International Research Journal of Oncology

Volume 7, Issue 2, Page 1-12, 2023; Article no.IRJO.97161

A Brief Review on Tumor Immunology

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/97161

Review Article

Received: 08/01/2023
Accepted: 13/03/2023
Published: 21/03/2023

ABSTRACT

The human immune system can eliminate unidentified proteins and contaminated tissues because it can discriminate between self and non-self proteins.

The potential for cancer immunotherapy is largely predicated on the idea that cancer cells express particular antigens recognized by T-lymphocytes, as these cells have been demonstrated in animal models to cause tumor rejection. The primary determinants of immune checkpoint inhibitor response can be believed to be T cells' capacity to identify tumor surface antigen and their subsequent migration to the tumor. Neoangiogenesis, a crucial stage in carcinogenesis, is stimulated by tumor related macrophages. Tumors have a variety of strategies for avoiding the immune response. The hunt for therapeutic treatments can benefit from a thorough grasp of these mechanisms.

A substantial corpus of clinical research demonstrates the growing importance of antibody-based cancer therapy.

Further emerging as a promising development in cancer immunotherapy is adoptive cell treatment following lymphodepletion.

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Keywords: Immunotherapy; tumor; antigen; evasion; immunoglobulin; macrophages; metastasis; adoptive cell therapy; monoclonal antibodies.

1. INTRODUCTION

"The immune system's capacity to discriminate between self and non-self is essential to its capacity to mobilize a response to an invasive infection, toxin, or allergy" [1]. "According to this immunoediting idea, the immune system is capable of identifying and eliminating subclinical cancers, but at some point - equilibrium is established, leaving the tumor in situ with a partially effective response" [2]. Certain cancer cells do, however, survive and develop into forms that are weakly immunogenic and capable of entering a steady-state phase. These cells either become clinically concealed or go into functional dormancy. It appears that neoplastic cells can direct immune cells to undergo modifications that encourage malignancy [3].

2. TUMOR IMMUNOLOGY

Understanding of the genetic events that give rise to tumor-specific antigens has improved with the characterization of the molecular structure of tumor antigens. In particular, primary open reading frames of gene products that are differentially expressed by tumors and not by normal tissues may encode tumor-specific antigens [4]. "This may also be represented by the products of gene translocation events, altered genes, intronic sequences, translated alternative open reading frames, pseudo-genes, antisense strands, or intronic sequences" [5]. Since T-lymphocytes have been proven to have a role in mediating tumor rejection in animal models, it is assumed that cancer cells express unique antigens that these cells can recognize and respond to [6]. When blood lymphocytes from patients with tumors are co-cultivated with radioactive tumor cells, autologous anti-tumor cytolytic T-lymphocytes (CTL) for human melanoma can be produced [7]. Melanoma cells exhibit numerous antigen expression, as shown by high activity and specificity anti-tumor CTL clones [8,9]. "Tumor antigens are proteins with unusual structures that are created by mutation in tumor cells. They serve as crucial diagnostic indicators for tumor cells and could be used as cancer therapeutic targets. Melanoma-associated antigen 1 (MAGEA1), which encodes the antigen MZ2E, was the first human tumor-associated antigen gene to be characterized at the sequencing level" [10]. Since then, additional tumor-specific antigens that are naturally processed and displayed on the surfaces of tumor cells have been discovered. These antigens are now included in the Cancer Immune Peptide Database.

2.1 Mechanisms of Tumor Evasion of the Immune System

2.1.1 First step of evasion

Lessening of tumor immunogenicity: Immune surveillance eliminates cancer clones that express potent neoantigens during tumor development. By removing immunogenic antigens or keeping cancer clones lacking cancer antigens, the tumor is now able to elude anti-cancer immune responses and is therefore unrecognizably by T cells. In other words, cancer clones that avoid immune monitoring contain less immunogenic antigens [2,11,12].

2.1.2 Second step of evasion

Blocking dendritic cell maturation:

Dead cancer cells' production of molecules including ATP and high-mobility group box 1 (HMGB1), which are damage-associated molecular patterns, can cause dendritic cell (DC) maturation. Cancer inhibits DC maturation by releasing tumor-derived factors like IL-10 [13], MCSF (Nefedova et al., 2004), VEGF [14], prostaglandin [15], TGF- [16], and indoleamine 2,3-dioxygenase [17]. Additionally, immune-suppressive cells in the tumor micro environment (TME), like Treg and myeloid-derived suppressor cells (MDSCs), express inhibitory molecules that prevent DC maturation by lowering the expression of MHC and co-stimulatory molecules in DCs. This lowers the production of inflammatory cytokines like IL-12, which in turn prevents the growth of T cells and IFN- [2,18-23].

