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Margatoxin (MgTX) and Its Effect on Immune Response and Disease Development

SALAUDDIN AL AZAD
MS student
Biotechnology and Genetic Engineering Discipline
Khulna University, Bangladesh
SAYEED SHAHRIYAR[1]
MS student
Department of Biotechnology
Bangladesh Agricultural University
Mymenshingh, Bangladesh
KANAK JYOTI MONDAL
Registrar, Medicine
Khulna Medical College Hospital, Khulna, Bangladesh

Abstract:

Margatoxin (MgTX) is a protein molecule which is generated from Central American Bark Scorpions (also called Centruroides margatitatus) as their defense agent, is very selective to the inhibition of Kv1.3 voltage-dependent potassium channel through the miss regulation of GLUT4 trafficking on the cell membrane via Ca^{2+} dependent mechanism. Consequently insulin production mechanism is hampered directly, a panic to the diabetic patients. The toxin molecule is the concern of many immunologists all over United States of America because there is seldom drugs are available to combat against the toxin. In the following passages the signs and symptoms of margatoxin invasion, biosynthesis, mechanism of the immune suppression, clinical aspects of MgTX and the future of drug design against the protein molecule are described stepwise. Synthetic MgTX

[1] Corresponding author: m15121415@bau.edu.bd

gene development and plasmid designing to insert it into E. coli for manipulating the desired amount of MgTX peptide is a master blessing of biotechnology where the main options of molecular or nanomedicine development lies on the structural modification analysis of the 39 amino acid sequence of the toxic protein molecule.

Key words: Margatoxin, immunization, disease, autoimmune

INTRODUCTION

Margatoxin is a much specified bio-molecule which can be considered as a peptide that selectively inhibits Kv1.3 voltage-dependent potassium channel. The venom is naturally stabilized by 3 disulfide bridges generated in the venom of *Centruroides margatitatus*, also known as the Central American Bark Scorpion. Margatoxin was discovered firstly in 1993. Then it was isolated from the venom of the scorpion and purified it. Afterwards its amino acid sequence was determined. Margatoxin (MgTX) is a molecule contains 39 amino acids and its molecular weight is 4185 Dalton (Garcia-Calvo *et al.,* 1993). Margatoxin demonstrates its similarities with many other molecules which are recognized as toxins and very functional in blocking the potassium channels. The sequence homological components are charybdotoxin (44%), kaliotoxin (54%), iberiotoxin (41%). But the very remarkable think is that the similarities from the sequential arrangements margatoxin relates to noxiustoxin, at around 79% (Garcia-Calvo, 1993). The peptide is widely used in ion channel research and often to verify Kv1.3 channel in the plasma membrane.

THE TOXIC ASPECTS OF MARGATOXIN

Margatoxin varies from organism to organism based on their features of metabolic activity and genotypic as well as phenotypic circumstances.

THE EFFECTS OF MARGATOXINS IN CASE OF HUMAN (ACUTE RESPONSE) ARE

i. Skin irritation (if absorbed through skin)
ii. Eye irritation (if exposed to eye)
iii. Irritating to mucus membrane
iv. Irritating to upper respiratory tract (if inhaled)
v. Allergic reaction to sensitive individuals (if prolonged exposure)
vi. Very fatal to survive (if enters bloodstream)

In case of chronic stage margatoxin means five crucial organs like muscles, nerves, lungs, skeleton and heart. Actually *Centruroides margatitatus* stings are not dangerous in major cases except as a result of possible anaphylactic response. The median dosage (LD50) of margatoxin is 59.9mg/kg. Usually pain and swelling lasts for 2-4.3 hours, for most of the subjects.

EFFECTS OF MARGATOXINS IN CASE OF ANIMALS

Inhibition of cell proliferation response is the main concern of invasion by margatoxins in case of animals including wild and domestic breeds. Often it distresses animals via interfering the proteins activity who are very short living and half life is around 2 hours, such as tuberculin in case of mini-swine (Koo *et al.,* 1997). Moreover it suppresses B cell response to allogenic immunization, thus delayed type hypersensitivity declined dramatically. In addition to this margatoxin leads to depolarize human and pig cells both *in vitro* (Koo *et al.,* 1997). The major effects are

i. Blockage in 99% of KV1.3-channels (if T-cell proliferation disrupted)
ii. Allogenic immunization response hampered
iii. Diarrhea and hyper- salivation (if continuously infused) (Suarez-Kurtz,*et al.,* 1999)

iv. Transient hyperactivity in pigs (if dosage is higher than 10nM)

