Original Article

In Silico Prediction of Continuous Epitopes on Human immunoglobulin Light Chains

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Abstract

Background & Objective: Immunoglobulins (Igs) have a vital role in body protection against germs. Igs contain heavy and light chains. Ig light chains consist of two isotypes: Kappa and lambda. Remarkable alterations in kappa to lambda proportion could occur in monoclonal growth of malignant B cells. Anti-human light chain monoclonal antibodies (MAbs) have medical implication in diagnosis and immunotherapy of B-cell proliferative disorders. In current study, prediction of continuous epitopes in constant part of human Ig light chain by immunoinformatics is explained.

Materials & Methods: Amino acid sequence and third structure of reference human IgG light chain was obtained in PDB database. Second IgG structure was identified by Phyre 2 software. Continuous epitopes of Ig light chains were delineated by Bepipred and Ellipro software programs.

Results: Four continuous epitopes situated to constant domain of human Ig light chain were predicted by Bepipred software. These continuous epitopes were located at amino acid sequences 110-130, 150-160, 160-175 and 180-205 of Ig light chain. The prominent epitope was sited at amino acids 160-175. Also, one continuous epitope situated in 198-203 amino acid sequences was predicted by Ellipro software.

Conclusion: In present study several continuous epitopes sited to constant part of human Ig light chain were determined. These epitopes are valuable for making specific monoclonal anti- Ig light chain antibodies and could have plausible implication in generation of specific diagnostic kits for human Ig light chain, monitoring the monoclonal light chain diseases, treatment of associated B cell malignancies and epitope mapping of Ig light chain.

Keywords: Continuous epitope, Immunoglobulins, Light chains, Immunoinformatics

Introduction

Antibodies (Abs) [Immunoglobulins (Igs)], a family of glycoproteins, are crucial tools for several usages including diagnosis and research (1). Furthermore, Abs have a main role in body defense against microbes (2-4). Recently antibodies have been one of the great areas in the treatment of some diseases including inflammatory disorders and autoimmunity (5- 7).

Igs include heavy and light chains. Ig light chains include two isotypes: kappa and lambda, based on differences in amino-acids of their carboxylic end. Each antibody has only one of these isotypes. The proportion of kappa/ lambda in antibodies is about 3/2 (8). Expression of light chains isotypes changes in some B lymphocytes tumors (9, 10). Role of light chains isotypes variations in non-secretory myeloma has been reported (11). Noticeable alterations in kappa to lambda ratio could take place in monoclonal growth of malignant B cells (12). Generally, determination the percentage of K^+/ λ^+ B cells is useful for diagnosis of B cell cancers (13). Also, specific targeting of light chain isotypes could be helpful for treatment of certain diseases such as multiple myeloma (14). Precise measurement of light chains isotypes needs specific and sensitive tools such as epitope-specific monoclonal

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antibodies (MAbs) (15). Accordingly, anti-human light chain MAbs has clinical significance in diagnosis and immunotherapy of patients with B-cell immunoproliferative abnormalities (16, 17). In order to optimizing the diagnostic tests of Ig- light chains and increasing effects of anti- Ig light chains therapies, exact recognition of light chains specific epitopes is of extreme importance (18- 20).

Epitopes (antigenic determinants) are divided into two types of continuous (linear) and conformational (spatial). Continuous epitopes are formed as a linear chain of covalently- linked amino acids whereas conformational epitopes are composed of some separate amino acids that are dispersed in protein sequence but are adjacent in the folded protein (21). In experiments that are completely/ partially denatured, target proteins are made throughout the sample preparation, for example western blotting, immunohistochemistry or immunofluorescence, continuous epitopes are preferred (22).

