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Cancer Therapeutic Antibodies

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Abstract

Cancer consistently ranks among the top causes of death worldwide. Traditional therapies include surgery, chemotherapy, and radiation. However, many patients either do not respond to or develop specific treatment resistance. Given the advent of genome, transcriptome, and proteome technologies, personalized medicine has gained tremendous recognition as a therapeutic field. Antibodies are Y-shaped proteins produced by activated B immune cells, featuring two substrate recognition sites. They identify and bind to invading pathogens, such as bacteria, viruses, and toxins to help prevent and eliminate infections. The concept and potential of therapeutic monoclonal antibodies (mAbs) in cancer was put forth by Paul Ehrlich over a century ago. A breakthrough by Köhler and Milstein (Cambridge, 1975) followed the development of hybridoma technology, allowing mass production of specific antigen-induced mAbs. MAbs exert their effect through various mechanisms to combat malignancies. Depending on their design, mAbs bind to specific cognate cell-surface receptors to modulate (insert = cell) growth, apoptosis, and immune recognition. MAbs targeting various cancer types have received clinical approval. For instance, rituximab binds CD20 expressed on B cell non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL), leading to immune-mediated target cell destruction. A class of mAbs known as immune checkpoint inhibitors (ICIs), activate the body's natural immune response against tumor cells by blocking their suppression. Notable ICI include pembrolizumab and nivolumab, which specifically target the programmed cell death receptor-1 (PD-1). Unlike traditional therapies which often cause damage to healthy cells, mAbs are intrinsically target-specific, reducing or eliminating harmful side effects. As such, they have emerged to provide more effective and less toxic options for cancer patients.

Keywords: cancer; personalized medicine; therapeutic monoclonal antibodies; tumor microenvironment

Introduction

Cancer therapeutic monoclonal antibodies (mAbs) are "a type of targeted (drug) therapy that recognize and bind specific antigen epitopes (i.e., regions) on cancer cells," exerting their effect through diverse mechanisms to combat malignancies [1-3]. Following their binding, critical intracellular molecular signal transduction pathways within target cells are modulated to influence their growth, survival, and death. Simultaneously, immune cells can recognize the antigen-bound mAbs and trigger a second cascade of effector functions. Antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) are two fundamental mechanisms by which mAbs lead to tumor mass reduction or elimination [2-5].

The Tumor Microenvironment

The tumor microenvironment (TME) is a complex and dynamic ecosystem consisting of various cell types, signaling molecules, and extracellular matrix components (e.g., glycoproteins) that interact with cancer cells [6, 7]. The immune system plays a critical role within the TME, influencing tumor progression, immune evasion, and response to therapy. Key aspects of the immune system's role in the TME include immunosurveillance, immune cell infiltration, and cytokine signaling. Immunosurveillance is the active monitoring of bodily tissues for damaged or malignant cells, which may involve infiltration by an army of relevant immune cells to the site of damage/malignancy guided by various soluble small molecule cytokines.

T ($CD4^+$ helper and $CD8^+$ cytotoxic [i.e., cell toxic]), natural killer (NK), dendritic, and macrophage immune cells are primary immune system components entering the TME. The type, density, and spatial distribution of such tumor-infiltrating cells can significantly impact tumor growth and progression. For instance, a high density of $CD8^+$ cytotoxic T cells is known to be associated with higher overall survival in breast cancer patients [8]. Macrophages are phagocytic (cell-engulfing) immune cells often exhibiting both anti- (M1) and pro-tumorigenic (M2)

phenotypes depending on cancer stage and TME context, coined as the M1/M2 duality [9]. M1 macrophages prevent tumor proliferation and promote immune activation. In contrast, M2 macrophages promote proliferation, suppress immune response, and contribute to angiogenesis (blood vessel formation) that help sustain TME [10]. TME-engaged immune cells produce various cytokines (e.g., IFN-γ, TNF-α, IL-12) and chemokines that regulate their further recruitment, activation, and effector functions [11, 12].

On the other hand, a T cell subset known as regulatory T cells (Tregs) play crucial roles in promoting immune tolerance (i.e., unresponsiveness) and preventing autoimmunity (self-reactivity) [14, 15]. Defined by FoxP3 expression, Tregs suppress excessive immune responses by secreting anti-inflammatory cytokines IL-10 and TGF-β, and inhibiting effector T cell activation. Tregs dysfunction can lead to autoimmune disorders, while their modulation is being explored as a strategy to enhance anti-tumor immunity in cancer therapy.

