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Research Article

Molecular Characterization of Tefimazumab Binding to the *Streptococcus pyogenes* Serotype M18 Superantigen SpeC as Basis for Vaccine Development

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Abstract

Streptococcus pyogenes is a facultative bacteria that is classified as a gram positive cocci which is the main human pathogen associated with local or systemic invasion and poststreptococcal immunologic disorders [1]. There are three antigenically distinct Pyrogenic extracellular exotoxins or superantigen implicated in streptococcal toxic shock syndrome and scarlet fever, namely (Spe): A, B, and C. SpeC bind to MHC Class II molecules, are presented to T cells, and bind to the variable region of the beta chain of T cell receptors [2]. Tefimazumab is a monoclonal antibody for the treatment of severe infections with *Staphylococcus aureus.* The possible effect of this antibody to the *Streptococcus pyogenes* Serotype M18 Superantigen SpeC will be discussed, specifically this study aims to characterize the Tefimazumab binding to the *Streptococcus pyogenes* Serotype M18 Superantigen SpeC as basis for vaccine production. Methodology and Theoretical Orientation: Amino acid sequence and secondary structure predictions were all performed using Protein Sequence Database (Uniprot) and Protein Structure Prediction Server. 3D visualization were performed using UCSF Chimera Multiple epitope predictions were all utilized from Immune Epitope Database and Analysis Resource (IEDB). The degree of disorder was then determined using GLOBPROT server. The molecular docking is simulated by the CLUS-PRO and UCSF Chimera. Findings: Docking model revealed the binding of the portions of the heavy chain and light chain of Tefimazumab with the epitope of interest. Since the epitope of *Streptococcus pyogenes* serotype M18 superantigen SpeC are mostly linear with a high degree of disorder, antibodies generally can bind to it easily. Conclusion and Significance: With the use of bioinformatics tools for epitope prediction and structural visualization, the epitope of interest of *Streptococcus pyogenes* serotype M18 superantigen SpeC located on residue number 6-26 using molecular docking models visually bind to the paratope heavy and light chain regions of the monoclonal antibody Tefimazumab. This can pave a way for vaccine development for the superantigen SpeC which can cause severe infections such as shock and scarlet fever.

Keywords: *Streptococcus pyogenes*; M18 Superantigen SpeC; Shock

Background

Streptococcus pyogenes is a facultative bacteria that is classified as a gram positive cocci which is the main human pathogen associated with local or systemic invasion and poststreptococcal immunologic disorders [1].

M protein in *S. pyogenes* isolates correlates with its capacity to resist phagocytic killing, binding of plasma fibrinogen to M protein molecules on the streptococcal surface interferes with complement (Low, 2017). There are three antigenically distinct Pyrogenic extracellular exotoxins or superantigen implicated in streptococcal toxic shock syndrome and scarlet fever, namely (Spe): A, B, and C. SpeC bind to MHC Class II molecules, are presented to T cells, and bind to the variable region of the beta chain of T cell receptors [2]. Once activated, the T cells release pro-inflammatory cytokines and chemokines [3].

Tefimazumab is a monoclonal antibody for the treatment of severe infections with *Staphylococcus aureus*. The possible effect of this antibody to the *Streptococcus pyogenes* Serotype M18 Superantigen SpeC will be discussed, specifically this paper aims to characterize the Tefimazumab binding to the *Streptococcus pyogenes* Serotype M18 Superantigen SpeC as basis for vaccine production.

Materials and Methods

Streptococcus pyogenes SpeC epitope prediction tools

Amino acid sequence and secondary structure predictions were all performed using Protein Sequence Database (Uniprot) and Protein Structure Prediction Server. 3D visualization were performed using UCSF Chimera. PS2-V2: Multiple epitope predictions were all utilized from Immune Epitope Database and Analysis Resource (IEDB). The degree of disorder was then determined using GLOBPROT server.

Tefimazumab prediction tools

Amino acid sequence and secondary structure predictions were all performed using EMBL-EBI and RCSB-PDB. Multiple epitope predictions were all utilized from PARATOME. 3D visualization were performed using UCSF Chimera.

Antigen- Antibody docking model

The molecular docking is simulated by the CLUS-PRO and UCSF Chimera.

