases in a much better way.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DCs: Dendritic Cells; **HSCs:** Hematological Stem Cells; **APCs:** Antigen-Presenting Cells; **MHC:** Major Histocompatibility Complex; **PCs:** Plasmacytoid Cells; **HLA:** Human Leukocyte Antigen; **CTLs:** Cytotoxic Lymphocytes; **CCR7:** CC-Chemokine Receptor 7; **CCR8:** CC-Chemokine Receptor 8; **PAMPs:** Pathogen-Associated Molecular Patterns; **TLRs:** Toll-Like Receptors; **NF-κB:** Nuclear Factor-Kappa B; **DAMPs:** Damage-Associated Molecular Patterns; **cDC1s:** Conventional Dendritic Cells 1; **cDC2s:** Conventional Dendritic Cells 2; **IPC:** Interferon Producing Cells; **PDCA-1C:** Plasmacytoid Dendritic Cell Antigen-1C; **CATs:** Cationic Amino Acid Transporters; **LATs:** L-type Amino Acid Transporters; **SLC1A5:** Solute Carrier Family 1 Member 5; **ASCT2:** Alanine, Serine and Cysteine-preferring Transporter 2; **GLS:** Glutaminase; **α-KG:** Alpha-Ketoglutarate; **Cys:** Cysteine; **Cys2:** Cystine; **ASCT1:** Alanine, Serine and Cysteine Transporter 1; **SLC15A4:** Solute Carrier Family 15 Member 4; **TLR7:** Toll-Like Receptor 7; TLR9**:** Toll-Like Receptor 9; **IFN-I:** Type I Interferon; **pDCs:** Plasmacytoid Dendritic Cells; **LPS:** Lipopolysaccharide; **TME:** Tumor Microenvironment; **MDSCs:** Myeloid-Derived Suppressor Cells; **Tregs:** Regulatory T Cells; **PD-L1:** Programmed Cell Death Ligand 1; **IDO1:** Indoleamine-2,3-Dioxygenase 1; **ARG:** Arginase; **JAK/STAT:** Janus Kinase/Signal Transducer and Activator of Transcription; **IL-10:** Interleukin-10; **TGF-β:** Transforming Growth Factor-Beta; **CTLA-4:** Cytotoxic T-Lymphocyte-Associated Protein 4; **CMI:** Cell-Mediated Immunity; **TADCs:** Tumor-Associated Dendritic Cells; **IL-12:** Interleukin-12.

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