Minireview Article

A Review on Tumor Immunology

ABSTRACT

The human immune system is able to distinguish between self and non-self proteins enabling it to take out unrecognized proteins and infected tissues.
The prospects for cancer immunotherapy are based mainly on the assumption that cancer cells expressed specific antigens recognized by T-lymphocytes, as these cells have been shown to mediate tumor rejection in animal model. The ability of T cells to recognize tumor surface antigen and their subsequent migration to the tumor can be assumed to be the main factors that influence reactivity to immune checkpoint inhibitors. Tumor associated Macrophages stimulates neoangiogenesis, a critical step in carcinogenesis.
A large body of clinical evidence highlights the increasingly prominent role of antibody-based therapy in cancer.
Adoptive Cell Therapy after lymphodepletion has also emerged as a promising advance in cancer immunotherapy.

Keywords: Immunotherapy, Tumor, Antigen, Evasion, Immunoglobulin, Macrophages, Metastasis, Adoptive Cell Therapy, Monoclonal Antibodies

INTRODUCTION

The ability of the immune system to distinguish self proteins from non-self proteins enables it to attack and destroy foreign non-self proteins and infected tissues. This forms the core of anti-microbial responses. This immunoediting theory suggests that the immune system is able to recognize and eradicate subclinical tumors but at some point equilibrium is reached and the tumor remains in situ, in a state of balance with a partially efficacious response (Dunn et al., 2002). However, cancer sometimes becomes clinically apparent because several tumors escape from this state of equilibrium. Deeper insights to the unraveling of mechanisms that enables cancerous cells to evade the immune system can prove useful in facilitating therapeutic interventions at critical points that would elicit the anti-tumor immune response.
These interventions which can be broadly referred to as "immunotherapy" could come as cancer vaccines, monoclonal antibodies, cytokine therapy etcetera. However, for the purpose of this

review, we would focus on monoclonal antibodies which can be administered to block certain immune checkpoints.

TUMOR IMMUNOLOGY

The characterization of the molecular structure of tumor antigens has enhanced understanding of the genetic episodes which result in tumor-specific antigens. In particular, tumor-specific antigens may be encoded by a primary open reading frame of gene products that are differentially expressed by tumors and not by normal tissues (Zarour et al., 2003). This may also be encoded by mutated genes, intronic sequences, or translated alternative open reading frames, pseudo-genes, antisense strands or represent the products of gene translocation events (Wolfel et al., 1995). The prospects for cancer immunotherapy are based mainly on the assumption that cancer cells expressed specific antigens recognized by T-lymphocytes, as these cells have been shown to mediate tumor rejection in animal models (Greenberg 1991). Autologous anti-tumor cytolytic T-lymphocytes (CTL) for human melanoma can be obtained when blood lymphocytes of the tumor bearing patients are co-cultivated with irradiated tumor cells (Boon et al., 1994). High activity and specificity anti-tumor CTL clones have demonstrated that melanoma cells express multiple antigen (Lehman et al., 1995, Wölfel et al., 1993). Tumor antigens are proteins with abnormal structures which are synthesized in tumor cells as a result of mutation. They are important markers for tumor cell diagnosis and potential targets in cancer therapy. The first human tumour-associated antigen gene to be defined at the sequence level was melanoma-associated antigen 1 (MAGEA1), which encoded the antigen MZ2E (van DER Bruggen et al., 1991). Ever since, several other tumor specific antigens which are processed naturally and presented on the surfaces of tumor cells have been identified and are listed in the Cancer Immunity Peptide Database.

2.1 Effective Mechanisms in Anti-tumor Immunity

Clinical successes have been achieved with engineered chimeric and harmonized antibodies in tumor immunotherapy (Vaughan and Osbourn 1998, Hooliger and Hoogenboom 1998) has elicited interest in the functions of immune effectors which are recruited by different subclasses and isotopes of antibodies. Antibody cytotoxic effect which is mediated by the interaction between complement proteins and their constant (Fc) regions and also with immunoglobulin (FcR) receptors present on the surface of various types of immune effector cells. Fc receptors are a family of cell surface molecules which can elicit intracellular signals after binding with antigen-antibody complexes. Three classes of leukocytes FcR for IgG, Fc-RI (CD64), Fc-RII (CD32) and Fc-RIII (CD16), have been identified, encompassing 12 receptor isoform (Heijnen and van de Winkel 1997, van de Winkel and Chapel 1993). FcγRI is expressed on monocytes and dendritic cells in peripheral blood and can be induced on Polymorphonuclear cells (PMNs) by interferon- or Granulocyte Colony Stimulating Factor (G-CSF) (Guyre et al., 1983).

