Monoclonal Antibody based Therapy against Cancer

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ABSTRACT

Cancer, as the most lethal illness, is characterized by the uncontrolled growth of cells that can be somewhat treated in the present day. Immunotherapy has been utilized to treat cancer as it has specificity against cancer cells. Apart from chemotherapy, monoclonal antibody (mAb) therapy has shown advanced effects in the treatment of cancer. mAb therapy is one of the recent developments that destroy tumor cells through different mechanisms such as antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, or blocking signaling pathways. This review gives a brief outline of the types, efficiency of action, challenges, and future perspectives of mAb therapy.

Key words: *Cancer therapy, Cancer, Immunology, Immunotherapy, Monoclonal antibodies*

The second leading cause of death worldwide is cancer, claiming one in six lives. The real challenge in treating the disease stems from its heterogeneity, complex immuno-suppressive microenvironment, metastasis, and resistance to therapy, resulting in a hopeless prognosis and leading to death [1]. The journey ahead does not seem to get easier, as the estimated new cases and cancer-related deaths predicted by the year 2040 are 27.5 million and 16.3 million, respectively [2].

Antibodies (Abs) are proteins that recognize specific Ags, as described by Heidelberger and Avery [3]. These are produced by plasma B-cells of the adaptive immunity system, as reported by Fagraeus in 1947 [4]. Abs were initially thought to be neutralizing substances present in the blood by Behring and Shibasaburo in the 1890s, when studied on animal models [5], leading to various scientific research that paved the way for Ab immunotherapy against cancer. Clonal selection theory, by Sir Nossal, proved that a single B-cell clone produces a specific Ab, which binds to a unique portion of an Ag, referred to as an epitope [6]. Thus giving rise to monoclonal Abs (mAbs).

MAbs have become a potential therapy against cancer and many other diseases. These Abs are an excellent example of precision medicine because they are made to specifically target proteins linked to cancer cells. There are five different forms of immunoglobulins in our blood serum which act against foreign Ags accordingly. In the same way, mAbs have more specificity against foreign Ags, hence called targeted therapy. In this review, our objective is to offer a concise overview of the potential implications of mAb therapy in terms of cancer treatment.

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MECHANISM OF PRODUCTION OF mAbs

An antibody called rituximab was approved by the US Food and Drug Administration (FDA) in 1997 as the first mAb to be used to treat cancer [7]. The major method to produce mAbs is hybridoma [Figure 1] technology, given by George Köhler and Cesar Milstein, in which the fusion of B cells with myeloma cells produces increased immunized Abs. According to Raghani *et al*., the production of mAbs starts with immunizing a mouse with a target antigen so that it produces Abs against it. After that, B cells, responsible for producing Abs, are collected and fused with myeloma cells through polyethylene glycol, which in turn forms a hybrid cell. This hybrid cell has the immortal property of myeloma cells, which are further selected on a hypoxanthine-aminopterin-thymidine culture medium [8].

TYPES OF mAbs USED IN CANCER TREATMENT

As of the latest data available, 162 mAbs have been approved to treat a wide range of illnesses. The advantages related to using antibody treatments come from their remarkable selectivity and superior binding affinity; therefore, antibody therapy is increasing rapidly in the US, Europe, Japan, and China healthcare markets [9]. The US FDA has approved a range of mAbs with diverse properties that target different types of cancer. The list below shows some of them.

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As new foreign Ags emerged, mAbs changed their characteristics and killing processes. Through the application of genetic engineering techniques, various categories of mAbs have been developed.

MODES OF ACTION OF mAbs CURRENTLY USED FOR CANCER TREATMENT

Blocking Ligand Binding

This mechanism involves the mAbs binding to the ligands or receptors on the cell surface, thereby inhibiting the ligand from binding to the cell surface [14]. This may be achieved by conjugated or unconjugated mAbs.

Non-conjugated mAbs

These achieve blocking of ligand binding by:

1. Steric hindrance, in which the mAbs bind in such a way that they occupy the region of interaction, thereby physically blocking the transmission of signals and the initiation of undesired biological responses [15].
2. Conformational changes, in which mAbs induce conformational changes in the structure of the target cell, leading to ineffective interaction with the ligand [15].
3. Internalization of the complex, in which the Ag-Ab complex is captured through endocytosis, inhibits the receptor and ligand from coming into contact with each other and, hence, blocks the initiation of unwanted biological processes [16].

