

HOMOLOGY MODELING AND COMPUTATIONAL MODEL FOR CELIAC DISEASE

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Abstract- Celiac Disease is an autoimmune disorder caused by the protein called Gluten found in the wheat and barley. The gluten will trigger autoimmune response in the small intestinal region. The 33mer gliadin part of Gluten protein influence the disease. The main intention of this paper is to find drug which will inhibit the autoimmunity in the body. The identification involves step by step process using computational methods. These computational methods makes process easier. The paper suggests that by blocking the tissue transglutaminase 2 using the drug molecule we can prevent autoimmunity in the body.

Keywords- Celiac Disease, tissue transglutaminase2.

1. INTRODUCTION

Celiac disease (CD) also called gluten-sensitive or autoimmune disorder results in damage to the lining of the small intestine when foods with gluten are consumed [1]. Gluten is a form of protein which is found in the grains like wheat, barley oats and etc. Characterisation of CD is by inflammation of the intestinal mucosa in the proximal small bowel. This will degenerate the villi like projections in the intestine wall. The CD causes mainly malabsorption, which is the result of injury to the small intestine with loss of absorptive surface area, reduction of digestive enzymes, and micronutrients such as fat-soluble vitamins, iron, and potentially [2]. The malabsorption will result in the diarrhoea and this leads to abdominal pain and weight loss in the CD active individual. Even symptoms like Anaemia and associated tiredness, headaches, mouth ulcers and skin problems are also common symptoms of CD [3].

The cause of the CD disease is not fully understood but still, the genetic factor plays a major role in the disease. Where the genetic disposition cause the CD in the patient [1]. Human Leukocyte Antigen (HLA) genes are linked to CD and even DQ2 and DQ8 play role in the active CD. It's not only genetic factors even environmental factors and external triggering factors can form active CD in the individual. Consuming diet food with rich gluten may trigger the CD and also other factors influence the CD. Even small amounts of gluten (50mg/day) can be immunogenic; therefore all food and food items and drugs that contain gluten and its derivatives must be eliminated completely from the diet [4].

As we know the gluten is found in the wheat, barley and etc., These food grains when consumed by a person with active CD the gluten present in grains is broken as Gliadin and glutenin. This gliadin contains the 33-mer peptide (LQLQFPQPQLPYQPQLPYQPQLPYQPQLPY) from $\alpha 2$ -gliadin [5]. The 33-mer is widely called the most immune dominant gluten peptide, because it contains three overlapping T-cell epitopes, namely PFPQPQLPY :DQ2.5-glia- $\alpha 1a$ - one copy, PYPQPQLPY :DQ2.5-glia- $\alpha 1b$ - two copies and PQPQLPY :DQ2.5-glia- $\alpha 2$ - three copies [5]. This result in the initiation of a strong immune response which enters the small intestine it binds with secretory IgA present in the mucosa of the small intestine. In a normal person, if this secretory IgA binds to any molecule in the small intestine it will destroy. But in active CD patient it won't destroy the Gliadin molecule instead of that it will transfer gliadin complex with secretory IgA to the intestinal receptor called Transferrin receptor. The main function of this receptor is to absorb the iron in the intestinal mucosa, but in inactive CD patient it binds to the Gliadin molecule and it is taken to the basal-lateral membrane. Once gliadin reaches inside the lamina tissue transglutaminase enzyme comes and cut out AMIDE group from the Gliadin protein. This deaminated gliadin will be eaten by macrophage and gliadin molecules will be placed on macrophage MHC II receptor. Now T-helper cell come in picture and identify gliadin molecules as antigen material and release inflammatory cytokines. These cytokines will destroy the lining of the small intestine. This inflammation will call up the killer T-cell which will destroy or degenerate the mucosal lining. CD is believed to directly target the skin. Gluten ataxia is another immune manifestation of CD indicating that it can also target the nervous system [6]. Joint and rheumatologically disease may also occur independently of intestinal involvement.

This disease found rare in childhood, but can have its onset at any age, and has lately emerged as a worldwide public health problem [7]. The most common age for diagnosis of CD is between forty and fifty years [3].

