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Monoclonal Antibody-Based Cancer Therapy: From Mechanistic Insights to Clinical Practice

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Abstract. Monoclonal antibodies (mAbs) are a cornerstone of cancer therapy. They offer high target specificity and diverse cytotoxic mechanisms, which render them superior to many conventional cytotoxic treatments. This review examines therapeutic mAbs from two aspects. First, their mechanisms of action are analysed, including direct target modulation (signaling inhibition and ADC payload delivery), Fc-mediated effector functions (ADCP, ADCC, and CDC), and immune checkpoint blockade (CTLA-4, PD-1/PD-L1, LAG-3, and TIM-3 pathways). In addition, engineering strategies that potentiate these effects are considered as well, such as Fc modification and optimised linker-payload design for antibody-drug conjugates. Second, the clinical landscape of approved mAbs is reviewed. Their remarkable success in hematologic malignancies (anti-CD20, anti-CD33, anti-CD38) are compared with the greater challenges in solid tumors, where tumour heterogeneity, immunosuppressive microenvironments and primary resistance frequently limit therapeutic efficacy. In solid tumours, biomarker-driven agents (anti-HER2, anti-EGFR) and immune checkpoint inhibitors are central. Immune-related adverse events also represent an important safety concern for checkpoint-blocking antibodies. It is critical to understand these mechanisms and clinical outcomes before optimizing current therapies and guiding next-generation antibody development, including novel ADCs and bispecific antibodies.

Keywords: Monoclonal antibodies, Cancer therapy, Antibody–drug conjugates, Immune checkpoint inhibitors, Fc-mediated effector functions

1. Introduction

Monoclonal antibodies (mAbs) originate from clones of a single parent immune cell. They specifically target a single epitope of an antigen. The evolution of monoclonal antibodies has been a long-standing process, with the first murine mAbs produced by Milstein and Köhler (Cambridge University), who were awarded the Nobel Prize in Physiology or Medicine in 1984 [1]. However, antibodies produced via hybridoma technology are entirely of murine origin, which provokes severe human-anti-mouse-antibody (HAMA) responses in patients. These responses accelerate drug clearance and give rise to toxic adverse effects. The subsequent development of chimeric antibodies substantially mitigated HAMA reactions. Chimeric constructs retain murine variable regions for antigen recognition and binding, whereas the Fc domain that mediates in-vivo effector functions is substituted with a human IgG constant region. Even so, variable-region-derived murine sequences

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can still trigger human-anti-chimeric-antibody (HACA) responses. This limitation spurred the advent of humanized antibody technology, in which only the three pairs of mouse-derived complementarity-determining regions (CDRs) are preserved, with all remaining sequences of human origin. Humanized antibodies exhibit markedly lower HACA rates and support repeated drug administration; many agents targeting solid tumours and immune-checkpoint molecules belong to this category, such as the anti-HER2 agent trastuzumab and the PD-1-targeting pembrolizumab. In the 1990s, phage-display platforms and transgenic mouse models enabled the generation of fully-human antibodies [2]. Devoid of heterologous animal-derived sequences, such antibodies show minimal immunogenicity and have become the preferred option for modern-day new-drug development.

To date, conventional full-length therapeutic mAbs have gained global regulatory approval against diverse molecular targets for a broad spectrum of diseases [3], most commonly cancer. Monoclonal antibody-based targeted therapies can reduce cancer cells by multiple direct and indirect cytotoxic mechanisms. By providing the required specificity, monoclonal antibodies can effectively broaden the therapeutic window. Some antibodies can even distinguish antigens with subtle difference of a single amino-acid residue or post-translational modification [4]. They can destroy tumour cells while keeping minimise damage to normal tissues. They also demonstrated a marked improvement compared to conventional cancer treatments, such as chemotherapy and radiation therapy. This review discusses therapeutic monoclonal antibodies in the aspect of mechanisms of action and clinical applications in cancer therapy.