Immunoinformatics, as a part of bioinformatics, uses biologic computational data for modeling and prediction of immune system function in health and diseases as well as resolving of many immunologic complications such as closer and more accurate diagnosis of diseases (23, 24). Bioinformatic approaches are useful to recognize novel molecules for diagnostic or therapeutic practices (25). Bioinformatics uses the computer as a laboratory and classifies the experimental data collected in computer and analyses them by computerized software programs (26). Immunoinformatics has been extended to all fields of immunology and has provided innovative occasions for forthcoming immunological researches (27, 28). Continuous epitopes could be predicted by bioinformatic tools and can be used in further experiments (25). Thus, ccomputational epitope prediction methods are valuable to find the epitopes which are anticipated to be more specific and effectual than other parts of molecule in stimulating Abs production. Immunoinformatics could be advantageous to solve the problems of experimentally mapping the epitopes (29). According to experimental surveys, human Ig light chains constant domain is very immunologic (30, 31). In present study we used immunoinformatics for analyzing the computerized experimental information about human Ig construction in order to define the continuous epitopes in constant domain of human Ig light chain for optimizing the Ig- light chains diagnostic tests and to improve anti- Ig light chains therapies.

Materials & Methods

1. Prediction of amino acid sequence of human immunoglobulin light chain with NCBI (National Center for Biotechnology Information) and PDB (Protein Data Bank).

Confirmed amino acid sequence of human immunoglobulin light chain was determined by NCBI in http://www.ncbi.nlm.nih.gov/ web site and with PDB data bank in http://www.rcsb.org/pdb/home/home.do web site (32). These sequences have been achieved by experimental and crystallographic techniques.

2. Prediction of second and third structure of human immunoglobulin light chain

The second structure of human immunoglobulin G light chain was determined by the Phyre2 (Protein Homology/analogy Recognition Engine V 2.0) available on the http://www.sbg.bio.ic.ac.uk/phyre website. These sequences have been found by experimental and crystallographic techniques of second structure of human immunoglobulin G light chain (33). The third structure of human immunoglobulin G light chain for reference amino acid sequence with 1IGT accessible code was obtained with PDB data bank in http://www.rcsb.org/pdb/home/home.do web site (32).

3. Prediction of continuous epitopes of human Ig light chain

I) Prediction of continuous epitopes based on amino acid sequence of protein by Bepipred software.

The continuous epitopes in constant portion of human Ig light chain were estimated by Bepipred software available at http://www.cbs.dtu.dk/services/BepiPred server. Bepipred software is used to predict linear epitope. Bepipred evaluates every amino acid individually and allocates it a score between −3 and 3. A higher score shows a greater possibility for it to be an epitope. The threshold was set at scores ≥ 0.35 and was considered as positive (34). Bepipred as one of the IEDB (Immune Epitope Database) web servers for the prediction of B-cell epitopes based on antigen sequences is found to be significantly better than other existing tools for sequence-based epitope on a big group of linear epitopes (35).

II) Prediction of continuous epitopes based on three-dimensional structure of protein by Ellipro software

The continuous epitopes in constant part of human Ig light chain were also anticipated by Ellipro software. Ellipro is a suitable investigation tool for recognizing the epitopes of antibody in protein antigens and is based on the geometrical characteristics of protein structure. Ellipro has been established on a standard dataset of epitopes concluded from 3D structures of antibody-protein complexes. Ellipro is accessible at http://tools.immuneepitope.org/tools/ElliPro. Ellipro outfits these algorithms: (i) estimation of protein outline as an ellipsoid; (ii) calculation of residue protrusion index (PI)for continuous epitope expectation. It approximates the protein exterior as an ellipsoid that can differ in sizes to comprise diverse proportions of the protein atoms (36).

Results

1. Amino acid sequence of human immunoglobulin light chain

Amino acid sequence of human immunoglobulin G light chain was determined with 1IGT name in PDB Bank illustrated in table 1. Amino acids were shown as single letter.

2. Second and third structure of human immunoglobulin light chain

Figure 1 shows the second structure of human immunoglobulin light chain obtained by phyre2 software.

Figure 2 shows the third structure of human immunoglobulin light chain found by PDB data bank.

3. Prediction of continuous epitopes of human Ig light chain

I) Prediction of continuous epitopes based on amino acid sequence of protein by Bepipred software

Table1. Amino acid sequence of human immunoglobulin light chain*

Sequence **
DIVLTQSPSSLSASLGDTITITCHASQNINVWLSWYQQKPGNIPKLLIYKASNLHTGVPSRFSGSGSGTGFTLTIS SLQPEDIATYYCQQGQSYPLTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGASVVCFLNNFYPKDINVKWKID GSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

* Amino acid sequence of human immunoglobulin light chain with NCBI (National Center for Biotechnology Information) and PDB (Protein Data Bank) .

