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REVIEW

Monoclonal Antibody Therapy in Asthma

By Arezoo Campbell, PhD

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ABSTRACT
Monoclonal antibodies (mAb) are biological molecules that have the unique capability of precisely binding to a single target. Technological advances have made it possible to design mAbs that bind to specific cellular components for therapeutic interventions. In this review, we will begin with a description of antibodies and how their unique structure and characteristics make them an accurate therapeutic tool. The second part of the review will summarize the production and nomenclature of therapeutic monoclonal antibodies. The last section will focus on asthma to elucidate the precise mechanism by which mAbs function to modulate the pathophysiology of a disease state.

Introduction

In 1975, the first monoclonal antibody was generated. However, it was more than a decade later (1986) that the first monoclonal antibody (Orthoclone OKT3 – muromonab-CD3) was licensed as a therapeutic agent in the prevention of kidney transplant rejection. Since then, the field has substantially grown and has become a multibillion-dollar industry.[1]

I. Endogenous antibody production and its role in the immune system:

B cells are a component of the adaptive immune response. The sole responsibility of these specialized cells is to produce secreted forms of immunoglobulins, commonly referred to as antibodies. In this review, the terms immunoglobulin and antibody will be used synonymously. Endogenously secreted immunoglobulins are present in five specific isotypes (IgG, IgM, IgD, IgA, and IgE). The most common and functionally versatile form is IgG, which is typically used as the isotype of choice for the production of therapeutic monoclonal antibodies.[2]

An immunoglobulin has a Y-shaped structure composed of two identical heavy chains and two identical light chains. The light and heavy chains associate together to form the two arms of the Y-shaped molecule. Cleavage of the molecule with protease yields two fragment antigen binding (Fab) and one fragment crystallizable (Fc) pieces (Figure 1). Antibodies have the capability of specifically binding to a variety of biological macromolecules, which is commonly referred to as the "antigen." These antigens are typically proteins or carbohydrates present on the surface of potential pathogens. The arms of immunoglobulins consist of two identical antigen-binding sites that are used to bind a wide variety of macromolecules. By doing so, not only do they neutralize a potential pathogen, but they also mark them for destruction by other components of the immune system. These components include macrophages, which can then opsonize the antibody-coated pathogens or natural killer cells that contain receptors for the Fc region of antibodies and can destroy cells by antibody-dependent cell-mediated cytotoxicity.[2] Biotechnology has taken advantage of the unique ability of antibodies to bind specific molecules in order to develop therapeutic strategies. The binding of mAb to specific molecular structures allows precise targeting of the therapeutic regimen, which is an advantage over traditional small molecule treatments.

II. Production and nomenclature of monoclonal antibodies:

The production of monoclonal antibodies was made possible by the creation of hybridoma technology described by Köhler and Milstein.[3] This process requires immunization of an animal (usually mice) with the desired target antigen. Once an adaptive immune response has been generated, spleen cells are isolated and fused with immortalized myeloma cells to form the antibody-producing hybridoma cells. Multiple drugs are added to the culture medium to prevent proliferation of all but the hybridoma cells. The hybridomas and antibodies produced are monitored by limited dilution to select the specific cell that is generating the mAb with the best capability of binding the target antigen.[4,5]

A limitation of using mouse-derived mAb for therapeutic purposes is the initiation of an immunological response in the human body against what is perceived as a foreign antigen. This is referred to as "immunogenicity." However, genetic engineering has made it possible to generate chimeric antibodies derived from both mouse and human species. Although

less immunogenic, chimeric antibodies still have the possibility of inducing an immune response. This has prompted the creation of humanized (minimal mouse-derived components) and fully human antibodies.[2]

The World Health Organization has created a rule for naming therapeutic monoclonal antibodies.[6] The prefix is usually random and unique so that it would be easy to distinguish one mAb from another. The substem A component of the name is related to the disease state or target of the mAb. Substem B is based on the species derivation of the antibody. Finally, a suffix of "mab " is added to all monoclonal antibody therapies (table 1).

