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Review Article

Dendritic Cell Functionin Cancer Immunity: A Systematic Review

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ABSTRACT

An emerging body of evidence indicates that the presence and functionality of Dendritic cells (DCs) within tumor microenvironment are critical determinants of the efficacy of various immune checkpoint blockade and,cancer therapies. The key concept of cancer immunotherapy is that the manipulation of the immune system can achieve cancer control and, ideally, cure. To make immunotherapies more effective, it is crucial to comprehend how DCs trigger tumor immune responses and the strategies cancers use to avoid DC surveillance. Tumor-associated DCs have a significant potential for boosting antitumor responses, but their functional activity is generally compromised, and they may also contribute to immune suppression in cancer. The present understanding involved in human cancer by several DC subsets, with an emphasis on their function in T-cell priming, migration into tissues and the Tumor Microenvironment (TME), and coordinated in vivo responses. Furthermore, the present study could pave the creation of novel therapeutic approaches that target DCs. Author's contributions: SMG,AFS, and OSY conceptualized and write the original draft edited the manuscript as well as performed the critical literature search and JOA supervised the manuscript. All authors read and approved the final manuscript.

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Introduction

An essential component of the immune system, dendritic cells (DC) serve as a link between innate and adaptive immunity. According to Baratin (2015) and Obleukhova et al. (2018), they are a varied group of functionally specialized myeloid-derived antigen-presenting cells (APCs) that coordinate antigen-specific immunity and tolerance, including self-tolerance and immunity against malignancy.

To start and adjust anti-tumor immune responses, DCs must first capture, process, and present tumor antigens to T cells. They live all across the body as important sentinel cells, although they are especially found in lymphoid organs and at environmental interfaces like the skin and intestine (Fig. 1). Although DCs have been linked to both positive and negative prognoses, their function is unknown despite the overwhelming evidence that they infiltrate a variety of solid human cancers (Mishinov et al., 2020).

The efficacy of current treatments may be increased, and more individualized and focused cancer therapies may result from a greater understanding of how DCs can be controlled to boost anti-tumor immunity (Patel et al., 2021).

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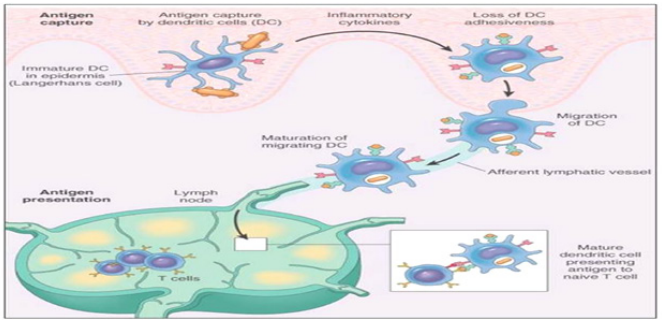


Fig. 1. Migration of dendritic cells to draining lymph nodes (Emmanuel, 2007)

DCs have been identified as important regulators that direct response to ICB (Immune Checkpoint Blockade) and other cancer immunotherapies due to their capacity to induce de novo T-cell immunity and their role in priming antigen-specific T-cells (Chen et al., 2013; Zilionis, 2019). By improving the role and effectiveness of DCs in cancer and anti-tumor immunity, ICB functions. Only a small percentage of patients respond to cancer immunotherapy, despite the fact that its success confirmed the idea that it promotes strong and long-lasting anti-tumor immunity by targeting immune checkpoints that activate or may reinvigorate neoantigen-specific T-cell clones (Obleukhova et al., 2018).

This is corroborated by multiple lines of evidence that link intratumoral DC or the expression of DC-specific transcriptional signatures with the T-cell inflamed phenotype and CD8 T-cell infiltration to a favorable prognosis among cancer patients and to response to various cancer immunotherapies (Zhang et al., 2020). Bristol Myers Squibb's Yervoy (also known as ipilimumab) was the first ICB to receive FDA approval for the treatment of metastatic melanoma in 2011, and more than 110 ICB-related medications have been developed for clinical trials or FDA-approved to treat cancer to date (Airhart et al., 2018). Despite progress in

cancer treatment, many tumors are able to evade immune detection and resist current therapies. The exact mechanisms by which DCs influence tumor immunity are not fully understood, and their dual role in either promoting or suppressing anti-tumor responses presents a challenge in developing effective immunotherapies(Ghasemi et al., 2023; Wu et al., 2023). In order to increase the number of patients who respond to ICB, especially those with non-inflammatory and poorly immunogenic tumor types, there is increasing interest in using the DC compartment to better activate and mobilize T-cells into the TME ((Garris et al., 2018).

