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Research Article

Homology Modeling of MMP11 in Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is the occurrence of chronic bronchitis or emphysema, a pair of commonly co-existing diseases of the lungs in which the airways become narrowed. This leads to a limitation of the flow of air to and from the lungs, causing shortness of breath (dyspnea). According to the World Health Organization, COPD kills more people than HIV-AIDS, Malaria and Tuberculosis all put together in the South East Asian region. COPD was classified in two broad categories chronic bronchitis and Emphysema. Cigarette smoking is the main environmental threat aspect for developing COPD, about 15% of smokers can develop clinically significant disease which suggest that there are also other influences on disease appearance. Subsequent work has suggested other important proteases, such as the matrix metalloproteinase (MMP's), cathepsin B and collagenases may also play a role, perhaps as part of a protease/anti-protease cascade MMPs are thought to be responsible for the turnover and degradation of connective tissue proteins, a function that is clearly performed by several family members. The mode of action of MMP11 proteins plays a critical role for causing the COPD disease by MMP11 gene. The MMP 11 has main potential drug target in Mink plasmacytosis and fibrosarcoma disease along with its related pathways and matrix. MMP11 play an important function in the development of epithelial malignancies. The main objective of this study to identification the role of MMP11 involvement in disease and its sequence and structure analysis by various In silico tools and database.

Keywords: *COPD; MMP11; Protein; In Silico*

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease that causes obstructed airflow from the lungs. The Symptoms incorporate breathing difficulty, cough, mucus (sputum) production and wheezing which caused by long-term experience to irritating gases or particulate matter, most often from cigarette smoke and it is phenotypically complex disease which is distinctive nature by small-airway disease and emphysema. The main reason of demise among COPD patients is lung disease. COPD is genetically difficult disease where the 1% of patients affected due to α-1 antitrypsin. approximately 24 million affected individuals. More than 24 million individuals affected in the world and more than 125,000 annual deaths in US by COPD disease. According to WHO, the COPD will become the third leading cause of death and fifth leading causes of worldwide by 2020 [1]. Smoking along with noxious particles like biofuel smoke are important cause of COPD and also main cause on inflammation in disease.

The risk of factors for COPD is air pollution, occupational exposure, and indoor biofuel pollution in worldwide. The genetic and biological characteristics are similar in COPD and lung cancer. The smoking history of patients has recorded 15% - 20% in COPD and 50 - 80% lung cancer in patients also the risk of COPD is six fold higher in lung cancer patients. COPD principally occurs in smokers above 40 years

of age, and its incidence is 2.5 times higher in those aged > 60 years [2]. It is major reason of chronic morbidity and mortality which represents a considerable economic and social burden throughout the world [3]. The tobacco smoking-induced inflammatory response yields an array of deregulated cells, cytokines, and growth factors that are conducive to the development of both chronic obstructive pulmonary disease (COPD) and lung cancer [4]. The cigarette smoke is main inducer for both COPD and lung cancer by increases the numbers of reactive oxygen species (ROS) in the lung also non-smokers may develop these diseases due to environmental factors. Normal patients can conquer from these stressors, whereas susceptible will extend the pathophysiological changes linked with COPD or lung cancer. A combination of immune-inflammatory signals and epigenetic actions may cause the improved threat of patients with COPD developing lung cancer [5].

