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In silico prediction of immunogenic epitope as vaccine target against fibronectin binding protein of Staphylococcus Aureus

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ABSTRACT

The initial step in an infectious disease is often adhered to and colonization of host tissue surfaces. Staphylococcus aureus, which is a major human and animal pathogenic organism, has been shown to bind to several host matrix proteins and plasma proteins, such as fibronectin, fibrinogen, collagen, elastin, laminin, prothrombin, thrombospondin, bone Sialoprotein and vitronectin . For each of these binding functions, a corresponding surface-associated protein has been identified. The existence of an S. aureus extracellular matrix binding protein with broad specificity that is capable of binding several extracellular glycoproteins has also been reported. The role of some of these proteins in the pathogenesis of staphylococcal infections has been shown in animal models. Most S. aureus strains bind to fibronectin and two highly homologous fibronectin binding proteins (FnBPs), and their corresponding genes (fnbA and fnbB) have been identified. Mutants defective in either of the two genes adhered equally well to fibronectin-coated surfaces in vitro, while a double mutant was completely unable to adhere, indicating that both genes are expressed and contribute to fibronectin binding. That's why we have chosen fibronectin possible target for vaccine design against Staphylococcus aureus. This proposed target protein for vaccine contained four coils and three strands.

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Introduction

The genus "Staphylococcus" is a common inhabitant of the skin and mucous membrane and it accounts for a considerable proportion of human infections. Approximately 20–30% of the general population are "staph carriers" (Heyman, 2004). It is still one of the four most common causes of nosocomial infections, often causing post-surgical wound infections. The emergence of antibiotic resistance in this microorganism and their spread is threatening the medical community.

The resistance development in Staphylococcus aureus dates back to the 1940s. The increasing gain of resistance to available antimicrobials and side effects associated with the drugs have attracted the attention of the scientific community towards the search and development of new cost effective drugs of natural and synthetic origin (Fine et al., 2000).

No effective vaccine is generally available that stimulates active immunity against staphylococcal infections in humans. However, vaccine therapies represent a new and innovative approach in broadening the available clinical tools against the global health problem of community and healthcare-associated *S. aureus* bacterial infections. So, it is cardinal to focus on designing a multi-epitope antigenic target specific against multidrug resistant Staphylococcus that may provide protection from a variety of infections caused by this deadly bacterium (Meri *et al.*, 2008). Thus, we investigated the possible vaccine candidate for the test organism using Bioinformatics tools.

Materials & Methods

An effort was made to analyze preventive measure against MRSA. So we performed in silico prediction of vaccine candidates of fibronectin binding protein through Bioinformatics approach. In this context, the sequences of Fibronectin binding protein were extracted from the NCBI protein database and were noted in FASTA format. Later on multiple sequence alignment of fibronectin binding protein sequences was done to find out the conserved sequence. Afterwards the conserved sequence was analyzed for B-cell epitope and T-cell epitope properties by EpiJen. Then, in the last part of the study, structural analysis was done by PSIPRED software.

Results & Discussion

The threat to the human population is that reservoirs of drug-resistant bacteria is abound. In the present study, S. aureus was indicated by the yellow halo produced around the colonies on Mannitol Salt Agar. This is caused by the ability of S. aureus to ferment mannitol to acids which is detected by a change of pH indicator from red to yellow (Leboffe and Pierce, 2002).

This study also showed that antimicrobial resistance of Staphylococcus aureus was high and alarming. Even though pharmaceutical companies have produced a number of new antibacterial drugs over the years, resistance to these drugs by Staphylococcus aureus has increased manifold and has now become a global concern. Therefore the identification of new effective antimicrobial agents is of paramount importance.

In the present study, it was found that the fibronectin binding protein of Staphylococcus can also be used as an effective candidate for the development of preventive measures against drastic diseases by blocking its binding efficiency. In fact in silico approach of vaccine target prediction is definitely less labor intensive, rapid and economic in relation to search for a lead antigenic molecule against the fibronectin binding protein (Stern & Markel, 2005). Multiple sequence alignment revealed various conserved regions of this protein. Analysis was done for finding out the potential of these conserved regions to work as B cell epitope and we found 41 potential B cell epitopes among the conserved sequence. For any predicted epitope, it is cardinal that it should induce T and B cell response. Such type of multi-epitope vaccine is a very recent experimental technique for

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predicting vaccine targets against HIV and Influenza virus (Bae *et al.*, 2009). We predicted one such type of multi-epitope peptide which was having very good potential to induce B cell response as well as a very good candidate for binding to MHC II molecule (Sette *et al.*, 2002 and Flower, 2003)