There is only one treatment available for CD which is Gluten Free diet. The patient with active CD should take only food without gluten. So the gluten-free food won't trigger the inflammation in the small intestine. But recently researchers have found gluten-free diet can cause several nerve-related disorders. This can lead to a patient in a critical problem in his life. The

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new approaches are coming to cure the CD using the drugs. The scientists mainly focusing on the particular regions of gluten molecule and tissue transglutaminase molecule as the main regions where the drug can inhibit the activity of the CD in patients. The major components of gluten are that it is not digested by the digestive enzymes in the stomach because of proline and glutamine bonds. To break these bonds external enzymes should be used to break bonds in the gliadin so the activity of the gluten will stop in the CD active person. The next is to block the transglutaminase activity using a drug. So the deamination of the gliadin molecule will be stopped. As the result, it won't influence the production of the immunoglobulins.

2. METHODOLOGY

The paper involves literature review on the CD and depending on research papers, the work has been carried out. The main intention is to stop or block the immunogenic response when a person consumes the gluten-rich food in CD patients. It's a big challenge to block immunogenic response in the CD patients. To block autoimmune response a target should be identified. According to researches carried out in the CD tells that targets found in the diseases are gluten molecule where it can be digested using a bacterial enzyme [8]. The second one is the reduction of exposure of gluten so that CD patient is exposed to less gluten food. Next one is blocking of HLA-DQ2 to prevent binding of Immunogenic Peptides and inhibition of the transglutaminase using the drug molecule [8].

In this paper we have worked on a method of blocking the tissue transglutaminase in a mucosal cell which is responsible for the de-aminated gliadin molecule in the immune response. The first task is to extract the structure of the transglutaminase 2 protein. The structure is modelled by homology modelling method using Swiss PDB viewers by submitting the request to Swiss modular. The obtained structure is validated using energy minimization processes, by mutating the odd residues and the Ramachandran plot to check the stability of the molecule. After finishing the homology modelling next is to find the preferable drug molecule to transglutaminase protein. After several study on papers a drug molecule was found which inhibited the transglutaminase in the intestine. The drug is called novel inhibitor which is a peptide-like drug, which inhibits the activity of the tissue transglutaminase [9].

3. RESULT

3.1 Homology modelling --

The sequence is submitted to the modelling request using the Swiss model work space [10]. After retrieving the model some basic mutations have been carried to bring the model to low energy. The structure gives force field energy as -57770.664 which is a good structure. Basically after Energy minimization the energy fall down to the -83724.186 and this structure can be good for the further processes. Next structure is validated using RAMPAGE to check the stability of the structure [11]. The result of RAMPAGE is given below and shown in Figure 1.

Number of residues in favoured region (~98.0% expected) : 1813 (88.5%)

Number of residues in allowed region (~2.0% expected) : 186 (9.1%)

Number of residues in outlier region : 50 (2.4%)

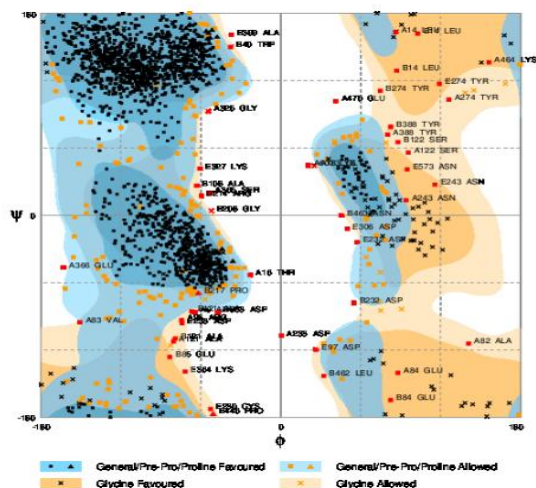


Fig 1. RAMPAGE graphical result

3.2 Docking

Hex offline tool is used for docking where receptor is given as the transglutaminase 2 and ligand given as inhibitor. The tool shows inhibitor binding to the transglutaminase molecule in the current Figure 2. Docking results give different parameters which have been shown below in Table 1 [12].

Table 1 – Docking results using Hex

	Cluste	Solution	Models	H-bonds	Bumps	RMS	Ettotal	Eshape	Eforce	Eair
Model 1	1	1	0:0	-1	-1	-1.00	-296.85	-296.85	0.00	0.00

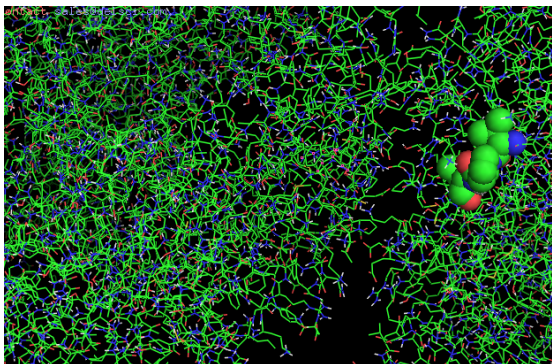


Figure 2. Docking figure using Hex

3.3 Swiss-ADME

Is an online tool used to give the property of drug in the body. This tool was used to calculate the Pharmacokinetics, drug-likeness, Medical Chemistry of inhibitor molecule [13]. Figure obtained is shown in figure 3 and physiochemical property in

Table 2.