2.1.3 Third step of evasion

Impairment of T cell activity:

Both antigen recognition and co-stimulatory signals are necessary for the complete activation of T cells. B7.1/B7.2:CD28, 4-1BBL:4-1BB, OX40L:OX40, CD70:CD27, and GITRL:GITR are co-stimulatory contacts between DC and T cells. These co-stimulatory interactions support T cell

survival, differentiation, proliferation, cytotoxicity, memory development, and cytokine production. By downregulating the expression of MHC and other co-stimulatory molecules, tumors reduce the co-stimulation needed for T lymphocytes, hence suppressing their activity. T cells become inactive (T cell anergy) when the TCR is activated without co-stimulation because of the excessive calcium/nuclear factor of activated T-cell (NFAT) signal [24-27].

2.1.4 Fourth step of evasion

Suppression of the migration and infiltration of T cells:

During the activation phase, cells produce chemokine receptors like CXCR3 on their cell surfaces in response to IFN- [28]. Cancer cells at this stage use posttranslational modification or breakdown of CXCR3 ligands, such as CXCL9, CXCL10, and CXCL11, to limit the production of these molecules as a significant evasion strategy, which prevents CD8+ T lymphocytes from migrating to the tumor [29]. These CXCR3 ligand fragments may also function as the receptor's antagonists. Another way that tumors prevent T cell migration is by altering the blood arteries in the area. Endothelial cells (ECs) are crucial for the migration of T lymphocytes, yet tumors release neoplastic agents like VEGF that inhibit their production [30,31]. Moreover, immunosuppressive substances such prostaglandin E2 and IL-10 are generated, which encourage the production of the Fas ligand in conjunction with VEGF and cause CD8+ T lymphocytes invading the tumor to die [32,33]. Moreover, tumor ECs express more endothelin-B receptors to prevent T cell migration [32,34-36]. “Even yet, it's possible that CD8+ T cells won't be able to reach the tumor's core despite their movement toward tumor tissue. This is because cancer-associated fibroblasts (CAF) and immunosuppressive immune cells create extracellular matrix (ECM) proteins to physically suppress T cells or to produce chemokines like CXCL12, which prevent the migration of T cells. In fact, analyses of human lung cancer tissue have confirmed that fibroblasts or collagen accumulates in the tumor substrate to prevent interactions between T cells and tumor cells” [37,38].

2.1.5 Fifth step of evasion

Immune cells' antigen recognition inhibition:

Cancer cells alter, decrease, or delete MHC-I from their surface in an effort to avoid being recognized by T cells. Cancer cells either directly or indirectly block peptide-MHC components or control MHC-I genes or proteins [39]. Moreover, by mutation, genetic loss, transcription inhibition, or epigenetic suppression of gene expression, cancer cells suppress the expression of antigens, proteasome components, TAP1/TAP2, MHC-I, and 2-microglobulin [40]. Current cancer genome investigations have confirmed that somatic mutations in the human leukocyte antigen cause the decrease in peptide-MHC-I expression on the surface of cancer cells [41,42]. Cancer cells may be able to avoid being recognized by T cells by reducing their MHC-I expression, however Natural Killer (NK) cells cannot be avoided. This is so that NK cells, which can recognize the level of MHC-I expression on the cell surface, can trigger an immune response against aberrant cells. To avoid being destroyed by NK cells, cancer cells instead secrete ligands to the active NK cell receptor NKG2D [43-45] (Terry et al. 2019).

2.1.6 Sixth step of evasion

Role of immunosuppressing cells:

Immune evasion also relies heavily on immunosuppressive cells in the TME. Tumor-associated macrophages are induced to develop into M2-type tumor-associated macrophages by the TME, and they produce IL-10 rather than IL-12 to suppress the CD8+ T cell response. When tumor-associated macrophages remove anti-PD-1 antibodies from PD-1+ CD8+ T cells in an FcR-dependent manner, they directly block immunological checkpoint inhibitor responses [46,47]. A collection of diverse cells known as MDSCs have the ability to significantly suppress the Teff response and activate Treg. By producing arginase, inducible nitric oxide synthase (iNOS), and TGF-, MDSCs suppress the immunological response. TGF- specifically inhibits cytotoxic T cells and NK cells by lowering the production of cytotoxic molecules like perforin and granzyme. Treg cells are immunosuppressive TME cells that are known to reduce the CD8+ T cell response and accelerate tumor growth when their population rises. A bad prognosis is typically correlated with a high Treg frequency. Strong anti-cancer immune responses, for instance, have been shown in mice models lacking Treg, and these findings imply that Treg cells are crucial in preventing anti-cancer immunity [48,49]. IDO, an immunosuppressive enzyme, generates kynurenine, a tryptophan metabolite with

immunosuppressive properties that is expressed in myeloid cells and different cancer cells. This is known to significantly increase the production and activity of Treg and MDSCs while significantly suppressing Teff function. Arginase 1, a different immunosuppressive enzyme, suppresses DC function by working with the IDO pathway. It is also recognized that inflammatory mechanisms and other metabolites can alter immunological and cancer cells, including glucose consumption, lactate production, and cholesterol metabolism [50-53].

