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Analysis and prediction of B-cell epitopes on ricin toxin A-Chain

Abstract

Two different computational methodologies used to determine the linear B cell epitopes necessary to development a ricin vaccine. First, identify the epitopes that were predicted using nine different programs, and the next step was obtained the B cell epitopes of ricin that were obtained from a database with experimental data-IEDB. With these two results, it was determined that a consensus of linear B cell epitopes it could be the best possible candidates for the design of a ricin vaccine.

Keywords: ricin, epitopes, toxin, vaccines, *Ricinus communis*

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Introduction

The ricin toxin is a glycoprotein extracted from the seeds of the castor bean plant (*Ricinus communis*). It is one of the most toxic substances that is found in nature and is currently being tested to kill cancer cells. Another widely used application is as a biological weapon because of its easy production. It does not require special conditions for its storage and it can be used in aerosol, liquid or solid form and only five hundred micrograms of ricin is enough to kill a person. Remember some terrorist events associated with ricin would include the murder of the Bulgarian journalist and writer Georgi Ivanov Markov on September 11, 1978 when ricin was supplied with the help of an umbrella when crossing the Waterloo Bridge in the middle of London.[1] Another incident was in April, 2013 when several letters containing small amounts of ricin were intercepted at the US Capitol in Washington, DC.[2] Recently, another event occurred in Germany when the police arrested a suspect for the manufacture of ricin on June 14, 2018. For this reason, the Joint Vaccine Acquisition Program (JVAP) of the US Military began a process of producing a vaccine against this toxin. To date, none has been approved and are only in the developmental stage. The most promising candidate is the one developed by Soligenix that is called RiVax with approximately $22 million grant from the NIH and FDA. The most recent test was in 2015[3] where exposing primates to the ricin toxin in the aerosol form was examined. Those animals treated with the vaccine survived an exposure with limited damage to the lung. The control group who were not vaccinated all perished.

Another experimental vaccine is one that is being tested by the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) called RVec that was developed in April, 2011. Experimental tests beginning 2015.[4] The hydrophobic face of truncating RTA was suppressed. To understand these developments, it is necessary to explain *grossomodo* which is the structure of the ricin toxin A-Cham. Remember that the holotoxin is composed of two protein subunits linked by a disulfide bond. The ricin-A chain (abbreviated as RTA) is an N-glycosidase that enters the cytosol of target cells. Once inside the cells, RTA acts as a ribosome inactivating protein (RIP) to remove a specific adenine based from a conserved region of rRNA, stopping the synthesis of new proteins, inducing apoptosis and the death of cells. The ricin B-chain (RTB) is a lectin that binds to the receptors of galactose or N-acetylgalactosamine on the surface of target cells to promote endocytosis and trafficking of the toxin through the trans-Golgi network.[5,6] In the next section, I explain a computational procedure to elucidate the best B cell epitope candidates that can be used to develop a ricin vaccine.

Materials and methods

We identify all linear B cell epitopes that are present in the ricin toxin A-chain that are currently available in the immune epitope database (IEDB), a curated database of free consultation available at www.iedb.org.[7] It was later determined to be the consensus according to the procedure described by Isea.[8,9] On the other hand, I determined the linear B cell epitopes with nine different prediction programs from the sequence XP_002534649 obtained in the NCBI. The programs employed in this studied were BePiPred,[10] Emini Surface Accessibility Prediction,[11] Kolaskar and Tongaonkar Antigenicity,[12] ABCpred,[13] SVMTriP,[14] BCpred,[15] FBCpred,[16] CBTOPE,[17] and AAP.[15] From the results obtained, only those epitopes predicted by four or more programs were selected such as length is equal to or greater than 4 mer. Finally, a consensus value ranging from zero (it means, not predicted by more than three prediction programs) to nine was determined, such that the epitopes of the linear B cells with a value equal to or greater than 3 must be the best candidates for vaccine design.