New evidence indicates that DCs are more closely related to the mechanisms of action of ICB and other cancer therapies than previously thought, including ligation of DC-expressed immune checkpoints and co-stimulatory molecules, as well as shaping adaptive immunity through immunogenic cell death (ICD) and activation of innate DNA or RNA sensing pathways (Chow, 2019). This study is important because it attempts to elucidate the function of DCs in the immune response to cancer, offering insights that could improve immunotherapeutic approaches.

2.0 MATERIALS AND METHODS

All relevant studies published before December 1, 2024 were searched on five databases, including Scopus, Web of Science, PubMed, Research Gate, and Google Scholar, with the keywords "Cancer Immunity" or "Dendritic Cell" or "Tumor Microenvironment" or "Immunity" or "immunogenic tumor" and "Immunotherapy for Cancer".

After the literatures were accumulated and analyzed, we screened and excluded non-tumor Microenvironment, particularly dendritic cell function in tumour microenvironment. We concluded that despite progress in cancer treatment, many tumors are able to evade immune detection and resist current therapies. The exact mechanisms by which DCs influence tumor immunity are not fully understood, and their dual role in either promoting or suppressing anti-tumor responses presents a challenge in developing effective immunotherapies.

3.0 RESULTS AND DISCUSSION

In total, 480 records in English were obtained through database searches with the keyword "Diabetes". After searching other keywords, screening titles, and abstracts, 54 papers relevant to Type 1 Diabetes Mellitus and 59 screened articles on immune function remain. The studies on Type 1 Diabetes Mellitus were both experimental and clinical research.

3.1 Biology of dendritic cell

The biology and functions of dendritic cells were first identified by Steinman in the 1970s as cells with a potent ability to stimulate allogeneic T cell responses (Steinman et al., 1973).DCs were later recognized as integral to activating antigen-specific responses. Later, it was discovered that DCs were essential for triggering antigen-specific reactions. It was acknowledged by the 1990s that "DCs" are actually a number of subtypes that were initially identified by different surface markers.

To differentiate classical (or conventional) DCs (cDCs) from plasmacytoid DCs, which are now believed to mediate responses through their cytokine secretion rather than directly taking part in the presentation of antigens to T cells, a broad classification was employed (Swiecki et al., 2015). More recently, proteins that serve as terminal selectors or lineage-determining factors in various lineages were identified (Sachien et al., 2016), and the underlying transcriptional foundation for the differences across DC subsets was found (Murphy et al., 2016).

In these lineages, proteins that serve as terminal selectors or lineage-determining factors were found (Sachien et al., 2016). These findings deepened the understanding that DCs are a collection of closely related cell types, and research into this long-standing topic, which dates back to the 1990s, is still ongoing.

According to Steinman et al. (2012), a DC's function as an immune cell is to process and deliver antigens on the surface of MHC Class-I and II molecules to T-cells. Their shape and expression of cell surface markers alter after antigen uptake, which starts the maturation and migration process to lymph nodes where multiple histocompatibility complex (MHC) molecules present the antigens to T cells. Using a variety of hydrolases and cathepsins, the foreign and pathogen-derived proteins are partially broken down in the DCs' endosomes, lysosomes, cytosol, and endoplasmic reticulum before appearing as antigenic peptides on MHC class I and class II molecules on the DC cell surface (Fig. 2).

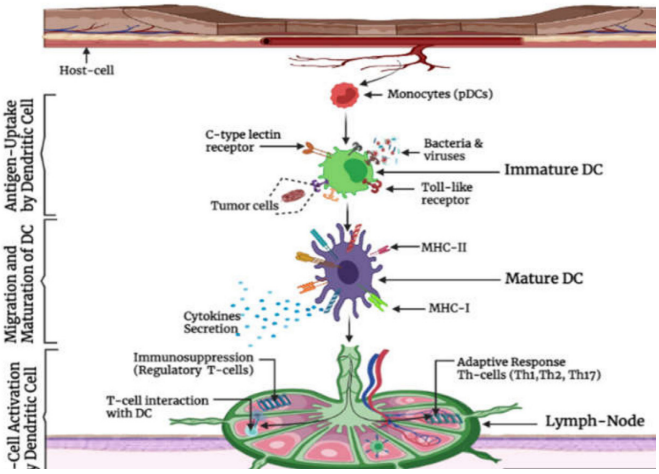


Fig. 2.T-cell activation by the dendritic cell (Zanna et al., 2021).