3. BIOLOGY OF MACROPHAGE-TUMOR INTERACTION

Macrophages can be described as a heterogeneous population of innate myeloid cells that are resident in all tissues and develop from monocytic precursors. They can undergo specific differentiation or polarization in the blood or within tissues, and depending on where they are found, they may have different names such as microglia or Kupffer cells. [54] (Current Biology 2020, Cell Press). Blood monocytes produced from bone marrow (MDMs, monocyte-derived macrophages) and tissue-resident macrophages (TRMs), which develop from specialized yolk sac progenitors, are the two origins of macrophages. Localized macrophages (TRMs) produced by specific yolk sac progenitors. The erythro-myeloid progenitors (EMPs) in the yolk sac and fetal liver, as well as the macrophage/dendritic cell progenitor cells (MDPs) in the bone marrow that give rise to monocytes, are at least three embryonic sources from which these tissue-resident macrophages develop. 2020 Current Biology: Cell Press Review. Macrophages are known to self-replicate, and the recruitment of macrophages from bone marrow in place of those from the yolk sac can alter their origins throughout life. Macrophages are also known to concentrate primarily in areas with poor blood flow and low oxygen levels due to the specific up-regulation of various chemoattractants. When macrophages reach the tumor location, they begin to create a unique collection of proteins that will draw in more leukocytes and have an impact on the angiogenesis process. (Anita E. M. et al, 2006). Among their many crucial functions are host defense, tissue homeostasis, and regulating inflammatory responses. Macrophages are innate immune cells [55,56]. “Immature macrophages with high plasticity respond to microenvironmental signals in order to carry out these functions, which causes them to adopt a variety of effector roles, of which M1-like and M2-like represent extreme polarization states” [57-59]. “Classically activated M1 macrophages exhibit pro-inflammatory behavior by migrating to inflamed tissues, targeting pathogens with the production of reactive oxygen species (ROS), and having high antigen-expressing potential” [60-62]. Anti-tumor macrophages are frequently referred to as M1 macrophages due to their inflammatory nature. These macrophages have the potential to be strong tumor cell-killing effector cells that can also attract cytotoxic T lymphocytes (CTLs) to trigger adaptive immune responses. On the other end of the spectrum of macrophage polarization, alternatively activated M2 macrophages release anti-inflammatory cytokines to promote immune tolerance and draw T regulatory cells (Tregs) and Th2 T cell subsets, which are capable of producing protective type 2 responses but lack cytotoxic capabilities. In cancer, M2 macrophages are thought to be pro-tumor because they accelerate conventional tissue repair processes, support tissue remodeling and repair, stimulate angiogenesis with vascular endothelial growth factor (VEGF), and increase tissue development with transforming growth factor beta (TGF-) [63]. The M1/M2 distinction represents idealized polarization states, although in nature, a wide spectrum of macrophage phenotypes exists. As a result, for the sake of simplicity, tumor-associated macrophages (TAMs) have been defined as either M1-like (anti-tumor) or M2-like (pro-tumor).

3.1 Macrophages and Tumor Metastasis

Tumor metastasis, which is the process by which tumor cells escape from the source sites, travel through lymphatic and/or blood circulations, and ultimately disseminate to the distant sites, is a major factor in the death of cancer patients. (Y. Lin et al. 2019). The processes by which tumor-associated macrophages (TAMs) actively and directly contribute to the development, spread, and metastasis of tumors include (1) the release of proteolytic molecules, such as MMPs, to promote ECM remodeling; (2) the expression of nonproteolytic proteins, such as chemokines, TGF-1, and hCAP/LL-37, to promote tumor cell proliferation, migration, and invasiveness; (3) the expression of angiogenic mediators, such as TGF-, VEGF-A, VEGFC, platelet-derived growth factor (PDGF), and MMP-9, to maintain the growth of [54].

