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INNOVATIONS IN IMMUNOTHERAPY: MONOCLONAL ANTIBODIES AND BIOLOGICS REDEFINING CANCER AND AUTOIMMUNE DISEASE TREATMENTS

Abstract

Cancer arises when the immune system fails to react to malignant cells, while autoimmune diseases result from the immune system attacking self-antigens. Traditionally viewed as distinct fields, research in autoimmunity has significantly contributed to cancer therapy advancements, notably through the identification of immune checkpoints and the development of PD-1 and CTLA-4 targeting drugs. Monoclonal antibodies (mAbs), a prominent class of biologics, have revolutionized treatment approaches for both cancer and autoimmune diseases. Structurally, antibodies are Y-shaped molecules with specific regions responsible for antigen binding and effector functions. Therapeutic mAbs, primarily of the IgG class, have shown efficacy in targeting cancer cells, modulating immune responses, and inhibiting inflammatory pathways. In cancer therapy, mAbs target specific antigens on tumor cells, such as CD20, EGFR, and HER2, or disrupt tumor microenvironment processes like angiogenesis. In autoimmune disorders, mAbs inhibit cytokines like TNF-alpha, IL-1, IL-6, and target B cell antigens like CD20 to reduce inflammation and autoimmunity. The successful application of mAbs in both domains underscores their potential in developing targeted and effective treatments.

Keywords: Cancer, Autoimmune Diseases, Monoclonal Antibodies in Cancer Therapy, Monoclonal Antibodies in Autoimmune Disorders.

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I. INTRODUCTION

Cancer arises when the immune system fails to react to malignant cells, whereas autoimmune illness is the outcome of the immune system's reaction against self-antigens. Therefore, for a long time, research on autoimmunity and cancer was seen as two distinct domains with little in common. However, research on autoimmune diseases can be very beneficial in the development of new anti-cancer medications, as demonstrated by the identification of immune checkpoints and the creation of anti-cancer medications that target the PD-1 (programmed cell death receptor 1) and CTLA-4 (cytotoxic T lymphocyte antigen 4) pathways. Consequently, it appears that cancer and autoimmunity are only two sides of the same coin [1].

Biologics is one of the newer areas of study for this subject. Any agent derived from a natural substance or live organism is considered a biologic. This group includes vaccines, blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. At the moment, monoclonal antibodies are one of the most well-known biologics [2]. Identical B cell clones create a class of antibodies called monoclonal antibodies (mAbs) that are directed against a specific antigen. The protein sequence, the location of the antigen-binding site, the binding affinity for the target, and the functional consequences downstream are all the same for monoclonal antibodies. These features set mAbs apart from polyclonal antibodies, which detect distinct epitopes on an antigen and have heterogeneous activity [3]. At the moment, monoclonal antibodies (mAbs) represent a significant class of therapeutic molecules that are being tested in clinical trials to treat a variety of conditions, including malignancies (like multiple myeloma, melanoma, breast cancer, and rheumatoid arthritis), infectious diseases, cardiovascular conditions, and inflammatory and autoimmune diseases [4].

II. STRUCTURE OF ANTIBODY

A molecule of an antibody is Y-shaped and has a molecular weight of about 150 kDa. It is made up of four polypeptide chains: two light (L) and two heavy (H) chains that are the same (Figure 1). Heavy and light chains next to each other are stabilised by covalent connections, primarily disulfide interactions. There are constant (CH and CL, respectively) and variable domains in each heavy or light chain (VH and VL, respectively). As antigen-binding sites, each antibody possesses two identical arms called "antigen binding fragments," or Fabs. The VH and VL domains combine to produce the variable region, or Fv, and the constant area that make up each Fab (formed by the CH and CL domains). The highly variable region known as Fv is in charge of the antibody's particular binding to the antigen, which helps the antibody's direct effects—like blocking or neutralising the antigen—to occur. The variable portions of the light and heavy chains contain three hypervariable regions that are referred to as complementarity determining regions, or CDR1, CDR2, and CDR3. These regions enable the recognition of various antigenic specificities. The constant portion of the antibody molecule is the stem of the Y structure, also referred to as the "fragment crystallizable region" or Fc. The antibody's functional characteristics and class are determined by its Fc region.. Immunoglobulin G (IgG), IgM, IgD, IgE, and IgA are the five classes of antibodies; each class has a unique effector mechanism for identifying and removing antigens. Furthermore,

the Fc region can engage in interactions with a wide range of receptors, including complement system components and Fc receptors, also known as FcRs, which are expressed on immune cells (such as C1q). When immune system components recognise Fc, the effector actions of antibodies, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cell cytotoxicity (ADCC), are triggered [5].