The antigens presented to T cells on MHC class I, and class II molecules will activate and induce the T cells to become cytotoxic T cells or helper T cells, respectively. Dendritic cells further enhance the immune response by presenting ligands on their surface, which bind to the T cells' co stimulatory molecules. Various types of cytokines, such as IL-12, further stimulate and optimize T-cell proliferation. Antigens from endogenous sources, such as viral proteins, are generally presented on MHC class I molecule to initiate cytotoxic T cell proliferation, while extracellular antigens are presented on MHC class II molecules. While other immune cells, such as macrophages and B cells are also involved in antigen presentation, DCs are versatile because of their ability to "cross present." Dendritic cells can present extracellular antigens on MHC class I molecules, initiating cytotoxic T cell proliferation.

Dendritic cells also contribute to the function of B cells and help maintain their immune memory. Dendritic cells produce cytokines and other factors that promote B cell activation and differentiation. After an initial antibody response has occurred due to an invading body, DCs found in the germinal center of lymph nodes seem to contribute to B cell memory by forming numerous antibody-antigen complexes. This provides a stable source of antigen that the B cells can take up themselves and present to T cells.

3.2. The role of dendritic cells in immunization against tumors

An essential conceptual framework for comprehending how DC promotes anti-tumor immunity, which, when effective, results in T-cell-mediated destruction of cancerous cells, is the cancer immunity cycle (Chen et al., 2013). Dendritic cells stimulate helper and cytotoxic effector T-cell populations, as well as long-lived memory cells, by delivering antigens to the tumor-associated draining lymph node (tdLN). As with antiviral memory responses, the quality of this initial priming event is frequently disregarded, yet it is probably crucial for controlling long-lasting protective immunity in cancer (Leal et al., 2021).

According to Wculek et al. (2020), DC are in charge of coordinating a number of activities that include: (1) antigen processing and capture; (2) licensing and activation in response to environmental cues and sensing; (3) maturation and migration to the tdLN; (4) antigen-presentation and

priming of naïve T-cells; (5) recruitment of T-cells into the TME via DC-derived chemotactic gradients; (6) in situ interaction with effector T-cells and local cytokine production in the TME.

Activated cDCs come in a variety of forms, and their functional characteristics are influenced by ontogenetic restrictions, the type of activation signal, and exposure to local immunological modulators, spatial organization, and time. Keep in mind that, as shown in fig. 3, cDC stimulation can also produce cDCs that suppress immunological responses and preserve tolerance

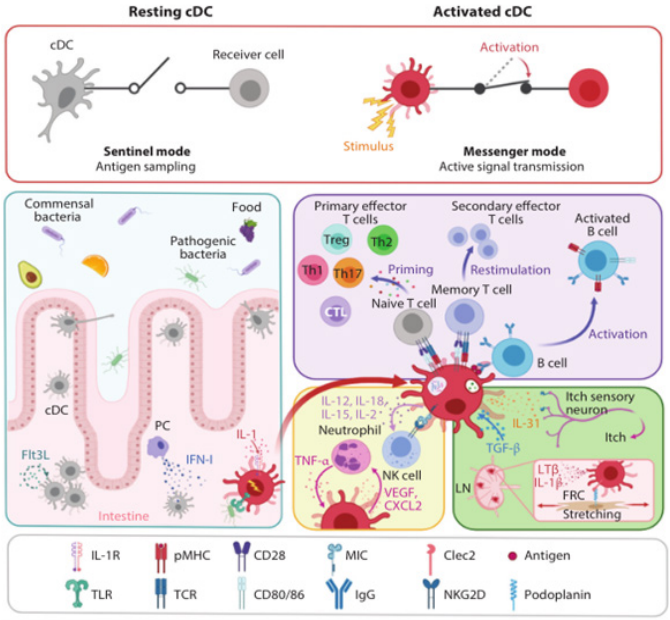


Fig. 3. Activated and dormant cDC (*Cabeza-Cabrerizo et al. 2021*).

