Int. J. Biol. Res., 11 (1-2): 25-29, 2023.

THE PROMISING ROLE OF MONOCLONAL ANTIBODIES IN CANCER TREATMENT: A MINI OVERVIEW

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ABSTRACT

Monoclonal antibodies are engineered proteins that specifically target cancer cells and are capable of initiating various therapeutic mechanisms, including apoptosis, immune system activation, and inhibition of angiogenesis. This review highlights the recent advances in mAb therapy, including their use as single agents, in combination with chemotherapy or radiation, and in conjunction with other immune therapies. We also discuss the challenges associated with mAb therapy, including resistance mechanisms and adverse effects. Despite these challenges, the efficacy and safety of mAb therapy offer hope for improving cancer treatment outcomes, and ongoing research is focused on developing new mAbs with improved selectivity and efficacy.

Key-words: Monoclonal antibodies, cancer, immune system, chemotherapy, radiation.

INTRODUCTION

The development of cancer is characterized by an anomalous increase in structural variations within cells, which can spread throughout the body. Over time, cancer treatment has shifted away from non-targeted approaches like surgery, radiotherapy, and chemotherapy, towards more specific methods like immunotherapy. This is because non-specific methods tend to damage healthy cells and are often insufficient for completely eradicating the disease. Immunotherapy has emerged as a critical option for cancer treatment, as it can selectively target the tumor and its surrounding microenvironment. This makes it possible to tailor treatment plans to each individual patient, resulting in lower toxicity and fewer adverse effects (Ahmad 2019; Alderson and Sondel, 2011). With the introduction of hybridoma technology in 1975 and subsequent advancements in producing chimeric, humanized, and human antibodies, the use of immunotherapy for cancer treatment has become more accessible and practical (Benavente *et al*., 2009). By directing attention towards tumors using unique or linked antigens, it is feasible to precisely eradicate cancer cells while keeping the level of toxicity at an acceptable level. Additionally, there are ongoing efforts to create therapeutic antibodies that focus on immune cells with the objective of disrupting the body's tolerance to the tumor and encouraging the patient's natural anti-tumor immune response (Chandarlapaty *et al*., 2012). At present, there are eleven antibodies that have been granted approval for use in cancer treatment, with nine of them being authorized within the last ten years (Cuyas *et al*., 2017).

Monoclonal antibodies (mAbs) have become a widely accepted and approved form of cancer immunotherapy in clinical settings. They are primarily employed to target various cancer types, including breast, colon, lymphomas, and other forms of cancer (Corraliza-Gorjon *et al*., 2017).To enhance the efficacy of cancer treatments, it is crucial to comprehend the mechanisms underlying the tumor-killing effects of monoclonal antibodies (mAbs). Despite variations in their mechanisms, these mAbs have been integrated into the conventional treatment regimen along with chemotherapy and/or radiotherapy (de Saint Basile *et al*., 2010).

1. Mechanism of action of monoclonal antibodies

Many antibodies can directly cause the death of tumor cells by blocking the signaling of growth factor receptors. These receptors are responsible for promoting the growth and survival of cancer cells, but when antibodies bind to them, they prevent their activation or binding of their ligands. One example of such a receptor is EGFR, which is often overexpressed in various types of cancer and drives the proliferation, migration, and invasion of tumor cells. Cetuximab, an anti-EGFR antibody, induces tumor cell death by inhibiting ligand binding and receptor dimerization, leading to apoptosis (Di Gaetano *et al*., 2003; Eischen and Libson, 1997). Monoclonal antibodies (mAbs) can have indirect effects on the body by engaging with the immune system, specifically through complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cellular cytotoxicity (ADCC). Many mAbs can activate the complement system to achieve their targeted effects. For example, rituximab's effectiveness in vivo depends in part on CDC. In a preclinical study, the anti-tumor