Conjugated mAbs

These comprise a class of therapies that can transport and release certain medicinal agents such as radioisotopes, specific proteins, cytotoxic molecules or payloads, and drugs [16,17]. The steps involved in achieving this feat are selective mating, wherein the mAb binds to a specific receptor; followed by internalization, wherein the mAb is engulfed within the cell by endocytosis, targeting specific endosomes or lysosomes in intracellular compartments; and finally leading to the release of the therapeutic agent bound to the mAb. The medicinal agent then begins its target-specific activity within the cell [17-19].

BLOCKING SIGNALING PATHWAYS

This mechanism is achieved by the Fab region of the mAbs, which binds to the receptor and blocks the signaling pathways producing growth factors [20]. This affects the survival of the tumor cells as it prevents their proliferation, adhesion, and angiogenesis, causing apoptosis and non-evasion of immune checkpoints [21,22]. Blocking the production of growth factors also neutralizes certain cytokines, which are vital for the growth and proliferation of tumor cells [23]. FDA-approved mAbs target mainly two members of the ERBB family: HER2 and the epidermal growth factor receptor (EGFR). Both of these receptors are commonly expressed in various solid cancers and are capable of unleashing several oncogenic signals through homodimerization and heterodimerization [19,21,24]. Examples of EGFR mAbs are cetuximab and the HER2 mAbs trastuzumab and pertuzumab [23].

DEPLETION OF TARGET BY FC INTERACTION

This mechanism involves interaction between the Fc domain on Ab and Fc receptors (FcR) on the effector cells [25]. These effector cells may be neutrophils, natural killer cells, dendritic cells, cytotoxic T cells, monocytes, or macrophages. This interaction may initiate Ab-dependent cellular cytotoxicity (ADCC), Ab-dependent phagocytosis (ADP), or complement-dependent cytotoxicity (CDC) [18,26] (Fig. 2). ADCC occurs when the Fc of the mAb binds to the FcR of natural killer cells, leading to the lysis of the target cell [25]. ADP occurs when mAbs interact with phagocytic cells such as neutrophils, macrophages, dendritic cells, and monocytes, causing opsonization of the malignant cell, leading

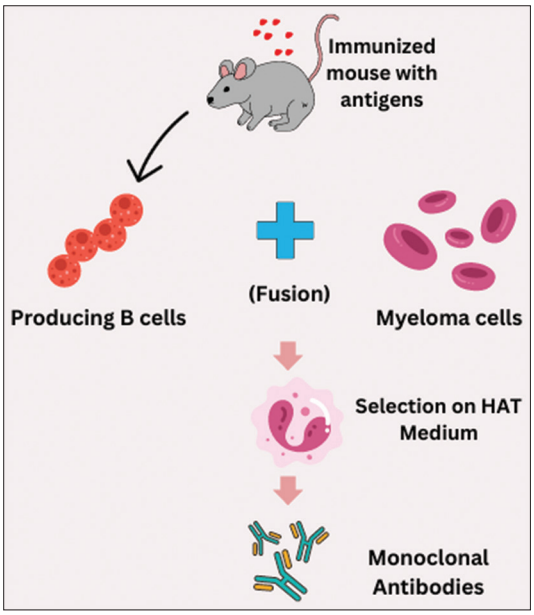

Figure 1: Steps of hybridoma technology to produce monoclonal antibodies

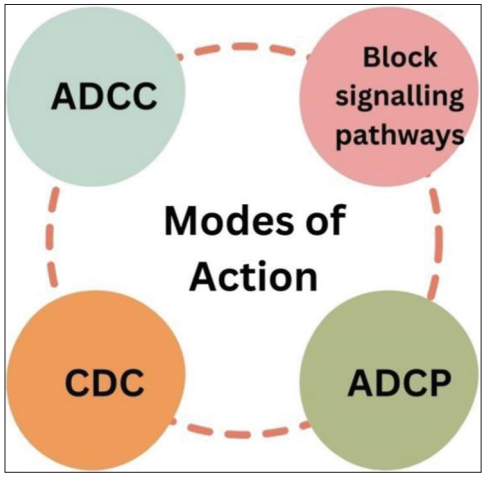

Figure 2: Modes of action of monoclonal antibodies

to its degradation [25]. Finally, CDC occurs when mAbs bind to the Ag on the target cell. A subtype of IgG, that is, IgG1, found abundantly in the plasma, can induce ADCC, ADP, or CDC [27].