3.3. Dendritic cells used therapeutically in tumors

The fundamental theory behind cancer immunotherapy is that cancer can be controlled and, ideally, cured by modifying the immune system. Coley was the first to demonstrate the potential of cancer immunotherapy when he treated patients with incurable sarcomas using a combination of bacterial toxins (Chaux 1996). Since then, numerous studies have demonstrated the clinical benefits of utilizing activators of the general immune system, including TLR agonists (Adams 2009) and bacterial products (Bernardes et al., 2010).

When anticancer activity does occur, it is ascribed to these chemicals' capacity to stimulate the immune system, which then gains the capacity to eliminate tumor cells. According to Burns et al. (2014), a large portion of this effect was demonstrated to be caused by DC activation followed by T cell response production.

Dendritic cells should play a major role in triggering anti-tumor immune responses since they are important activators of the adaptive immune response. The numerous functional abnormalities these cells exhibit in cancer patients highlight the potential significance of dendritic cells in triggering anti-tumor immune responses (Fig. 4). Given these facts, it would seem reasonable to use DC's immune-stimulating pro.

Given these findings, it makes sense to use DC's immune-stimulating properties to help cancer patients develop antitumor responses. However, therapeutic approaches utilizing DC were only made feasible after techniques for the in vitro creation of these cells were described, due to the challenge of collecting large numbers of these cells through non-invasive means (Sidorov et al., 2020).

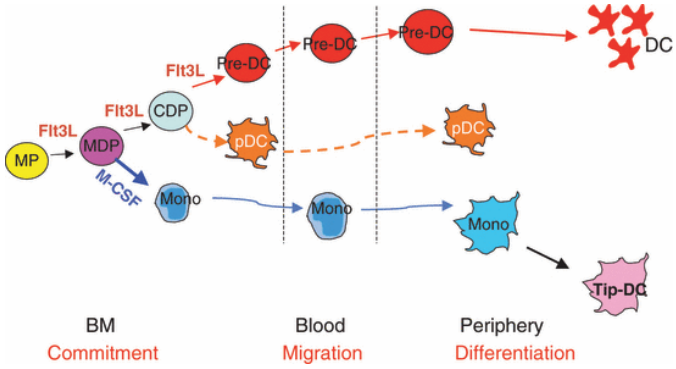


Fig. 4. Origin and development of dendritic cells (Emmanuel, 2007)

Abbreviatioons; MP: Myeloid progenitor, MDP: monocyte dendritic cell progenitor, CDP: committed DC progenitor, Flt3L: fms-like tyrosine kinase 3 ligand

3.4. Immune responses against tumors

Tumor stem cells are among the diverse cancer cells seen in tumors that interact with immune and micro environmental cells (Koido et al., 2013). Escape from immune regulation is linked to progressive tumor growth (Xin et al., 2012).The impact of malignant cells and their surroundings on immune cells, which results in their suppression and altered activity, is linked to the development of the tumor process(Chevolet et al., 2015). It has been demonstrated that the ratio of myeloid to plasmacytoid dendritic cells varies and that the quantity of circulating dendritic cells, particularly myeloid dendritic cells, falls in cancer patients. Patients with pancreatic cancer, melanoma, and breast cancer should undergo these modifications (Lim, 2020; Patel et al., 2021).

The primary populations of dendritic cells have changed in number and ratio, and their maturation and differentiation have been violated, and their functional activity has been suppressed (Gabrilovich et al., 2012). Patients with cervical cancer (Reuben et al., 2006), hepatocellular carcinoma (Ormandy et al., 2006), lung cancer (Perrot et al., 2007), colonic cancer (Chaux et al., 1996), and breast cancer (Pinzon-Charrey et al., 2007) had lower accumulations of mature dendritic cells. VEGF, a tumor microenvironmental factor that promotes tumor angiogenesis, is most frequently linked to the inhibition of dendritic cell differentiation in cancer patients (Chen et al., 2015).

T cell exhaustion has been shown to be a major factor in tumor-induced immunosuppression in a number of cancer patients (Hodi et al., 2012). The negative influence of tumor cells and their microenvironment is manifested in the differentiation of effector cells and dendritic cells into suppressor cells, mediated by "checkpoint" molecules, which are highly expressed in tumor-infiltrating dendritic cells and inhibit T-cell activation and cytokine production (Salmon et al., 2016).

