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Monoclonal Antibodies and Clinical Use in the Field of Cancer Treatment

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Abstract:

Monoclonal antibody-based cancer therapy has now been proven successful and effective in the therapeutic treatment of both haematological malignancies and solid tumours. Antibodies are proteins that bind to specific antigens naturally circulating in the body, and monoclonal antibodies are designed to mimic this biological process. Possessing high specificity, monoclonal antibodies can be engineered to directly target cancerous cells, making them highly valuable in clinical settings as they cause minimal damage to non-cancerous cells. As an emerging technology in cancer treatment, they are used alongside established methods such as surgery, radiotherapy, and chemotherapy. This paper explores the historical development of monoclonal antibodies, detailing their production processes and examining current clinical applications in cancer treatment, along with the controversies surrounding their use. It also assesses the balance between the economic costs associated with monoclonal antibody therapies and their clinical success, while drawing comparisons with other newly emerging therapeutic technologies in the field. By synthesizing these elements, the paper aims to provide a comprehensive overview of the role of monoclonal antibodies in cancer treatment and their position within the broader landscape of oncology therapies.

Keywords: Monoclonal therapeutics; personalised treatments; monoclonal antibody production; cancer treatment; cancer immunotherapy.

1. Introduction

Monoclonal antibodies are laboratory-manufactured molecules designed to bind to antigens and have proven revolutionary in medical treatment and clinical applications for numerous fields such as immunology, cancer and infectious diseases. These lab-created proteins mimic the body's immune system to which can be programmed to specifically bind and target cancerous cells. The innovative combination of serological techniques for cancer cell surface antigen discovery, along with hybridoma technology, made monoclonal antibodies a pivotal technology within biotechnology, producing highly specific antibodies

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[1]. Since the licensing of the first monoclonal antibody muromonab-CD3 (Orthoclone OKT3) in 1986 by the US Food and Drug Administration (FDA), combined worldwide sales have reached 125 billion dollars [2]. Now, as medicine has improved to a new era of specialised therapy, as of November 10, 2014, forty-seven different monoclonal antibody-related treatments and products have been approved for clinical therapy in the US or Europe for a wide variety of diseases [2].

However, despite their widespread usage, the clinical advancement of these molecules is largely stunted by the production and purification process involved in their manufacturing. This high economic cost, paired with the potential accompanying risk of side effects, puts monoclonal antibodies into an area of controversy. Furthermore, monoclonal antibodies, despite having the ability to be highly specific, have a limited penetration ability, reducing the overall effectiveness. These challenges have prompted the continued development of next-generation alternative clinical therapeutics. Newly emerging technologies such as bispecific antibodies, nanobodies and anti-drug conjugates aim to reduce these obstacles in the medical treatment of cancer.

2. History of Monoclonal Antibodies

The success of monoclonal antibody production marks a revolutionary breakthrough within medical history and the advancement of personalised therapy. The journey of monoclonal antibodies officially began when, on August 7th, 1975, César Milstein and Georges J.F. Köhler published a report in Nature involving a detailed methodology for the large-scale production of these molecules [3]. This innovative technique fused B-lymphocyte cells and immortal myeloma cells, forming a hybrid cell typically referred to as the hybridoma cell. Later in 1986, the first therapeutic monoclonal antibody product, muromonab-CD3 (Orthoclone OKT3), was approved by the US Food and Drug Administration (FDA) for commercial use in treatment. Since then, monoclonal antibodies have left a lasting impact on medicine, providing a practically unlimited source of diagnostic and therapeutic reagents.