EFFICIENCY OF mAbs USED CLINICALLY IN CANCER THERAPY

For the past three decades, mAbs, as an immunotherapy for cancer, has been used clinically [Table 1] in an attempt to extract its capability of being a targeted therapy. The concept of a therapy that targets Ag on the surface of tumor cells led to the belief that it could be less toxic and more effective than regular chemotherapy. At present, mAbs targeting EGFR and HER2 receptors have seen wide clinical acceptance for the treatment of colorectal and breast cancer, respectively [28,29]. In addition, mAbs are also used in cancer therapy as antibody-drug conjugates (ADCs), bispecific T cell engagers (BiTEs), targeting pro-tumorigenic compounds in the microenvironment of the tumor mass, and inhibitors of immune checkpoints. Clinically, their ability to be tumor Ag-specific helps in delivering cytotoxic compounds to target cells.

The first ADC to be approved by the FDA in 2011 was brentuximab vedotin [30]. It targets CD30 cells expressed on the surface of lymphoma cells. In 2013, another ADC, ado-trastuzumab emtansine, composed of trastuzumab and the maytansine derivative DM1, was approved for patients with metastatic breast cancers (HER2 positive) [31]. ADCs have gained popularity over time, owing to a better understanding of their mechanism and the finding that they may also induce antitumor immunity by T cells [32].

In targeted cancer therapy, pseudomonas exotoxin A (PE) and ricin toxins are most commonly under clinical trials [33]. Moxetumomab pasudotox is the only mAb linked to PE, which has gained FDA approval for the treatment of hairy-cell leukemia [34]. Radioimmunotherapy involves labeling mAbs with a radionuclide to initiate targeted radiotherapy. The FDA has currently given its approval to two such radionuclides labeled mAbs: Yttrium-90-ibritumomab tiuxetan and iodine–131-tositumomab. Both of them target CD20 cells expressed by lymphoma cells. As life-threatening side effects have been reported clinically by their use, radioimmunotherapy as a treatment modality has become restricted, leading to the discontinuation of tositumomab by its parent company [35].

Several growth factors are present within the microenvironment of the tumor mass, which aid in its growth and vascularization and evade antitumor responses. The aim to target and block such growth factors has proven to be clinically efficacious. The most pertinent target in the microenvironment of the tumor mass documented is vascular endothelial growth factor (VEGF) binding to its VEGF receptor (VEGFR). Bevacizumab is the mAb, which targets VEGF and prevents its binding to its receptor, VEGFR, and is approved for the treatment of numerous cancers [36]. Another growth factor, transforming growth factor beta, secreted by certain tumor cells, blocks immune effector cell function within the tumor microenvironment [37]. To inhibit this growth factor, fresolimumab is undergoing clinical trials [38].

Another successful domain being explored, which is based on the objective of targeting immune cells to strengthen the antitumor response, is BiTE Abs. These Abs target CD19 Ag and its activating receptor CD3 on T cells [39]. Blinatumomab, a CD19-CD3 BiTE, was approved by the FDA in 2017 for the treatment of lymphoblastic leukemia [40].

Immune checkpoints are a form of inhibitory receptors that are responsible for stimulating the immune response to maintain the self-tolerance of the immune system and evade collateral tissue damage [41]. Blocking of immune checkpoints by mAbs is a mechanism that holds promise and is widely gaining popularity among researchers and clinicians. This mechanism involves generating severe signaling pathways that produce co-inhibitory and costimulatory signals to modify the immune response toward tumors Ag. The first T-cell checkpoint to be identified was cytotoxic T lymphocyte Ag-4 (CTLA-4). It is significantly expressed by Treg cells and also becomes upregulated on activated T cells. CTLA-4 competes for the binding of the costimulatory ligands CD80 and CD86 [42]. Thus, it was inferred that by blocking CTLA-4, the antitumor response of the T cells can be amplified. Based on this theory, mAbs against CTLA-4 were actively tested on animal models and developed for clinical trials [43]. Finally, in 2011, the FDA approved Ipilimumab, an anti-CTLA-4 mAb, for melanoma patients [44].