Enhancing T-cell immunoglobulin and mucin domain-containing protein-3 (TIM-3) activity on dendritic cells is another method that prevents immunological signal transmission (Soliman et al., 2018). It was demonstrated that VEGF, CCL1, CCL2, and CXCL5 inhibited dendritic cell maturation and IL-12 production in a conditioned media derived from colorectal cancer explants, but boosted IL-10 secretion(Vander et al., 2015). It has been discovered that melanoma cells that express β-catenin increase tumor growth, decrease dendritic cell and T-cell infiltration, and create resistance to immunotherapeutic drugs. Additionally, prostaglandin E2 promoted tumor growth by interfering with intratumoral CD103+ dendritic cell accumulation (Vander et al., 2015).

In cancer patients, metabolic disruption may also impact the development of dendritic cells. Normal dendritic cell function is hampered by hypoxia, lactic acid generation, and a lower pH (Ebner et al., 2006). It has been demonstrated that metabolites from the tumor microenvironment cause

lipid peroxidation, which in turn causes dendritic cells to accumulate lipids (Zelenay et al, 2015). These lipid particles hinder T lymphocytes' ability to cross-present and prevent the peptide-MHC I complex from migrating to the surface of dendritic cells, hence preventing their activity (Veglia et al., 2014). It has been demonstrated that tumor-infiltrating plasmacytoid dendritic cells actively express ICOSL and indoleamine 2, 3-dioxygenase (IDO) and stimulate Treg cells, but they are unable to produce type I IFN.

This promotes the growth of tumors (Ito et al., 2007). A poor prognosis is linked to a high number of tumor-infiltrating plasmacytoid dendritic cells in cancer patients. Furthermore, because CCR7 expression is regulated, dendritic cells in the tumor microenvironment have a diminished capacity to transport antigens, which in turn reduces their capacity to stimulate T cells in lymph nodes (Roberts et al., 2016).

4.0 Methods of cellular immunotherapy

Getting functionally mature dendritic cells that can convey tumor antigens to effector cells and trigger cytotoxic immune responses is the foundation of current cellular immunotherapy strategies (Steinman et al., 2007). Obtaining functionally mature dendritic cells in vitro is the best choice for inducing them, given the significant reduction of immunity in cancer patients and the need to remove the influence of tumors (Dauer et al., 2005). The majority of clinical trials use ex vivo-derived dendritic cells from peripheral blood monocytes. Dendritic cell development from progenitor cells is usually induced by IL-4 and GM-CSF in 5-7 days (Mohty et al., 2003) or for "fast" dendritic cells (Vitsin et al., 2018) in 2-3 days. Patients with metastatic prostate cancer saw a 4-month increase in median survival, according to clinical trials (Dauer et al., 2005).

4.1. Proteins or peptides and tumor cell lysates

The use of lysates and tumor proteins (peptides) from autologous tumor cells to prime dendritic cells (Li et al., 2010)—which express a greater variety of tumor antigens appropriate for individualized treatment—as well as tumor cells fused with dendritic cell vaccines (Hao et al., 1986; Koido et al., 2013) are among the oldest techniques for delivering tumor-associated antigens. One possible benefit of using tumor lysates as a source of tumor immunogens is that they can elicit responses against several distinct tumor-associated antigens(Liu et al., 2008).

This method stimulates both, enabling the generation of a polyclonal immune response. By activating both CD4+ and CD8+ T cells, this method enables the generation of a polyclonal immunological response. By using tumor lysates, dendritic cells can naturally digest tumor antigens, saving time and effort needed to find and manufacture particular immunodominant protein epitopes. This method's drawback is that in certain clinical scenarios, it is impossible to get tumor material for lysate preparation (Liu et al., 2008).

4.2. Vaccinating against cancer using dendritic cells

previously, melanoma and other highly immunogenic malignancies were protected against by dendritic cell vaccines (Butterfield et al., 2003). They have now been widely employed in a number of clinical trials. Hematopoietic stem cells or monocytes generated from patients are frequently gathered and in vitro developed into DCs. DCs are then cultivated with maturation cytokines after being pulsed with TAAs or tumor lysates (Santos et al., 2018; Yang et al., 2019). The decreased number of immune cells in cancer patients (Tjomsland et al., 2010) is a barrier to this approach and may result from other therapies like chemotherapy or radiation. This issue can be resolved by using monocyte-derived DCs (MoDCs) produced from healthy donors.