** Each letter demonstrates a single letter code of an amino acid

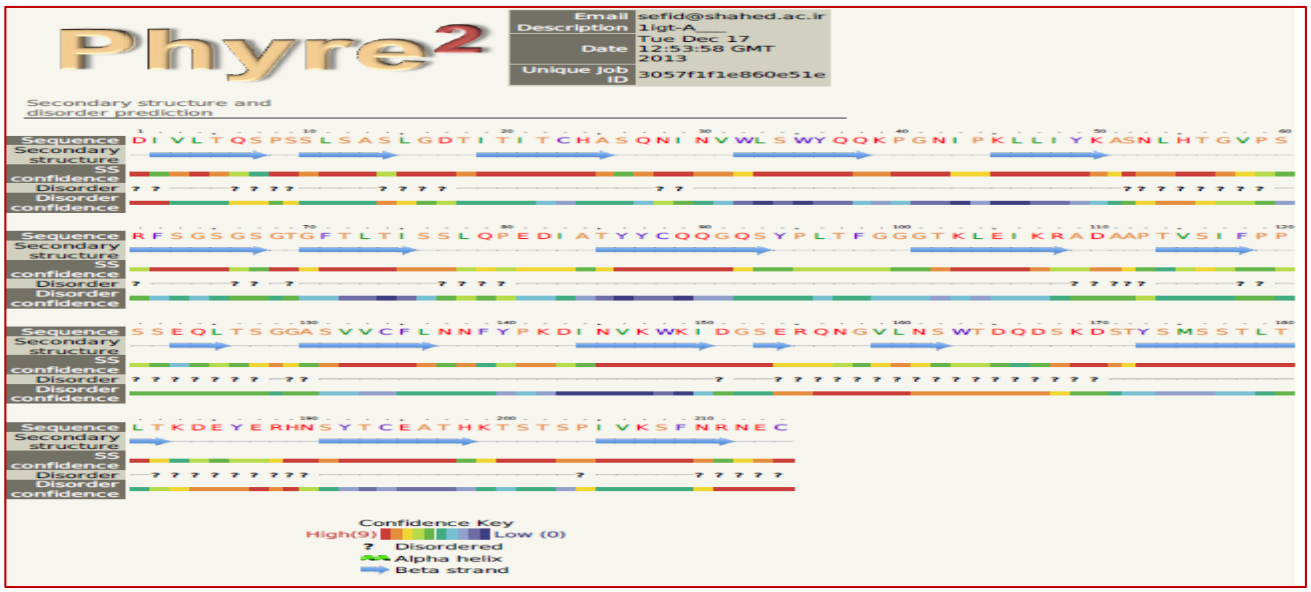

Figure 1. Second structure of human immunoglobulin light chain determined by phyre2 software. *B* sheets and *a* helix are shown by blue and green colors respectively.

Four continuous epitopes located in constant domain of human Ig light chain were determined by Bepipred software. These epitopes were ranked by mean residue score (mean residue score was averaged by every residue in the predicted peptide. The higher the score of the available amino acids for the possible epitope in a part of the sequence, the higher the probability that this part of the sequence will be epitope.