FcγRII being constitutively present on platelets, monocytes, dendritic cells, B cells, eosinophils, neutrophils and basophils, shows the broadest cell distribution. FcγRII is found as a trans-membrane molecule (FcγRIIIa) on monocytes/macrophages and also on natural killer cells. It is also present on Polymorphonuclear (PMNs) cells as a glycosylphosphatidylinositol-linked protein (FcγRIIIb). The ability of immunoglobulin molecules to activate immune effector functions is further influenced by binding to the inhibitory Fc receptor FcγRIIb expressed on macrophages, B cells and basophils (Hulett and Hogarth 1994). The FcγRIIb molecules bear a unique IT I'M signaling motif in their cytoplasmic tails (Amigorena et al., 1992) whose phosphorylation leads to the recruitment of down-regulating type phosphatases, activation of receptor clusters SH2 domain containing protein tyrosine phosphatase and SH2 domain-containing inositol phosphatase (Ono et al., 1996, D'Ambrioso et al., 1995, Dαeron et al., 1995).
Like Fc-RI, cross-linking of FcαRI results in ADCC, phagocytosis, endocytosis, induction of respiratory burst and release of inflammatory mediators and cytokines (Morton et al., 1996, Shen 1992).
Comparison of the distribution of FcγR and FcαR on cytotoxic and non-cytotoxic cell types suggests a more favorable distribution for therapeutic effect of the latter. FcαRI expression primarily is limited to immune effector cells that demonstrate cytotoxic activities, whereas FcγR receptors are also expressed on non-cytotoxic cells (B lymphocytes, platelets) or on effector cells that do not efficiently trigger cytotoxic function (for example, FcγRIIIb on PMNs). Experiments with bi-specific antibodies recognizing FcαRI on effector cells and antigens on tumor cells have demonstrated that in vitro, FcαRI effectively mediated ADCC by PMNs and isolated monocytes (Valerius et al.z 1997, DEO et al., 1998). Several in vivo studies have suggested an active role for PMNs in the immune-surveillance against malignant tumors (Collombo et al., 1991, Midorikawa et al., 1990). To achieve efficient PMN-mediated killing through Fc-RI, the PMNs must be pre-activated with cytokines (D'Qmbrioso et al., 1995, Valerius et al., 1993) whereas a functional FcαRI is constitutively expressed by PMNs.

2.2 Mechanisms of Tumor Evasion of the Immune System

Tumors generally can be divided into two - Cold tumors and Hot tumors. Cold tumors are tumors that do not have the likelihood of triggering a strong immune response. They tend to be surrounded by cells that are able to suppress the immune response and prevent T cells from attacking the tumor cells and killing them. They do not usually respond to immunotherapy. Examples include most breast cancers, prostate, ovarian and pancreatic cancers. On the other hand, hot cancers have a high chance of triggering a strong immune response because they have many molecules on their cell surfaces that allow T cells to attack and kill tumor cells. Examples include cancers of the bladder, kidney, liver, head and neck.

The early stages of the cancer-immune cycle being the successful recognition and activation of antigen by T cells, alongside the more distal infiltration of T cells into the tumor are very important conditions for "hot tumors".
This type of immune infiltration is usually characterized by reactivity to immune checkpoint inhibitors. “Cold” tumors in contrast which are characterized by immune non-infiltration, reflect a defect in the initial stage of the cancer-immune cycle, and consequently most cold tumors do not respond to immune checkpoint inhibitors. Therefore, the ability of T cells to recognize tumor surface antigen and their subsequent migration to the tumor can be assumed to be the main factors that influence reactivity to immune checkpoint inhibitors

2.2a First step of evasion:

Lowering of tumor immunogenicity: During tumor formation, immune-surveillance removes cancer clones that express strong immunogenic neoantigens. At this point, the tumor evades anti-cancer immune responses by eliminating immunogenic antigens or maintaining cancer clones without cancer antigens so that they are not recognized by T cells. In other words, cancer clones that evade immune-surveillance have fewer immunogenic antigens (Dunn et al., 2004; Coulie et al., 2014; Kim and Chen, 2016).