As a result, many ways in which antibodies might eradicate a specific antigen are explained, and both variable and constant regions of antibodies play a part in this reaction. The usefulness of immunoglobulins for the production of therapeutic monoclonals is mostly determined by the stability, flexibility, and effector actions of antibodies, such as activating CDC, ADCC, and interacting with C1q. IgG mAbs make up the bulk of those that are clinically available. As previously mentioned, IgG is a 150 kDa glycoprotein made up of two heavy and two light chains. The amino acid arginine297 (N297) in the CH2 domain contains a conserved glycosylation site that is crucial for the structural conformation of the Fc and its interaction to complement component C1q and FcRs. As a result, many ways in which antibodies might eradicate a specific antigen are explained, and both variable and constant regions of antibodies play a part in this reaction. The usefulness of immunoglobulins for the production of therapeutic monoclonals is mostly determined by the stability, flexibility, and effector actions of antibodies, such as activating CDC, ADCC, and interacting with C1q. IgG mAbs make up the bulk of those that are clinically available. As previously mentioned, IgG is a 150 kDa glycoprotein made up of two heavy and two light chains. The amino acid arginine297 (N297) in the CH2 domain contains a conserved glycosylation site that is crucial for the structural conformation of the Fc and its interaction to complement component C1q and FcRs. IgG3 is the IgG subclass that is not suitable for target binding because it has a longer hinge region than the other subclasses. However, in contrast to other subclasses, IgG3 has the highest allotypic polymorphism, the shortest half-life (about 7 days), and cannot be isolated using protein A. Therefore, in order to modify the amino acid composition of the IgG3 hinge region for the creation of therapies, engineering techniques are needed. Conversely, the majority of mAb therapies available on the market are made up of IgG1, IgG2, or IgG4 and have extended half-lives and delayed elimination. Since most therapeutic mAbs bind to C1q, ADCC, and CDC, IgG1 has strong stability and powerful effector activities. When it comes to the Fc receptor, IgG1 has a stronger affinity than the other subclasses (IgG1 > IgG3 > IgG4 > IgG2, correspondingly). Since IgG4 has a low affinity for C1q, it may become a useful therapeutic mAb in situations when the host effector function is undesirable. Furthermore, the exchange of Fab arms is an undesirable biological activity that can happen in IgG4 and is a natural procedure. Therapeutic IgG4 for multiple sclerosis (MS) and acute myeloid leukaemia (AML) includes natulizumab (Tysabri) and gemtuzumab ozogamicin (Mylotarg), respectively [6].

Compared to IgG1, IgG2 has a lower affinity for interacting with antigens and shows less functional activity. IgG2-A, IgG2-A/B, and IgG2-B are the three isoforms of IgG2 antibodies that are distinguished by the kinds of disulfide links that connect the antibody chains. It is possible to transform these isoforms into one another. Disulfide shuffling is the term for this process, which may control serum IgG2 activity [8,9].

III. APPLICATION OF MONOCLONAL ANTIBODIES IN CANCER THERAPY

By specifically targeting antigens expressed on cancer cells, monoclonal antibodies (mAbs) have revolutionised cancer therapy by eliciting potent immune responses against malignancies. The first monoclonal antibody (mAb) licenced in 1997 for the treatment of non-Hodgkin B cell lymphoma was rituximab, an anti-CD20 chimeric antibody. It interacts with B cell cancers' CD20 antigen, causing immune systems to eradicate cancerous cells. Ibritumab, Obinutuzumab, and Ofatumumab provide more alternatives for addressing CD20-positive malignancies by broadening the spectrum of anti-CD20 mAbs, others like Daratumumab a CD38 targeting mAb in approved for Multiple myeloma and Alemtuzumab a CD52 targeting mAb is approved for Chronic lymphocytic leukaemia [10].

In addition to these, EGFR is an essential antigen that is expressed on many types of cancer cells and promotes the growth and metastasis of cancer. Metastatic colorectal cancer (mCRC) can be treated with EGFR-targeting monoclonal antibodies (mAbs) such cetuximab and panitumumab, whereas metastatic squamous non-small cell lung cancer can be treated with enectuzumab, which also targets EGFR [11]

There are also antibodies that are specifically designed to target crucial events in the tumour microenvironment. For example, Bevacizumab blocks binding of vascular endothelial growth factor A VEGF-A to its receptor and inhibit angiogenesis. It is approved for treatment of Metastatic colorectal cancer, metastatic lung cancer, ovarian cancer fallopian tube or peritoneal cancer, glioblastoma multiforme, metastatic renal cell cancer. Ramucirumab binds to VEGF receptor (VEGF-R2) and blocks receptor activation. It is approved for the management of advanced gastric and gastroesophageal adenocarcinomas [12].