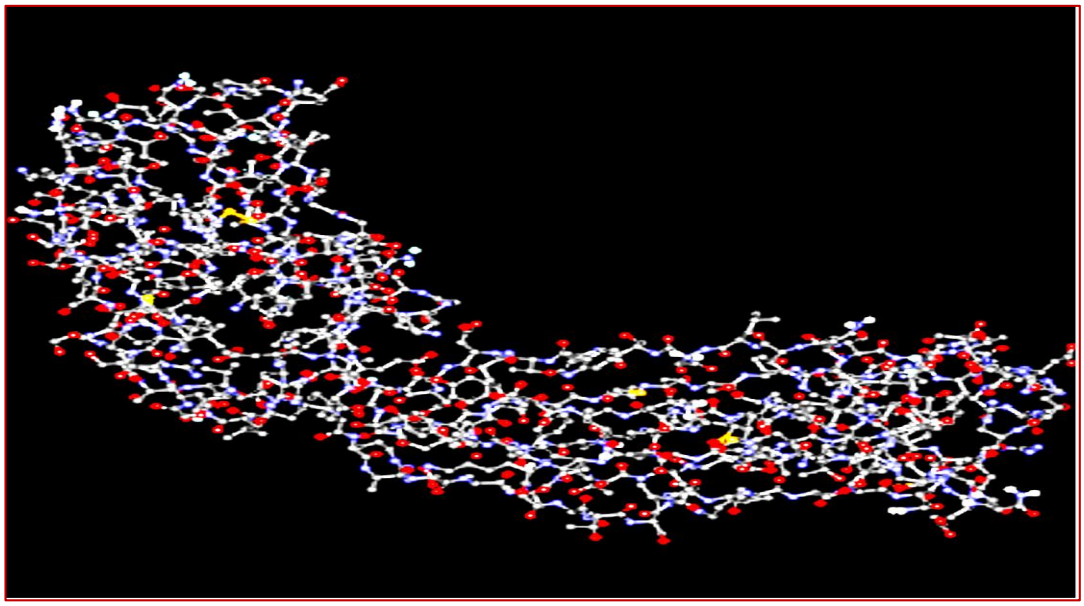

Figure 2. Third structure of human immunoglobulin light chain determined by PDB data bank and depicted by bullet and rod model.

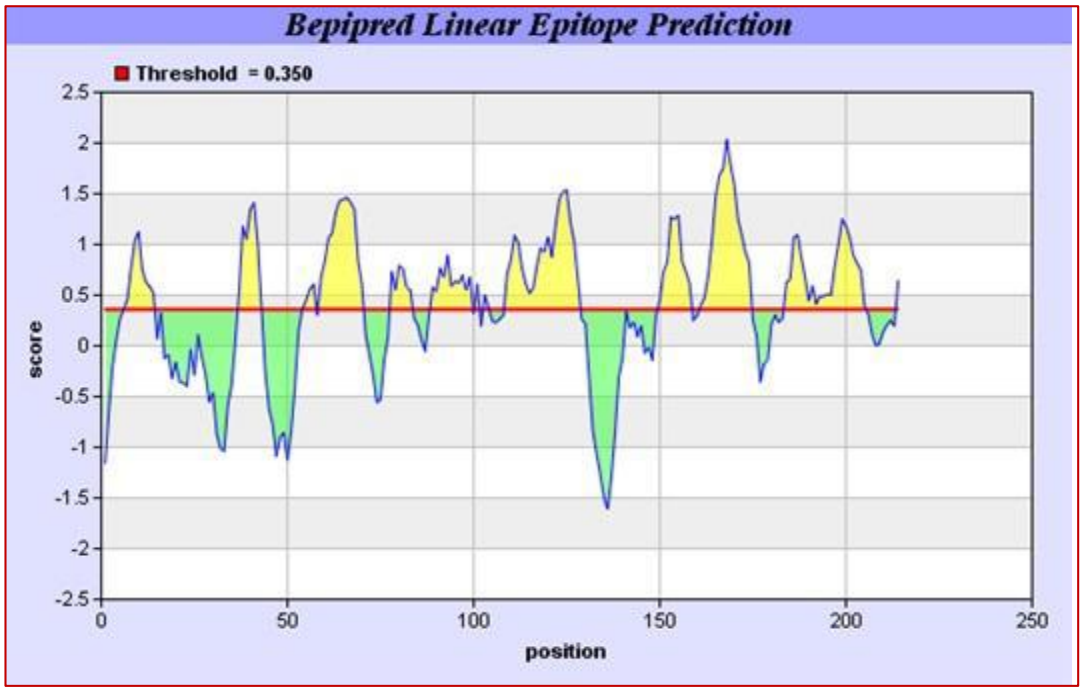

Figure 3. Prediction of continuous epitopes in the human Ig light chain. This is the output image of amino acid sequence analysis of reference human Ig light chain by Bepipred software. The 4 peaks of the map in the constant domain, formed by consecutive amino acids were regarded as 4 predicted linear epitopes. They were ranked by mean residue score (mean residue score was averaged by every residue in the predicted peptide). The higher the score of the available amino acids for the possible epitope in a part of the sequence, the higher the probability that this part of the sequence will be epitope. The 3th peak (amino acids 160-175) was the most likely epitope to be predicted by Bepipred.

