BAOJ Microbiology

Abdullah Farhan ul haque Saeed, et al., BAOJ Microbio 2016 2: 2
2: 015

Research Article

Monoclonal Antibody in Quest of Cancer Therapeutics

Abdullah Farhan ul haque Saeed[1*] and Saima Ashraf Awan[2]

[1]Key Laboratory of Biopesticide and Chemical Biology of Education Ministry, School of Life Sciences, Fujian Agriculture and Forestry University, Fuzhou-350002, China

[2]Fujian Agriculture and Forestry University, Fuzhou-350002, China

Abstract

Monoclonal antibodies (mAbs) have been an essential part of cancer therapy and one of the most vital approaches for current cancer treatment. These essential immune molecules function through on-target antigen specificity, complement or antibody dependent cell mediated cytotoxicity, structural and physiological modifications in host immune system towards the malignant cells and their effective removal from the human patients. The mAbs are of great scientific and practical significance being homogeneous and monospecific. Currently, more than 20 recombinant antibody drugs based on immune checkpoint antagonists, bi-specific antibody, and antibody drug conjugates have been approved for the successful cancer or malignant tumor treatment. The current study will help to understand the significance of mAbs and cytotoxic drugs against cancer or tumor related malignancies and to build better therapeutic strategies.

Keywords: Monoclonal Antibody; Oncology; Cytotoxicity; Cancer; Tumor; Therapy

Introduction

The use of mAbs was first described by Köhler and Milstein in 1975. Since then, the understanding of remarkable potential of antibodies has been established, that began more than two centuries ago in comparison with polyclonal antibodies which were being used against infectious diseases for decades. The mAbs comprise two heavy (V_H) and two light chains (V_L) and are divided into many isotypes on the basis of the heavy chain they contain (Figure 1). Therapeutic mAbs are typically of the g-immuno- globulin (or IgG) isotype. The mAbs are being used to treat cancers, tumors and other related fatal diseases since 15 years. They are saving millions of lives each year; instead, there is still room for the improvement of these essential therapeutic drugs. Since the discovery of mAbs by Köhler and Milstein, it was broadly assumed that, these unique molecules would be perfect biological reagents for imaging and therapeutic just like the magical bullets fantasized by Paul Ehrlich at the beginning of the 20th century. The mAbs are selected on the basis of their high specificity, stability and their affinity to wide range of molecules and are useful for targeting the specific antigens and many kinds of other foreign reagents. They were used against many diseases extensively, but later on, their origin and production mechanisms revealed their murine nature which proved to be incompatible for the human immune system components, and subsequently are eliminated. The biological effectiveness of mAbs became strictly limited and lead to disappointment since the murine antibodies are not as good as human antibodies in the elicitation of human immune system and to destroy the malignant cells, bacteria and virus of interest [1-7]. Since their discovery, these invaluable unique biological entities were quickly applied in many areas of diagnostics and treatment in oncology, immunohistochemistry, flow cytometry and related molecular tools. They have the exceptional ability to bind with specific antigen epitopes due to their distinctive molecular structure to the molecules known as cluster of differentiation (CDs) [8,9].

Cancer is evolved by the incidence of tumor-promoting inflammation, escape from immune surveillance, favored by immunodeficiency and sustained immunosuppression. A study revealed association of 40% increased cancer risk with low natural toxicity of peripheral blood natural killer (NK) cells as compared to the individuals harboring high cytotoxicity activity. The tumor surveillance and novel immunotherapeutic success is supported by the finding of correlation of the decreased NK-cell activity in the patients which are diagnosed with familial melanoma [10-21]. The present study describes the applications of cytotoxic drugs, mAb-based therapeutics and their mechanism against cancer/tumor therapy.

Cytotoxic Drugs

The cytotoxic drugs are being used broadly under specific conditions for the treatment of hematological, solid malignant tumors and have no exposure limits. Consequently, they have changed the natural progress of the diseases considerably. Anti-

***Corresponding author:** Abdullah Farhan ul haque Saeed, Key Laboratory of Biopesticide and Chemical Biology of Education Ministry, School of Life Sciences, Fujian Agriculture and Forestry University, Fuzhou-350002, China, E-mail: abdullahfarhan@hotmail.com

Sub Date: July 15, 2016, **Acc Date:** August 4, 2016, **Pub Date:** August 5, 2016.

Citation: Abdullah Farhan ul haque Saeed and Saima Ashraf Awan (2016) Monoclonal Antibody in Quest of Cancer Therapeutics. BAOJ Microbio 2: 015.