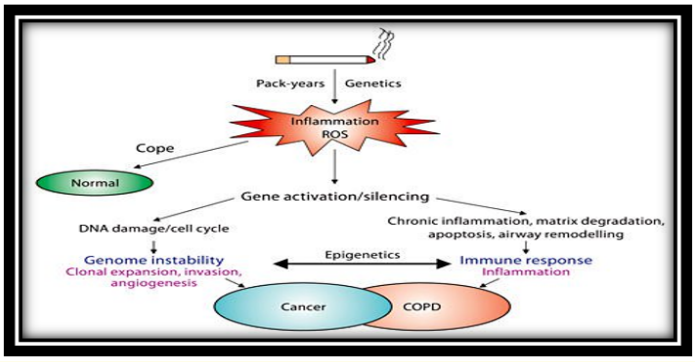

Figure 1: *COPD Infection.*

MMP families are actively concerned in the breakdown of extracellular matrix in normal physiological processes. The mainly MMP's are acting as secreted and inactive proprotein they are activate by cleaved extracellular proteinases and actively involved in constitutive secretary pathway also degrades structural proteins of the extracellular matrix. In vertebrates MMPs comprise a family of 28 matrix degrading enzymes that contain a zinc atom in their active site and are able to cleave all components of the extracellular matrix (ECM) and basement membranes (BM) including collagen, laminin, and elastin. The ECM is a complex network of different molecules sustaining collagens, laminin, fibronectin, entactin/nidogen and proteoglycans, and serving a mechanical role by supporting and maintaining tissue structure and modulating different cell functions including development, migration and proliferation [6]. cigarette smoke and oxidative stress is main factors for activation of MMPs. MMP-11 (stromelysin-3) and their Molecular weight latent/active (kDa) 58/28 and Main substrates are Fibronectin, laminin, gelatin, aggrecan, elastin, collagens IV, V, IX, X [7]. MMPs are a large family of zinc-dependent proteases that have the ability to degrade several components of the extracellular matrix and thus are likely to play a role in cell migration and tissue destruction. They are produced as inactive pro-enzymes by both inflammatory and structural cells and become activated by proteolytic cleavage of an N-terminal domain. MMPs can activate cytokines and chemokines, thereby further contributing to the inflammatory reaction in COPD [8]. The biological mechanism of MMP-11 is not known, but possibly involve in proteolytic cleavage to promote cell survival, but it is significantly differ from other MMPs. The ECM proteins such as collagens, gelatin and fibronectin can be degraded by MMP-11 also it exhibit an anti-apoptotic result [9]. The main substrates of MMP-11 have been shown that mainly protease inhibitors such as a1 proteinase inhibitor and a2 macroglobulin activity also it shows weak caseinolytic activity and insulin-like growth factor-binding protein-1 (IGF-BP-1) [10].

Objective of the Study

The main objective of this study to identification of MMP11 protein and it play a critical role for causing the COPD disease with its structure analysis by In silico tools and database.

Methods and Material

Sequence Retrieval

The protein matrix metalloproteinase 11 (MMP11) sequence was retrieved from the Uniprot Sequence Database and it is a central access point for extensive curated protein information, including function, classification and cross references. It consists of large amount of information about the biological function of protein derived from research literature [11].

Primary Sequence Analysis

The various physicochemical parameters of matrix metalloproteinase 11 were analyzed such as theoretical PI, amino acid Composition, extinction coefficient, instability index, aliphatic index and grand average of hydropath city (GRAVY) was done by using ExPASy's protparam tool [12].

Secondary Structure Prediction

The secondary structure prediction of matrix metalloproteinase 11 carried out by using SOPMA (The Self-Optimized Prediction method With Alignment) server. The method is employed for calculating the secondary structural elements of the selected query sequences. SOPMA will predict the secondary structure based on the query sequence [13].

Tertiary Structure Prediction

The tertiary structure of matrix metalloproteinase 11 was predicted by using SWISS MODEL [14]. SWISS MODEL is a fully automated protein structure homology modeling server and the predicted model were validated using PROCHECK tool [15].

Structure Visualization

The predicted 3D structures of matrix metalloproteinase protein 11 were visualized using RasMol [16]. RasMol is bioinformatics programme for visualization of protein 3D structure.

Domain Analysis

The domains of matrix metalloproteinase 11 were predicted by using pfam database. The pfam domain database which contain the information of families and annotation [17].

Results and Discussion

Sequence Retrieval

The sequence of protein matrix metalloproteinase 11 (MMP11) were retrieved from database such as UniprotKB Database with amino acid in FASTA file format given in below in table 1.

Uniprot ID	FASTA file format
P24347	>sp|P24347|MMP11_HUMAN Stromelysin-3 OS=Homo sapiens OX=9606 GN=MMP11 PE=1 SV=3 MAPAAWLRSAAARALLPPMLLLLLQPPPLLARALPPDAHHLHAERRGPQPWHAALPSSPA PAPATQEAPRPASSLRPPRCGVPDPSDGLSARNRQKRFVLSGGRWEKTDLTYRILRFPWQ LVQEQVRQTMAEALKVWSDVTPLTFTEVHEGRADIMIDFARYWHGDDLPFDGPGGILAHA FFPKTHREGDVHFDYDETWTIGDDQGTDLLQVAAHEFGHVLGLQHTTAAKALMSAFYTFR YPLSLSPDDCRGVQHLYGQPWPTVTSRTPALGPQAGIDTNEIAPLEPDAPPDACEASFDA VSTIRGELFFFKAGFVWRLRGGQLQPGYPALASRHWQGLPSPVDAAFEDAQGHIWFFQGA QYWVYDGEKPVLGPAPLTELGLVRFPVHAALVWGPEKNKIYFFRGRDYWRFHPSTRRVDS PVPRRATDWRGVPSEIDAAFQDADGYAYFLRGRLYWKFDPVKVKALEGFPRLVGPDFFGC AEPANTFL

Table 1: *Sequence of MMP11.*

Primary Sequence Analysis

The various physicochemical parameters of matrix metalloproteinase 11 were analyzed by protparam tool. The parameters shown in table 2.

