ROLES OF A$_1$ ANTITRYPSIN DEFICIENCY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Alpha$_1$ antitrypsin deficiency (α_1ATD) is a genetic disorder that affects 1 in 1500-3000 of European origin population. Mutation in SERPINA$_1$ gene appears to be the main cause of α_1ATD. This disorder increases the risk of Chronic Obstructive Pulmonary Disease (COPD) due to the proteolytic action of serine proteases on the alveolar cells and accumulation of α_1AT consequent immune response. In addition, the effects of immune response to the accumulated enzyme in the Endoplasmic reticulum (ER). Patients aged 20-50 years having α_1ATD are at a high risk for developing COPD. This review focuses on the molecular pathophysiology of α_1ATD and how it leads to COPD. It is concluded that factors accelerating α_1AT release in the peripheral circulation lead to a better outcome.

KEY WORDS: SERPINA$_1$ gene, proteases, alveolar cells, Endoplasmic reticulum (ER), immune response.

INTRODUCTION

Alpha$_1$ antitrypsin (α_1AT) is a protein belongs to serine protease inhibitor (Serpin) super family[1,2]. This protein plays a major role in maintaining the stability of lung tissue[1]. α_1AT blocks the activity of different proteases, one of which is Neutrophil elastase (NE) which known to be one of the important factor in the development of COPD[3, 4]. Destruction of lung elastic tissue by neutrophil elastase (NE) will subsequently lead to loss of elastic recoil of the lung and causes (Emphysema)[5,6]. Emphysema is one of the main pictures of chronic obstructive pulmonary disease[5].

α_1AT deficiency is due to genetic disorder that inherited as an autosomal codominant condition[7]. It was first documented by Laurell and Eriksson in 1963 in Sweden when they noticed the relation between the absences of alpha$_1$ antitrypsin and Emphysema[4]. After one decade, different phenotype / genotype of α_1ATD was detected[8]. The allelic variations are due to single nucleated polymorphism (SNPS) in SERPINA$_1$ gene on chromosome 14q32[7]. SERPINA$_1$ gene is highly polymorphic gene consists of 7 exons and 6 introns with more than 100 SNPs[7,9]. α_1ATD is due to Mutation in SERPINA$_1$ gene[2]. This gene most of the time produce normal level of α_1AT in the blood. M variant (normal) is the most common variant with gene frequency of 0.95 among the people[7], normal serum level of M variant α_1AT is 20-53 μM/L[2]. The degree of α_1ATD primarily depend on the site of mutation and subsequent effect of (substituted / deleted) amino acid on α_1AT protein structure and function. Substitution of Glutamic acid by Valine at position 264 of α_1AT polypeptide is a result of S Allele which associated with moderate decrease in α_1AT level in the blood[7]. On the other hand, Z allele is due to the substitution of Glutamic acid by Lysine at the position 342 of α_1AT[7].

Z allele associated with significant reduction in α_1AT blood level (<11 μmole/L) due to inability of the cell to release the accumulated polymerized protein in the endoplasmic reticulum. The lower limit of the protective threshold of α_1AT in the blood is 11 μmole/L[2,8], so the quantitative availability of this concentration is required to abolish the destructive effect of neutrophil elastase. Respiratory epithelium secretes α_1AT which play a local significant protective role in the respiratory system beside what mainly secreted by hepatocyte[10]. Not only low level can increase the risk of COPD, but also the accumulation of the non-secreted α_1AT in the endoplasmic reticulum of respiratory cells[10]. This review focuses on molecular pathophysiology of α_1ATD and subsequent cell responses.

α_1AT structure and function associations:

α_1AT protein consists of 394 amino acid with 52 kDa[7]. As other Serpins protein α_1AT fold consists of nine alpha helices (A-I), three β -pleated sheets (A-C) and reactive center loop (RCL)[11]. RCL contain PI-PI' and Methionine at 358 which act as a target site for neutrophil elastase inhibition. Changes in β -pleated sheet A in Z variant mutation are gap formation in beta sheet A itself and increasing the mobility of RCL. Polymerization occur when the highly mobile RCL of one α_1AT molecule got inserted in the gap of β-pleated sheet A of another molecule[4]. Factors lead to changes in RCL affects the protein function as an antiprotease. Accumulation of Mutant α_1AT in the endoplasmic reticulum will lead to two negative effects. First, Low level of α_1AT in the blood which leads to unopposed effect of proteases specially neutrophil elastase[7]. Second, accumulated α_1AT in the endoplasmic reticulum leads to ER stress which result in different translational changes[12]. The polymerized form (ZZ phenotype) acts as chemotactic factor for inflammatory cells[10].

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Those effects are greatly explaining why α$_1$AT deficient patient at a greater risk of developing COPD.

Intracellular response to the accumulated non polymerized and polymerized α$_1$AT:

Physical structure of the accumulated α$_1$AT determines different pathways of intracellular responses[12]. Asparagine linked modification of newly synthesized α$_1$AT augments association with glycoprotein folding machinery[13]. Unassembled or misfolded α$_1$AT glycoprotein is degraded by Endoplasmic Reticulum Associated Degradation (ERAD) which involves removal of mannose by ER mannosidaseI[1]. ER mannosidaseI is involved in proteasomal degradation of misfolded α$_1$AT[14]. The target of ERAD is to release misfolded protein to 26S proteasomes in the cytosol in normal situations. When the ER got overwhelmed and over loaded with the misfolded α1AT protein unfolded protein response UPR will take over because ERAD is easily saturated[1].