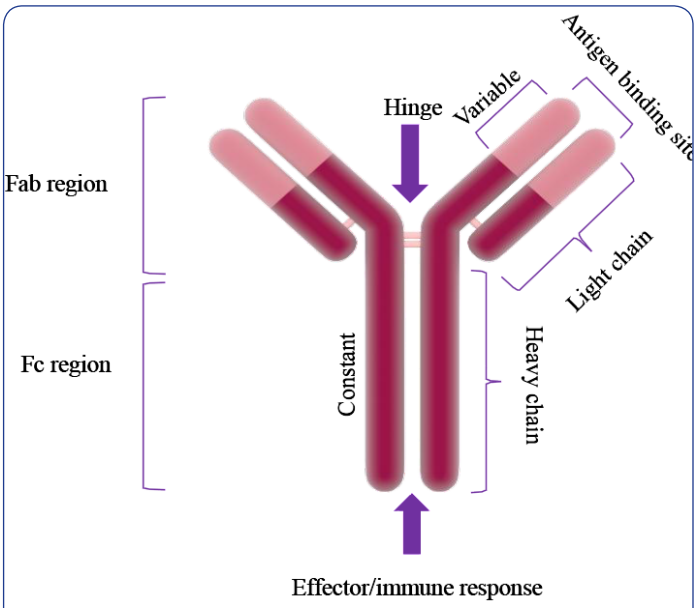

Figure 1: Monoclonal antibody and its components.

neoplastic is the most common form of cytotoxic drugs in used. These drugs inhibit or prevent the cells physiology, rapid growth and division of the cells. They can influence the growth of other cells (hair follicles and digestive epithelial cell layer), damages normal cells during period of treatment and target cancer cells as chemotherapy administration. Recently, they have been used to treat various diseases such as psoriasis, rheumatoid, juvenile rheumatoid arthritis, and steroid-resistant muscle conditions. Their clinical efficacy is altered in terms of early cessation of treatment and increased risk of tumor relapse by on-target adverse events due to their elementary mode of action. Various anticancer drugs such as brentuximab vedotin and trastuzumab emtansine have greatly transformed the outlook for the technique of cancer therapy Numerous novel alternative approaches such as the conjugation of cytotoxic agents to humanized antibodies (also known as Antibody–drug conjugates, ADCs) have been established to improve the quality of cancer treatments. Several features such as the target antigen, antibody linker and cytotoxic payload must be considered, evaluated and thoroughly checked for the design and synthesis of ADC drug [22,23].

Therapeutic MAbs

The mAbs have significant influence on medical care for a number of diseases, including inflammatory diseases and cancers. These have been an essential part in basic research of immunology, pharmaceutics, medical sciences, biotechnology and cancer therapeutics due to high specificity/affinity for the target antigens and their removal by methods such as complement-dependent cytotoxicity (CDC) or antibody dependent cell-mediated cytotoxicity (ADCC). Various mAbs have been approved by United States Food and Drug Administration (US-FDA) (Table 1). The antibodies impart therapeutic benefit to target antigens in the case of trastuzumab (Herceptin®), bevacizumab (Avastin®), and cetuximab (Erbitux®). However, tumor-specific mAbs are usually deprived of the therapeutic activity [24-27].

History and Success of Therapeutic MAbs

The mAbs are first generated in 1975 using the hybridoma technology by immunizing animal species against a specific antigen and fusion (by chemical- or virus-induced methods) of B-lymphocytes from spleen and immortal myeloma cell line. They are produced from single B-lymphocyte clone and bind to the same epitope. With the introduction of new therapeutic mAb products, the global mAb market has been elevated to compound annual growth rate (CAGR) of 5.3% to nearly $58 billion [2,28,29].

OKT3 was first antibody that was developed to prevent acute organ transplant rejections in recipients. It was generated from hybridoma technology and subsequently approved by US-FDA in 1986. The murine mAb induces human anti-mouse antibody (HAMA) response, toxicity, short half-life and reduced efficacy in the human patients. For that reason, various portions of murine antibody were replaced with human counterparts in 1980s or fully humanized antibodies have been generated in 1990s to reduce the immunogenicity of the murine antibody (chimerization and humanization) by recombinant DNA technology, phage display libraries [30-34] and transgenic mice [35-37].

The Fc function of antibodies is significant for CDC and ADCC mediated therapy to kill the malignant tumor cells that have been successfully applied in the clinic. The repeal of tumor cell signaling (cetuximab and trastuzumab), ADCC effector function (rituximab) and the T cell immune modulation (ipilimumab) have been most successful therapeutic approaches that led to the approval of antibodies [38-42].

Various therapeutic antibodies are currently being tested in numerous stages of clinical trials. The use of FDA-approved therapeutic antibodies in patients with solid tumors has been successfully treated with class of the ErbB family including EGFR and VEGF [43-48]. Colorectal cancer patients with wild-type KRas tumors have been effectively treated with anti-EGFR that showed enhanced responses, survival and disease control [49-51].

