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Dendritic cells as a basis for designing anti-cancer vaccines

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ABSTRACT

Dendritic cells (DCs) have been shown to play a pivotal role in orchestrating the immune response against tumors, thereby acting as a link between innate and adaptive immunity. DCs capture, process, and present tumor antigens to T cells, which triggers a specific immune response aimed at destroying cancer cells. DCs are a heterogeneous population that includes several subtypes, such as conventional DCs (cDC1, cDC2) and plasmacytoid DCs (pDC). Each subtype has unique functions: cDC1s specialize in activating CD8⁺ T cells, while pDCs produce interferons in response to viral infections. In a tumor microenvironment, DCs are often depleted of their functionality due to immunosuppressive factors, such as IL-6 and PGE₂, which impedes their ability to activate T cells. Furthermore, an imbalance between oxidative phosphorylation and glycolysis regulated by the AMPK/mTOR axis may lead to the immunosuppressive phenotype of DCs.

A promising direction in cancer immunotherapy is the creation of DC-based vaccines that can restore the immunogenicity of cold tumors lacking T cell infiltration. Such vaccines can be created by generating DCs *in vitro* or modifying them to enhance the presentation of tumor antigens.

Despite significant advances, the biology of DCs remains poorly understood. This lecture highlights the importance of DCs in developing new cancer treatment strategies and opens up prospects for more effective immunotherapeutic approaches.

Keywords: dendritic cells, antitumor vaccine

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Дендритные клетки как основа конструирования противораковых вакцин

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РЕЗЮМЕ

Дендритные клетки (ДК) играют ключевую роль в организации иммунного ответа против опухолей, выступая связующим звеном между врожденным и адаптивным иммунитетом. Они захватывают,

обрабатывают и представляют опухолевые антигены Т-клеткам, что запускает специфический иммунный ответ, направленный на уничтожение раковых клеток. Представляют собой неоднородную популяцию, включающую несколько подтипов, таких как обычные ДК (cDC1, cDC2) и плазматоидные ДК (pDC). Каждый подтип выполняет уникальные функции: cDC1 специализируются на активации CD8⁺ Т-клеток, а pDC вырабатывают интерфероны. В микроокружении опухоли ДК часто теряют свою функциональность из-за иммуносупрессивных факторов, таких как IL-6 и PGE2, что затрудняет их способность активировать Т-клетки. Кроме того, нарушение баланса между окислительным фосфорилированием и гликолизом, регулируемым осью AMPK/mTOR, может приводить к иммуносупрессивному фенотипу ДК.

Перспективным направлением в иммунотерапии рака является создание вакцин на основе ДК, которые могут восстанавливать иммуногенность «холодных» опухолей, лишенных инфильтрации Т-клеток. Такие вакцины созданы путем генерации ДК *in vitro* или их модификации для усиления презентации опухолевых антигенов.

Несмотря на значительные успехи, биология ДК остается недостаточно изученной. Эта работа подчеркивает важность ДК в разработке новых стратегий лечения рака и открывает перспективы для создания более эффективных иммунотерапевтических подходов.

Ключевые слова: дендритные клетки, противоопухолевая вакцина

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INTRODUCTION

The immune system plays a key role in recognizing and destroying tumor cells, and in recent years, significant advances have been made in developing therapeutic strategies aimed at activating the immune system to fight tumors [1].

Cell-based therapeutic anti-cancer vaccines use autologous tumor cells derived from the patient, allogeneic tumor cell lines, or autologous antigen-presenting cells to mimic the natural immune process and stimulate an adaptive immune response against tumor antigens. Such vaccines have been developed over decades and various approaches have been used to create vaccine constructs for anticancer therapy. In general, they can be divided into cell-based vaccines, viral vector-based vaccines, and molecular vaccines consisting of peptides, deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) [2].

Tumor cell-based vaccines have an important advantage: they contain multiple neoantigens, thus avoiding the need for prior identification of specific target antigens. However, their efficacy may be limited by inadequate presentation of antigens to the immune system. If the antigens are not effectively

presented by dendritic cells, the immune response may be weak, reducing the efficacy of the vaccine [3]. Tumor neoantigens are proteins produced as a result of mutations in tumor cells that can undergo processing and presentation for recognition by T lymphocytes [4].

The aim of this lecture was to discuss the use of dendritic cells in the development of novel cancer treatment strategies.

THE ROLE OF DENDRITIC CELLS IN ANTITUMOR IMMUNITY

Dendritic cells (DCs) play a key role in producing effective T-cell responses against tumors and are the basis of modern immunotherapy strategies aimed at replenishing depleted T cells in the tumor microenvironment. Cancer therapy with DC-based vaccines has attracted considerable attention. However, their functional behavior is determined by multiple factors. The type of DCs, transcription program, location, intratumor factors, and inflammatory environment all influence DCs, which may result in enhancement or suppression of antitumor immunity [5].