3. Specific Monoclonal Antibody Production

Monoclonal antibodies are produced upon the fusion of spleen B cells to myeloma cells, which form hybridoma cells. These hybridoma cells are then equipped with the specificity provided from the B-lymphocytes, as well as the indefinite division that the cancer cells are capable of; these can then be cloned and screened for the desired antibodies. The B cell is crucial within host cell defence, as it secretes antigen-specific immunoglobulin, which is a 'Y-shaped' protein produced by plasma cells that binds to the specific antigen. B-cell production initiates from immunizing the host organism, which is typically a laboratory mouse, over several weeks. This period allows the full stimulation of the differentiation of plasma B cells from deactivated B cells [1]. These activated B cells are isolated from the spleen of the mice under highly aseptic conditions. Then, prior to cell fusion, metastatic tumour cells are incubated in 8-azaguanine for the formation of the non-functional hypoxanthine-guanine phosphoribosyl transferase genes of the myeloma cells [1]. Afterwards, fusion with the myeloma cells occurs, which is initiated by fusogenic agents; polyethylene glycol and Sendai virus [4]. Polyethylene glycol, also referred to as PEG, can be used to create PEGylated antibodies, is a fusogen that can increase the circulatory in vivo half-lives of antibodies, and also promote membrane fusion [4]. The Sendai virus is a viral agent that can destroy cell membranes, a fundamental step in the merging of the spleen B cells and the myeloma cells.

Upon fusion of the lymphocyte and cancer cells, we require a selection to extract the hybridoma cells that have been fused successfully. The fused mixture of cells undergoes the HAT medium, also referred to as hypoxanthine-aminopterin-thymidine, for the selection, as cells that were unsuccessfully fused will fail to survive in this solution. The hybridoma cells that successfully survived will then be cloned to create numerous identical antibodies specific to the antigen it was primarily exposed. Finally, the clones are screened to ensure they produce antibodies that are correct and exhibit the required specificity. This is an extensive and laborious procedure; hence, numerous processes have been developed since 1975 for more efficient selection to speed up monoclonal antibody generation. The ELISA testing method can be effectively used during screening, also known as the enzyme-linked immunosorbent assay, which can detect and count the quantity of specific antibodies within a sample [5]. Other substances, such as flow cytometry, can also be used, which is a technique that uses lasers to produce light sources, then signals for detection to be converted into electrical signals to have samples analysed according to their light scattering capabilities [6]. Once validated, they can be cultured in vitro for long-term antibody production. Modern advancements, such as humanization (via recombinant DNA technology to reduce immunogenicity) and large-scale cultivation in Chinese hamster ovary (CHO) cells, have further optimized production efficiency and clinical compatibility.

4. Clinical Usage of Monoclonal Antibodies

Monoclonal antibodies are a crucial aspect of diagnosis and treatment in personalised therapy of numerous pathogenic microorganisms and diseases. One of the most valuable aspects of these artificially cultured proteins is the monoclonal antibody-based immunotherapy, which is now one of the most used types of synthetic treatment, along with chemotherapy and hormonal therapy. Of those specifically engineered antibodies, several have been approved by the FDA to target and kill cancer cells.

Alemtuzumab is a humanized monoclonal antibody (IgG1) targeting CD52, a glycosylphosphatidylinositol-anchored glycoprotein expressed on most malignant lymphoid cells [7]. Approved in 2001 in the EU and US for fludarabine-refractory chronic lymphocytic leukemia (CLL) unresponsive to alkylating agents, it is also used for Relapsing Remitting Multiple Sclerosis (RRMS), which involves myelin sheath damage[8]. According to information released by the NHS regarding dosages, Alemtuzumab is intended to be used in treatment by administration in vitro across a span of 2 weeks.

Bevacizumab, a humanized IgG1 monoclonal antibody, binds to vascular endothelial growth factor (VEGF), a protein that promotes tumor growth and metastasis. By blocking VEGF from binding to its receptors on cancer cells, it inhibits tumor blood vessel formation, stunting cancer growth [9]. Initially approved by the FDA for metastatic colorectal cancer in combination with chemotherapy, clinical trials with 829 patients showed a 25% reduced risk of death [10]. It is now licensed for metastatic colon cancer, kidney cancer, non-small cell lung cancer, and glioblastoma [9]. Administered via intravenous push, it is often combined with chemotherapy. Notably, VEGF inhibition can cause hypertension, bleeding, or gastrointestinal perforation, limiting its use in high-risk patients.