The predicted continuous epitopes are located in amino acid sequences 110- 130, 150-160, 160-175, and 180-205 of the human Ig light chain. The prominent epitope is sited at amino acids 160-175 as are illustrated in Figure 3.

I) Prediction of continuous epitopes based on amino acid sequence of protein by Ellipro software

Discussion & Conclusions

In this study, a panel of four continuous epitopes on human Ig light chain constant domain were predicted by Bepipred software whereas only one continuous epitope was predicted by Ellipro software.

Bepipred assesses every amino acid separately and assigns it a score between −3 and 3. A higher score shows a greater possibility for being an epitope (34). Ellipro is suitable for recognizing the epitopes based on the geometrical characteristics of protein structure. Ellipro estimates the protein outline as an ellipsoid and calculates the residue protrusion index (PI) for continuous epitope anticipation (36).

Table 2. Prediction of continuous epitope in human Ig light chain constant domain by Ellipro software

Initial amino acid NO	End amino acid NO	Amino acid sequence**	Number of Amino acids	Score
198	203	HKTSTS	6	0.503

**Each letter demonstrates a single letter code of an amino acid

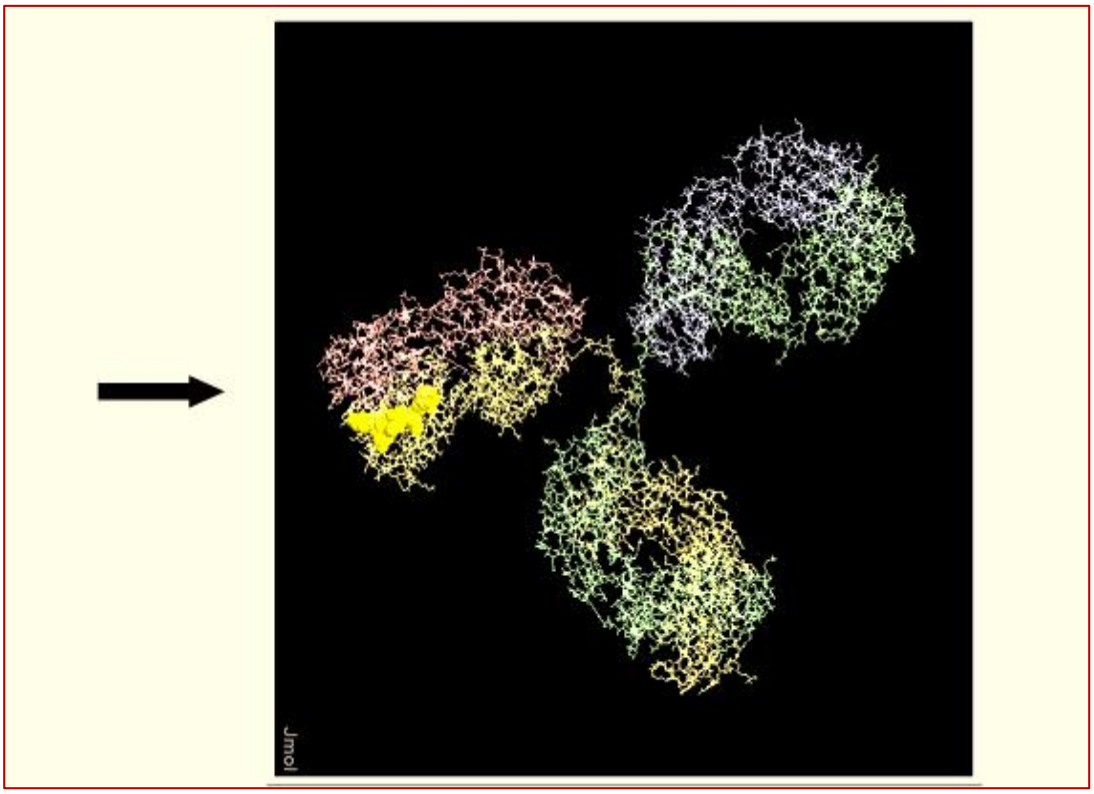

Figure 4. Prediction of continuous epitope on human Ig light chain constant domain by Ellipro software. The epitope is designated by yellow color.