Non-polymerized α$_1$AT does induce (UPR) as described by Hidvegi et al. UPR results in wide spectrum of gene activation triggered by accumulation of unassembled, unfolded or misfolded protein in the ER. The objectives of gene activation is to increase the ER membrane synthesis to contain the load, to increase synthesis of ER chaperons that augment the folding process in the ER, and to increase synthesis of different proteins supporting glycosylation system and degradative machinery[12]. There are three important transmembrane proteins of the ER involved in UPR; Ire1, ATF-6 and PERK. Grp78 (Bip) binds to the luminal domain of those transmembrane protein keeping them inactivated. Bip dissociated from the luminal domain to bind with the misfolded protein during ER stress[12,15]. Dissociation of Bip activates trans membrane protein which leads to activation of targeted UPR genes[12]. On the other hand, accumulation of polymerized α$_1$AT doesn't lead to UPR, in a study conducted by BelaZ. Schmidt et al. has shown the interaction of ER chaperons like Bip with non-polymerized α$_1$AT is identical to polymerized α1AT protein[1,15]. The interaction of Bip with polymerized form in mammalian cells is unknown and may not functionally related[15]. Auotophagic response and specific signaling pathway get activated due to accumulation of polymerized α$_1$AT. A polymerized α$_1$AT protein activates caspase4, BAP31 and NFKB. NFK B gets activated by accumulation of both mutant α$_1$AT Z and S protein[12]. Expression of polymerized α$_1$AT protein is associated with up regulation of RGS16 which interact with anti-phagocytic factor Gα$_{i3}$ and may repress its activity[16]. This may explain why Up-regulation of RGS16 is correlated with high phagocytic activity.

Pathophysiology:

The exact risk for α$_1$AT deficiency individual to develop COPD is unknown[2]. The central part of COPD is the inflammatory process. Neutrophil plays a major role as a part of inflammatory process in COPD specially Neutrophil elastase[17,18]. Neutrophil elastase activate toll like receptor TLR which subsequently augment the production of IL8[2]. IL8, Myeloperoxidase and LTB$_4$ concentration was increased in sputum of patients with ZZ mutant α$_1$AT as described by A.T.Hill et al. IL8 with LTB$_4$ play major role for Neutrophil recruitment[18]. In addition, Polymerized Z α$_1$AT protein acts as potent neutrophil chemo-attractive factor. Polymerized α$_1$AT is produced by the lung epithelial in patient with liver transplant[10]. Polymerized α$_1$AT is found in lung epithelial lining fluids. Alveolar tissue destruction by neutrophil elastase causes air trapping (Emphysema) with a decrease in lung function including significant decrease in forced expiratory volume (FEV$_1$)[2]. David G et al. has shown that basal emphysema according to CT scan pattern in α$_1$AT deficiency (Piz phenotype) associated with a greater impairment of FEV$_1$ than whom have apical emphysema[19].

Epidemiology:

α$_1$AT is generally underdiagnosed genetic disorder[20]. Approximately 3.4 million persons worldwide have α$_1$ATD if ZZ, SZ or SS included[7]. Northwest European countries and North America recorded the highest prevalence of Z mutation deficiency. The gene frequency in Europe decreases from the Northwest toward the Southeast[2]. The Z allele frequency in the United State is equal to the lowest frequencies in Europe which is 0.012[2,8]. The S allele frequencies in The United State is 0.35; which is higher than the frequencies of the same allele in Northwest Europe[8]. One study in Spain documented the gene frequency of Z Allele is 1.5%[20]. Hungary, Portugal and Spain carry the highest frequencies of S allele which associated with mild deficiency of α$_1$AT blood level[8]. Southern Scandinavian is thought to be the origin of Z mutation[2,8]. 4000 to 7000 years ago this mutation distributed to Europe by population movements[8,2]. Other alleles like Siiyama allele (Ser53Phe) which form polymers in ER is a rare and specific for Japanese[8]. Asia, Africa, and Middle Eastern population have less frequent α$_1$ATD disorder[8].

Optional management of α$_1$ATD:

It is known that smoking is the most common risk factor associated with COPD. Low level of α$_1$AT and smoking will accelerate the risk of development of COPD. According to Sam Alam et al. smoking extracts accelerate polymerization of ZZ phenotype α$_1$AT by oxidative modifications[21]. He is also shown the risk of premature emphysema is increased in ZZ phenotype smoking individual. Risk factor modification by smoking cessation is highly recommended in homozygous ZZ phenotype individuals and It is also recommended for homozygous ZZ phenotype individuals. COPD patients with α$_1$ATD or non α$_1$ATD patients are similarly treated accord-

ing to the American Thoracic Society and European respiratory society ATS / ERS recommendations[2]. Nonspecific treatments like bronchodilators, anti-inflammatory (inhaled steroids), and portable oxygen for some cases had shown symptomatic bene-fits[7].

Augmentation therapy is a Specific therapy for α_1ATdeficient patients[22]. It is FDA approved therapy in United State[2]. It has two different route of administration; one is intravenous route and the other through inhalation route. Intravenous route and inhalation route used according to ATS / ERS guidelines. Different studies stated that Augmentation therapy shown decline in decreasing FEV$_1$ in COPD patients[23]. Contaminating factor in both forms may induce allergic reaction.

CONCLUSION

Augmentation therapy can only replace the deficient α_1AT but cannot interfere with the accumulated mutant α_1AT in the ER. ER stress response is the target of current researcher for a better understanding the ambiguity behind mechanical impeding of different kind of mutant α_1AT in the ER in order to aid its release. A better outcome is expected from future studies on mutant α_1AT in lung tissue with disease specific induced pleurae potential stem cell (iPSC) that has the ability to differentiate to lung epithelial precursor in vitro.

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