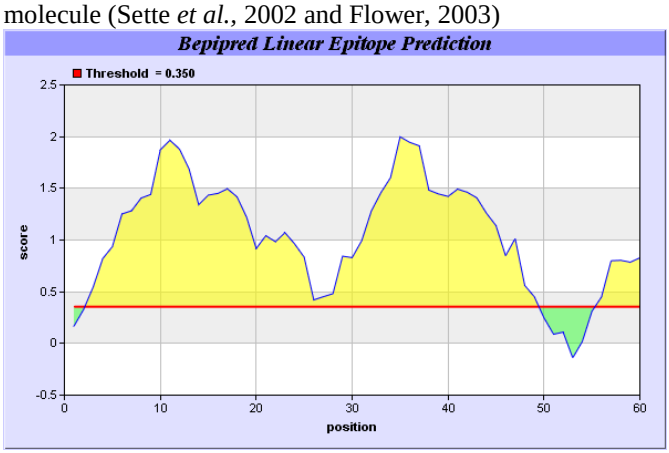

Figure 1. Predicted B-cell epitope by the BepiPred Epitope prediction method. The area under yellow peaks showed the conserved sequences among the analysed sequences which have values above threshold for being a B-cell epitope candidate

Among 51 MHC II alleles analyzed, the conserved region of the protein showed binding affinity with all the 51 alleles with one or more than one paratope found in each. As per the results of ProPred, 47 sequences were found to bind with MHC I alleles. During the last step of the study, this protein sequence was also analyzed for its binding affinity with T-cell receptors using the EpiJen server. The following epitope sequences were identified as the smallest set of most promiscuous epitopes: A*0101- 62, 571, 511, 161, 365, 612, 215, 433, 235, 656, 524, 43, 13, 361, 372, 562, 358, 488, 166, 233, 237, 636, 124, 581, 461, 491, 507, 580, 264, 154, 279, 493, 329. A*0201- 518, 587, 445, 495, 22, 424, 182, 365, 643, 222, 104, 379, 372, 219, 656, 498, 20, 440, 640, 478, 336, 115, 268, 61, 168, 466, 108, 328, 399, 306, 350, 12, 165. A*0203-126, 224, 59, 187, 20, 84, 105, 323, 250, 240, 91, 277, 292, 130, 180, 122, 338 and 139. A*0206-222, 187, 240, 158, 126, 323, 180, 338, 200, 33, 26, 250, 71, 292, 137, 146, 286 and 326. A*0301- 255, 201, 147, 149, 186, 260, 116, 343, 136, 110, 13, 254, 76, 344, 62, 138, 229 and 60. A*1101- 179, 137, 134, 186, 330, 147, 149, 345, 26, 17, 116, 299, 18, 309, 53, 201, 255, and 337. A*3101-254, 44, 246, 60, 277, 299, 286, 344, 116, 179, 53, 255, 13, 201, 36, 19, 330 and 39. A*6801- 60, 344, 186, 246, 76, 254, 93, 184, 256, 223, 134, 139, 293, 234, 201, 62, 282 and 109. A*6802-158, 146, 200, 71, 17, 139, 18, 330, 222, 33, 179, 345, 288, 126, 299, 337, 247 and 240. B*07- 47, 288, 194, 61, 71, 38, 131, 278, 283, 247, 326, 153, 265, 20, 18, 28, 24 and 42. B*3501- 131, 38, 283, 24, 20, 320, 26, 347, 10, 207, 326, 265, 61, 234, 105, 247, 47 and 288. B*51- 265, 47, 28, 234, 61, 105, 323, 33, 38, 10, 20, 131, 217, 187, 347, 119, 233 and 283. Structure prediction of this sequence by PSIPRED revealed that there are four coils and three strands present in this sequence. This data can be very helpful for generating antigenic candidate by wet lab researchers.

The results presented in this report were encouraging, although clinical controlled studies are required to define the real efficacy and possible toxic effects in vivo. Also the focus of this study was on a Bioinformatics based approach as a means to enhance the optimal selection of potential target of immune response that can then be validated by experiment that test the biological function of these antigen sequences in immune system based assays.

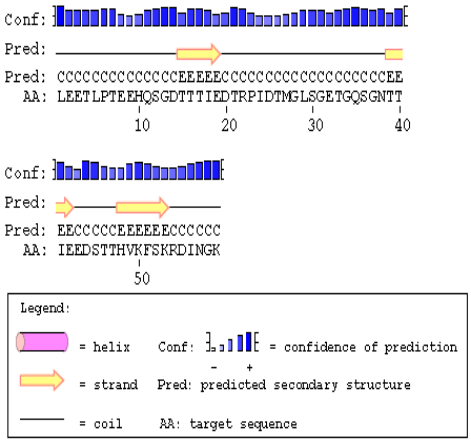

Figure 2. A part of the structure of the proposed vaccine target against MRSA predicted by PSIPRED

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