2. Mechanisms of action of therapeutic mAbs

Therapeutic monoclonal antibodies (mAbs) affect tumours through multiple complex and interrelated mechanisms. Three types can be summarized, i.e., direct modulation of target antigens, Fc-fragment-mediated immune effector functions, and blockade of immune checkpoints to reactivate anti-tumor immune responses. It is critical to understand these mechanisms for optimizing existing antibody therapies and developing next-generation drugs.

2.1. Direct target modulation

Direct binding of monoclonal antibodies to antigens on the surface of tumor cells affects direct target modulation. It will thus interfere with physiological functions or acting as carriers for the delivery of cytotoxic drugs.

Firstly, Signaling Inhibition means that monoclonal antibodies bind to growth factor receptors on the surface of tumor cells, competitively or via steric hindrance to block ligand-receptor binding, or inhibit receptor dimerization, thereby abrogating downstream oncogenic signaling and suppressing tumor-cell proliferation and survival, for instance, the antibody targeting human epidermal growth factor receptor 2 (HER2). HER2 is overexpressed in approximately 15-20% in the treatment of breast cancers. It acts as a key driver of tumour progression [5]. Trastuzumab (Herceptin) binds to subdomain IV of HER2, subsequently delaying its homodimerization. This action further suppresses the downstream PI3K/Akt signaling pathway. It also upregulates the cyclin-dependent kinase inhibitor p27. Ultimately, cell proliferation is inhibited [6]. Pertuzumab, another anti-HER2 antibody, binds to subdomain II of HER2. Through preventing heterodimerization between HER2 and other HER family members, such as HER3 via steric hindrance. It can achieve more comprehensive blockade of downstream signaling.

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In addition to HER2, epidermal growth factor receptor (EGFR) has become a well-established therapeutic target. Cetuximab, panitumumab and other anti-EGFR monoclonal antibodies interfere with ligand binding to EGFR. They can prevent downstream RAS-RAF-MEK-ERK and PI3K-AKT signaling. They can provide clinical benefits for patients diagnosed with colorectal cancer and head and neck squamous cell carcinoma [7]. However, unlike anti-HER2 antibodies, anti-EGFR antibodies primarily function via signal blockade. Because they target specifically the extracellular EGFR domain, mutations in downstream genes, such as KRAS, NRAS and BRAF give rise to primary drug resistance. This further shows that inhibition of signaling pathways is the core basis of their therapeutic efficacy.

Secondly, Antibody-drug conjugates (ADCs) combine the target specificity of antibodies with the potent cytotoxic potency of chemotherapeutic agents. Their mechanism includes: ADCs are bonded to target antigens on the surface of tumor cells. They are then internalized via receptor-mediated endocytosis. Subsequently, they are degraded within lysosomes, or cytotoxic payloads are released through cleavable linkers. This approach enables the accurate delivery of highly toxic drugs into tumor cells, thereby reducing systemic toxicity toward normal tissues. Three key components need to be optimized to meet the requirements of ADCs design. They are the antibody, the linker and the cytotoxic payload. The linker must remain stable during systemic circulation to prevent premature drug release. It can also enable efficient payload release once inside tumor cells. Most currently approved ADCs adopt cleavable linkers, such as peptide linkers and hydrazone linkers, or non-cleavable linkers [8]. The drug-to-antibody ratio (DAR) is one of the critical factors governing therapeutic efficacy. For instance, trastuzumab emtansine (T-DM1) with a DAR of approx. 3.5 conjugates the microtubule inhibitor DM1 to trastuzumab via a non-cleavable linker. In contrast, the next-generation ADC trastuzumab deruxtecan (T-DXd) employs a cleavable linker to attach the topoisomerase I inhibitor DXd. It features a markedly higher DAR of around 8.0. It has thus been regarded as a partial contributor to its superior therapeutic efficacy [9].