Conventional DCs (cDCs) are formed in the bone marrow from a common monocyte – dendritic cell progenitor (MDP), from which a common DC progenitor (CDP) originates. In the bone marrow, it gives rise to cDC1 (pre-cDC1) and cDC2 (pre-cDC2) precursors, whose terminal differentiation occurs in peripheral tissues under the influence of the antigenic and inflammatory microenvironment. Plasmacytoid DCs (pDCs) are thought to develop from a separate CDP subpopulation; however, there is an alternative view that their progenitor may be an IL-7R⁺ lymphoid precursor [6–8]. Using technologies based on the study of single cells, it was found that rDCs originating from lymphoid and myeloid tissues have different functional and transcriptional profiles despite similar phenotypic markers [9].

Immature DCs localize in the bloodstream or peripheral tissues and are activated by signals delivered through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), retinoic acid-inducible gene-I (RIG-I)- like receptor, nucleotide-binding oligomerization domain-like receptors, and C-type lectin receptors (CLRs). These PRRs allow DCs to respond rapidly to pathogen-associated molecular patterns (PAMP) or danger-associated molecular patterns (DAMP). Under conditions of homeostasis, DCs take up harmless antigens that are to be transferred. When DCs are activated through PRR stimulation, they increase the expression of chemokine receptors, such as chemokine C-C receptor type 7 (CCR7), which promotes DC migration to the draining lymph node. In addition, PRR activation leads to increased expression of MHC molecules, co-stimulatory surface molecules (CD40, CD80, CD86), and cytokines (IL-12, IL-10, IL-23, TNF α), which promotes the transition from resting immature DCs to functional mature DCs capable of activating T cells in the lymph node [10].

Possessing multiple PRRs, DCs recognize DAMP signals and safety-associated signals, which is crucial for triggering appropriate T-cell responses. In addition, they efficiently integrate signals from the local tissue microenvironment to fine-tune T cell responses. Under normal physiologic conditions, DCs play a key role in maintaining immune homeostasis by activating T cells to destroy infected or malignant cells and stimulating regulatory T cells to attenuate chronic inflammation. Immune dysregulation contributes to cancer and tumor-induced immunosuppression, including T-cell depletion, which poses significant obstacles to cancer

immunotherapy. Restoration of functional activity of depleted T cells to stimulate antitumor response is the main goal of modern immunotherapeutic strategies [11].

DCs are professional antigen-presenting cells optimized for activation of T-cell responses. DCs play a central role in orchestrating effective CD8⁺ T-cell responses against tumors [12]. At the initial stage of antitumor immune responses, recognition of tumor antigens by T cells depends on their presentation by DCs. This process begins with the capture of tumor antigens by DCs, which intracellularly bind to major histocompatibility complex (MHC) molecules. These MHC peptide complexes (pMHC) are then transported to the cell surface to prime and activate effector T cells in the lymph node draining the tumor. DCs are professional antigen-presenting cells (APCs). Their expressed major histocompatibility complex type I (MHC-I) molecules present antigens for recognition to CD8⁺ and MHC-II – to CD4⁺ T lymphocytes, where, with the participation of costimulatory molecules, proliferation of a clone of T cells specifically recognizing a certain antigen takes place. The assistance of CD4⁺ T cells, especially activated effector memory Th1 cells, enhances the activation of CD8⁺ T cells through CD40 signaling to DCs [13]. This interaction promotes antigen cross-presentation, migration of T cells to the tumor, and induction of their effector functions and immunological memory formation [14]. In the tumor microenvironment (TME), cytotoxic T cells (CD8⁺) recognize specific antigens on the surface of tumor cells, leading to their destruction. Following tumor cell death, new antigens are released and captured by APCs, which restarts the cycle of anti-tumor immune responses. Importantly, APCs that capture and process tumor antigens may differ from those that activate tumor antigen-specific T cells in lymph nodes. Several mechanisms of antigen transfer between different types of DCs have been proposed, including cross-presentation of phagocytized fragments from donor DCs, presentation via MHC, and synaptic transmission of antigen-loaded vesicles [15].