III. Mechanism of action of monoclonal antibodies used in the treatment of asthma:

Asthma is an inflammatory airway disease that causes constriction of the bronchi, which leads to coughing, wheezing, and difficulty breathing. In the United States, there are more than 25 million individuals living with asthma, and the prevalence is increasing (7.3% in 2001 compared to 8.4% in 2010).[7] Complex interactions between genetic predisposition and environmental factors contribute to the etiology of asthma. The genes most associated with asthma are ones that influence the immunological process and bronchial hyperreactivity. Environmental factors that have been linked to asthma include history of smoking and exposure to secondhand smoke, living in urban areas that experience high air pollution, obesity, and stress.[8] It is suggested that epigenetic factors such as DNA methylation status, chromatin remodeling that dictates DNA transcription, and microRNA regulation of translation may all contribute to the complexity of the gene-environment interactions that underlie asthma pathogenesis.[9]

Atopy is a predisposition to develop allergic responses to innocuous antigens such as plant pollen, dust mite, or cat dander. Atopic individuals have an increased chance of developing asthma. They have higher levels of the IgE immunoglobulin isotype. IgE is unique because, unlike other antibody isotypes, it binds tightly to the surface of cells that express the specific receptor subtype (FcεRI). These include mast cells, basophils, and activated eosinophils. Atopic individuals also have a greater number of eosinophils in their blood compared to normal people. Eosinophils, along with mast cells, are specialized granulocytes that evolutionarily are believed to have developed as a means of defending against parasitic infections. Normally, the number of eosinophils are tightly regulated, and they are only recruited from the bone marrow when necessary. This is because they contain highly toxic mediators that can inadvertently damage host tissue as bystander effects.[2]

The production of eosinophils are induced by the cytokines IL-3, IL-5, and GM-CSF. These cytokines are produced by type 2 helper T cells (TH2). TH2 cells also produce IL-4 and IL-13, which promote isotype switching to IgE in antigen-specific B cells. This antigen-specific IgE binds to the Fc receptor on mast cells. This sensitization step is necessary for priming mast cells to carry antigen-specific IgE on their surface. Upon subsequent antigen encounter, mast cell release the content of their granules. These granules contain histamine, which causes smooth muscles of the bronchi to constrict and vasculature to become permeable to the entry of other immune competent cells. Once activated, mast cells and eosinophils synthesize and release leukotrienes, which additionally contribute to smooth muscle contraction, vascular permeability, and mucus production in the airways that result in the symptoms observed in asthmatic individuals.[2] Because the pathogenesis of asthma is complex and incorporates many cell type and mediators, for simplicity, the immunological players that are targeted by FDA-approved monoclonal antibody therapy are selectively displayed in Figure 2.[2,10]

Presently, asthma is controlled by treatment with a combination therapy consisting of targeting ß2-adrenergic receptor agonists and corticosteroids. The former results in relaxation of airway smooth muscles, and the latter contributes to dampening the inflammatory response. Approximately 5-10% of asthmatics do not always respond well to these therapeutic interventions, and thus the use of monoclonal antibodies provides a more targeted approach that may be useful in controlling asthma in this subset of individuals.[11,12] In 2003, Xolair (omalizumab) became the first FDA-approved monoclonal antibody for the treatment of severe asthma. Omalizumab binds to soluble IgE molecules and inhibits the binding of antigen-specific IgE to Fc receptors on mast cells and basophils.[13] Nucala (mepolizumab) is another therapeutic monoclonal antibody that was approved in 2015 for treatment of severe asthma in patients 12 years or older. This therapeutic mAb binds to IL-5 and thus blocks the binding of the cytokine to cell surface receptors on eosinophils. The inhibition of IL-5 binding reduces both the production of eosinophils from the bone marrow and the survival of the cells.[14] In March of 2016, the FDA approved the third therapeutic monoclonal antibody, Cinqair (reslizumab), for the treatment of patients with severe asthma age 18 years and older. The mechanism of action of this humanized IL-5 binding mAb is the same as mepolizumab.[15] Figure 2 shows the specific pathological pathway that is modulated by the three FDA-approved mAbs.

A number of other monoclonal antibodies, specifically targeting other molecules that are thought to be involved in the pathogenesis of asthma, are presently undergoing clinical trials. Examples of these are listed in table 2. The efficacy of the humanized mAb benralizumab has been evaluated in two phase III clinical trials for treatment of severe uncontrolled asthma with eosinophilic inflammation. AstraZeneca announced on May 17, 2016, that the phase III studies show that the mAb is well tolerated and reduces the asthma exacerbation rate compared to the placebo.[16] This mAb specifically targets the α-chain of the IL-5 receptor expressed on eosinophils and basophils, leading to their demise by antibody-dependent cellular cytotoxicity.[17] The company is planning on submitting the regulatory applications in the second half of 2016.