Thirdly, Trastuzumab is another humanised monoclonal antibody, which is a form of targeted therapy for Human epidermal growth factor receptor 2 HER2-positive breast cancers. Trastuzumab is highly responsive to the HER2 protein, which is within 20-30% of human breast cancers and higher risk of death [11]. Trastuzumab, marketed as Herceptin, is making an evolutionary leap in the medicinal advancements in breast cancer care. Trastuzumab was primarily administered intravenously directly into the vein; a subcutaneous formulation alternative was later developed [12]. First-line Trastuzumab doubled with chemotherapy portrayed a 25% higher survival rate in relative to chemotherapy only [11]. However, although Trastuzumab is classified as the most effective clinical treatment in oncology, it still has its limitations. Mechanisms limiting the capability of this antibody include challenges in the binding of trastuzumab to the HER2 antigen, the high activity of HER2 downstream signalling pathways, or signalling through alternate pathways, as well as a failure to trigger an immune response or the destruction of the cancerous body cells [13].

5. Limitations of Monoclonal Antibodies

Monoclonal antibodies reaching hospitals were an evolutionary step in cancer treatment advancements. Regardless, there are still many remaining limitations which reduce therapeutic efficiency in the treatment of solid tumours, a crucial problem is the poor tumour tissue penetration. This major drawback exists as these antibodies must overcome both physical and physiological obstacles for penetration into cancerous body cells. The large size of the monoclonal antibody leads to diffusion being difficult, making it more challenging to reach the target tumorous cell. Another limitation is the immunogenicity of reagents, causing issues as there is insufficient uptake within deposits of solid cancerous tumours. Once again, this problem is a result of the size of the monoclonal antibodies, making it difficult to achieve effective drug delivery. A third issue surrounding monoclonal antibodies is the high cost in production and manufacturing, as they require a sophisticated eukaryotic machine in order to maintain their active form [14]. Furthermore, studies show molecules must be injected with large volumes of Rituximab for development, meaning the need for large cultures of mammalian cells, all of which are economically costly [14]. Following a thorough selection and purification process further makes monoclonal antibodies less financially viable. Due to the high cost during manufacturing, the annual cost per patient can reach 35,000 dollars for antibodies specific to cancer treatment. This acts as a challenge, preventing monoclonal antibodies from reaching a wider audience of patients, stopping many from receiving this treatment, which can be critical to prolonging life and reducing mortality rate.

6. Future Technological Alternatives

To overcome the limitations of monoclonal antibodies, alternatives have been developed by scientists to provide the finest care for patients. Nanobodies have been developed as an option with the potential to substitute monoclonal antibodies, which have a significantly reduced size. Nanobodies have identical structures to the heavy chain variable domain as human immunoglobulins, hence are still equipped with the capability of being able to bind to

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specific antigens. Nanobodies are incredibly petite in size, as well as highly specific with flexible delivery routes [15]. The achievement of manufacturing an antibody of such reduced size is a key milestone within medicinal discovery, as this allows easier diffusion of membranes to reach target cancerous cells, making therapy of difficult-to-reach tumours plausible. Furthermore, nanobodies are developed at a reduced cost relative to conventional monoclonal antibodies as they utilise E. coli, which is a low-cost resource of a rapid fermentation cycle, making production more efficient [15]. The combined advantages of nanobodies make this therapy more effective in treatment, as they both have more effective diffusion to target cancerous cells and are more accessible to patients due to the lower cost.

7. Conclusions

Monoclonal antibodies are formulated from lymphocyte B cells with myeloma cells to produce hybridoma cells, which are then selected and screened for the desired monoclonal antibody. Since the first monoclonal antibody was approved by the FDA for personalised therapy, numerous more treatments have been granted for marketing. Such as Alemtuzumab, Bevacizumab and Trastuzumab, all of which are used for cancer treatment at different types of tumours. These treatments have all been clinically proven to be successful. Bevacizumab has been shown by the FDA to cause a 25% reduction in deaths when trialled with 829 patients. However, many controversies still reside with monoclonal antibodies as they are one of the most expensive medicines for patients and also lack ideal penetration from their large size, making drug delivery more difficult. Nanobodies have since then been discovered as an alternative which overcomes these limitations, but still hold the same functions of being able to provide personalised therapy for cancers. Nanobodies are not only cheaper in production but also smaller in size, making the diffusion of these substances across membranes easier and more efficient. Regardless of monoclonal antibody discovery marking a huge milestone in the development of personalised therapy, replacement technologies have been created, demonstrating the undiscovered potential of medicinal practice.

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