SUBTYPES OF DENDRITIC CELLS

DCs are a heterogeneous population consisting of multiple subtypes with unique functions that have been identified over the past decade in both mice and humans. However, the exact number of DC subtypes, their interrelationships, and differences from other mononuclear phagocytes remain a subject of research

[16]. DCs can be divided into subtypes depending on their function and phenotypic markers. Initially, conventional DCs (cDCs) were distinguished from plasmacytoid DCs (pDCs) on the basis of their ability to directly present antigens to T cells [17]. Current studies of transcription factors regulating DC differentiation in mice have greatly expanded the understanding of their subtypes. The development of advanced technologies, such as single-cell RNA sequencing (scRNA-seq), has made it possible to clarify and improve the classification of DCs [16]. DCs are classified into three major subtypes: type 1 conventional DCs (cDC1), type 2 conventional DCs (cDC2), and plasmacytoid DCs (pDCs). These subtypes, interacting with one another, play a key role in the formation and regulation of the adaptive immune response.

Numerous studies have shown that human DCs express high levels of MHC class II molecules, such as HLA-DR, a molecule required for antigen presentation, and lack key markers of T cells, B cells, natural killer cells (NK cells), granulocytes, and monocytes. In the blood, DC subtypes include CD11c⁺ cDCs, composed of CD141⁺ or CD1c⁺ cells, and pDCs, composed of CD123⁺ cells. Conventional DCs efficiently stimulate antigen-specific CD4⁺ and CD8⁺ T cells, while pDCs specialize in the production of type I interferons in response to viruses. The pDC and cDC subtypes differ in the expression of numerous receptors, signaling pathways, and effectors and play different roles in the immune response [19].

However, the definition of DCs can still be distorted by the limited number of markers available for cell identification, isolation, and manipulation. Such distortions, in turn, may affect the definition of the function and ontogenesis of each DC subtype.

The study by A.K.Villani et al. [16] allowed to develop a more accurate classification of DCs, including six DC subtypes and four monocyte subtypes, as well as to identify a circulating, dividing dendritic cell precursor. In contrast to previous studies that categorized human blood DCs as one population of pDCs and two populations of cDCs, the authors identified six DC populations: DC1 corresponds to CD141/BDCA-3⁺ cDC1, which specializes in antigen cross-presentation and is labeled with CLEC9A; DC2 and DC3 represent subpopulations of CD1c/BDCA-1⁺ cDC2; DC4 corresponds to CD1c-CD141-CD11c⁺ DC, which is best labeled with CD16 and shares signatures with monocytes; DC5 is a unique DC subtype such as DCs; and DC6 is an interferon-

producing pDC that has been isolated in a purer form than previously identified pDCs defined by standard markers (e.g., CD123, CD303/BDCA-2⁺) but containing an admixture of other DCs (AS DCs).

Given the unique ability of cDC1 to present tumor antigens to CD8 T cells, as well as their ability to interact with CD4 T cells, they are considered to be the main subset of DCs that regulate antitumor responses of T cells. However, cDC2 has been shown to be a critical factor in antitumor immunity under certain conditions [5]. In one preclinical model with diphtheria toxin receptor (DTR) knockout cDC1, depletion of intratumor regulatory T cells (Treg) enhanced migration of cDC2 into the tumor-draining lymph node and eliminated the dysfunction, leading to productive priming and activation of effector CD4 T cells [19].

Tumor-infiltrating DCs are characterized by different functional states that play a key role in antitumor immunity. To identify DC states associated with productive antitumor T-cell immunity, E. Duong et al. [20] compared spontaneously regressing and progressing tumors. In Batf3-deficient (Batf3^{-/-}) mice lacking type 1 DCs, CD8⁺ T-cell responses to tumor were lost in progressing tumors but preserved in regressing tumors. Transcriptional profiling of intratumor DCs in regressing tumors revealed an activation state of CD11b⁺ conventional DCs (DC2) characterized by interferon-stimulated gene expression (ISG⁺ DCs). ISG⁺ DCs demonstrated an enhanced ability to activate CD8⁺ T cells *ex vivo* compared to DC1. In contrast to DC1, which perform antigen cross-presentation, ISG⁺ DCs presented intact tumor cell-derived peptide-MHC class I complexes. Continuous production of type I interferon by regressing tumor cells resulted in an ISG⁺ DC state, and activation of these cells with exogenous interferon β restored antitumor immunity in Batf3^{-/-} mice. The genetic signature of ISG⁺ DCs was also detected in human tumors, suggesting their potential role in antitumor protection. At the same time, under conditions of high IL-6 and PGE2 expression, intratumor cDC2 may acquire a pro-tumor phenotype characterized by CD14 expression and impaired antigen presentation [21].

