ROLES OF $\alpha_1$ ANTITRYPSIN DEFICIENCY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Alpha $\alpha_1$ antitrypsin deficiency ($\alpha_1$ATD) is a genetic disorder that affects 1 in 1500-3000 of European origin population. Mutation in SERPINA1 gene appears to be the main cause of $\alpha_1$ATD. 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 $\alpha_1$AT 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 $\alpha_1$ATD are at a high risk for developing COPD. This review focuses on the molecular pathophysiology of $\alpha_1$ATD and how it leads to COPD. It is concluded that factors accelerating $\alpha_1$AT release in the peripheral circulation lead to a better outcome.

KEY WORDS: SERPINA1 gene, proteases, alveolar cells, Endoplasmic reticulum (ER), immune response.

INTRODUCTION

Alpha $\alpha_1$ antitrypsin ($\alpha_1$AT) 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(3). $\alpha_1$AT 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(7).

$\alpha_1$AT 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 absence of alpha antitrypsin and Emphysema(8). After one decade, different phenotype / genotype of $\alpha_1$ATD was detected(8). The allelic variations are due to single nucleated polymorphism (SNP) in SERPINA1 gene on chromosome 14q32(7). SERPINA1 gene is highly polymorphic gene consists of 7 exons and 6 introns with more than 100 SNPs(7,9). $\alpha_1$ATD is due to Mutation in SERPINA1 gene(2). This gene most of the time produce normal level of $\alpha_1$AT 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 $\alpha_1$AT is 20-53 µM/L(12). The degree of $\alpha_1$ATD primarily depend on the site of mutation and subsequent effect of (substituted / deleted) amino acid on $\alpha_1$AT protein structure and function. Substitution of Glutamic acid by Valine at position 264 of $\alpha_1$AT polypeptide is a result of S Allele which associated with moderate decrease in $\alpha_1$AT 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 $\alpha_1$AT(7).

Z allele associated with significant reduction in $\alpha_1$AT 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 $\alpha_1$AT in the blood is 11 µmole/L(12,28), so the quantitative availability of this concentration is required to abolish the destructive effect of neutrophil elastase. Respiratory epithelium secretes $\alpha_1$AT 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 $\alpha_1$AT in the endoplasmic reticulum of respiratory cells(10). This review focuses on molecular pathophysiology of $\alpha_1$ATD and subsequent cell responses.

$\alpha_1$AT structure and function associations:

$\alpha_1$AT protein consists of 394 amino acid with 52 kDa(7). As other Serpins protein $\alpha_1$AT 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 $\alpha_1$ATmolecule got inserted in the gap of β-pleated sheet A of another molecule(6). Factors lead to changes in RCL affects the protein function as an antiprotease. Accumulation of Mutant $\alpha_1$AT in the endoplasmic reticulum will lead to two negative effects. First, Low level of $\alpha_1$AT in the blood which leads to unopposed effect of proteases specially neutrophil elastase(7). Second, accumulated $\alpha_1$AT 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).
Those effects are greatly explaining why α1AT deficient patient at a greater risk of developing COPD.

**Intracellular response to the accumulated non polymerized and polymerized α1AT:**
Physical structure of the accumulated α1AT determines different pathways of intracellular responses[12]. Asparagine linked modification of newly synthesized α1AT augments association with glycoprotein folding machinery[13]. Unassembled or misfolded α1AT glycoprotein is degraded by Endoplasmic Reticulum Associated Degradation (ERAD) which involves removal of mannose by ER mannosidase1[1]. ER mannosidase1 is involved in proteasomal degradation of misfolded α1AT[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 α1AT 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 chaperones 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. Gp78 (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[12,13]. Dissociation of Bip activates trans membrane protein which leads to activation of targeted UPR genes[12]. On the other hand, accumulation of polymerized α1AT 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 α1AT is identical to polymerized α1AT protein[11,15]. The interaction of Bip with polymerized form in mammalian cells is unknown and may not functionally related[15]. Autophagic response and specific signaling pathway get activated due to accumulation of polymerized α1AT. A polymerized α1AT protein activates caspase4, BAP31 and NFKB. NFK B gets activated by accumulation of both mutant α1AT Z and S protein[12]. Expression of polymerized α1AT protein is associated with up regulation of RGS16 which interact with anti-phagocytic factor Gαi3 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 α1AT 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 LTB4 concentration was increased in sputum of patients with ZZ mutant α1AT as described by A.T.Hill et al. IL8 with LTB4 play major role for Neutrophil recruitment[18]. In addition, Polymerized Z α1AT protein acts as potent neutrophil chemo-attractive factor. Polymerized α1AT is produced by the lung epithelial in patient with liver transplant[10]. Polymerized α1AT 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 (FEV1) [2]. David G et al. has shown that basal emphysema according to CT scan pattern in α1AT deficiency (Piz phenotype) associated with a greater impairment of FEV1 than whom have apical emphysema[19].

**Epidemiology:**
α1AT is generally underdiagnosed genetic disorder[20]. Approximately 3.4 million persons worldwide have α1ATD 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[21]. 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 α1AT blood level[19]. 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[2,8]. 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 α1ATD disorder[8].

**Optional management of α1ATD:**
It is known that smoking is the most common risk factor associated with COPD. Low level of α1AT and smoking will accelerate the risk of development of COPD. According to Sam Alam et al. smoking extracts accelerate polymerization of ZZ phenotype α1AT 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 α1ATD or non α1ATD patients are similarly treated accord-
Augmentation therapy is a Specific therapy for α1-ATDeficient patients. It is FDA approved therapy in United State. 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 FEV1 in COPD patients. Contaminating factor in both forms may induce allergic reaction.

CONCLUSION
Augmentation therapy can only replace the deficient α1-AT but cannot interfere with the accumulated mutant α1-AT 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 α1-AT in the ER in order to aid its release. A better outcome is expected from future studies on mutant α1-AT in lung tissue with disease specific induced pleurae potential stem cell (iPSC) that has the ability to differentiate to lung epithelial precursor in vitro.

REFERENCES