Advantages of MAbs

The success of mAb therapeutics began with the progress in genetic and molecular techniques to produce recombinant chimeric mouse-human or humanized mAbs in parallel to naturally occurring human IgG [52]. These molecules are developed from single hybridoma clone which reacts with the same epitope on antigens and have widespread applications in targeting advanced tumor related diseases [53,54]. The therapeutic mAbs allow unlimited production of recombinant human IgG (or bispecific IgGs) with highly specific properties. They are not needed to be pure or characterized, thus, are not needed to produce large quantities of specific antibody. The mAbs are selected for specific epitope specificities to generate antibodies against extensive number of antigenic determinants. IgGs are naturally occurring globular immune proteins which are accepted as therapeutic agents by the host immune system. IgG binds with the molecular epitopes of target antigen and relates with effector arms of the immune system [55]. They have long half-lives, modification capacity, on-target specificity, tumor associate binding, signal alterations, tumor angiogenesis blockade, effective

Tablel 1: FDA-approved monoclonal antibodies in oncology.

Scientific name	Common name	Origin and isotype	Company	Target	FDA approval
Ranibizumab	Lucentis	humanized Fab	Genentech	Age-related macular degeneration	2006
Panitumumab	Vectibix	human IgG2κ	Amgen	Metastatic colorectal carcinoma	2006
Eculizumab	Soliris	humanized IgG2/4κ	Alexion	Paroxysmal nocturnal hemoglobinuria	2007
CertolizumabPegol	Cimzia	Peglated humanized Fab	UCB, Inc	Crohn's disease, rheumatoid arthritis	2008
Golimumab	Simponi	human IgG1κ	CentocorOrtho Biotech	Rheumatoid and psoriatic arthritis and ankylosing spondylitis	2009
Canakinumab	Ilaris	human IgG1κ	Novartis	Cryopyrin-associated periodic syndromes	2009
Ustekinumab	Stelara	Human IgG1κ	Centocor Ortho Biotech	Plaque psoriasis	2009
Catumaxomab	Removab	Murine/rat hybrid IgG	TRION Pharma	Malignant ascites	2009
Ofatumumab	Arzerra	Human IgG1κ	Glaxo Grp Ltd	Chronic lymphocytic leukemia	2010
Tocilizumab	Actemra	Humanized IgG1κ	Roche/Chugai	Rheumatoid arthritis	2010
Denosumab	Prolia	Human IgG2κ	Amgen	Malignant osteoporosis	2010
Edrecolomab	Panorex	Murine IgG2a	Wellcome/Centocor	Colon cancer	
I^{131}-TNT	Cotara	I^{131}-chimeric IgG1	MediPharm Biotech	Lung cancer	
Nimotuzumab	Theracim	Humanized IgG1	CIM/CIMAB/YM Bioscience	Nasopharyngeal carcinomas, head and neck tumors	
trastuzumab	Herceptin	Humanized IgG1	Genentech	Breast cancer	2010
Ipilimumab	Yervoy	Humanized IgG1	Bristol-Myers	Metastatic melanoma	2011
Pertuzumab	Perjeta	Humanized IgG1	Genentech	Breast cancer	2012
Cetuximab	Erbitux	Human/mouse IgG1	ImClone	Colorectal, head and neck cancer	2012
Rituximab	Rituxan	Humanized IgG1	Genentech	non-Hodgkin lymphoma, chronic lymphocytic leukemia	2012
Bevacizumab	Avastin	Humanized IgG1	Genentech	Epithelial ovarian, cervical, colorectal, breast and lung cancer, renal cell carcinoma andglioblastom	2014

bio-distribution in circulatory systems, and prolonged anticancer responses. Clinical modifications such as Immunoconjugates including antibody-drug conjugates and radio immunoconjugates that can deliver toxic payload to the cancer cell are beneficial. Bifunctional antibodies and chimeric antigen receptor T cells retarget cellular immune system towards cancer cells by using specificity of the mAbs [56-58].

Mechanisms of Tumor Targeting Clinical Efficacy of MAbs

The mAbs are really efficient in tumor targeting which is the best immunotherapeutic strategy and have shown impressive responses against malignant tumors in cancer patients. They can specifically bind with the antigens, exerting anti-neoplastic effects to the transformed cells or neutralize trophic signals released by the tumor stroma, they also activate and play an essential role in effector or regulatory components of the immune system [59-64].

There are numerous mechanisms for the tumor targeting clinical efficacy of the mAbs immunotherapeutics: (i) the mAbs can inhibit the cancer cell-intrinsic signal transduction pathways which are important for the survival/proliferation (ii) they activate the pro-apoptotic receptors which are specifically expressed by the neoplastic cells i.e., tumor necrosis factor receptor super family, member 10B, TNFRSF10B, which are best known as TRAILR2 or DR5, (iii) Initiation of the innate response by selective opsonization of malignant cells which is based on ADCC, cellular phagocytosis, and CDC (Figure 2) [65-74], (iv) mAbs specific for tumor associated antigen (TAA) and T-cell marker recruit or activate T lymphocytes in the proximity of the cancer cells (v) the targeted delivery of toxins or radionuclides to neoplastic lesions (vi) trophic factor released by stromal or malignant components of the tumor mass are effectively and efficiently neutralized by the specific mAbs [75-83].