METABOLIC PROGRAMMING OF DENDRITIC CELLS

In DCs, metabolism is closely linked to maturation signals and is therefore a key factor in the activation or tolerogenicity of DCs in the tumor microenvironment. In general, differences in the

regulation of glycolysis and oxidative phosphorylation programs are associated with anti-inflammatory or proinflammatory DC phenotypes. The metabolic needs of DCs have only recently been discovered, and metabolic phenotypes, dependent on subtype and environmental conditions, are closely related to their functions. In immature DCs, the mammalian AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) axis is thought to play a key role in maintaining the metabolic balance. AMPK promotes oxidative metabolism and counteracts mTOR, which activates glycolytic pathways after TLR signaling [5].

The analysis of metabolic pathway activation at the level of individual cells revealed simultaneous involvement of several metabolic pathways at different stages of monocyte-derived DC differentiation. GM-CSF/IL4 induce rapid glycolysis-dominated reprogramming of monocytes, accompanied by temporary joint activation of glycolysis and mitochondrial pathways, which subsequently leads to TLR4-dependent DC maturation. Disruption of the balance between mTOR and AMPK phosphorylation, as well as increased activity of oxidative phosphorylation, glycolysis, and fatty acid metabolism lead to two key features of tolerogenic DCs – hyperactivity and an immunosuppressive DC phenotype. These cells are resistant to maturation, meaning that they fail to fully develop into mature DCs, but instead retain an immature, dedifferentiated phenotype and express unique immunoregulatory receptors that enhance their immunosuppressive properties. Data obtained at the individual cell level provide important information on the metabolic pathways that regulate the immune profiles of human DCs [22].

In recent years, more and more studies have confirmed that immune cells depend on certain metabolic characteristics to perform their functions, and that the extracellular environment can influence their metabolism and vice versa. DC subtypes move in a variety of environments from the bone marrow, where they develop, to peripheral tissues, where they differentiate and capture antigens before migrating to the lymph node for antigen presentation and T cell activation. It is likely that DC subtypes regulate their ability to stimulate the immune response depending on the unique metabolic programs that are activated in them. The metabolic needs of DCs have been studied relatively recently, and their metabolic phenotypes, which depend on cell subtype and environmental

conditions, are closely related to their functional properties [10].

DENDRITIC CELLS OF CANCER PATIENTS

DCs play a key role in the tumor microenvironment (TME). As the main antigen-presenting cells in tumors, DCs modulate the antitumor immune response by regulating the intensity and duration of responses carried out by infiltrating cytotoxic T lymphocytes. Unfortunately, due to the immunosuppressive nature of TME, and high plasticity of DCs, tumor-associated DCs often acquire a dysfunctional phenotype that contributes to the evasion of the immune response. Recent advances in the study of intratumor DC biology have identified potential molecular targets to improve their functional activity, which is involved in cancer immunotherapy [23]. The data indicate that both the number and function of DCs are reduced in cancer patients, and to a greater extent in metastatic tumors than in localized tumors [24]. Moreover, the powerful immunosuppressive environment created by tumors suppresses antigen presentation, maturation and normal function of DCs by several mechanisms, preventing an effective immune response to the tumor [25]. Given what is known about DC development and function, therapeutic anti-cancer vaccines based on these cells have been developed [26]. Vaccines based on DCs are able to transform the so-called cold tumors, characterized by the absence of infiltration by T cells, their dysfunction or exhaustion, into hot tumors, which stimulates the development of an effective anti-tumor immune response.

It has been shown that DCs can be generated *in vitro* in cancer patients or can be isolated from peripheral blood (natural DCs) and modified to enhance their functional competence. The use of DCs that have been activated by tumor antigens to induce the immune response has been proposed as a therapeutic strategy for certain tumors. The goal of DC-based vaccines is to stimulate the patient's own immune system to trigger an antitumor response that destroys malignant cells. In addition, this response can form immunological memory that can prevent recurrence of the disease [27].

CONCLUSION

Although the importance of dendritic cells in antitumor immunity is becoming increasingly clear, the biology of dendritic cells is still not fully understood. The functional behavior of dendritic cells is determined

by multiple factors, including their subtype, transcriptional programs, localization, intratumor conditions, and inflammatory environment. All of these influence whether dendritic cells will promote an effective T cell response or, conversely, inhibit it.

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Author Contribution

Frantsiyants E.M. – conception and design; final approval of the manuscript for publication. Bandovkina V. A. – justification of the manuscript and critical revision of the manuscript for important intellectual content. Surikova E. I. – critical revision of the manuscript for important intellectual content. Cheryarina N. D. – critical revision of the manuscript for important intellectual content. Kaplieva I. V. – justification of the manuscript and critical revision of the manuscript for important intellectual content. Menshenina A.P. – critical revision of the manuscript for important intellectual content. Shikhlyarova A.I. – justification of the manuscript and critical revision of the manuscript for important intellectual content. Neskubina I.V. – critical revision of the manuscript for important intellectual content.

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