2.2b Second step of evasion

Blockage of dendritic cell maturation:
Damage-associated molecular patterns, such as ATP and high-mobility group box 1 (HMGB1) (Zhu et al., 2009), released from dead cancer cells can induce DC maturation. Cancer inhibits DC maturation through tumor derived-factors such as IL-10 (Williams et al., 2004), macrophage colony-stimulating factor (MCSF) (Nefedova et al., 2004), vascular endothelial growth factor (VEGF) (Gabrilovich et al., 1996), prostaglandin (Sá-Nunes et al., 2007), TGF-β (Zong et al., 2016), and indoleamine 2,3-dioxygenase (IDO) (Munn and Mellor, 2016). In addition, immunosuppressive cells in the TME, such as Treg and myeloid-derived suppressor cells (MDSCs) express inhibitory factors that suppress DC maturation, reducing the expression of MHC and co-stimulatory factors in DCs, resulting in reduced production of inflammatory cytokines, such as IL-12, and ultimately inhibiting the proliferation of T cells and IFN-γ (Dunn et al., 2004; Hwang et al., 2005; Novitskiy et al., 2008; Steinman, 2012; Lindau et al., 2013; Kim and Chen, 2016; Li et al., 2020).

2.2c Third step of evasion

Impairment of T cell activity:
For full activation of T cells, both antigen recognition and co-stimulatory signals are required. Co-stimulatory interactions between DC and T cells include B7.1/B7.2:CD28, 4-1BBL:4-1BB,

OX40L:OX40, CD70:CD27, and GITRL:GITR. These co-stimulatory interactions promote proliferation, differentiation, survival, cytotoxic function, memory formation, and cytokine generation of T cells. Tumors inhibit the activity of T cells by reducing the expression of co-stimulatory factors and MHC, limiting the co-stimulation required for T cells. When the TCR is activated without co-stimulation, excessive activity of calcium/nuclear factor of activated T-cell (NFAT) signals induces the expression of negative modulating factors and T cells become unresponsive (T cell anergy) (Gimmi et al., 1993; Macián et al., 2002; Williams et al., 2006; Chen and Flies, 2013).

2.2d Fourth step of evasion

Suppression of the migration and infiltration of T cells:

Cells express chemokine receptors such as CXCR3 on the cell surface in response to IFN-γ during the activation process (Kuo et al., 2018). As a major evasion mechanism at this stage, cancer cells reduce the expression of CXCR3 ligands such as CXCL9, CXCL10, and CXCL11, and/or carry out posttranslational modification or decomposition of CXCR3 ligands, thereby inhibiting the migration of CD8+ T cells to the tumor (Karin, 2020). These fragments of cleaved CXCR3 ligands may also act as antagonists of the receptor. As another mechanism for inhibiting the migration of T cells, tumors transform nearby blood vessels. Tumors produce neoplastic factors such as VEGF, reducing the expression of adherent factors in endothelial cells (ECs), which are important for the migration of T cells (Gupta and Qin, 2003; Zarychta and Ruszkowska-Ciastek, 2022). In addition, IL-10 and prostaglandin E2, which are immunosuppressive factors, are produced and promote Fas ligand expression along with VEGF, thereby inducing apoptosis of CD8+ T cells infiltrating the tumor (Motz et al., 2014; Lee et al., 2020b). Moreover, the endothelin-B receptor expression of tumor ECs is increased to inhibit the migration of T cells (Motz et al., 2014; Slaney et al., 2014; Joyce and Fearon, 2015; Mikucki et al., 2015). However, even if CD8+ T cells move toward tumor tissue, they may not be able to infiltrate the center of the tumor. This is because immunosuppressive immune cells and cancer-associated fibroblast (CAF) around the tumor produce extracellular matrix (ECM) proteins to physically suppress T cells or produce chemokines such as CXCL12, inhibiting the migration of T cells to tumors. 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 (Salmon et al., 2012; Turley et al., 2015).