An IgG1 mAb called trastuzumab targets the HER2 protein that is expressed in breast tumour cells, providing HER2-positive breast cancer patients with a tailored treatment. The choices for HER2-targeted therapy are further expanded by Pertuzumab, intratrastuzumab and ado-trastuzumab emtansine [13].

Immunocheckpoint inhibitors (mAbs) that target the protein known as programmed cell death protein 1 (PD-1) have demonstrated impressive efficiency against a variety of cancer types. Approved for the treatment of lymphoma, lung cancer, and melanoma, nivolumab and pembrolizumab are humanised IgG4 mAbs that target PD-1. Furthermore, ipilimumab suppresses CTLA-4, a protein that is associated with cytotoxic T lymphocytes, which boosts T cell activation and the immune system's ability to fight malignancies. Apart from these for advanced merkel cell carcinoma, Avelumab is approved and for advanced urothelial cancer, Atezolizumab and Durvalumab are approved [14].

By imitating tumor-associated antigens, anti-idiotype monoclonal antibodies present a fresh strategy. For example, ACA125 imitates CA125 in ovarian cancer, eliciting anti-idiotypic immune responses linked to extended survival. In a similar vein, anti-idiotype mAbs that imitate carcinoembryonic antigen epitopes have shown encouraging outcomes in advanced colorectal cancer and disialoganglioside GD2 in melanoma [14].

Another tactic for cancer treatment is the use of recombinant immunotoxins, which are fusion proteins made of bacterial toxins and the Fv region of mAbs. These immunotoxins, which come from Pseudomonas enterotoxin, have been effective in treating leukemias, lymphomas, and solid tumours [15].

Using mAbs labelled with radioisotopes such as yttrium-90 and iodine-131, radioimmunotherapy offers a focused method of exposing cancer cells to radiation. This method has been applied to the treatment of lymphoma and Hodgkin's disease, as well as in cancer diagnosis through immunoscintigraphy [16].

IV. APPLICATION OF MONOCLONAL ANTIBODY IN AUTOIMMUNE DISORDER

Monoclonal antibody may potentially inhibit the immune system's activity in autoimmune disorders or following organ donation. Therapeutic applications of monoclonal antibodies (mAbs) have demonstrated success in treating a number of inflammatory disorders, including multiple sclerosis, psoriasis, rheumatoid arthritis (RA), juvenile arthritis, and Crohn's disease [17].

1. Anti-TNF- Alpha

TNF alpha is associated with several autoimmune disorders like Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Inflammatory Bowel Disease (IBD), Psoriasis (PS), Non-infectious Uveitis (NIA). Because of the crucial role in inflammatory responses, TNF-a is considered as an important cytokine involved in pathogenesis of several disorders such as RA, Crohn’s disease, and spondyloarthritides and, therefore, anti-TNF agents have become an efficient approach used in treatment for these diseases. Infliximab is a human chimeric IgG1 anti-TNF antibody that interacts with soluble and transmembrane forms of TNF-a resulting in inhibiting proinflammatory cascade signaling. Binding infliximab to cells expressing TNF led to cell destruction through antibody and CDC, infliximab was also approved to treat crohn’s disease, psoriasis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis [18].

Adalimumab is approved for use in RA, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, Crohn’s diseases, ulcerative colitis, and Psoriasis. Golimumab, a fully human mAb, has been approved for RA, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, and juvenile idiopathic arthritis. Certolizumab is approved for the treatment of Crohn’s disease, RA, psoriatic arthritis, and ankylosing spondylitis. Etanercept and Ozoralizumab prevents the progression of RA in patients [19].

2. Anti IL-1 and Anti-IL-1R

Anakinra is an antagonist for IL-1RI which prevents the interaction of IL-1α as well as IL-1β to IL-1R1 resulting in reducing inflammatory response and tissue damage. Anakinra is currently approved for the treatment of RA and cryopyrinassociated periodic syndromes. Other anti-IL1 mAbs are also under investigation for clinical use such as Gevokizumab (anti-IL-1β IgG2 mAb), LY2189102 (anti-IL-1β IgG1 mAb), MABp1 (anti-IL-1α IgG1 mAb), and MEDI-8968 (blocking IL-1RI) [20].