Another inhibitory immune checkpoint that has been identified is programmed death receptor-1 (PD-1), which is associated with the programmed death pathway in T cells [45]. It is highly expressed by CD8+T cells, Tregs, activated B-cells, and NK cells. The corresponding ligand to PD-1 on tumor cells is PD-L1, which is produced by T cells in large numbers to block the infiltration of lymphocytes [46]. Nivolumab, an anti-PD-1 mAb, gained FDA approval in 2014 for melanoma patients [47]. Gradual clinical trial success with anti-PD1 mAbs also led to the approval of pembrolizumab for the treatment of several malignancies [48-50].

CHALLENGES AND LIMITATIONS OF mAb THERAPY IN CANCER

Despite having efficacy against cancer, mAbs still have certain limitations, like any other therapeutic modality. Their route of administration or the class to which they belong can be a few of the many challenges surrounding them [51]. Signs and symptoms ranging from rashes at the site of administration to weakness, fever, headaches, diarrhea, nausea or vomiting, and hypotension have been commonly observed. Severe side effects like renal failure, delayed or improper wound healing, excessive bleeding, and hypertension have been reported with bevacizumab, a mAb used against blood vessel tumors. Drowsiness, allergic reactions like itching and rashes, and severe pain have been observed after the administration of raxibazumab, a mAb used for the treatment of inhalational anthrax [52]. The availability of FDA-approved mAbs on the market and their cost are areas of concern as well [53].

It has been observed that the penetrating efficacy of mAbs and their conjugates is poor in solid tumors, serving as a limitation [54].

Table 1: Clinically approved mAbs for the treatment of cancer

Monoclonal Antibodies	Type	Target cancer	References
Gemtuzumab	CD-33 specific mAb	Acute myeloid leukemia	[10]
Trastuzumab	Anti-HER2 mAb	Breast cancer	[11]
Cetuximab	Chimeric IgG1 mAb	Colorectal cancer	[12]
Olaratumab	Human IgG1 mAb	Soft-tissue Sarcoma	[13]

MAb: Monoclonal antibody, IgG: Immunoglobulin G

On the contrary, research has shown that the concentration of mAbs used in solid tumors is 100 μg/mL, which is sufficient for mAbs to target every cell in the tumor mass [55]. The tumor cells follow different mechanisms to shed cancer-specific Ag from their surface, which are otherwise supposed to be targets for mAbs to be effective against cancer. As these shedding mechanisms are not entirely understood, it limits the anticipated efficacy of the mAbs and their immunoconjugates [55]. The cell surface proteins present in tumor cells have been shown to change rapidly during the course of disease progression [55]. This may lead to a loss of expression of Ag on tumor cells, resulting in the inability of mAbs to recognize the cells and act against them effectively. Another factor to take into consideration is the level of toxicity that may be encountered due to the various combinations of mAbs, largely depending on the patterns of expression of Ag, wherein Ag having restricted expression (e.g., CCR9) has exhibited lower toxicity levels as compared to Ag having a wider range of expression on tumor cells [56]. Finally, as evolution has progressed, the ability of the immune system to fight disease has evolved as well. It has been demonstrated that the immune system produces polyclonal responses to a single Ag. This feature may limit the efficacy of therapeutic mAbs, as currently a monoclonal approach is being followed to target tumor cells [57].