effects of rituximab were eliminated when the complement cascade component C1q was removed (Fanger *et al*., 1989). ADCP happens when FcγRI present on certain cells, like macrophages, connect with IgG1 or IgG3 monoclonal antibodies that have marked a tumor cell for destruction. Although there is limited research on ADCP, some evidence suggests that this process is crucial in eradicating tumor cells that are circulating in the body after monoclonal antibody therapy (Gul *et al*., 2014). Through their Fab regions, antibodies can form links with target cells by binding to the antigens on their surfaces. By utilizing their Fc sections, they can also connect with effector cells, making them crucial for mediating ADCC. Although IgG, IgA, and IgE can all be involved in this process, IgG1 is the primary subclass used in cancer therapy. For ADCC to take place, effector cells must express FcR, which is necessary for the antibody to attach to them (Harris and Drake, 2013; Li *et al*., 2005). Natural killer (NK) cells are the primary type of effector cells responsible for antibody-dependent cellular cytotoxicity (ADCC). However, other types of myeloid cells, including monocytes, macrophages, neutrophils, eosinophils, and dendritic cells, are also capable of mediating ADCC. These effector cells cause the death of target cells by releasing cytotoxic granules, signaling through Fas receptors, and generating reactive oxygen species. Although various myeloid cell types have been shown to mediate ADCC in immunotherapy, the clinical effectiveness of most monoclonal antibodies targeted to cancer cells primarily relies on the activity of NK cells (Linares *et al*., 2016; Loi *et al*., 2019; McLaughlin *et al*., 1998; Melero *et al*., 2015; Mishima *et al*., 2011).

2. Structure of Monoclonal antibodies

Antibodies are large proteins belonging to the immunoglobulin family that play a crucial role in the immune system by recognizing and neutralizing foreign antigens. They have a Y-shaped structure made up of two heavy and two light chains. The tip of the Y contains the fragment antigen-binding (Fab) region, responsible for recognizing specific antigens. The fragment crystallizable (Fc) region located at the base of the Y structure interacts with other immune system components through Fc receptors (FcRs) (Murphy, 2012). There are five classes of antibodies based on the type of heavy chain, with IgG being the most used for therapy. IgG interacts with FcγR, found on immune cells such as NK cells, neutrophils, monocytes, dendritic cells, and eosinophils to mediate specialized functions like ADCC and CDC. Monoclonal antibodies are clones of a specific antibody isotype targeted to a unique antigen epitope (Nimmerjahn and Ravetch, 2008a).

3. Types of monoclonal antibodies used in cancer treatment

3.1. Unconjugated antibodies

Unconjugated or "naked" monoclonal antibodies (mAbs) are a type of antibody that can function independently. They are widely used for cancer treatment, where they attach to antigens on cancer cells. This means that they do not require any additional components to be effective. The possible outcomes of using monoclonal antibodies (mAbs) in cancer treatment are varied. One of them is the enhancement of the person's natural immune response against cancer cells. This happens because mAbs help attract immune cells and improve the recognition of cancer cells, leading to an increase in their destruction. Another mechanism involves targeting immune system checkpoints, while other types of mAbs prevent cancer cells from using antigens to expand and multiply (Nimmerjahn and Ravetch, 2008b).

3.2. Conjugated antibodies

A conjugated monoclonal antibody refers to the combination of an mAb with a chemotherapy agent or a radioactive particle. This allows the mAb to act as a carrier and transport the chemotherapy or radioactive particle to the specific target antigen in the patient's body (Nimmerjahn and Ravetch, 2008b?).

3.3. Bispecific antibodies

This special monoclonal antibody is created by combining two different types of antibodies. This allows the antibody to attach to two different types of proteins at once. One protein is found on cancer cells, while the other is found on immune cells. By bringing these two cells together, the hope is to stimulate a stronger immune response and ultimately eliminate cancer cells (Nimmerjahn and Ravetch, 2008b?).