Properties	MMP11
Number of amino acid	488
Molecular weight	54589.93
Positive charge	49
Negative charge	54
Total number of atoms	7613
Instability index	51.62
Aliphatic index	74.08
Theoretical PI	6.38
Gravity	-0.332

Table 2: *Physicochemical parameters of MMP11.*

Secondary Structure Prediction

The secondary structure prediction of matrix metalloproteinase 11 is done by using SOPMA server. The secondary structural elements like percentage of alpha helix, beta sheets and coils were enlisted in table 3.

Properties	MMP11
Alpha helix	23.98%
Beta bridge	0.00%
Random coil	59.63%

Table 3: *Secondary structure of MMP11.*

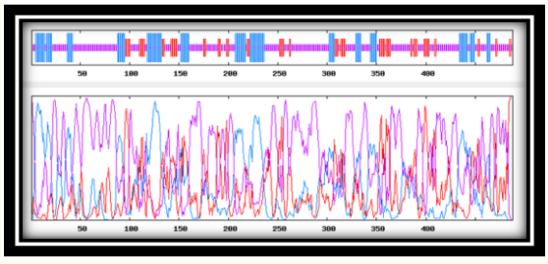

Figure 2: *Secondary structure of MMP11.*

Tertiary Structure Prediction

The tertiary structure of matrix metalloproteinase 11 was predicted by using SWISS MODEL automated modeling server. The table 4 given below represents favored regions in target proteins. As per table the number of amino acids residue in favored region predicts the

quality of newly generated model. Further, this model was gives the structural insight the identification of binding residue for the structure based drug design.

Uniprot ID	No. of residues in most favored region
P24347	88.8%

Table 4: *Validation score of MMP11.*

Structure visualization

The predicted 3D structure of matrix metalloproteinase protein 11 were visualized using RasMol. The 3D structure of MMP11 were shown in figure 3 and its represents the alpha helix, beta sheet and coiled region along with the evolutionary conserved region in protein MMP11. The 3D structure quality was checked using PROCHECK. The PROCHECK analyses provide an idea of the stereo chemical quality of the protein it shown in a figure 4.

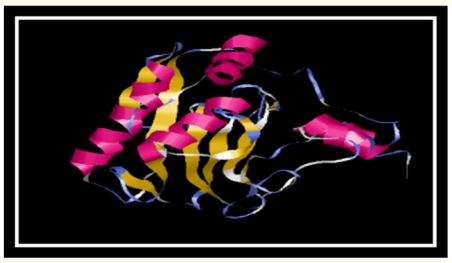

Figure 3: *3D Structure of MMP11 Protein.*

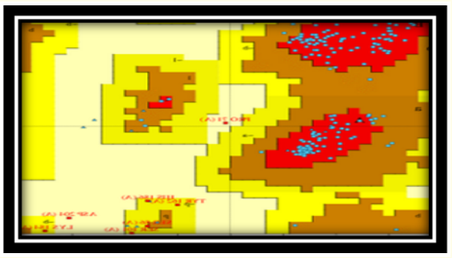

Figure 4: *Procheck Analysis.*

Domain Analysis

The domains of matrix metalloproteinase 11 were predicted by using pfam database which contain the information of families and annotation were shown in the figure 5.

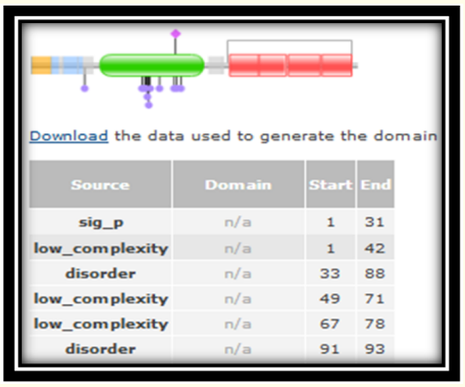

Figure 5: *Domain Analysis.*

Conclusion

MMP11 protein is involved in the breakdown of extracellular matrix in Chronic Obstructive Pulmonary disease. Mainly MMP11 is secreted protein and it is activated by extracellular proteinase. Thus In silico sequence and structural analysis of MMP11 which pave details inside the as novel drug target in COPD. The further study continue to find the potential natural inhibitor for MMP11 by Computer based Drug Design (CADD).

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