Monoclonal Antibody Mechanisms of Action

ADCC is one mechanism of action (MOA) by which antibody-tagged cells (e.g., cancer cells) are destructed by NK, macrophage, or neutrophil immune cells [15]. ADCC MOA entails two identical Fab (fragment antigen-binding) domains on MAb that recognize and bind to target antigen expressed on cancer cell surface. Following, immune cell recognition of Fc (fragment crystallizable) domain on MAb results in immune cell effector function. These functions include cytotoxic granule release to induce cell death (e.g., by $CD8^+$ T and NK cells), chemokine secretion to recruit more or other immune cells (e.g., dendritic cells), or induction of tolerance via Treg recruitment. Granules released by activated NK and $CD8^+$ T cells contain perforin and granzyme, the former of which creates membrane pores allowing entry of the latter to cleave pro-apoptotic proteins in the targeted cell. In ADCP, the mAb Fc domain is recognized by macrophages, leading to its internalization and degradation in acidic vesicles [14-15]. As such, mAbs are designed to recognize and interact with abnormal, over-, or alternatively expressed antigens to achieve specific tumor targeting.

Antibody-drug conjugates (ADCs) comprise a mAb linked to a cytotoxic drug via a stable linker [16]. The mechanism involves mAb binding to specific tumor antigens, leading to receptor-mediated endocytosis (i.e., cellular internalization). Once inside the cell, the linker is cleaved—often by enzymatic action—releasing the cytotoxic drug, which disrupts critical processes like DNA replication or microtubule formation, depending on MOA of the specific compound. One example is mAb conjugation to Monomethyl auristatin E (MMAE), which disrupts microtubule assembly crucial for cell division, leading to cell cycle arrest or apoptosis.

Immune checkpoint inhibitors (ICI) are a class of mAb with clinical translation potential [17, 18]. They function by targeting key regulatory pathways that suppress T cell activity, thereby enhancing anti-tumor immunity. For example, pembrolizumab and nivolumab specifically inhibit the PD-1 receptor on T cells, preventing it from binding to PD-L1 expressed on tumor cells. This blockade effectively releases the "brakes" on the immune system, allowing T cells to proliferate, produce cytokines, and mount a vigorous attack against cancer cells. In contrast, ipilimumab targets CTLA-4, another checkpoint molecule that dampens T cell activation in lymph nodes. By blocking CTLA-4, this inhibitor promotes T cell activation and expansion, further amplifying the immune response. Ongoing research is focused on increasing our understanding of ICI mechanism and evaluating variable patient response in different tumor types.

Monoclonal Antibody Mechanisms in Cancer

In blood cancers (e.g., plasma-, red- and white blood cells) known as hematologic malignancies, mAbs far-ranging in mechanism have been developed [19, 20]. Rituximab mAb binds to CD20 antigen on B cell lymphoma and chronic lymphocytic leukemia (CLL) cells, leading to ADCC [21, 22]. Obinutuzumab mAb MOA is analogous to rituximab, with the added feature of enhanced ADCC and direct cell death induction [19, 22]. Brentuximab Vedotin ADC combines anti-CD30 mAb and MMAE via a linker, which delivers its cytotoxic payload upon binding to CD30-expressing lymphoma cells. Daratumumab mAb binds to CD38, a marker highly expressed on multiple myeloma (MM) cells, inducing ADCC and direct apoptosis. Elotuzumab targets CD319 (SLAMF7), an inhibitory ligand on myeloma cells, to enhance NK cell-mediated cytotoxicity.

In solid malignancies such as breast, colon, and lung cancer, mAbs with diverse mechanisms have also been developed [23]. For instance, trastuzumab mAb binds to human epidermal growth factor receptor 2 (HER2) on breast cancer cells, inhibiting downstream signaling pathways crucial for cell growth and survival [19]. Pertuzumab mAb binds to a different epitope on HER2 than trastuzumab, inhibiting its dimerization and downstream cell proliferation signaling [19, 24]. Bevacizumab mAb binds to vascular endothelial growth factor A (VEGF-A), preventing its interaction with VEGF receptors on endothelial cells, thereby inhibiting angiogenesis [19, 20]. Importantly, pembrolizumab and nivolumab ICI bind to PD-1 on T cells, restoring their ability to recognize and attack cancer cells [25].

Clinically Approved Monoclonal Antibodies

Cancer therapeutic mAbs are employed in various cancer types broadly divided into hematologic (e.g., NHL, CLL, MM) and solid tumors [19, 20]. NHL and CLL are clinically treated with rituximab (anti-CD20),

obinutuzumab (anti-CD20), and/or brentuximab vedotin (anti-CD30 ADC) mAbs [19]. MM is often treated with daratumumab (anti-CD38) and/or elotuzumab (anti-SLAMF7). Rituximab is currently approved for both first-line and relapsed/refractory settings in NHL and CLL [2, 19]. It is often used in combination with chemotherapy regimens and/or as maintenance therapy in follicular lymphoma (FL) [18]. Obinutuzumab is approved for CLL in combination with chemotherapy (e.g., chlorambucil) and as first-line treatment for FL [19, 26]. Brentuximab vedotin is approved for relapsed/refractory Hodgkin lymphoma and anaplastic large cell lymphoma [19]. For the treatment of MM, daratumumab is approved in combination with lenalidomide (an immunomodulatory drug) and dexamethasone (inflammation reducer) or bortezomib (protein degradation inhibitor) and dexamethasone for relapsed/refractory myeloma and as a single agent in heavily pretreated patients [19, 27]. Similarly, elotuzumab is approved in combination with lenalidomide and dexamethasone for relapsed/refractory myeloma [28].