2.2e Fifth step of evasion

Immune cells' antigen recognition inhibition:

Cancer cells remove, reduce, or transform MHC-I on the surface of cancer cells as a mechanism to evade recognition by T cells. Cancer cells directly regulate MHC-I genes or proteins or

indirectly inhibit peptide-MHC components (Dhatchinamoorthy et al., 2021). In addition, cancer cells down regulate the expression of antigens, proteasome components, TAP1/TAP2, MHC-I, and β2-microglobulin through mutation, genetic loss, transcription inhibition, or epigenetic inhibition of gene expression (Taylor and Balko, 2022). Recent cancer genome studies have confirmed that the reduction of peptide-MHC-I expression on the surface of cancer cells due to somatic mutations in human leukocyte antigen (Campoli and Ferrone, 2008; Lawrence et al., 2013). Even if cancer cells can evade recognition by T cells through reduced MHC-I expression, NK cells cannot be evaded. This is because NK cells can induce an immune response to abnormal cells by recognizing the degree of MHC-I expression on the cell surface. As an alternative to this, cancer cells release ligands to NKG2D, an active receptor of NK cells, to evade lysis by NK cells (Ljunggren and Kärre, 1990; Groh et al., 2002; Terry et al., 2019; Hu et al., 2020).

2.2f Sixth step of evasion

Expression of immune checkpoint molecules:
The CD8+ T cells that infiltrate a tumor can simultaneously express several additional co-inhibitory receptors in addition to PD-1, including B and T lymphocyte attenuator (BTLA), lymphocyte activation gene 3 protein (LAG-3), T-cell immunoglobulin domain, mucin domain-3 (TIM3), T-cell immunoglobulin, and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT). Other co-inhibitory receptors are expressed simultaneously, and T cells become exhausted T cells (Tex) that are unresponsive to immune checkpoint inhibitors.

2.2g Seventh step of evasion

Role of immunosuppressing cells:
Immunosuppressive cells in the TME are also an important mechanism of immune evasion. The TME induces macrophages to differentiate into M2-type tumor-associated macrophages that promote tumor formation, and tumor-associated macrophages generate IL-10 instead of IL-12 to inhibit the CD8+ T cell response. Tumor-associated macrophages directly inhibit immune checkpoint inhibitor responses by removing anti-PD-1 antibodies from PD-1+ CD8+ T cells in an FcγR-dependent manner (Garris et al., 2018; Chen et al., 2019). MDSCs are a group of heterogeneous cells that can strongly inhibit the Teff response and induce Treg. MDSCs inhibit the immune response by generating arginase, inducible nitric oxide synthase (iNOS), and TGF-β. In particular, TGF-β inhibits the cytotoxic activity of cytotoxic T cells and NK cells by reducing the expression of cytotoxic factors such as perforin and granzyme. Treg cells are among the immunosuppressive cells of the TME; when their number increases, they are known to inhibit the CD8+ T cell response and promote tumor progression. A high Treg frequency is generally associated with a poor prognosis. For example, strong anti-cancer immune responses have been reported in Treg-deficient mouse models, and these results suggest that Treg cells play an

important role in inhibiting anti-cancer immunity (Han et al., 2019; Verma et al., 2019). IDO, an immunosuppressive enzyme expressed in myeloid cells and various cancer cells, induces kynurenine, which is a tryptophan metabolite that exerts immunosuppressive actions. This is known to strongly suppress Teff function while promoting the generation and activity of Treg and MDSCs. Another immunosuppressive enzyme, arginase 1, inhibits the function of DCs through cooperation with the IDO mechanism. Other metabolites (e.g., glucose consumption, lactate generation, cholesterol metabolism) and inflammatory mechanisms (e.g., cyclooxygenase-2/prostaglandin E2) are also known to affect cancer cells and immune cells (Rodriguez et al., 2004; Ohta et al., 2006; Kalinski, 2012; Munn and Mellor, 2013).