Results

Figure 1 shows the epitopes that were obtained from the sequence of the ricin toxin A-Chain that was selected for the present study and it is identified with the label "Seq". Subsequently, the B cell epitope predicted by at least four different predictors and the next rows indicated the epitopes found in the IEDB. Subsequently, a numerical consensus is determined based on the frequency of appearance of the amino acids present in these epitopes as being the best candidates for the design of a vaccine which must have a consensus equal to or greater than three (fixed in an arbitrary manner) with an extension equal to or greater than four (arbitrarily selected). From this figure, we observe six epitopes: TGADVRHEIPVLPNRVG, RFILVE, NQED, EQLAGNLRENIELGNGPL, MISEAARFQYIEGEMRTRIRYNRRSAPDPSVITLENS and GAFASPIQLQR which are the best candidates for creating a ricin vaccine.


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Seq: IFPKQYPIINFTTAGATVQSYTNFIRAVRGRLTTGADVRHEIPVLPNRVGLPINQRFILVELSNHAELSVTLALDVTNAY
                              IRAV GRLTT      EIPVLP         RFILVE                  Y
                                          GADVRHEIPVLPNRVGLPINQRFIL
                                               EIPVLPNRVGLPINQRFILVELSNHAELSV
                                         DVRHEIPVLPNR            ELSNHAELSVTLALDVTNAY
                                       TGADVRHEIP
                           YTNFIRAVRGRLTTGADVRHEIPVLPNRVG
Cons:                      1111222212222333444466655544332222233332322222222211111111112

Seq: VVGYRAGNSAYFFHPDNQEDAEAITHLFTDVQNRYTFAFGGNYDRLEQLAGNLRENIELGNGPLEEAISALYYYSTGGTQ
     VVG           PDNQED                                          GNGPLEEAIS LYYYSTGGTQ
     VVGYRAGNSA      NQEDAEAITHLF            GNYDRLEQLAGN      LGNGPLEEAISA
                                                DRLEQLAGNLRENIELG
                                                   EQLAGNLRENIE
                 YFFHPDNQEDAE                          LRENIELGNGPL
Cons:2211111111111122333322111111           1112223333333333333433332222211111111111

Seq: LPTLARSFIICIQMISEAARFQYIEGEMRTRIRYNRRSAPDPSVITLENSWGRLSTAIQESNQGAFASPIQLQRRNGSKF
     LP                                                        QESNQG  ASPIQLQR
                          FQYIEGEMRTRIRYNRRSAPDPSVITLENS            QGAFASPIQLQR
                    ISEAARFQYIE EMRTRIRYNRRS                        QGAFASPIQLQRRNGSKF
                    ISEAARFQY               APDPSVITLENS                SPIQ
                   MISEAARFQYI
     LPTLARSFIICIQMI         IEGEMRTRIRYNRRSAPDPSV
       TLARSFIICIQM       FQYIEGEMRTRIRYNRRSAPDPSVITLENS
Cons:22222222222223433333555543444444444444444444333333        1111322344443331111111

Seq: SVYDVSILIPIIALMVYRCAPPPSSQF
     SVYDVSILIPII      CAPPPSSQF
                  IIALMVYRC  PPSSQF
Cons:11111111112211111211222222
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Figure 1 The sequence of the ricin toxin had been identified with the label "Seq". The next line indicates the consensus sequence of the B cell epitope obtained with the nine programs. Immediately after the epitopes found in IEDB. Finally, the numerical consensus according to the methodology published by Isea.[8,9]

Conclusion

The ricin is a terrorism agent with just one gram being six thousand times more poisonous than cyanide. Currently, there is a lack of a vaccine and hence the importance of developing computational strategies to develop effective vaccines against it should be obvious. In view of this, I proceeded to determine the best candidates for linear B cells that can be used in a vaccine obtained from the consensus of nine epitope predictors as well as from the different studies published in the scientific literature that are available free of charge in the IEDB. The next step is the experimental verification that would indicate, for example, the appropriate cut-off value for the selection of the best candidates for epitopes B that was arbitrarily placed as 3, as well as the extension that was chosen to be 4. Finally, this computational methodology can be used for the development of other vaccines.

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Conflict of interest

The author declares that there are no conflicts of interest regarding the publication of this manuscript.

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