Results

Streptococcus pyogenes SpeC epitope prediction tools

The sequence of *Streptococcus pyogenes* serotype M18 superantigen *SpeC* was obtained by UNIPROT. It has 235 amino acids, with mass of 27, 372 daltons. It has 2 domains (Figure 1), with sequences 19-109 forming the Staphyloccal/Streptococcal OB Fold and sequences 122-214 forming the beta grasp domain (Figures 2 and 3). There are 3 available 3D structure of *Streptococcus pyogenes* serotype M18 superantigen *SpeC*. In order to model exact structure predictions using PS2-V2: Protein Structure Prediction Server was applied, using a known dimer template of SpeC (1an8A). Figure 4 reveals the structure.

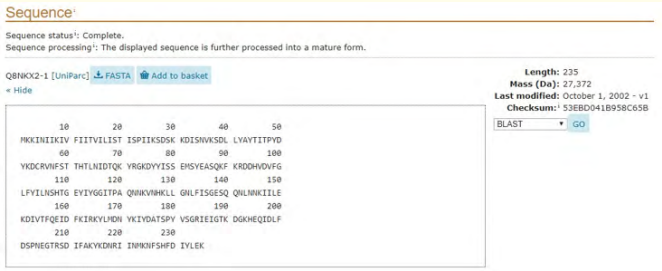

Figure 1: Sequence of *Streptococcus pyogenes* serotype M18 superantigen *SpeC* (UNIPROT).

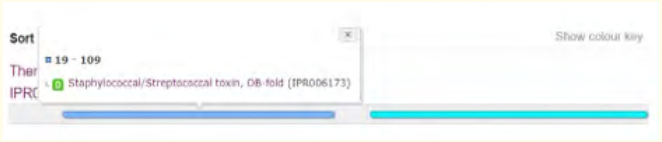

Figure 2: OB fold domain (AA 19-109) of *Streptococcus pyogenes* serotype M18 superantigen SpeC (www.ebi.ac.uk).

Figure 3: Beta grasp domain (AA 122-214) of *Streptococcus pyogenes* serotype M18 superantigen SpeC (www.ebi.ac.uk).

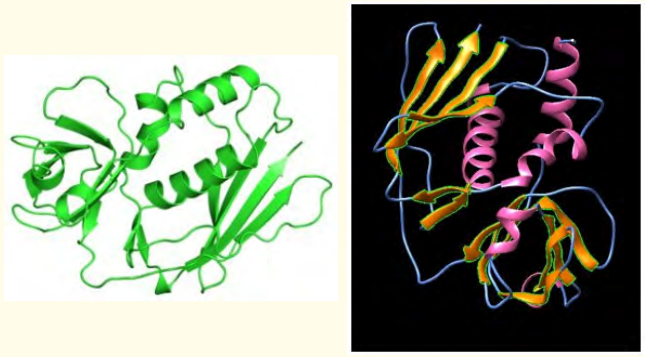

Figure 4: Left. Template used- 1an8. (EMBL-EBI). Right. 3D Structure Visualization of *Streptococcus pyogenes* serotype M18 superantigen SpeC dimer secondary structure. Coils are shown in blue, Helices are shown in pink and Strands are shown in orange (UCSF Chimera).

For the epitope prediction tools, the Immune Epitope Database and Analysis Resource (IEDB) was utilized by incorporating both sequences and predicted structure of *Streptococcus pyogenes* serotype M18 superantigen SpeC**.** Kolaskar and Tongaonkar Antigenicity method was used which predicts physicochemical properties of amino acid residues in order to predict antigenic determinants on proteins based on experimentally known segmental epitopes, the sequence IIKIVFIITVILISTISPIIK was the selected epitope marker. Figure 5 below shows the epitope prediction and 3D visualization.