Interleukin-17 (IL-17) is a cytokine that is produced by type 17 helper T cells (TH17). IL-17 interacts with IL-17 receptor A (IL-17RA), expressed on the smooth muscle of the airways, and modulates lung inflammatory processes . Brodalumab is a human anti-IL-17 receptor A mAb that binds the receptor and does not allow binding of IL-17. It is thought that brodalumab also blocks binding of IL-25. In a phase II, double-blind, placebo-controlled study, it was shown that brodalumab was not able to control moderate to severe asthma, although a subpopulation of patients were identified who may benefit from the use of this mAb.[18] Ligelizumab is a humanized mAb that binds IgE. In a double-blind, randomized, placebo-controlled study, it was shown that ligelizumab was more effective compared to omalizumab (an FDA-approved drug with the same mechanism of action) in patients with mild allergic

asthma.[19]

Roche has developed lebrikizumab, which is a humanized mAb targeting IL-13. IL-13 is a cytokine that has been associated with eosinophil survival and migration, as well as mediating the class switching of B cells to IgE.[20] A recent investor update from the company indicated that the mAb significantly reduced exacerbations in patients with severe asthma in one of two phase III clinical trials. The second clinical trial failed to show efficacy, and the company is further analyzing the results.[21] Tralokinumab is another IL-13 binding mAb that has been evaluated for safety and efficacy. The phase II randomized, double-blind, placebo-controlled study showed that, in patients with severe uncontrolled asthma, this mAb failed to significantly reduce asthma exacerbations. However, in the study, a subpopulation of asthmatics was discovered to have benefited from the therapy. A phase III study is further determining the possibility of using tralokinumab in this group of patients.[22]

Conclusion

Considering that more than 25 million individuals in the United States are asthmatic, it is not surprising that biotech companies are investing top dollars in developing new monoclonal antibody therapies for the treatment of asthma. Because the immunological processes that underlie asthma are complex, demonstrating safety and efficacy of specific monoclonal antibodies have proven difficult. Although conceptually promising, clinical trials with mAbs that specifically blocked IL-17 or IL-13 showed mixed results. Notwithstanding, there are several mAbs that are in phase III clinical trials. As research discovers more specific markers in the pathogenesis of asthma, it is likely that there will be more mAbs developed for the treatment of patients with asthma.

About the Author

Arezoo Campbell received her Ph.D. in Toxicology from the University of California, Irvine (UCI). She is an Associate Professor of Pharmaceutical Sciences in the College of Pharmacy at Western University of Health Sciences. She is also an Associate Adjunct Professor at the University of California Irvine, School of Medicine. The main focus of her laboratory is to determine how aberrant induction of innate immune responses may accelerate the pathogenesis of neurodegenerative disorders. Dr. Campbell is the Speaker of the Assembly appointee to the Department of Toxic Substances Control Independent Review Panel. She is the current president of the Southern California Chapter of the Society of Toxicology.

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Table 1. Nomenclature of Therapeutic Monoclonal Antibodies

Prefix	Substem A		Substem B		Suffix
Random	Based on the target of the mAb:		Based on species derivation of the immunoglobulin:		-mab
	-c(i)-	Cardiovascular	*o*	Mouse	
	-k(i)-	Interleukin	*u*	Human	
	-l(i)-	Immunomodulating	*xi*	Chimeric	
	t(u)	Tumor	*zu*	Humanized	

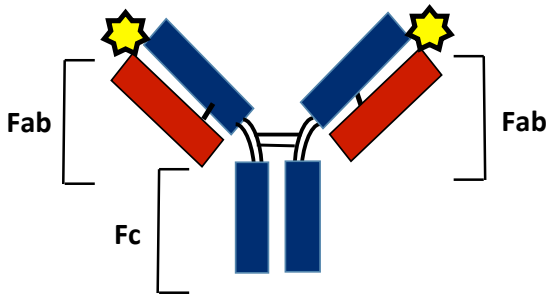
The information in table 1 is derived from the World Health Organization INN Working Document 09.251.