4.3. In vitro platforms

The majorities of cancer immunotherapy agents were first characterized and evaluated in vitro using 2D and 3D models. Human cancer cell lines, cancer cell-derived organoids, primary tumor cells, or patient-derived tumor organoids are either cultured alone or co-cultured with human peripheral blood mononuclear cells (PBMCs), TILs, CAR-T, TCR-T, or CAR-NK cells for screening the efficacy of the cancer immunotherapy. For the 2D screening system, specific cancer cells or organoids are co-cultured with the immune cells on flat dishes. Subsequently, cancer immunotherapy agents are added to examine the phenotypic modulation of cells and the underlying molecular mechanisms through various immune cell assays (for T cells, NK cells, macrophages, DCs, and neutrophils) and tumor cell assays.

However, the 2D system represents an artificial and simplified cultural environment, while the 3D system is capable of reflecting the complexity of tumors in patients, since the tumors also consist of immune cells, stromal cells, epithelial cells, and endothelial cells (Zhou, 2016). The 3D culture system can be classified as a scaffold system and a scaffold-free system. The former system supports cell growth, proliferation, and survival through a specific extracellular matrix (ECM), such as hydro gel.

The essential nutrients and growth factors are supplemented to the cells through some small pores in the ECM, which is similar to their primary microenvironment in vivo(Yanget al., 2014). In contrast, 3D a scaffold-free system generates spheroids and cell aggregates by forced-floating, hanging drop or agitation-based technology in the absence of ECM, which provides a better physiological model when compared to the scaffold system.

4.4. In vivo models

The aforementioned in vitro platforms allow us to promptly evaluate the efficacy of cancer immunotherapy drugs. However, the in vitro models barely reproduce the complexity of the tumor microenvironment, which consists of human tumor cells, immune cells, and stromal cells. Hence, there is an urgent need to develop sophisticated in vivo models that can mimic the tumor microenvironment in patients for the assessment of novel cancer immunotherapy agents.

Humanized Mouse Tumor Models: Humanized mouse tumor models can be divided into humanized oncology models and humanized immune-oncology models.

4.5. Humanized Oncology Models

The humanized oncology models are established by the injection or engraftment of human cancer cell lines (from human tumors or oncogene-generated) or human PDX tumors into immunodeficient mice, including but not limited to athymic nude mice, severe combined immunodeficiency (SCID) mice, non-obese diabetic (NOD) mice, and NOD scid gamma (NSG) mice (Liet al., 2018). Recently, the models have been used to screen the immunotherapy agents against cancers, such as monoclonal or bispecific antibody therapies, CAR-T cells, oncolytic viruses and cytokine therapies(Linet al., 2015; Chen et al., 2017; Suet al., 2019).

Apart from CAR-T cells therapy, it was reported that the delivery of oncolytic virus using modified neural stem cells was more efficient and able to extend the survival of mice in the mouse glioma-PDX model (GBM43 and GBM) (Yuet al., 2016). However, the major drawback is that ICBs, or cancer vaccines, cannot be evaluated in these models due to the absence of a human immune microenvironment. Therefore, there is a growing interest in developing human immune-oncology models for the studies of cancer immunotherapy.

4.6. Models of Humanized Immune-Oncology

Engrafting human cancer cell lines or human PDX tumors into immunodeficient mice with HLA-matched human immune systems creates humanized immune-oncology models. Human PBMCs or hematopoietic stem cells (HSCs) could be transplanted into these models to create a human immune system.

5.0 Conclusion

A growing amount of data suggests that the existence and activity of dendritic cells (DCs) in the tumor microenvironment are important factors that affect how well certain cancer treatments, such as chemotherapy, radiation, and immune checkpoint inhibition, work. The fundamental theory behind cancer immunotherapy is that cancer can be controlled and, ideally, cured by modifying the immune system. It is vital to analyze the mechanisms underlying therapeutic response and resistance in order to comprehend how DC immunobiology might be used to enhance response rates and treatment outcomes for cancer patients, given the rapidly growing clinical use of immunotherapy.

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