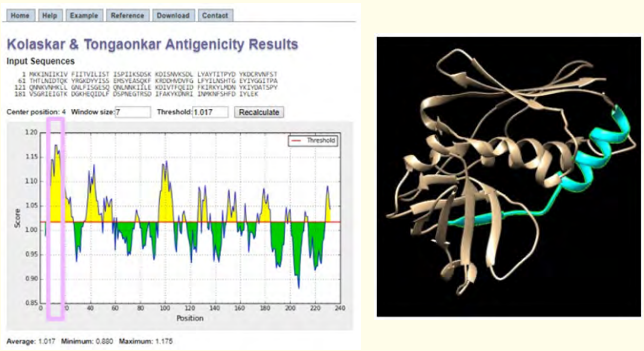

Figure 5: Left: Prediction result using Kolaskar and Tongaonkar Antigenicity (IEDB), the epitope of interest is highlighted (pink). **Right:** 3D visualization of the linear epitope using UCSF Chimera, linear epitope is shaded in cyan.

Tefimazumab prediction tools

Secondary structure and Sequence of the antibody was obtained by EMBL-PDB and RCSB PDB, respectively. Heavy chain is made up of 222 amino acids while the light chain is made up of 216 residues. The secondary structure and sequence are shown below.

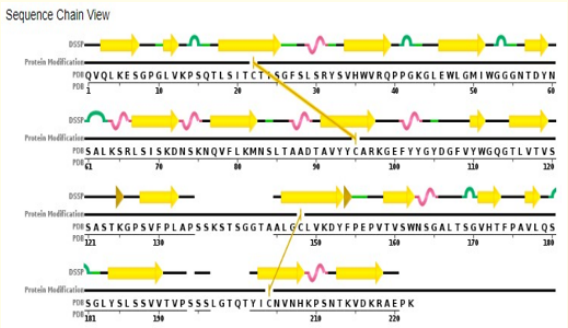

Figure 6: Sequence of Tefimazumab (RCSB PDB) Heavy chain.

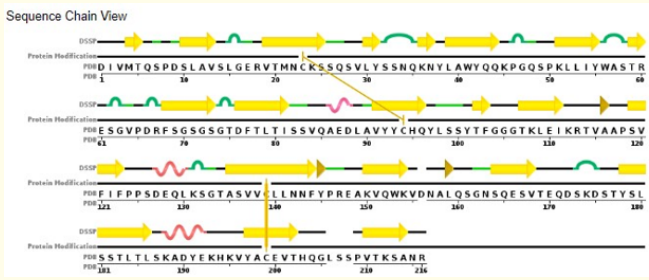

Figure 7: Sequence of Tefimazumab (RCSB PDB) Light chain.

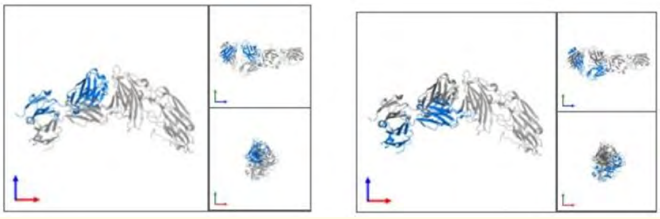

Figure 8: 3D Structure of Tefimazumab (EMBL-EBI) Left: Heavy chain. Right: Light chain.

Paratope prediction tool PARATOME was used, it is a tool which identifies antigen binding regions based on a set of consensus regions derived from a structural alignment of a non-redundant set of all known antibody-antigen complexes. Here are the paratope predictions for the Heavy chain: FSLSRYSVH at locations (27,28,29,30,31,32,33,34,35), WLGMIWGGGNTDY at locations (47,48,49,50,51,52,53,54,55,56,57,58,59) and RKGEFYYGYDGFVY at locations (97,98,99,100,101,102,103,104,105,106,107,108,109,110).

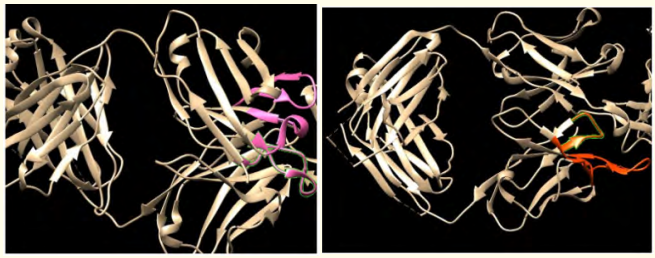

Figure 9: 3D Structure of Tefimazumab paratopes (UCSF Chimera) Left: Heavy chain, shaded in pink. Right: Light chain, shaded in orange.