One continuous epitope located at constant domain of human Ig light chain was determined by Ellipro software. This continuous epitope is shown in table 2 and Figure 4. The predicted continuous epitope is located at amino acid sequences 198- 203, in human Ig light chain.

Our results are compatible to Jespersen et. al study (2017) (35). Because in our study the predicted epitopes by Bepipred software were much more (4 epitopes) than the predicted epitope by Ellipro software (only 1 epitope). Jespersen et. al (2017) reported that Bepipred web server which predicts B-cell epitopes based on antigen sequences is significantly better than other existing tools for sequence-based epitope prediction on a big group of linear epitopes (35).

According to our results the most important continuous epitopes on human Ig light chain constant domain are located at amino acid sequences 110- 130, 150-160, 160-175, and 180-205. The prominent epitope is sited at amino acids 160-175.

According to some laboratory researches, the human immunoglobulin light chain constant region has a relatively high immunogenicity (30, 31) (similar to our data). In our study, several continuous epitopes were predicted in human Ig light chain constant domain.

Expression of light chains isotypes changes in some B lymphocytes tumors (9, 10). Role of light chains isotypes variations in non secretory myeloma has been reported (11). Noticeable alterations in kappa to lambda ratio could take place in monoclonal growth of malignant B cells (12). Generally, determination of the percentage of K^+/ λ^+ B cells is useful for diagnosis of B cell cancers (13). Also, specific targeting of light chain isotypes could be helpful for treatment of some diseases (14). Exact measurement of light chains isotypes needs specific and sensitive tools such as epitope-specific MAbs (15). Accordingly, anti-human light chain MAbs has clinical significance in diagnosis and immunotherapy of patients with B-cell immunoproliferative abnormalities (16, 17). Anti-human Ig light chains MAbs are useful to study the structure and its relationship to the antigenic properties of Ig light chains. A number of MAbs to human Ig light chains have been previously produced in mice (31, 37), some of which have shown cross-reactivity with other species of Igs (37). However, the position and features of the epitopes recognized by these MAbs have not been fully described. In order to optimize the diagnostic tests of Ig-light chains and increasing effects of anti-Ig light chains therapies, exact recognition of light chains specific epitopes is of extreme importance (18-20).

In experiments that are wholly/ partly denatured, target proteins are produced during sample preparation, for example western blotting, immunohistochemistry or immunofluorescence, continuous epitopes are favored (22).

Immunoinformatics, as a part of bioinformatics, uses biologic computational data for modeling and predicting immune system function in health and diseases as well as resolving of many immunologic complications including closer and more careful diagnosis of diseases (23, 24). Bioinformatic techniques are useful to recognize unique molecules for diagnostic or therapeutic practices (25). Bioinformatics uses the computer as a laboratory and categorizes the experimental data gathered in computer and analyzes them by computerized software programs (26). Immunoinformatics has been overextended to all fields of immunology and has provided innovative occasions for upcoming immunological researches (27, 28). continuous epitopes could be predicted by bioinformatic tools and can be used in further experiments (25). Thus, ccomputational epitope prediction tools are valuable to find the epitopes which are anticipated to be more specific and efficient than other parts of molecule in stimulating Abs production. Immunoinformatics could be benefit to solve the problems of experimentally mapping the epitopes (29).

