

Insilico characterization of cd59 like snake venom peptide inhibitors to treat au...

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INSILICO CHARACTERIZATION OF CD59 LIKE SNAKE VENOM PEPTIDE

INHIBITORS TO TREAT AUTO IMMUNE DISORDERS
Abstraction
Present work is aimed for the intervention of car immune diseases with particular mention for the intervention of Rheumatoid Arthritis (RA) which is normally seen all over the universe. One such cause for the car immune disease is the cascade activation of complement system which in bend activates CD59 which is called MAC inhibitory protein. This CD59 resembles the construction of snake venom neurolysin (three finger toxin) .

Docking surveies of assorted neurolysin from Indian cobra has revealed that engineered neurolysin can be targeted towards C8 and C9 which binds irreversibly and is really specific in nature. Introduction
Autoimmune diseases are the 3rd most common class of disease in the United States after malignant neoplastic disease and bosom disease (NIH2002) . The National Institutes of Health (NIH) estimates that it affects about 8 % of the US population (or 23. 5 million) and the prevalence is lifting every twelvemonth. Rheumatoid Arthritis (RA) is one of the major discrepancy of car immune upsets. Harmonizing to WHO 1 % of universe population and 3 % of Indian population is enduring from RA. The complement system is portion of both innate and adaptative unsusceptibility, made up of a big figure of distinguishable plasma proteins that react with one another to opsonize pathogens and bring on a series of inflammatory responses that help to contend infection. However, it may do significant hurt when activated unsuitably and leads to autoimmune diseases (Kuby, 2000) .

In worlds, complement system is good controlled by the host and is chiefly mediated by complement regulative proteins. One such regulative
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glycoprotein called CD59, besides known as MAC-inhibitory protein (MAC-IP), is a cell-surface molecule that protects host cells from complement-mediated lysis, by adhering to and forestalling the normal operation of the complement proteins C8 and/or C9 which form portion of a membrane penetrating assembly called the membrane onslaught composite (MAC) . CD59 besides has limited sequence homology to snake venom neurolynsins (Harrison, 1993) , which are members of three-fingered proteins' (TFPs) superfamily. Hence, toxins from serpent venom sharing similar construction with CD59, which are members of three-fingered proteins, could go possible curative peptides to handle complement mediated immune upsets.

Presently available drugs to handle complement mediated immune system upsets like corticoids (Orasone) and non-steroid drugs such as Imuran, cyclophosphamide, mycophenolate, sirolimus or tacrolimus are frequently prescribed to command or cut down the immune system ' s response (as immunosuppressive agents) (Niethemmer 1999) . Monoclonal antibodies based interventions are expensive and their drawn-out uses have proven side effects (Trevor T. Hansel 2010) . Hence there is an immediate demand for alternate efficacious and selective therapy. The figure of venom constituents in deadly animate beings like serpent, Scorpio or cone snail ranges from 50-200 toxins (Tan *et Al.* , 2003) . The natural library of toxins is therefore estimated to incorporate 1000000s of different toxins and discrepancies. Since there is turning figure of identified serpent venom neurolysin sequences, it is really hard to analyze them by experimentation merely.

Detailed bioinformatics analysis offers a convenient methodological analysis for efficient *in silico* preliminary analysis of possible map of toxins. The common name 'Cobra' is applied to about 30 species of serpents in 7 genera within the household Elapidae. Following are the genera *Boulengerina*, *Hemachatus*, *Naja*, *Ophiophagus*, *Aspidelaps*, *Pseudohaje* and *Walterinnesia*. *Naja* comprises about 25 species and is the most widespread. Snakes are equipped with venomous armoury to undertake different quarry and marauders in inauspicious natural universe. The composing of snake's venom is a cocktail of active proteins and polypeptides and non-enzymatic polypeptide like cytotoxins and short neurolysin. These two constituents structurally resemble to three-finger protein superfamily specific scaffold. Neurotoxins are the chemical or natural or man-made agents which disrupt the transmittal of signals between Neurons, doing legion jobs.

Neurotoxins can impact the cell at any measure of nervous transmittal i. e., presynaptic or postsynaptic.

Present work is concentrated on the α -neurotoxins from the Indian cobra belonging to *Naja* genera. The α -neurotoxins from Indian cobra are categorized to be postsynaptic neurolysin which occurs on the having terminal of a discharge across the synapse. These neurolysin mimic the form of the acetylcholine molecule and tantrum into the acetyl choline receptors block the ethanoyl group choline flow ensuing in numbness and palsy. Depending on their amino acid sequence and third constructions, α -neurotoxins can be classified into short concatenation α -neurotoxins, long

concatenation ? -neurotoxins, which have important sequence homology and portion the same 3-dimensional construction, but differ in association or dissociation with the receptor. A neurolysin can be called strong when its consequence on its receptor is rapid and weak when its consequence is slow.

- Short Type: Contain four disulfide Bridgess ; composed of 60-62 amino acids.
- Long Type: Contain five disulfide Bridgess ; composed of 66-75 amino acids.