BIOSYNTHESIS OF MARGATOXIN

It is weird to listen that scorpion produces very small quantity of venom which is not enough to design drug or to use another research purposes, but it is manipulated through chemical synthesis approach, which renders the opportunity to generate moderately (Lecomte *et al.*, 1998). The 39 amino acid peptide, margatoxin (MgTX), a potent inhibitor of the voltage-activated potassium channel (Kv1.3) in human T lymphocytes, was initially synthesized by a solid phase technique. Formation of the disulfide bridges was rapid at pH 8.2. The final product was purified to homogeneity and was physically and biologically indistinguishable from the toxin prepared biosynthetically. The most popular and effective way in the twenty first century is the recombinant DNA technology for synthesizing margatoxin following by the amino acid sequence determination of margatoxin (MgTX) (Garcia-Calvo *et al.*, 1993). The procedure of designing synthetic MgTX gene and its expression on *E. coli* is a reliable way today for the synthesis of margatoxin with various innate and adaptive traits. To obtain significant quantity of this peptide with selective traits rMgTX (recombinant margatoxin) is expressed in *E. coli* as part of a fusion protein with the T7 gene and 9 products (Figure 1). *E. coli* multiplies it for hundreds of time and finally the considerable amount of protein product found. rMgTX is purified to homogeneity by ion-exchange and reversed phase chromatography which follow the partial purification of fusion protein and cleavage with factor X_a protease. The indication of identical feature of rMgTX to native peptide by amino acid analysis followed by sequence determination. The significance is that the equivalent level of potentiality and selectivity to the native in blocking potassium Kv1.3 ion-channel. In the same

way rMgTX (recombinant margatoxin) displays the same protocol to the native margatoxin in the prohibition of ChTX binding to brain membranes. ChTX is a blocker of K+ channel but its biosynthesis and mode of action is slightly different where MgTX has effects on ChTX binding to the K+ channels (Leonard *et al*., 1992).

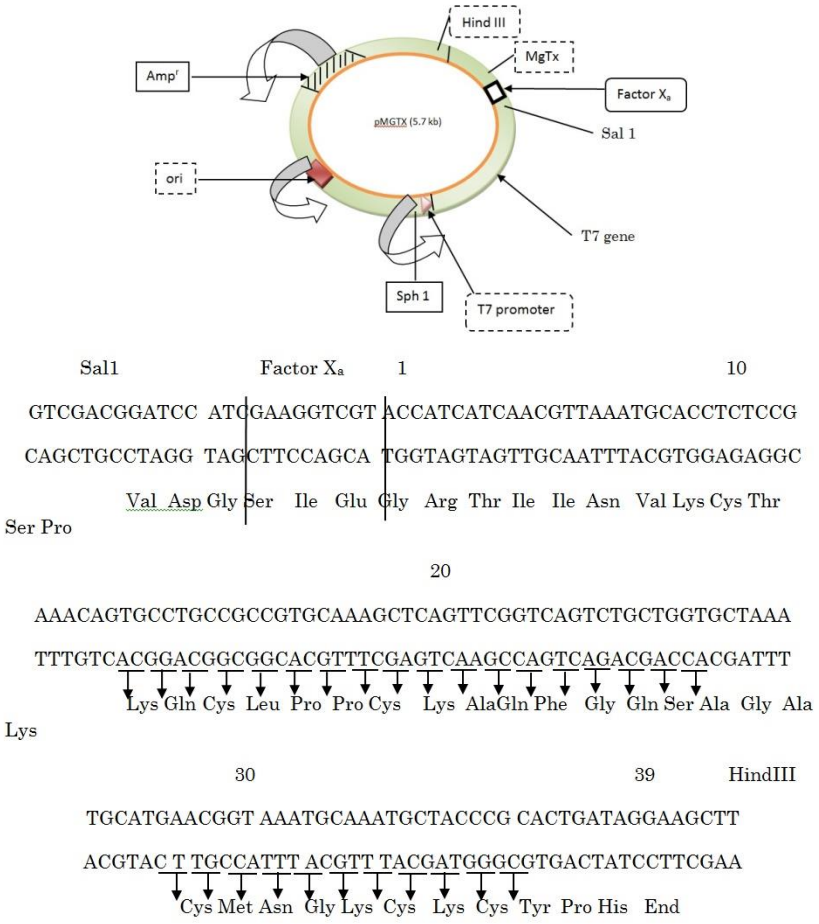
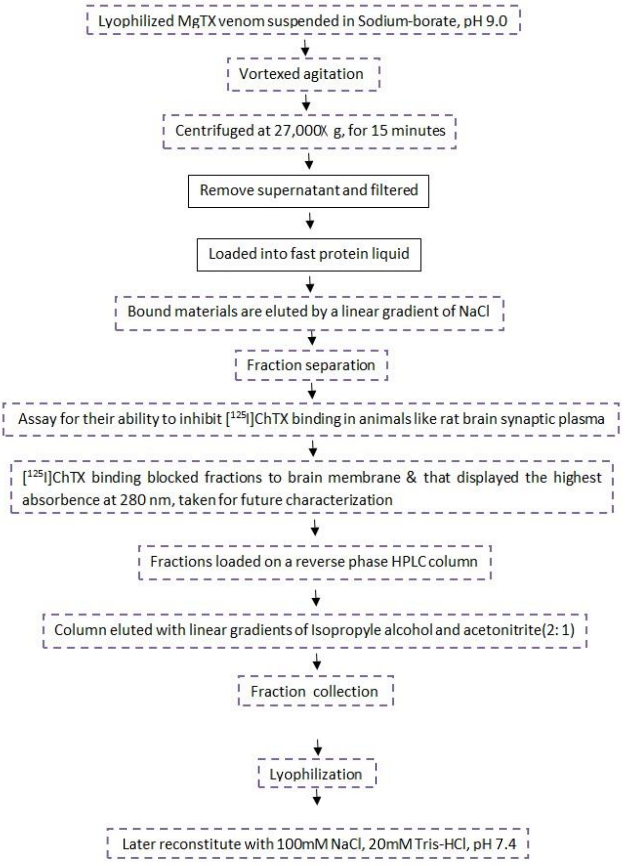