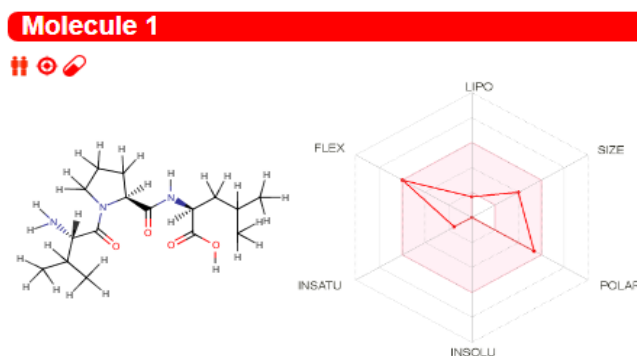


Figure 3. Figure obtained using Swiss-ADME

Table 2: physiochemical property

Formula	C ₁₆ H ₂₉ N ₃ O ₄
Molecular weight	327.42 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	0
Fraction Csp ³	0.81
Num. rotatable bonds	9
Num. H-bond acceptors	5
Num. H-bond donors	3
Molar Refractivity	91.40
TPSA	112.73 Å ²

Table 3: Lipophilicity

Log Po/w (iLOGP)	Log Po/w (XLOGP3)	Log Po/w (WLOGP)	Log Po/w (MLOGP)	Log Po/w (SILICOS-IT)	Consensus Log Po/w
2.13	-2.62	0.20	0.24	0.70	0.13

Table 2 shows lipophilicity of the inhibitor molecule in iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT and are different freely available predictive models to calculate Lipophilicity.

Table 3: Water Solubility

Log S (ESOL)		Log S (Ali)		Log S (SILICOS-IT)	
Solubility	7.76e+02 mg/ml ; 2.37e+00 mol/l	Solubility	2.07e+03 mg/ml ; 6.31e+00 mol/l	Solubility	2.15e+01 mg/ml ; 6.58e-02 mol/l
Class	Highly soluble	Class	Highly soluble	Class	Soluble

Table 3 shows three different model (ESOL, Ali *et al.*, and SILICOS-IT) have been used to predict the water solubility of novel inhibitor.

Table 4: Pharmacokinetics

GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation)
high	No	Yes	No	No	No	No	No	-10.16 cm/s

Table 4 shows the novel inhibitor Pharmacokinetics calculation of molecule which shows that the GI absorption is high. This will be a good benefit in the CD. There is no Blood-Brain Barrier Permeability. Novel inhibitor being a substrate to P-Glycoprotein shows good absorption and bioavailability. Log Kp (skin permeation value) -10.16 cm/s shows that skin permeation is very low which shows that administration through skin also fails in delivering the drug. The molecule also acts as a non-substrate to 5 isoforms of cytochrome P450 (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4) which is crucial for the elimination of the drug from the body. The overall result obtained signifies that the oral drug administration is not of much use, which leaves the intravenous administration of novel inhibitor the better option.

Table 5: Druglikeness

Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
Yes; 0 violation	yes	Yes	yes	No; 1 violations: XLOGP3<-2	0.55

Table 6: Medicinal Chemistry

PAINS	Brenk	Leadlikeness	Synthetic accessibility
0 alert	0 alert	No; 1 violation: Rotors>7	3.43

4. CONCLUSION

As we know the celiac disease is autoimmune disorder. There is an only one cure present its gluten free diet. But when a person with active CD travels he was unable to get Gluten free food daily. Depending on these factors the drug have to be discovered to be aware of disease. As above mentioned novel inhibitor is used to block the activity of tissue transglutaminase2 in the CD. As the results of the literature review, the inhibitor is a peptide-like drug which blocks the de-amidation of gliadin molecule as the result autoimmunity is not mediated. These are the computationally predicted it makes work easier then these methods can be applied through the experimental approaches. We suggest this computational method for the other allergy disease which does not have the proper treatment of Celiac Disease which will be helpful for the further studies.

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