3.2 Macrophages in Neoangiogenesis

Neoangiogenesis, a crucial stage of carcinogenesis that also involves macrophage infiltration, is the capacity of cancer to develop a new vascular network to feed metabolic substrates to cancer cells. Different studies have suggested that TAMs are primarily located near the blood vessels of malignant solid tumors, and TAMs numbers are typically positively correlated with blood vessel density. This suggests that TAMs are primarily located near the blood vessels of malignant solid tumors due to the rapid proliferation of cancer cells, which results in an increased demand for nutrients and oxygen, which results in the fast growth of tumor mass. Growth factors released by cells in the TME control the development of new blood vessels. When this process is not properly controlled, abnormalities in the structure and function of newly formed vessels lead to increased vessel permeability, which speeds up the progression of disease. Rapid and unchecked cell proliferation results in the formation of hypoxic areas in tumor tissue, which are associated by a higher rate of cancer cell apoptosis. TAMs invade these hypoxic areas to restore homeostasis by stimulating the growth of new blood vessels. Research has also shown that TAM removal can reduce neoangiogenesis, while TAM enhancement can speed up this process [64,65]

4. REGULATORY MECHANISMS OF PHAGOCYTOSIS IN TUMOR CELLS

“Tumor-associated macrophages make up a sizable portion of the immune infiltration of most solid tumors (TAM). They can be supplied with the essential building blocks by blood monocytes recruited by chemokines like CCL2 or CSF-1 as well as tissue-resident macrophages. In the context of cancer, the tumor microenvironment (TME), which influences TAM performance and promotes a response analogous to wound healing, actively promotes tumor growth” [66].

The mechanisms that have been investigated and characterized the most include the synthesis of growth factors by TAM, stimulation of angiogenesis in tumors, and the development of an immunosuppressive or anti-inflammatory microenvironment. TAM release a variety of anti-inflammatory cytokines, such as Transforming Growth Factor (TGF) and Interleukin (IL)10, express a variety of immune checkpoint ligands, such as Programmed Death- Ligand 1 (PD- L1), and starve cytotoxic CD8 T cells by depleting essential amino acids by expressing arginase in order to achieve this. Moreover, TAM attract regulatory T cells (Treg) that take involvement in suppressing the antitumor immune response. (Valérie Dutoit, et al. 2020).

TAM's primary method of action is phagocytosis, which can inhibit the spread of tumors. Small particles can be endocytosed by the majority of eukaryotic cells, but only specialist phagocytes, including macrophages and DC, are able to phagocytose particles bigger than 0.5 m.

The "eat-me" and "don't eat-me" ligands expressed on the surface of tumor cells, such as calreticulin, SLAMF7, opsonizing antibodies, and phosphatidylserine (PtdSer), as well as CD47, PD-L1, and major histocompatibility complex (MHC), interact with TAM by binding to specific receptors on macrophages to regulate phagocytosis.

Chemicals known as "eat-me signals" are released from or made visible on a target cell and promptly trigger phagocyte phagocytosis. The bulk of eat-me signals, like phosphatidylserine, are anchored in the target cell membrane, although some soluble proteins linked to cell surfaces, such calreticulin, can be released and bind back to the target cell. Because they resemble opsonins in part, these could be called "self-opsonins". Tom O. J. Cockram and others, [67].

Don't eat me signals are released by the majority of cells in the body to ward off phagocytes from devouring them. Signals on or coming from target cells that deter phagocytosis are known as "don't-eat-me" signals. Certain soluble proteins, like calreticulin, which are linked to cell surfaces, can, however, be released and bind back to the target cell. Because they resemble opsonins in part, these could be called "self-opsonins". Don't eat me signals are released by the majority of cells in the body to ward off phagocytes from devouring them. Based on the balance between these several functional groups of chemicals exposed on cancer cells, phagocytosis is started. "Eat-me" signals encourage cell engulfment by causing phagocytes to rearrange their actin cytoskeleton if they are effective. (Guy C. Brown, et al. 2021).

5. MONOCLONAL ANTIBODIES AND TUMOR PHAGOCYTOSIS

“Monoclonal antibodies are now widely utilized in the treatment of a number of tumor types;

pertinent examples including trastuzumab (anti-Her-2) for the treatment of breast cancer, rituximab (anti-CD20) for the treatment of lymphoma, and the recently approved immunoconjugate T-DM1, which fuses trastuzumab to a highly potent chemotherapy, emtansine (DM1 [deacetyl maytansine]) to facilitate local delivery and minimize systemic toxicity" [68].

The use of antibody-based immunotherapeutics as targeted treatments is supported by the Fc region of antibodies' capacity to interact with host immune system components and the varied and nanomolar level affinity of the Fv region of the antibody for its target.