Fig.1. Design of synthetic MgTX gene for expressing inside *E. coli*. The plasmid is designed with MgTX gene, origin of replication, T7 promoter site, T7 gene9 fusion proter, Factor X_a cleavage site, ampicillin resistance. The corresponding amino acid sequence is also shown with the MgTX peptide sequence from residues Thr^1 to His^{39}.

This plasmid is then inserted into *E. coli* thus it is generated in huge amount because *E. coli* have the power to produce thousands of copies each containing MgTX peptide.

Only bio-synthesis of margatoxin doesn't mean to be utilized where purification is a major precursor of consuming margatoxin. The process of purification is run through a complex multistage procedure. The basic of the purification procedure as follows:



The rate of toxin biosynthesis varies from organism to organism. Similarly the intensity of venoms varies from one another. Few organisms can be featured as both greater amounts of toxin producing and with higher intensity of

pathogenesis. There are ten deadliest organisms involved in venom production as their metabolic product and to get better defense. These poisonous organisms have a differential mode of relativity with the venomous scorpion species; in some extent with the *Centruroides margatitatus* generated toxin potentiality. Literally most of the aforementioned organisms mean formation of paralysis and few are for respiratory failure, such as Death Stalker Scorpion, Blue Ringed Octopus and Marble Cone Snail. Scorpion generally produces a range of toxic molecules which contain modes of action. But interestingly the affinity the toxins generated is very unique in nature and possesses the properties corresponding to the invasion on the receptor protein molecules engaged in ion transmission (Lecomte *et al.,* 1998). Subsequently retardation on cardio vascular function, immune system suppression, malfunction on lymphocytic ion channels and many other concerns relating to fatal disease creation become regular sufferings for the individuals possessing the aforementioned toxins. The effect of margatoxin (MgTX) superficially on human nervous system relates with the other neurotoxic substances, found from Banana Spider and Inland Taipan, but action potential is quite different. Here the Puffer Fish generate tetrodoxin which is the ultimate infective precursor for cardiac failure and arrhythmia and is very decent with the activity of MgTX. But it is common to around 85% of scorpions' venoms that pain and respiratory failure as exposed to our body environment.