CD59 is a membrane edge protein nowadays in assorted cells which binds to C8 and C9 of the terminal complement system. CD59 is a little glycoprotein made of 77 aminic acids and has a molecular weight of 18 to 25kD. CD59 is besides called as theMembrane Attack Complex Inhibitory protein. The less common map of CD59 is to act upon the proliferation capacity of T cells and their ability to bring forth cytokines, act uponing T cells response to a given antigen that enters the blood stream.

CD59 works in the both innate immune system and besides in the adaptative immune system. Material and MethodBelow mentioned sequences and constructions were obtained from databases like Uniprot and PDB. Protein – protein moorage was carried out by on-line tool ClusPro and the analysis was done utilizing tools PYMol and SPDB Viewer.

Multiple sequence alliance of neurolysin was carried out by ClustalW and Superimposition surveies were done by SPDB Viewer.

SI Neurotoxin(lig PDB ID Lengt Molecular Weight(in

No.	and)		h	Dalton)
1	Long Neurotoxin 1	2CTX	71	7847
2	Weak Neurotoxin 5	1LN7	62	6943
3	Weak Neurotoxin 6	1LN9	65	7568
4	Weak Neurotoxin 7	1LQ3	65	7637
5	Weak Neurotoxin 8	1LMG	65	7581

Table 1: Detailss of Neurotoxins used for Docking surveies

Sl. No	Name of Receptor	PDB ID	Lengt h	Molecular Weight(in Dalton)
1	CD59	1CDQ	77	14177
2	C8	2QQH	334	65163
3	C9	Theoretical Model	559	
4	Acetyl Choline	4D01	218	

Receptor

Table 2: Detailss of different receptor marks for Rheumatoid Arthritis and Natural Targets of Neurotoxins Protocol for the work is illustrated in the Flowchart below Fig 1. Fig 2: Multiple Sequence Alignment consequence utilizing ClustalW

	2CTX - LN2	1LN7 - WN5	1LN9- WN6	1LQ3- WN7	1LMG - WN8
2CTX - LN2	-	1. 17A49 Atoms	1. 25 A49 Atoms	1. 31 A49 Atoms	1. 29 A51 Atoms
1LN7 - WN5	-	-	1. 09 A61 Atoms	1. 21 A59 Atoms	1. 08 A57 Atoms
1LN9- WN6	-	-	-	1. 03 A64 Atoms	1. 13 A63 Atoms
1LQ3- WN7	-	-	-	-	1. 13 A56 Atoms

Table 3: Superimposition Surveies between ligands for C-? Atoms

	2CTX - LN2	1LN7 - WN5	1LN9- WN6	1LQ3- WN7	1LMG - WN8
2CTX - LN2	-	1.	1. 27	1. 26	1. 32

LN2		28A196	A196 Atoms	A192 Atoms	A204 Atoms
1LN7 -	-	-	1. 1 A248 Atoms	1. 24 A236 Atoms	1. 11 A228 Atoms
WN5					
1LN9-	-	-	-	1. 08 A256 Atoms	1. 18 A268 Atoms
WN6					
1LQ3-	-	-	-	-	1. 16 A228 Atoms
WN7					

Table 4: Superimposition surveies between ligands for all atoms

Number of Interactions within 5A	2CTX - Long Neurotox in	1LN7 - Weak Neurotox in 5	1LN9 - Weak Neurotox in 6	1LQ3 - Weak Neurotox in 7	1LMG - Weak Neurotoxi n 8
Acetyl	8	7	7	7	8
Choline					

Receptor

CD59	9	5	9	11	9
C8	7	11	8	10	13
C9	14	13	10	22	19

Table 5: Interaction tabular array of Neurotoxins with different marks. With the above interaction chart for 2CTX and LIGPLOTs for 1LN7, 1LN9, 1LQ3 and 1LMG we found that Proline 7 dramas built-in function in adhering to its natural receptor Acetyl Choline Receptor hence we modified the construction of all neurolysins and removed amino acid 1 to Proline 7 from every neurolysin and docked it once more and found the interactions which is been tabulated below.

Number	Modified	Modified	Modified	Modified	Modified
of	2CTX -	1LN7 -	1LN9 -	1LQ3 -	1LMG -
Interactio	Long	Weak	Weak	Weak	Weak
ns within	Neurotox	Neurotox	Neurotox	Neurotox	Neurotoxi
5A	in	in 5	in 6	in 7	n 8

Acetyl

Choline	8	7	9	18	11
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Receptor

CD59	8	6	10	10	9
C8	8	11	12	17	14

C9 17 16 17 15 15

Table 6: Interaction tabular array of modified Neurotoxins with different marks
 Consequences and Discussion
 The above interaction tabular arrays do give a clear image that modified long neurolysin with PDB ID 2CTX and weak neurolysin 6 with PDB ID 1LN9 can be used to aim C9 and therefore can suppress the polymerisation of C9. This suppression of polymerisation of C9 will suppress the formation of Membrane Attack Complex which is responsible for the devastation of self-cells.

So the modified neurolysin can be used as CD59 miming agent and these neurolysin are readily soluble in the blood hence they can make their marks with higher efficiency. Mentions

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