4. Mechanism of resistance in mAb therapy

Monoclonal antibody (mAb) therapy has shown effectiveness in treating cancer, but resistance to this therapy remains a significant challenge. Resistance can be innate (already present in the tumor cells) or acquired (develops during therapy due to immune selection pressure). Different mechanisms contribute to each type of resistance (Papaioannou *et al*., 2016; Patel *et al*., 2009; Reichert, 2011; Sathyanarayanan and Neelapu, 2015). One limitation of

mAb therapy is that its efficacy depends on the expression of target molecules by tumor cells. For instance, mutations in CD20 can make lymphoma patients resistant to rituximab (Sathyanarayanan and Neelapu, 2015), while a mutation in the EGFR ectodomain confers resistance to cetuximab but not panitumumab (Sforza *et al*., 2016). Downregulation of the target protein, mutations in downstream signaling pathways, epithelial to mesenchymal transition (EMT), and impaired effector cell responses are some of the other mechanisms of resistance to mAb therapy (Schreiber *et al*., 2011)

Mutations of the antibody target and downstream signaling molecules can activate alternative growth or survival signaling pathways, leading to acquired resistance. For example, mutations in KRAS, NRAS, BRAF, and PIK3CA bypass EGFR signaling inhibition by cetuximab in colorectal cancers (Seledtsov *et al*., 2015). These mutations enhance signaling through MAPK and PI3K/AKT pathways and increase expression of anti-apoptotic BCL-2 proteins, leading to resistance to mAb-induced apoptosis (Shuptrine *et al*., 2012). In breast cancer, activating mutations of the PI3K/AKT/mTOR pathway and overexpression of compensatory growth factors contribute to resistance to trastuzumab (Sickmier *et al*., 2016). Aberrant activation of the tyrosine kinase SRC and cyclin E/CDK 2 pathway have also been implicated in trastuzumab resistance (Society, 2016).

5. Combination therapies

Monoclonal antibodies (mAbs) have shown success as a monotherapy for some patients, but the current trend is to use them in combination with other treatment modalities such as chemotherapy, radiation, targeted drugs, immune checkpoint inhibitors, vaccines, and/or cellular therapies. These combination therapies are currently being investigated in preclinical studies and clinical trials (Stagg *et al*., 2011). One key mechanism of mAb action is their ability to trigger immune effector cell responses. For instance, the efficacy of cetuximab has been attributed in part to ADCC, which can lead to more effective anti-tumor immune responses. Patients with durable responses to cetuximab have shown sustained anti-tumor specific immune responses. Combining anti-PD-1/PD-L1 mAbs with cetuximab has shown promise in HNSCC patients, as has combining pembrolizumab or avelumab with cetuximab, which are currently undergoing clinical trials (Teillaud, 2012; Weiner *et al*., 2010). Similarly, the combination of ICB and HER2-targeted mAbs is a promising strategy for breast cancer treatment, with preclinical evidence suggesting that resistance to trastuzumab monotherapy can be overcome by combination with ICB (Vernieri *et al*., 2019). Clinical trials investigating the relationship between ICB and HER2-targeted mAbs have shown positive preliminary results (Zahavi and Weiner, 2020).

CONCLUSION

Monoclonal antibodies are showing promise in the treatment of cancer due to their selectivity in targeting cancer cells and inducing tumor cell death. While they offer advantages over traditional chemotherapy, limitations such as high cost, immunogenicity, and limited effectiveness in certain cancers still persist. To overcome these challenges, research is underway to improve the efficacy of monoclonal antibody therapy by studying their mechanisms of action and identifying new approaches to increase clinical efficacy. One such approach is engineering strategies to augment ADCC activity. Combining tumor-targeted monoclonal antibodies with ICB has also shown promise in maximizing clinical benefits. Identifying biomarkers of efficacy and resistance will be crucial in developing future treatment strategies that incorporate inhibitors of alternative signaling pathways to abrogate resistance. With evolving treatment paradigms, monoclonal antibodies hold great potential in offering curative therapy for many cancer patients and paving the way for a brighter future in cancer treatment.

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