Unconjugated monoclonal antibodies' mechanisms of action include blocking a pro-survival signal and facilitating tumor cell lysis by binding to the Fc portion of natural killer (NK) cells' Fc Receptors. This enhances NK cells' capacity to lyse their targets through a process known as antigen-dependent cytotoxicity (ADCC).

"Complement-dependent cytotoxicity is a process in which monoclonal antibodies attach to complement receptors on effector cells and cause cytotoxicity (CDCC). Monoclonal antibodies of the human IgG4 isotype largely serve as "blocks" because the immunological mechanisms that are induced are heavily influenced by the Fc component of a monoclonal antibody. While higher antibody affinities result in increased target engagement and ADCC, they can also lead to decreased tumor penetration and compromised efficacy" [69-71]. A substantial corpus of clinical research demonstrates the growing importance of antibody-based cancer therapy. For instance, Yul et al showed that there was an 11% absolute benefit in the 2 year survival in patients with advanced neuroblastoma who were treated with a combination of IL-2, GM-CSF, and an antibody targeting GD2 (disialoganglioside 2) (P = 0.02).

As a result, many researchers are becoming more and more interested in conjugating monoclonal antibodies to either a cytotoxic agent, such as trastuzumab emtansine (anti-HER2-DM1) for breast cancer or glembatumumab vedotin (anti-GPNMB-MMAE) for breast cancer [68,72,73]. Moreover, T cells can be modified to express chimeric (antibody-based) antigen receptors (CARs), which allows the lethal cytotoxic lymphocyte killing apparatus to be directed directly at the tumor antigen [74]. Several antigens, including as CEA, CAIX, EGFR, HER2, and CD19 and CD20, have been targeted by CAR transformed T cells, but major adverse effects have been noted [75,76]. A CAR that targets CD19 was recently demonstrated to be able to generate a significant clinical response in a patient with chronic lymphocytic leukemia by Porter et al. [75]. "Another extremely intriguing use of monoclonal antibody technology is the production of bi-specific antibodies, where one arm is specific for a tumor antigen and the other arm bears specificity for the CD3 complex on T cells. The idea behind this method is to physically co-localize lymphocytes with tumors in order to stimulate anti-tumor T cell responses. In Phase I-II investigations, bi-specific antibodies against CD19 (blinatumomab) have demonstrated promise" [77,78].

6. CONCLUSION AND AVENUE FOR FURTHER RESEARCH

After lymphodepletion, adoptive cell therapy (ACT) has become a promising development in cancer immunotherapy.

We now have a better knowledge of the mechanisms underlying effective immunotherapies, and the best T cell populations have been identified thanks to new information from preclinical and clinical research. Also, the target population that might gain from ACT-based immunotherapies has grown thanks to gene engineering.

Significantly, ACT-based therapies are only offered in a few places throughout the world and are not FDA-approved. The expensive cost of these therapies, as well as the need for specialized cell-production facilities and highly skilled laboratory and medical staff, is a major drawback. Yet, despite these restrictions, progress has been made in bringing customized cell therapies into the clinic (including advancements in cell isolation and culture procedures), which has stimulated the development of numerous new experimental treatments. It is conceivable that blood banks may manufacture tumor-specific T cells for use in medical settings or that a central facility could be used to mass create autologous or even allogeneic cells, possibly by a for-profit organization [79,80].

It will be crucial to investigate strategies for enhancing immune ablation in the future.

Randomized studies to compare high-intensity lymphodepleting regimens are now being conducted, despite pilot studies suggesting that total-body radiation can boost the effectiveness of ACT-based therapy (see ClinicalTrials.gov; study identifier NCT01319565).

The identification of patient-specific tumor antigens may soon change cancer immunotherapy thanks to inexpensive and common DNA sequencing techniques.

Last but not least, there is a compelling case for combining ACT-based therapy with other cancer treatments [81]. Research on mice have demonstrated that acute T cell activation can increase those cells' anticancer effectiveness [82] By giving a vaccine together with the transferred cells in vivo, this can be achieved [83]. During "oncogene withdrawal," tumor cell death may offer the antigenic stimulation that might activate T lymphocytes [84,85]. Removing oncogenes may also lessen tumor cells' production of immunosuppressive cytokines [86].

Using targeted drugs may alter the ratio of pro- and anti-apoptotic chemicals in tumor cells, leading to a bias for these cells to die when they come into contact with T cells that are specifically designed to attack the tumor or its metabolites. Vemurafenib, a small-molecule inhibitor of the RAF-MEK-ERK signaling pathway, has also been demonstrated to increase the expression of tumor-associated antigens on melanomas, facilitating T cell-mediated tumor detection [87,88].

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/97161