Chapter 27
Molecular-Docking-Based Anti-Allergic Drug Design

Anamika Basu
Gurudas College, India

Piyali Basak
Jadavpur University, India

Anasua Sarkar
Jadavpur University, India

ABSTRACT

Allergens are foreign proteins that when come in contact of part(s) of human body stimulate the production of immunoglobulin types of proteins (antibodies). These allergens react with antibodies (immunoglobulin type E or IgE) produces allergic reactions, also known as immediate-type hypersensitivity reactions. As much as 20% of the general population may be affected by grass pollen as a major cause of allergic disease. EXPB class of proteins are known in the immunological literature as group-1 grass pollen allergens Molecular docking method can be used to identify the predicated the interaction of pollen allergen EXPB1 (Zea m 1), a beta-expansin and group-1 pollen allergen from maize with IgE molecules of human. The World Health Organization recognised allergen immunotherapy, as therapeutics for allergic diseases. RNA Interference (RNAi) is a biological process in which RNA molecules e.g. Small Interfering RNAs (siRNAs) inhibit gene expression, by cleavage and destruction of specific mRNA molecules. Use of Small Interfering RNA (siRNA) is a novel method in the induction of RNA Interference (RNAi), which is a potent method for therapeutics of allergic reactions. Due to various effects of STAT 6 proteins during hypersensitivity reactions caused by pollen allergens, mRNA of STAT6 gene is selected as target gene for allergy therapeutics via Post-Transcriptional Gene Silencing (PTGS). Using molecular docking study a specific sense siRNA is identified as anti allergic drug to treat allergic asthma during immediate type of hypersensitivity reaction, caused by Zea m 1 pollen allergen.

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INTRODUCTION

Allergens are foreign proteins that when come in contact of part(s) of human body stimulate the production of immunoglobulin types of proteins (antibodies). These allergens react with antibodies (immunoglobulin type E or IgE) produces allergic reactions, also known as immediate-type hypersensitivity reactions (Kay, 2008). As much as 20% of the general population may be affected by grass pollen as a major cause of allergic disease. An evolutionary conserved protein in plant developmental biology, expansins play an important role in cell wall expansion by slippage or rearrangement of matrix polymers during plant cell growth (Basu, 2013). But among the four classes of expansin protein family, EXPB class of proteins are known in the immunological literature as group-1 grass pollen allergens (Anderson, 2003). These EXPBs proteins cause hay fever and seasonal asthma in humans (Ball, 2005). Allergy symptoms are caused by these proteins when these allergens come into contact with the moist surface of the human respiratory tract (Knox, 1996). Molecular docking method can be used to identify the predicated the interaction of pollen allergen EXPB1 (Zea m 1), a beta-expansin and group-1 pollen allergen from maize with IgE molecules of human. Antibodies, expressed on the surface of B –cell of human immune system, recognize antigenic determinants, also called epitopes on their antigen. The interacting part of the antibody involved in the antigen-antibody interaction, is called the paratope (Stave, 2013). Paratope is formed in combination of different amino acids in the complementarity Determining Regions (CDRs) of antibody or immunoglobulin (Collis, 2003).

At present drugs such as antihistamines, leukotriene receptor antagonists, and corticosteroids are used for symptomatic treatment, but they do not prevent the allergic response (Natt, 2011). The World Health Organization recognised allergen immunotherapy, as therapeutic vaccines for allergic diseases, also known as desensitisation or hyposensitisation. The use of chemically altered allergens, allergoids, recombinant allergens, and relevant T-cell epitope peptides are some common approaches for immunotherapy.RNA interference (RNAi) is a biological process in which RNA molecules e.g. small interfering RNAs (siRNAs) and microRNAs (miRNAs) inhibit gene expression, by cleavage and destruction of specific mRNA molecules. Small interfering RNAs (siRNAs) are 21-25 nucleotide single-stranded RNAs containing 2 nucleotide 3′ overhangs produced by cleavage of longer double-stranded RNAs by the enzyme Dicer. After cleavage by Dicer the 21-25 nucleotide double-stranded product is loaded into an Argonuate protein (humans contain 4 Argonautes) and rendered single-stranded.

Small interfering RNAs (siRNAs) can regulate eukaryotic gene expression when transcribed endogenously or preformed, synthetic siRNA introduced into cells. Among two strands of siRNA, the guide strand pairs with a complementary sequence in a messenger RNA molecule and induces cleavage of mRNA molecule with the help of catalytic component of the RNA-induced silencing complex (RISC) complex. The siRNA component guides RISC to mRNA molecules containing a homologous antisense sequence, resulting in cleavage and degradation of that mRNA. RISC is composed of dicer protein, the double-stranded RNA binding protein TAR RNA Binding Protein (TRBP), and Argonaute2 (AGO2) and does not required ATP for its activity. Dicer protein converts long double-stranded RNAs into siRNAs by the endonuclease activity and Argonaute protein performs the cleavage of the mRNA. At first the process of RNA interference is initiated through Dicer protein by converting double-stranded RNA into small interfering RNA (siRNA). Then the siRNA guide strand after binding with the Argonaute protein in RISC recognizes its complementary sequence in mRNA and targets mRNA for its cleavage.

RNA interference or RNA silencing occurs due to endonucleolytic cleavage of the mRNA specifically by AGO2 protein, when RISC complex binds with a perfectly complementary mRNA (Kandeel, 2013).