3. BIOLOGY OF MACROPHAGE-TUMOR INTERACTION

Macrophages can be defined as heterogeneous population of innate myeloid cells which originate from monocytic precursors that are resident in all tissues, they can undergo specific differentiation/polarization in the blood or within tissues and have multiple roles and often different names such as (microglia, Kupffer cells, and so on) based on their locations. (Sainz, B. J., et al 2016: Cell press current biology 2020). Macrophages originate from two sources: blood monocytes derived from the bone marrow (MDMs, monocyte-derived macrophages) or tissue-resident macrophages (TRMs) arising from dedicated yolk sac progenitors. These tissue-resident macrophages originate from at least three embryonic sources: erythro-myeloid progenitors (EMPs) in the yolk sac and in the fetal liver, and macrophage/dendritic cell progenitor cells (MDPs) in the bone marrow that give rise to monocytes. (Cell press current biology 2020: Cell press review). Macrophages are known to self-replicate and their origins can be changed through life by the recruitment of bone-marrow-derived macrophages replacing those of yolk sac origin, macrophages are also known to accumulate mainly in poorly vascularized, hypoxic areas as a result of specific up-regulation of various chemo attractants. Once macrophages arrive at the tumor site, they start to produce their own set of proteins to attract more leukocytes and to influence the process of angiogenesis. (Anita E. M. et al 2006).

Macrophages are innate immune cells and play a myriad of important roles such as host defense, tissue homeostasis, and modulating inflammatory responses (Wynn et al., 2013, Okabe and Medzhitov 2016). To perform these functions, immature macrophages with high plasticity respond to micro environmental cues, causing them to adopt a spectrum of effector function, among which M1-like and M2-like represent extreme polarization states (Gordon and Taylor 2005,Mantovani et al., 2002,Xue et al.,2014). 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 (Chavez-Galan et al., 2015, Kapellos et al.,2019,Haloul et al.,2019). Due to their inflammatory behavior, anti-tumor macrophages are commonly called M1 macrophages. These macrophages can be potent effector cells that kill tumor cells and can recruit cytotoxic T lymphocytes (CTLs) to activate adaptive immune responses. On the opposite side of the macrophage polarization spectrum, alternatively activated M2 macrophages secrete anti-inflammatory cytokines to induce immune tolerance and attract T regulatory cells (Tregs) and Th2 T cell subsets capable of protective type 2 responses but devoid of cytotoxic functions. M2 macrophages facilitate canonical tissue repair

functions and in cancer are regarded as pro-tumor where they promote tissue remodeling and repair, stimulate angiogenesis with vascular endothelial growth factor (VEGF), and encourage tissue growth with transforming growth factor beta (TGF-β) (Jayasingam et al., 2019). Therefore, for simplicity, tumor-associated macrophages (TAMs) have been described as either M1-like (anti-tumor) or M2-like (pro-tumor), but it should be recognized that the M1/M2 dichotomy represents idealized polarization states, while in nature, there exists a broad spectrum of macrophage phenotypes.

3.1 Macrophages and Tumor Metastasis: Tumor metastasis is a major contributor to the death of cancer patients, with metastasis being a process whereby tumor cells escape from the primary sites, spreading through lymphatic and/or blood circulations and ultimately disseminating to the distant sites. (Lin, Y. et al 2019). TAMs participate actively and directly in tumor initiation, progression, and metastasis via several mechanisms such as (1) the secretion of proteolytic molecules such as MMPs to facilitate ECM remodeling, (2) the expression of nonproteolytic proteins like chemokines, TGF-β1, and hCAP/LL-37 to facilitate tumor cell proliferation, migration, and invasiveness, (3) the expression of angiogenic mediators such as TGF-β, VEGF-A, VEGFC, platelet-derived growth factor (PDGF), and MMP-9 to sustain the growth of the tumor stroma and promote *de novo* tumor blood vessel formation, or (4) the expression of immunosuppressive factors including TGF- β, inducible nitric oxide synthase (iNOS), arginase-1, IDO (indoleamine 2,3-dioxygenase), and IL-10 to facilitate T-cell proliferation and activity. (Sainz, B. J., et al 2016)

3.2 Macrophages in Neoangiogenesis: Neoangiogenesis is the ability of cancer to generate a new vascular network to supply metabolic substrates to cancer cells and it considered as a critical step during carcinogenesis, in which macrophage infiltration is also involved. Due to the rapid proliferation of cancer cells, there is an increased demand for nutrients and oxygen which results in the fast growth of tumor mass, essential nutrients are delivered to the tumor by a capillary network formed in the process of neoangiogenesis, different studies have suggested that TAMs are predominantly sited near the blood vessels of malignant solid tumors, and TAMs numbers are usually positively correlated with blood vessel density. The formation of new vessels is regulated by the growth factors released by cells in the TME, because of poor regulation, the structure and function of newly formed vessels are abnormal with increased vessel permeability, which enhances the disease progression. Hypoxic regions of tumor tissue are formed due to the rapid and uncontrolled cell growth and are accompanied by an increased rate of cancer cell death. TAMs infiltrate these hypoxic regions to regain homeostasis through stimulation of new blood vessel formation, studies have also demonstrated that TAMs elimination can cause the reduction of neoangiogenesis, while TAMs enhancement can aggravate this process. (Wang, N., et al 2021: Cendrowicz, E., 2021)