MECHANISM AND EFFECTS OF MARGATOXIN IN DISEASE DEVELOPMENT

In case of excitable and non-excitable cells, the responsibilities of K^+ ion channels for cellular signaling and regulation purposes are very crucial. To the following way more than 50 genes encoding various K^+ channels have utilized and cloned. Genetic linkage analysis is very effective to determine the disease oriented loci as consequences of K+ channels mutations

(Shieh *et al.*, 2000). The voltage-gated Potaiium Kv1.3 ion channel and the Calcium activated IKCa 1K^+ channels are expressed in T-cells in a distinct pattern that depends on the activation and differentiation (Chandy *et al.*, 2004). There is a very intensive correlation between ionic movements and mitogen activation of lymphocytes (Iversen 1976). K+ channels are very important for T-cell activation but several chemically unrelated K^+ channel blockers suppress T-cell proliferation and cytokine production with potencies paralleling channel blockade. There are four types of K^+ channels in human where one is voltage-gated and the rest three are Ca^{2+}- activated. Margatoxin (MgTX) attracts Kv1.3 voltage channel selectively where Charybdotoxin (ChTX) possesses the property of blocking all four types of potassium channels (Leonard *et al.*, 1992). In the same way, the margatoxin, another scorpion toxin charybdotoxin has been shown to block voltage gated K^+ (Kv) channels (Price *et al.,* 1989). In case of using labeled ChTX binding, there is very transparent evidence of having higher affinity sites associated with K^+ channels in human T-cells (Deutsch *et al.,* 1991). Noxiustoxin (NxTX) and margatoxin (MgTX) both are generated from the same species (organism) and are engaged in blocking Kv1.3 voltage channel but both of them are adverse to any of the other ChTX sensitive channels, yet they like ChTX and can depolarize resting T cells (Leonard *et al.*, 1992). In case of insulin production mechanism the importance of Kv1.3 voltage channel is very crucial as it regulates GLUT4 trafficking on the membrane via Ca2+ dependent mechanism (Wang *et al.*, 2006) (Figure 3). Kv1.3 inhibition by margatoxin actually makes a way in which glucose is up taken by the adipose tissues and skeletal muscle and that the effect of margatoxin in transporting glucose is additive to that of insulin. Kv channels regulate cell membrane potential (Vm) by controlling the rate of K^+ exit from the cell and can therefore modulate a number of cellular processes. Kv1.3 is a shaker related Kv channel that is expressed in

insulin sensitive tissues. For instance, in the olfactory bulb Kv channel experiences inhibition which is mediated by phosphorylation of multiple tyrosine residues, in case of insulin (Fadool *et al.,* 2000).

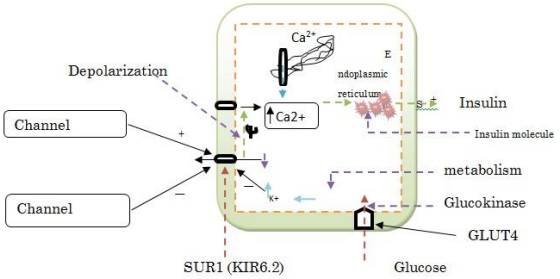


Fig. 3. Schematic demonstration of basic insulin production process and activity of K^+ and Ca^{2+} channel. Initially glucose enters into the cell through GLUT4, after that it is converted into glucose-6-PO_4 and metabolized as glycolysis and gives ATP. When the ratio of ATP to ADP increase then K+ closed and Ca^{2+} activated and forces the system generate insulin molecules. If K+ remains opened then the mechanism should be impossible for pancreatic beta cell.

Margatoxin destroys the proliferation mechanism of Jurkat T lymphocyte like it does for the others via affecting the ion channels. Whole-cell K^+ outward currents (IK) with an outward rectification found in these cells are identified as Kv1.3 current. Ion channels are responsible for a growing number of diseases including cancer. In some extent of disease development, voltage gated potassium channels (VGPCs) that exhibit oncogenic properties, either-a-go-go type 1 (Eag 1). Generally Eag 1 is expressed almost exclusively in tissue of neural origin but its epitopic expression leads to uncontrolled proliferation (Pardo *et al.,* 2005). Margatoxin does the thing fruitfully. In case of cellular abnormalities like cancer or other fatal diseases K^+ channels controls the variation of membrane potentials, could not only be the regulation of Ca^{2+} influx which is well established as a critical factor for cell proliferation but also