Table 2. Therapeutic Monoclonal Antibodies in Development for the Treatment of Asthma

mAb	Target	Mechanism of Action
Benralizumab	α chain of the IL-5 receptor	Binds to eosinophils and basophils and destroy them by antibody-dependent cellular cytotoxicity
Brodalumab	IL-17 receptor A	Blocks interaction of IL-17 (and IL-25) with the IL-17 receptors present on airway smooth muscle
Ligelizumab	IgE	Binds to IgE and prevents its binding to Mast cells and basophils
Lebrikizumab	IL-13	Binds IL-13 and prevents its function in eosinophil activation and IgE production
Tralokinumab	IL-13	Binds IL-13 and prevents its function in eosinophil activation and IgE production

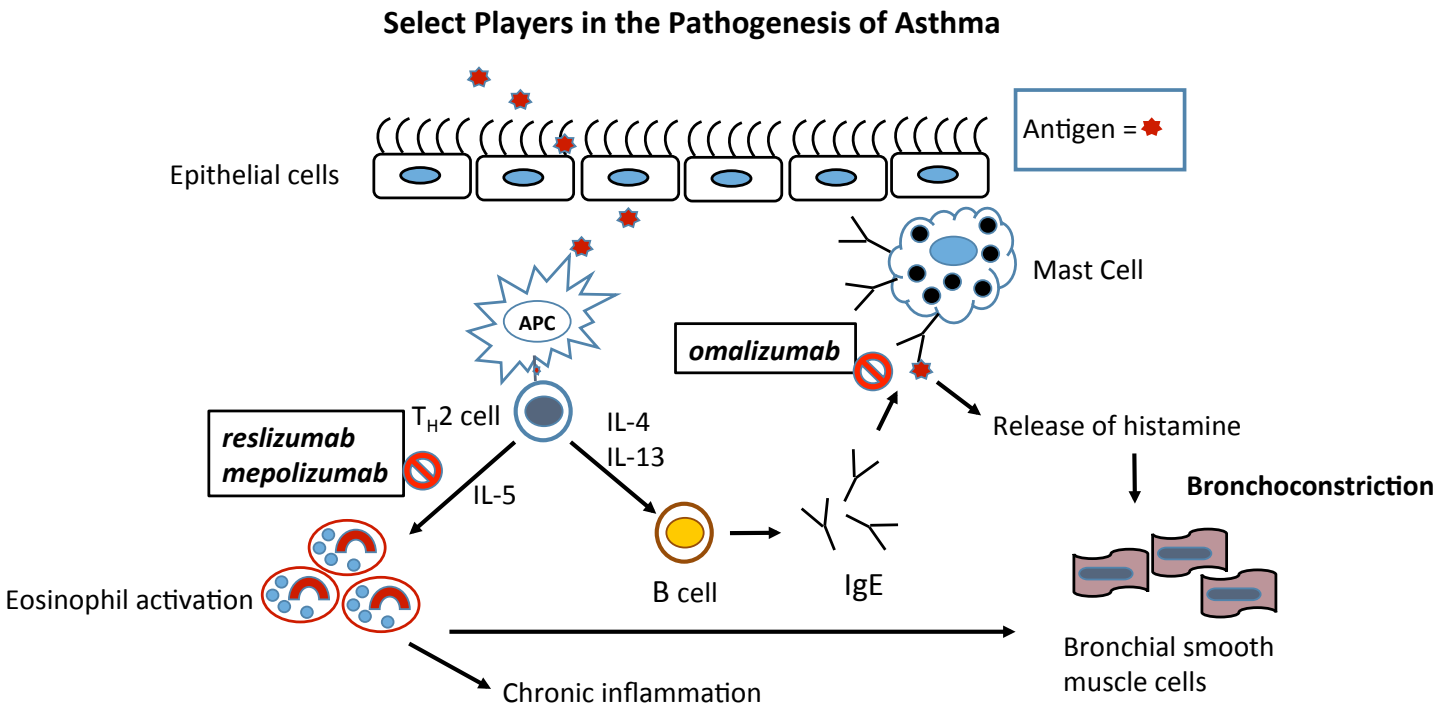
Figure 1

Structure of an Antibody (Immunoglobulin) Molecule



An antibody molecule is composed of two identical heavy chains (dark blue) and two identical light chains (red). In the most commonly present isotype (IgG – which is represented in this figure), the heavy chains are joined together at a hinge region. The yellow stars represent antigens that bind to the identical antigen-binding sites of the two arms of the antibody molecule.

Figure 2



A simplified view of cells and molecular mediators that play a role in the pathogenesis of asthma. The pathways influenced by FDA-approved mAb are indicated. APC = antigen presenting cell; IL = interleukin; TH2 = T helper subtype 2; IgE = Immunoglobulin E.