For solid tumors, various biomolecules have been developed [19, 29]. The most common mAbs include trastuzumab (anti-HER2), pertuzumab (anti-HER2), and bevacizumab (Avastin) [19]. Trastuzumab is the standard-of-care in $HER2^+$ breast cancers, used in combination with chemotherapy (e.g., docetaxel; cell division inhibitor) or as part of dual $HER2^-$ targeted therapy (e.g., with pertuzumab) [30]. Pertuzumab is approved in combination with trastuzumab and chemotherapy (e.g., docetaxel) as the following treatment modalities in $HER2^+$ breast cancer: neoadjuvant (before main therapy), adjuvant (following main therapy), and metastatic (for advanced cancer). Bevacizumab, which inhibits angiogenesis, has been approved for use in combination with chemotherapy (e.g., paclitaxel) for the treatment of $HER2^-$ metastatic breast cancer. In some cases, bevacizumab has been used off-label in combination with chemotherapy for the treatment of triple-negative breast cancer (TNBC), which is negative for estrogen, progesterone, and HER2 receptors. The rationale behind using bevacizumab in TNBC lies in its ability to limit blood supply to the tumor, hence targeting TME to improve treatment outcomes. Bevacizumab has also been studied in clinical trials for use in neoadjuvant and adjuvant therapies in breast cancer. However, its use in these settings is less established compared to its role in metastatic disease.

Colorectal cancer is another common solid tumor treated with mAbs. Cetuximab (anti-EGFR) is approved in wild type-KRAS (healthy KRAS/cell proliferation signalling pathway) and metastatic colorectal cancer, often coupled with chemotherapy [19, 20, 31]. Bevacizumab (anti-VEGF) is approved in combination with chemotherapy for metastatic colorectal cancer and in combination with paclitaxel (microtubule inhibitor) for metastatic breast and non-small cell lung (NSCL) cancer [32]. In lung cancer, which frequently ranks as the most prevalent cancer type globally, pembrolizumab (anti-PD-1), nivolumab (anti-PD-1), and atezolizumab (anti-PD-L1) have been used in clinical practice [19, 25]. Pembrolizumab and nivolumab are approved for NSCL cancer, both as a monotherapy in $PD\text{-}L1^+$ tumors and in combination with chemotherapy.

Future Directions

The use of mAbs has revolutionized cancer treatment by improving efficacy and reducing side effects compared to traditional therapies [33, 34]. However, mAbs have several limitations. They can be costly to develop and manufacture, narrowing access to these therapies. MAbs are also relatively large biomolecules, limiting their penetration into solid tumors, and many require frequent dosing due to short half-lives. Patients may develop immune responses that reduce efficacy or cause allergic reactions, and tumor cells may develop resistance. These shortcomings need to be addressed and considered when considering mAbs as a treatment modality for cancer patients.

Efforts to improve cancer therapies are focusing on innovative strategies [35-37]. Novel conjugation methods, including cleavable linkers that respond to specific intracellular conditions, enhance precision and efficacy. For example, pH-sensitive linkers remain stable in the bloodstream but are cleaved in the acidic environment of tumor cells, releasing cytotoxic drugs precisely where needed. Additionally, bispecific antibodies can bind to two different antigens, recruiting immune cells to target tumors and reducing resistance in heterogeneous cancers. Nanobodies, derived from camelid antibodies, are small enough to penetrate tissues and reach previously inaccessible targets, allowing for rapid clearance and minimizing off-target effects. Together, these advancements significantly enhance specificity and reduce side effects in cancer treatment.

List of Abbreviations

ADCC: antibody-dependent cellular cytotoxicity
ADCP: antibody-dependent cellular phagocytosis
ADCs: antibody-drug conjugates
CLL: chronic lymphocytic leukemia
Fab: fragment antigen-binding
Fc: fragment crystallizable
ICI: immune checkpoint inhibitors
MAbs: monoclonal antibodies
MM: multiple myeloma cells
MMAE: monomethyl auristatin e
NHL: B cell non-Hodgkin lymphoma
NK: natural killer cells
NSCL: non-small cell lung cancer
PD-1: programmed cell death receptor-1
PD-L1: programmed cell death ligand-1
TME: tumor microenvironment
TNBC: triple-negative breast cancer
Tregs: regulatory T-cells

Conflicts of Interest
The author declares that they have no conflict of interest.

Authors' Contribution
ZS: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.

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