2.2. Fc-mediated effector functions

The fragment crystallizable (Fc) region of antibodies acts as a bridge connecting humoral immunity and cellular immunity. Following antibody binding to target cells, the Fc domain can be recognized by Fcγ receptors (FcγRs) on immune effector cells or trigger activation of the complement system, initiating potent antitumor immune responses mainly categorized into three pathways: Antibody-Dependent Cellular Phagocytosis (ADCP), Antibody-Dependent Cellular Cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (CDC). (Table 1) Due to its high affinity for activating FcγRs, the IgG1 subtype serves as the primary isotype responsible for mediating these effector functions.

Table 1. Three primary Fc-mediated effector functions of therapeutic monoclonal antibodies: a comparison

Feature	ADCP	ADCC	CDC
Definition	Phagocytes such as macrophages recognize and engulf antibody-coated tumor cells via Fcγ receptors.	NK cells recognize antibody-coated tumor cells via FcγRIIIa and release cytotoxic granules to eliminate target cells.	The complement system recognizes antibody-coated tumor cells via C1q and forms the membrane attack complex (MAC) to lyse target cells.

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Table 1. (continued)

Effector cell	Macrophages	NK cells	Complement proteins; no specific cells
Fc receptor/molecule	FcγRIIa (CD32a), FcγRI (CD64)	FcγRIIIa (CD16a)	C1q
Preferred IgG isotype	IgG1 > IgG3 > IgG4 > IgG2	IgG1 > IgG3 > IgG4 > IgG2	IgG1 > IgG3 >> IgG2, IgG4
Representative mAbs	Trastuzumab, Rituximab	Trastuzumab, Rituximab, Cetuximab	Rituximab, Daratumumab
Mechanism of killing	Target cells are degraded within lysosomes following phagocytosis.	Perforin and granzymes mediate apoptosis/lysis of target cells.	MAC triggers cell membrane lysis.
Enhancement strategies	Block CD47-SIRPα "don't eat me" signal; Fc engineering (point mutations: S239D/I332E) [10]	Afucosylation; Fc point mutation engineering [10]	Induce antibody hexamerization to boost C1q binding; combination of distinct antibodies targeting one antigen
Resistance mechanisms	Upregulation of CD47 (enhanced "don't eat me" signal) [11]	FcγRIIIa polymorphism (158V/F) affects affinity; tumor microenvironment suppresses NK cells [12]	Overexpression of complement regulatory proteins (CD46, CD55, CD59) on tumor cells [13]

In conclusion, ADCP, ADCC and CDC, the three Fc-dependent effector functions, do not exclude one another. Antibodies like rituximab and trastuzumab elicit synergistic anti-tumor activity through diverse pathways. Fc modification and combination regimens are utilized to amplify these functions and enhance clinical outcomes.

2.3. Immune checkpoint blockade

Immune checkpoint blockade targets inhibitory receptors expressed on immune cells, most notably T cells, to reverse tumor-mediated immunosuppression and reinstate anti-tumor immune responses. Its primary pathways include the CTLA-4 pathway, the PD-1/PD-L1 pathway, as well as the LAG-3 and TIM-3 pathways.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is the first successfully targeted immune checkpoint. Induced upon T cell activation, CTLA-4 binds ligands CD80/CD86 on antigen-presenting cells (APCs) with greater affinity than the co-stimulatory receptor CD28. By competing for binding sites, it interrupts CD28-triggered co-stimulation and inhibits T cell activation. Anti-CTLA-4 antibodies such as ipilimumab interfere with the above interaction via CTLA-4 binding and rescue T cell activation [14].Structurally, the binding interface between CTLA-4 antibodies and their target protein is extensive, enabling effective competition with natural ligands. In addition, a

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proposed mechanism observed in preclinical models is that its functional Fc domain mediates the depletion of regulatory T cells (Tregs) via ADCC, further alleviating immunosuppression [15].