3.3 Recruitment of Monocytes and Macrophages to Breast Tumors

TAMs represent a significant component of the inflammatory infiltrate in breast tumors (O'Sullivan and Lewis 1994, De Palma and Lewis, 2013). Tumor-derived growth factors such as chemokines and cytokines facilitate recruitment of monocytes and macrophages into tumors (Leek and Harris, 2002). One of the best-characterized cytokines responsible for recruiting TAMs into the tumor is chemokine (C-C motif) ligand 2 (CCL2), also known as monocyte chemoattractant protein 1 (MCP-1). CCL2 is expressed by both stromal cells and tumor cells (Ueno et al., 2000) and is associated with poor prognosis in breast cancer (Tsuyada et al., 2012, Goede et al., 1999). Through recruitment of CCR2-expressing monocytes, CCL2 has been shown to promote pulmonary metastasis in mouse models of breast cancer (Qian et al., 2011). Activation of the CCL2–CCR2 axis promotes CCL3 production from macrophages, enhancing metastatic seeding of breast cancer cells (Kitamura et al., 2015). CCL5, also known as Regulated upon Activation, Normal T Cell Expressed and Secreted (RANTES), is another well-known factor that recruits TAMs to the breast tumor. CCL5 is expressed by malignant epithelial cells in breast carcinoma and is associated with advanced disease progression (Luboshits et al., 1999, Soria G, Ben-Baruch et al., 2008, Bieche et al., 2004). Macrophages express high levels of its receptor (CCR5) and respond to CCL5 produced by tumor cells by infiltrating to the TME (An et al., 2019,Walens et al., 2019). Importantly, CCL5 has been reported to alter the functionality of TAMs toward a tumor-promoting phenotype in colorectal cancer (Halama et al.,2016)

4. REGULATORY MECHANISMS OF PHAGOCYTOSIS IN TUMOR CELLS

The immune infiltration of the majority of solid tumors contains a significant amount of tumor-associated macrophages (TAM). Both tissue-resident macrophages and blood monocytes drawn by chemokines like CCL2 or CSF-1 can provide them with the necessary building blocks. The tumor microenvironment (TME), which has an effect on TAM performance and encourages a response akin to wound healing, actively encourages tumor growth in the context of cancer. (Marc Lecoultre, et al 2020)

The growth factor production by TAMs, the encouragement of angiogenesis in tumors, and the formation of an immunosuppressive or anti-inflammatory microenvironment are the mechanisms that have been studied and characterized the most. In order to accomplish this, TAM release various anti-inflammatory cytokines, including as Transforming Growth Factor (TGF) and Interleukin (IL)10, express various immune checkpoint ligands, such as Programmed Death-Ligand 1 (PD- L1), and starve cytotoxic CD8 T cells by depleting essential amino acids through arginase expression. In addition, TAM recruit regulatory T cells (Treg) that participate in antitumor immune response inhibition. (Valérie Dutoit et all 2020)

TAM can slow the growth of cancer by phagocytosing tumor cells, which is a key mechanism. Most eukaryotic cells have the ability to endocytose tiny particles, but only specialized phagocytes, such as macrophages and DC, can phagocytose particles larger than 0.5 m.

The "eat-me" ligands (such as calreticulin, SLAMF7, opsonizing antibodies, and phosphatidylserine (PtdSer)) and "don't eat-me" ligands (such as CD47, PD-L1, and major

histocompatibility complex (MHC)) expressed on the surface of tumor cells interact with TAM by binding to particular receptors on macrophages to control phago

Eat-me signals are chemicals that are released from or exposed on a target cell to immediately cause phagocyte phagocytosis. The target cell membrane is where the majority of eat-me signals are anchored (such as phosphatidylserine), however, some soluble proteins attached to cell surfaces, such calreticulin, can be released and bind back to the target cell. These could be referred to as "self-opsonins" because they partially resemble opsonins. (Tom O. J. Cockram, et al 2021)

The vast majority of cells in the body emit don't-eat-me signals to deter phagocytes from devouring them. Don't-eat-me signals are signals on or emanating from target cells that prevent these cells from being phagocytosed. However, some soluble proteins attached to cell surfaces, such calreticulin, can be released and bind back to the target cell. These could be referred to as "self-opsonins" because they partially resemble opsonins.