In our previous studies, a number of conformational epitopes located at constant part of human immunoglobulin light chains (38) or heavy chain (39) have been determined by immunoinformatics. Also, several linear epitopes located at constant part of human immunoglobulin heavy chains were identified by immunoinformatics software programs (40). The results of this study are in agreement with our previous data (38) in this respect that 4/5 conformational epitopes located at constant part of human immunoglobulin light chains were determined in our previous study (38) included amino acid sequences 151-170 and this sequences are overlapped by the prominent linear epitope predicted by Bepipred software in present study which is sited at amino acids 160-175. Accordingly, it seems that the amino acid sequences 160-170 may form the more immunogenic part of the epitopes in the constant part of human immunoglobulin light chains. Thus, we recommend that special attention be directed to this area for the production of specific

diagnostic and therapeutic tools for human Ig light-chains. Antibody therapy with high effectiveness is one of main approaches in antibody thereatments. In this regard, computational tactics may well predict antibody-antigen constructions, manufacturing function of antibodies and increasing antibody-antigen complex characteristics. In silico planning of antibodies can improve affinities and physicochemical properties of antibodies in experimental studies (41-43).

Therefore, prediction of Ig light-chain linear epitopes could optimize the production of high affinity- specific anti-light chains MAbs and raise the sensitivity of existing diagnostic tests.

The Ig light-chain linear epitopes predicted in this study could be suitable tools for production of specific MAbs with high affinity in order to optimize the current light chain diagnostic tests and treatment methods in which the human immunoglobulin light chain is specifically targeted. In addition, these epitopes can be utilized to epitope drawing of the human immunoglobulin light chain, along with evolutionary studies.

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Conflict of Interests

The authors declare no conflict of interest.

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مقاله پژوهشی

پیشگویی اپی توپ های پیوسته زنجیره های سبک ایمونوگلوبولین انسان توسط ایمونوانفورماتیک

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چکیده

زمینه و هدف: ایمونوگلوبولینها که نقش حیاتی در دفاع علیه میکروارگانیسم ها دارند, از زنجیره های سبک و سنگین تشکیل شده اند. زنجیره های سبک به دو ایزوتیپ کاپا و لامبدا تقسیم می شوند. تغییرات قابل توجهی در نسبت زنجیره های کاپا به لامبدا در برخی بدخیمی های لنفوسیتهای B روی میدهد. آنتی بادیهای منوکلونال ضد زنجیره های سبک, در تشخیص و ایمونوتراپی ناهنجاری های پرولیفراتیو سلولهای B کاربرد دارند. هدف مطالعه حاضر تعیین اپی توپهای پیوسته زنجیره سبک ایمونوگلوبولین انسان توسط ایمونوانفورماتیک میباشد.

مواد و روش ها: توالی اسیدهای امینه و ساختار سوم زنجیره سبک ایمونوگلوبولینG (IgG) مرجع انسان در پایگاه اطلاعاتی PDB، ساختار دوم IgG توسط نرم افزار Phyre2 و اپی توپهای پیوسته زنجیره های سبک توسط نرم افزار های Bepipred و Ellipro تعیین شدند.

نتایج: چهار اپی توپ پیوسته در دومین ثابت زنجیره سبک ایمونوگلوبولین انسان توسط نرم افزار Bepipred شناسایی شدند . این اپی توپها درناحیه قرارگیری اسیدهای آمینه شماره ۱۱۰-۱۳۰, 150-160, 160-۱۷۵ و۱۸۰-۲۰۵ واقع شده اند. شاخص ترین اپی توپ در موقعیت اسیدهای آمینه 160-۱۷۵ قرار گرفته است. همچنین یک اپی توپ پیوسته در ناحیه اسیدهای آمینه ۱۹۸- ۲۰۳ توسط نرم افزار Ellipro شناسایی شد.

نتیجه گیری: در این پژوهش تعدادی از اپی توپهای پیوسته دومین ثابت زنجیره سبک ایمونوگلوبولین شناسایی شدند. این اپی توپها ابزارهای بسیار ارزشمندی جهت تولید آنتی بادیهای مونوکلونال شناسایی کننده اختصاصی زنجیره سبک ایمونوگلوبولین بوده و میتوانند برای تولید کیتهای تشخیصی اختصاصی زنجیره سبک، کنترل بیماریهای مونوکلونال زنجیرههای سبک, درمان برخی بدخیمی های لنفوسیت B و تعیین نقشه اپی توپهای زنجیره سبک مفید باشند.

کلمات کلیدی: اپی توپ پیوسته، ایمونوگلوبولین ، زنجیره سبک، ایمونوانفورماتیک

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