FUTURE PERSPECTIVES

Combination Therapies

MAbs, as a monotherapy, has proven to be effective against cancer, but the direction of research toward combining mAbs with various other treatment modalities is intriguing. Combining mAbs with chemotherapy, radiotherapy, other Abs, vaccines, cellular therapies, or molecularly targeted drugs is being extensively studied, which has been covered in great detail in an article by Corraliza-Gorjón *et al*., [58] as it is beyond the scope of this review. Another area being explored for combination therapy is biological substances such as recombinant proteins, genetic material, and microorganisms such as bacteria, viruses, and other cells to activate the host immune system against the tumor cells [59]. The various mechanisms being explored in combination with biological substances are as follows: (i) Ab identifies tumor-specific Ag, which may be used as ADC or immunotoxin, (ii) Ab in combination with cytokines to disrupt the immune response against tumor cells or with anti-cytokines to balance the immune and antitumor response, (iii) a combination, which directly targets the angiogenesis within the tumor cells, thereby inhibiting neovascularization essential for tumor growth, (iv) combination of mAbs with effector cells to boost the immune response against tumor cells, and (v) combination with immunostimulatory or immunomodulatory proteins, which block the signaling pathways generated by tumor cells to disrupt the antitumor response. Several clinical trials are needed to establish the effectiveness of these mechanisms [58].

Potential Protein Biomarkers for Designing mAbs for Cancer Therapy

Alpha-1 collagen (XI) (UniProtKB-P12107), a polypeptide chain encoded by the COL11a1 gene, belongs to the cartilage family, is classified as a minor fibrillar collagen subgroup, and is responsible for forming alpha-collagen XI [60-62]. In several aggressive cancers, which are resistant to chemotherapy and have a poor prognosis, the overexpression of COL11a1 has been noticed [61,62]. This has been significantly observed in glioblastomas, mesenchymal tumors derived from scleroderma and keloids [63], lung cancers [64], and breast carcinomas. Developing mAbs to inhibit COL11a1 can prove to be a beneficial therapeutic modality.

Claudin 18 (UniProtKB-P56856), also known as CLDN18, is a membrane protein belonging to the claudin family, found largely in gastric, pancreatic, and pulmonary tissues, with the primary function being the maintenance of tight junctions that regulate the exchange of molecules between cells [65-68]. In gastric carcinomas (GC), especially the ones caused by the Epstein–Barr virus, the overexpression of this protein has been noticed [69]. To block a variant of this protein, that is CLDN18.2, a chimeric IgI mAb-zolbetuximab was clinically tested [70,71]. Zolbetuximab triggers ADCC, resulting in apoptosis and inhibition of cell proliferation [65]. Clinical efficacy as the first-line treatment for GC as compared to chemotherapy alone was observed [72,73]. Hence, CLDN18.2 can serve as a potential target for treating various other malignancies.

B7 homolog 3 (B7-H3) (UniProtKB-Q5ZPR3) Ag, also known as B7-H3, encoded by the CD276 gene, has a primary biological function of interacting with the CD28 receptor on T cells to stimulate deregulation, differentiation, and activation of T cells [74,75]. As B7-H3 is significantly expressed in ovarian, cervical, colorectal, breast, lung, and brain cancers and neuroblastomas, accelerating tumor growth, causing metastasis, drug resistance, and poor survival rates, it can be used as a potential biomarker for creating anti-B7-H3 mAbs [76].

CD73 (UniprotKB-P21589) is found in the cell membrane with hydrolase activity and is expressed in endothelial cells, epithelial cells, and T and B lymphocytes [77,78]. CD73 is overexpressed in several malignancies, as per research, and its presence makes the prognosis hopeless [79]. CD73 leads to the generation of increased levels of adenosine, creating a microenvironment within the tumor mass, resulting in faster tumor growth, angiogenesis, immune suppression, and metastasis [80,81]. This

is what makes CD73 a potential target for producing anti-CD73 mAbs. Anti-CD73 therapy has shown promising results on mice models, and further clinical trials are needed to make it available as a therapeutic modality against cancer [82,83].

CONCLUSION

The journey of mAbs as an effective cancer therapy has been astonishing. Although rigorous research and advancements are still needed to improve its safety and efficacy and make it more cost-effective and readily available, mAbs have come a long way. They have served as a beacon of light in the lives of people suffering from cancer, which was earlier considered to be an incurable disease. With several formulations readily gaining FDA approval and deemed fit for human use, it shows that modern engineering techniques, advancements in hybridoma technology, and biomolecular sciences are producing mAbs with better features and characteristics. Thus, the future of mAbs is promising, not only as a therapeutic modality in cancer but also in certain infectious diseases and conditions such as Alzheimer's and Parkinsonism, depending extensively on technological advancements and clinical trials.

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