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Phagocytosis is initiated based on the balance between these several functional groups of chemicals exposed on cancer cells. If "eat-me" signals are successful, they cause phagocytes to reorganize their actin cytoskeleton, which promotes cell engulfment. (Guy C. Brown, et al 2021)

Among the "don't eat me" ligands, CD47 suppresses myosin II conformational changes, which prevents the formation of phagosomes, by binding to its receptor signal- regulatory protein (SIRP) on macrophages. 22 By blocking CD47 or SIRP with antagonistic antibodies, tumor growth is inhibited in a variety of preclinical models, including those for glioblastoma, melanoma, lymphoma, breast, colorectal, and melanoma. 27 More than a dozen phase I clinical investigations are in progress as a result of these encouraging outcomes. 28 It is still unclear, though, whether TAM on their own can stop tumor growth or if T cells must also get involved.

5. CRISPR TECHNOLOGIES AND ROLE IN TUMOR IMMUNOLOGY

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) can be defined as a family of DNA sequences found in the genome of some prokaryotic organisms such as bacteria and archaea, these sequences are derived from DNA fragments of bacteriophages that had previously infected the prokaryote. Cas9 or CRISPR-associated protein 9 is an enzyme that has the ability to recognize and cleave specific strands of DNA that are complementary to the CRISPR sequence using the CRISPR sequences as a guide, Cas9 together with CRISPR sequence form the basis of a technology known as CRISPR-Cas9 that can be used to effectively edit targeted genes within organisms. (Redman, M., et al 2016). The first component is the single-effector Cas9 protein which is an enzyme which acts as a molecular scissors to cut strands of DNA at specific locations, it contains the endonuclease domains RuvC and HNH. RuvC cleaves the DNA strand

non-complementary to the spacer sequence and HNH cleaves the complementary strand. Together, these domains generate double-stranded breaks (DSBs) in the target DNA. The second component of effective targeted gene editing is a single guide RNA (sgRNA) carrying a scaffold sequence which enables its anchoring to Cas9 and a 20-base pair spacer sequence complementary to the target gene and adjacent to the PAM sequence. This sgRNA guides the CRISPR/Cas9 complex to its intended genomic location. The editing system then relies on either of two endogenous DNA repair pathways: non-homologous end-joining (NHEJ) or homology-directed repair (HDR). NHEJ occurs much more frequently in most cell types and involves random insertion and deletion of base pairs, or indels, at the cut site. This error-prone mechanism usually results in frame-shift mutations, often creating a premature stop codon and/or a non-functional polypeptide. (Uddin, F., et al 2020)

6. 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. (Verma et al., 2012)

The ability of the Fc region of antibodies to engage components of the host immune system and the diverse and nano-molar level affinity of the Fv region of the antibody for their target are the basis of using antibody-based immunotherapeutics as specific treatment tools.

The mechanisms of action of unconjugated monoclonal antibodies include blocking a pro-survival signal, as well as facilitating tumor cell destruction by the binding of the Fc portion of the antibody to Fc Receptors on natural killer (NK) cells—promoting the ability of NK cells to lyse their targets through a process known as antigen-dependent cytotoxicity (ADCC).

Monoclonal antibodies can also mediate cytotoxicity by binding to complement receptors on effector cells, a process known as complement-dependent cytotoxicity (CDCC). The Fc portion of a monoclonal antibody plays a major role in determining the immune mechanisms induced, with monoclonal antibodies of the human IgG4 isotype primarily functioning as “blockers”. One interesting aspect involved in the development of monoclonal antibodies for the clinic involves their affinity, while higher antibody affinity results in increased target engagement and ADCC, higher affinities can also result in decreased tumor penetration and compromised efficacy [Fujimori et al.1990, Adams et al., 2001, Rudnick et al., 2011]. A large body of clinical evidence highlights the increasingly prominent role of antibody-based therapy in cancer. For example, in patients with advanced neuroblastoma who were treated with a combination of IL-2, GM-CSF, and an antibody targeting GD2 (disialoganglioside 2) ($P = 0.02$), Yul et al demonstrated that there was an 11% absolute benefit in the 2 year survival in such class of patients.