maintaining the driving force for Na^+ dependent nutrient transport and influencing the intracellular pH (Nilius *et al.,* 1993). Blockage on K^+ flux leads to inhibit hyper polarization. To attend into any hyper polarizaton function, an adequate threshold of action potential activation required to the K^+ channels, but just the effect of membrane potential would be sufficient to alter the cell cycle progression and if blocking any K^+ channel impairs proliferation, the opposite effect should also be expected as accelerated cycle progression by an increase in the expression levels of endogenous K^+ channels. If its implementation is true then the K^+ channel openers would be oncogenic and this can also be transformed through the activity of strong promoters. But the fact of being oncogenic openers for K^+ channels is not so remarkably experienced but in many cases the openers enhance the synthesis of DNA (Harmon *et al.,* 1993 and Malhi *et al.,* 2000).

In case of animals K^+ channel inhibition is very identical. Margatoxin (MgTX) and iberio toxin (IbTX) are almost equally K^+ channel inhibitors, can induce c-fos like protein and mRNA in rat organotypic dorsal striatal slices (Saria *et al*., 2000). MgTX was recently found to increase the release of dopamine (Saria *et al.,* 1998) and acetylecholine (Fischer and Saria, 1999) in rat striatal slices. Immediate early genes (IEG) act as transcription factors, which are considered to be important initial factors for plastics and potential cytoskeletal changes in response to neurotransmitters and toxins like margatoxin (Morgan and Curran, 1989 and Zhang *et al.,* 1992). There's hardly any mechanism in case of cellular miss-regulation and disease development than damage on ion channels through the application of drugs, neurotransmitters, and toxins, where K^+ voltage-channels malfunction due to margatoxin invasion would be a very efficient example.

Usually non-metabolized glucose is up taken by our adipose tissues and skeletal muscles when the activity of Kv1.3 channel function is disrupted due to the potentiality of

margatoxin after infection (Figure 4). There are eight analogs of MgTX can be synthesized and applied for inhibition of ^{125}I margatoxin binding to voltage-activated potassium channels. The results indicate that the three C-terminal residues of MgTX are important for the efficient toxin binding to Kv1.3 (Bugianesi *et al.,* 1994).

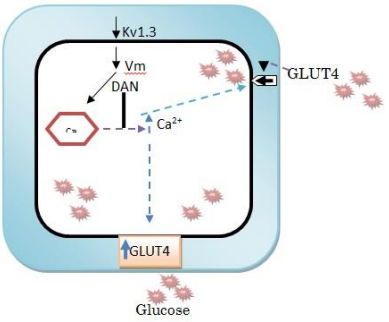


Fig. 4. Scheme demonstrating the mechanism of increased glucose uptake in adipocytes with Kv1.3 inhibition

For the HIV and diabetic patients margatoxin infection should be fatal because HIV patients have no ability to generate adequate quantity of antibody against the toxin while lack of insulin secretion can damage the heart and other essentially sensitive organs. Margatoxin blocks potassium channels Kv1.1, Kv1.2 and Kv1.3. Kv1.2 channel which regulates releasing of neurotransmitter associated with many specific functions. The functional sides are:

i. Neural excitability (uncontrolled)
ii. Epithelial electrolyte transport (reduced)
iii. The secretion of insulin (reduced)
iv. Heart rate regulation (imbalanced)
v. Inhibition of T-cell proliferation

Any changes in potassium channel type due to margatoxin infection especially for human, the vascular smooth muscle cells switch from the contractile to proliferating phenotype. This is quite transparent that Kv1.3 is important in proliferating

vascular smooth muscle cells. Inhibitors of such channels suppress vascular smooth muscle proliferation, stenosis following injury, and neo-intimal hyperplasia.