Here are the paratope predictions for the Light chain: QSVLYSSNQKNYLA at locations (27,28,29,30,31,32,33,34,35,36,37 ,38,39,40), LLIYWASTRES at locations (52,53,54,55,56,57,58,59,60 ,61,62) and HQYLSSY at locations (95,96,97,98,99,100,101). Figure 9 below shows the 3D visualization of the paratopes

Antigen- Antibody Docking Model

The Degree of disorder were determined by GLOBPLOT2, which identifies inter-domain segments containing linear motifs, and also ordered regions that do not contain any recognised domain, using a known dimer template of SpeC (1an8A) the regions of degree of disorder are locations 1-42, 53-65,181-190, 264-277. The selected epitope IIKIVFIITVILISTISPIIK is part of the disordered region. This can serve as the epitope that can be used for antibody development.

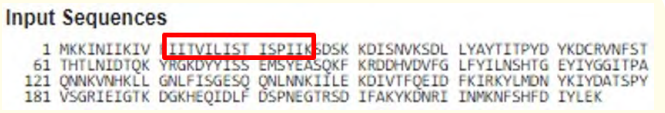

Figure 10: Degree of disorder of Streptococcus pyogenes serotype M18 superantigen SpeC (UNIPROT) 1an8. The epitope of interest is highlighted in red (Globprot).

Molecular docking was visualized using Cluspro 2.0 and UCSF Chimera. Docking model revealed the binding of the portions of the heavy chain and light chain of Tefimazumab with the epitope of interest. Since the epitope of *Streptococcus pyogenes* serotype M18 superantigen *SpeC* are mostly linear with a high degree of disorder, antibodies generally can bind to it easily [4-6].

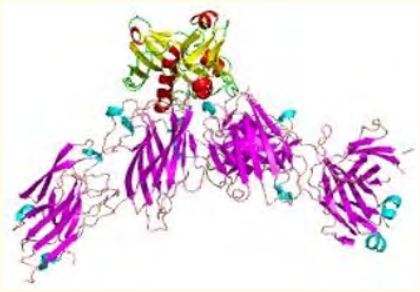

Figure 11: Antigen-Paratope docking of the Streptococcus pyogenes serotype M18 superantigen SpeC (UNIPROT) 1an8 and Tefimazumab heavy and light chain visualized in Cluspro.

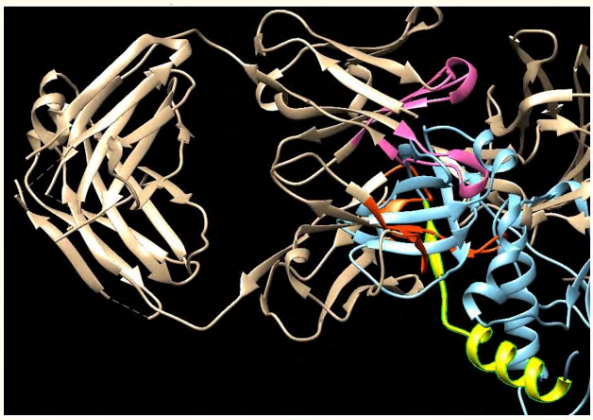

Figure 12: Antigen-Paratope docking of the Streptococcus pyogenes serotype M18 superantigen SpeC (UNIPROT) 1an8 and Tefimazumab heavy and light chain visualized in UCSF Chimera. Epitope of interest is shaded in yellow, Light chain paratopes are shaded in blue and Heavy chain paratopes are shaded in pink.

Conclusion

With the use of bioinformatics tools for epitope prediction and structural visualization, the epitope of interest **(**IIKIVFIITVILISTISPIIK) of *Streptococcus pyogenes* serotype M18 superantigen SpeC located on residue number 6-26 using molecular docking models visually bind to the paratope heavy and light chain regions of the monoclonal antibody Tefimazumab. This can pave a way for vaccine development for the superantigen SpeC which can cause severe infections such as shock and scarlet fever. *In vitro* testing can confirm findings of this study. The use of multiple epitope alignment can also contribute to the findings.

Bibliography

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