Conclusions

The mAbs have been extensively used for the treatment of cancer or tumor related diseases on the basis of tumor targeting antigen specificity, cell mediated cytotoxicity and immune modifications. Cytotoxic therapeutic drugs with mAb payload are efficient for the treatment of hematological and solid malignant tumors. They

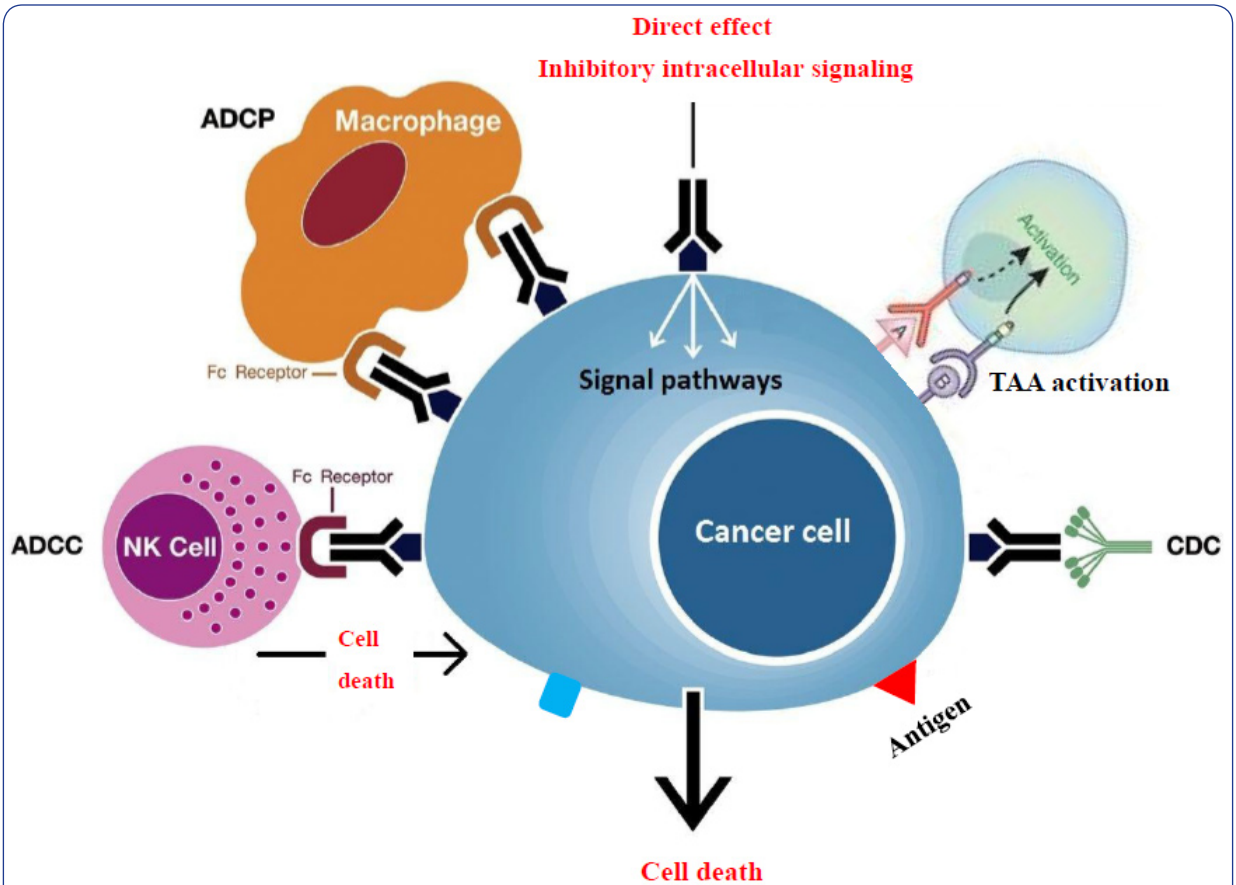

Figure 2: The mechanisms of tumor targeting clinical efficacy of the mAbs immunotherapeutics and cytotoxicity.

have no exposure limits that effect physiology, specific antigen binding, neutralization of trophic signals, and prevention/division of rapid growth of malignant tumor cells. The present study aims to extend the applications of mAbs into many exciting malignancies treatments with advanced antibody mediated cytotoxic techniques, ensuring a significant position for these powerful molecules at the forefront of research and cancer therapeutics.

Acknowledgements

The author thanks Miss. S. A. A. for assistance in illustrations.

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