Consequently, many researchers are more increasingly developing interest in conjugating

monoclonal antibodies to either a cytotoxic agent, like brentuximab vedotin (anti-CD30-MMAE [monomethyl auristatin E]) for anaplastic large cell and Hodgkin lymphoma, trastuzumab emtansine (anti-HER2-DM1) for breast cancer, and glembatumumab vedotin (anti-GPNMB-MMAE) for breast cancer [Verma et al., 2012, Pro et al., 2012, Rose et al., 2010].

Besides, T cells can be re-engineered to express chimeric (antibody-based) antigen receptors (CARs) to target the powerful killing machinery of cytotoxic lymphocytes directly to tumor antigen [Sadelain et al., 2009]. CAR transformed T cells have been developed against a variety of antigens, including CEA, CAIX, EGFR, HER2, CD19, and CD20, but serious adverse events have been reported [Porter et al., 2011, Morgan et al., 2010]. In an interesting research work recently done by Porter et al., they showed that a CAR specific for CD19 could mediate a major clinical response in a patient with chronic lymphocytic leukemia [Porter et al., 2011]. In addition ,the engineering of bi-specific antibodies, in which one arm is for a tumor antigen and the other arm carries specificity for the CD3 complex on T cells, is another very interesting application of monoclonal antibody technology. The working principle behind this technology is to induce anti-tumor T cell responses by co-locallizing lymphocytes to tumors physically. Bi-specific antibodies against CD19 (blinatumomab) have shown promise in Phase I-II studies
[Bargou et al., 2008,Topp et al., 2012]

7. AVENUE FOR FURTHER RESEARCH

Adoptive Cell Therapy (ACT) after lymphodepletion has emerged as a promising advance in cancer immunotherapy.

Emerging data from preclinical and clinical studies have increased our understanding of the mechanisms that underlie successful immunotherapies and have helped us to identify the most effective T cell populations. In addition, gene engineering has expanded the potential target population that could benefit from ACT-based immunotherapies.

Importantly, ACT-based therapies are not FDA-approved and are only available in a limited number of locations worldwide. A major limitation of these therapies is their expense, and the treatments require specialized cell-production facilities and highly trained laboratory and medical staff. However, despite these limitations, there have been improvements in translating personalized cell therapies into the clinic (including advances in cell isolation and culture techniques), which have led to a proliferation of new experimental therapies. It seems plausible that blood banks could grow tumour-specific T cells for use in the clinic, or that autologous or even allogeneic cells could be mass-produced in a central facility, perhaps by a commercial enterprise (Boni et al., 2008, Restifo & Bachinski 2011)

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In the future, it will be important to explore methods for improving immune ablation.

Although pilot trials have suggested that total-body irradiation can improve the efficacy of ACT-based therapies, randomized trials to compare high-intensity lymphodepleting regimens are currently underway (see ClinicalTrials.gov; study identifier NCT01319565).

Inexpensive and routine DNA sequencing techniques may soon revolutionize cancer immunotherapy by enabling the identification of patient-specific tumour antigens.

Finally, there is a strong rationale for using other cancer therapies in combination with ACT-based therapy (Blank et al., 2011). Studies in mice have shown that acute activation of T cells can augment their antitumour efficacy (Klebanoff et al.,2009). This can be accomplished in vivo by administering a vaccine together with the transferred cells (Overwijk et al.,2003). Tumour cell death after 'oncogene withdrawal' may provide the antigenic stimulation that can drive T cells (Restifo, 2010, Rakhra et al., 2010). Oncogene withdrawal may also reduce the production of immunosuppressive cytokines by tumour cells (Sumitomo et al., 2006). The use of targeted agents might change the balance of pro- and anti-apoptotic molecules in tumour cells to bias these cells towards death following encounter with tumourspecific T cells or their toxic metabolites. In addition, it has been shown that the administration of vemurafenib (a small-molecule inhibitor of the RAF–MEK–ERK signalling pathway) can lead to the upregulation of tumour-associated antigens on melanomas, thereby promoting T cell-mediated recognition of the tumour (Boni et al., 2010).

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