PD-1 serves as an inhibitory receptor on T cells; its ligands PD-L1 and PD-L2 are overexpressed on tumor cells and tumor microenvironment-resident immune cells. The ligation of PD-1 and its ligands recruit tyrosine phosphatase SHP-2 to dephosphorylate pivotal components of the TCR signaling cascade, hampering T cell proliferation and effector activity and inducing T cell exhaustion. Anti-PD-1/PD-L1 antibodies restore TCR signaling and reawaken the anti-tumor activity of exhausted T cells by blocking receptor-ligand interactions. Structurally, anti-PD-1 antibodies such as pembrolizumab and nivolumab bind to an epitope on PD-1 that overlaps with the PD-L1 binding interface, exerting therapeutic effects via competitive blockade.Distinct from CTLA-4 antibodies, PD-1 antibodies are designed as IgG4 isotypes. The S228P Fc mutation weakens FcγR binding and prevents ADCC-mediated depletion of PD-1-expressing tumor-infiltrating T cells.

LAG-3 is an inhibitory receptor expressed on the surface of T cells and NK cells. Upon binding to MHC class II molecules and FGL1, it transmits inhibitory signals to negatively regulate T cell proliferation and cytokine [16].TIM-3 is another inhibitory receptor expressed on exhausted T cells, NK cells, dendritic cells and monocytes. Binding to its ligands including galectin-9, HMGB1 and phosphatidylserine (PtdSer) triggers T cell apoptosis or functional suppression [17]. Anti-LAG-3 antibodies (such as relatlimab) and anti-TIM-3 antibodies block ligand-receptor binding, thereby abrogating the aforementioned inhibitory signals and restoring T cell function.

3. Clinical applications and approved mAbs

3.1. Hematologic malignancies

Anti-CD20 antibodies rituximab and obinutuzumab are indicated for B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia in hematological malignancies. Polatuzumab vedotin (anti-CD79b) is used in the treatment of DLBCL. In leukemia, gemtuzumab ozogamicin (anti-CD33 antibody-drug conjugate) is indicated for acute myeloid leukemia (AML). Blinatumomab (CD19×CD3 bispecific antibody) and inotuzumab ozogamicin (anti-CD22 antibody-drug conjugate, ADC) are approved for acute lymphoblastic leukemia (ALL). In multiple myeloma, daratumumab and isatuximab (anti-CD38 monoclonal antibodies), elotuzumab (anti-SLAMF7), and teclistamab (BCMA×CD3 bispecific antibody) have been approved for clinical use. These therapeutics rely on targeting B-lineage surface antigens, utilizing naked mAbs, ADCs and bispecific antibodies to mediate malignant cell elimination.

3.2. Solid tumors

In breast cancer, the anti-HER2 antibodies trastuzumab and pertuzumab are indicated for HER2-positive breast cancer. The antibody-drug conjugate (ADC) T-DXd has further expanded its indications to include HER2-low breast cancer.In colorectal cancer and head and neck squamous cell carcinoma, the anti-EGFR antibodies cetuximab and panitumumab are administered to patients with wild-type KRAS/NRAS [18].Among immune checkpoint inhibitors, the anti-PD-1 antibodies pembrolizumab and nivolumab are approved for more than 20 cancer types including melanoma, non-small cell lung cancer, renal cell carcinoma, and MSI-H solid tumors. The anti-PD-L1 antibodies atezolizumab, durvalumab and avelumab are indicated for urothelial carcinoma, non-small cell lung cancer and Merkel cell carcinoma. These solid-tumor antibodies comprise biomarker-driven tumor-targeting agents and broadly-active immune-checkpoint modulators.

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4. Conclusion

In summary, therapeutic monoclonal antibodies have become a cornerstone of cancer therapy owing to their properties of direct targeted binding and precise payload delivery. Nevertheless, antibody therapies achieve remarkable efficacy in hematological malignancies yet still encounter substantial obstacles in solid tumors, including target heterogeneity and immunosuppression within the tumor microenvironment. Immune-related adverse events (irAEs) constitute the primary limiting factor for the clinical use of immune checkpoint inhibitors. In the future, novel antibody-drug conjugates (ADCs), bispecific antibodies and combinatorial therapeutic strategies are expected to further expand the population of patients who can benefit from treatment, by improving payload selectivity for ADCs, refining molecular architectures of bispecific agents, and overcoming primary or acquired resistance via rational combination regimens.

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