3. Anti IL-6 and IL-6R

Tocilizumab or atlizumab, is a humanized anti-IL-6 receptor mAb and binds to both soluble and membrane-bound IL-6 receptor. Its efficacy is currently being explored in the treatment of RA, systemic juvenile idiopathic arthritis in children, Castleman's disease, systemic lupus erythematosus (SLE), juvenile dermatomyositis (DM), vasculitis, and juvenile scleroderma. Sarilumab is another human IgG1 mAb against IL-6 receptor developed for the treatment of RA [21]. Sirukimab, olokizuman, and clazakumab are the inhibitors of IL-6 that are currently under development for treating inflammatory disorders.

4. Anti-CD20

CD20 antigen is a phosphoprotein expressed on B lymphocytes involved in B cell proliferation and activation by initiating an intracellular signaling pathway. Targeting CD20 by mAbs induces B cell apoptosis and could inhibit B cell function through antibody-dependent cell mediated cytotoxicity and complement-dependent cytotoxicity. Rituximab, a chimeric mAb against CD20 antigen, has been first approved for the treatment of lymphomas. Rituximab was approved for treating RA in combination with methotrexate, which could improve symptoms in patients. Rituximab is also approved for systemic lupus erythematosus dermatomyositis, severe autoimmune hemolytic anemia, refractory immune thrombocytopenic purpura, Wegener's granulomatosis, Ocrelizumab is another humanized anti-CD20 antibody that targets CD20 molecules on B lymphocytes. It was approved for the treatment of the primary progressive form of multiple sclerosis. Ofatumumab, a fully human anti-CD20 antibody, has been shown to be effective and safe in treating patients with autoimmune diseases. Phase II and III trials are ongoing to evaluate the efficiency of ofatumumab in patients with multiple sclerosis and rheumatoid arthritis, respectively [22,23].
Others

Secukinumab, an IgG1 human mAb, binds to IL-17A and is approved for the treatment of psoriasis and ankylosing spondylitis. Ixekizumab also neutralizes IL-17 and was developed for the treatment of moderate to severe plaque psoriasis. Brodalumab also interacts with IL-17 and prevents its binding to IL-17 receptor [24].

Guselkumab, Risankizumab, and Tildrakizumab are IgG1 mAbs targeting IL-23 p19 approved for the treatment of patients with plaque psoriasis [25].

Targeting adhesion molecules which play an important role in leukocyte activation, circulation, and localization to inflammatory sites is also considered as an efficient therapeutic approach in treating autoimmune diseases [26]. Natalizumab, a humanized mAb against the cell adhesion molecule α4-integrin, was the first mAb approved for treatment of Multiple Sclerosis. Natalizumab is also used for treating Crohn's disease [27].

V. CONCLUSION

The intersection of cancer and autoimmune disease research has opened new avenues for therapeutic innovations, particularly through the development of monoclonal antibodies (mAbs). These biologics have revolutionized the treatment landscape for both malignancies

and autoimmune disorders by specifically targeting molecular pathways involved in disease pathogenesis. Structurally, mAbs are Y-shaped molecules with distinct antigen-binding and effector regions, which enable them to perform various immunological functions such as blocking antigens, neutralizing pathogens, and mediating immune cell interactions.

In cancer therapy, mAbs target specific antigens on tumor cells, disrupt key processes in the tumor microenvironment, and harness the body's immune system to combat malignancies. Notable examples include anti-CD20 mAbs like rituximab for lymphomas, anti-EGFR mAbs for metastatic cancers, and anti-HER2 mAbs for breast cancer. Additionally, immune checkpoint inhibitors like nivolumab and pembrolizumab have shown remarkable efficacy by targeting PD-1, enhancing T cell responses against tumors.

For autoimmune diseases, mAbs have proven effective in modulating immune responses and reducing inflammation. Anti-TNF-alpha mAbs, such as infliximab and adalimumab, have become standard treatments for conditions like rheumatoid arthritis and Crohn's disease. Other mAbs target interleukins (e.g., IL-1, IL-6) and B cell antigens (e.g., CD20), demonstrating the versatility and therapeutic potential of these agents.

The shared mechanisms underlying the immune system's regulation in both cancer and autoimmune diseases underscore the interconnectedness of these fields. The continued exploration and application of mAbs promise to yield even more targeted and effective treatments, offering hope for improved patient outcomes across a wide range of conditions. As research progresses, the boundary between oncology and immunology will likely continue to blur, driving further advancements in both disciplines.

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