THE WAYS OF USING AS DRUGS

It was found in 2010 that scorpion venom have painkiller properties. But this isn't all; actually it was also found that scorpion venom could assist in fighting cancer. Seattle researchers developed something called "tumor paint" out of scorpion venom, which was successful in identifying brain cancer and lighting it up for doctors to see (Bushak, 2015). The scorpion toxin finds the cancer cells and drags the flashlight into them and makes them glow brilliantly. Many drugs have been developed from neurotoxins in snake venom, which are used to treat Alzheimer's and Parkinson's, as well as stroke and brain injuries. In this sense margatoxin activity is different because it has target specificity. Scorpion venom lethality varies with species where a range of toxins have neuro-toxic, nucleo-toxic, nephrotoxic, cardiotoxic, hemolytic-toxic, phosphodiasterase and hyaluronidase mediated toxic nature, but margatoxin contains a typical cytotoxin regulated by K^+ channels blocking. Multiple toxins may be present in the venom of a same species capable to produce potential synergic effect on victim (Possani *et al.,* 1999 and Gwee *et al.,* 2002). The success of antivenom therapy depends on antivenom application (dose, route and time of injection after envenomation). MgTX has anti-proliferative, cytotoxic, apoptogenic and immunosuppressive properties, which make margatoin as a thepapeutic agent (Joseph and George, 2012). MgTX can also be utilized as anti-epilectic, antimicrobial and channel blocking agent. Scorpion toxins can be very effective in the treatment of glioma and tumour on brain and spine. The most common glioma is the brain (Mamelak *et al.,* 2007). Margatoxin selectively inhibits Kv1.3 voltage-dependent

potassium channels. It increases the time necessary to conduct action potentials in the cell in response to stimulus. Acetylcholine (Ach) gets a key role in activation of nicotinic and muscarinic Ach receptors. MgTX forces nicotinic Ach receptor agonist-induced norepinephrine release. Upon activation muscarinic Ach receptors bethanechol, MgTX-sensitive current is suppressed. Kv1.3 affects the function of postganglionic sympathetic neurons. This Kv1.3 influences sympathetic control of cardiovascular function. In this case margatoxin can be considered as a key medicine (Sukumar *et al.,* 2010). For margatoxin, the treatment of autoimmune diseases are possible because this scorpion derived peptide, blocker of Kv1.3 channel in effector memory T cells might have use in multiple sclerosis, rheumatoid arthritis, bone resorption and others. Genetically engineered toxins can penetrate into insects and attack the nervous system, leading to paralysis and deaths. These toxins are very acute against some insects like leaf eating moths, locusts, flies and beetles. In this case the beneficial insects and mammals should be uninfected. MgTX is used in insecticides, vaccines and protein engineering scaffolds and is very effective (Joseph and George, 2015). In some extent, plasma of horses immunized with the scorpion venoms like MgTX can be used as vaccine against viruses that could infect human. In case of inflammatory neuropathies and cancer K^+ channels blocking toxins like margatoxin would be a better therapeutic component (Petricevich *et al.,* 2013).

It should be possible to increase the affinity and selectivity of the toxins once the precise modes and interactions between MgTX and the channel are fully understood. In this type of interaction, involves formation of the toxin channel complexes would be valuable for further developments of MgTX and other scorpion toxins as drug scaffolds. MgTX-Lys-35 acts as the pore blocker. Still now only few structures-activity relationship have been found for margatoxin and accurate modles for describing the binding of this toxin to Kv1.3 and

other closely related channels has not yet been established (Chen and Chung, 2014).

DIRECTIONS FOR THE FUTURE EXPOSURE

Margatoxin can be considered as one of the best weapons of destroying cancer, cardiological disorders, allergy problems and remedy from any types of tumors. There are many ways, how we should isolate and manipulate margatoxin and apply it in drug production. Already isolation and manipulation through chemical synthesis approach have got the attentions of the scientists (Garcia-Calvo *et al.*, 1993 and Lecomte *et al.,* 1998). Few approaches might be taken in future to develop more suitable drugs from margatoxin. The approaches are:

i. Change on the 39 amino acids structure might change the cell receptors of margatoxin. Then it won't be able to bind with the location of interest as receptor has changed. Then it may be used as a vector or carrier molecule.
ii. Margatoxin can be utilized with monoclonal antibody, containing cell targeting properties. Thus it will contribute in the destruction of cancer and tumors.
iii. A virulence suppressor gene can be designed and engineered with MgTX molecule, therefore vaccines using this procedure will enhance our immunity on scorpion toxins. For future exposure via pre-generating antibodies because intensity of virulence will be suppressed by the suppressor gene and the small virulence will just increase immune response.
iv. Induced mutation and side specific mutation might be possible to reduce the pathogenecity and design vaccines with proenzymes. Here pro-enzyme should be inactive in interaction with margatoxin because it needs to be matured. In the correspondence margatoxin will be a

carrier and pro-enzyme will be activated moving far from non-pathogenic margatoxin.

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