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# Structural Features, Biological Functions of the Alpha-1 Antitrypsin and Contribution to Esophageal Cancer

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## 1. Introduction

Alpha-1 antitrypsin (AAT) is a member of the serine protease inhibitors (serpin) family. Hepatocytes are the major source of synthesis and secretion of AAT into the blood stream, however macrophages of the lungs also take part in this process to a lower extent [1]. AAT is a proteolytic enzyme which plays major role in the normal physiological processes such as angiogenesis, intravascular fibrinolysis, and wound healing. However it may also participate in pathological conditions such as tumor invasion and metastasis which require degradation of the basement membrane, stimulation of angiogenesis, and migration [2, 3].

Following to synthesis AAT diffuses into tissues where it targets neutrophil elastase, a powerful protease capable of cleaving elastic fibers of alveolar walls and other structural proteins [4]. Apart from synthesis in the liver, AAT may also be synthesized and secreted by the epithelial cells of stomach, intestine, pancreas, and respiratory tract. Additionally, it can be produced by certain cancer cells, including cancers of gastric, colon, and lung. Tumor cells synthesize and release not only an intact native form of AAT, but also a variety of cleaved and/or degraded forms of alpha-1 antitrypsin. AAT has multiple effects on tumor cell viability and play diverse roles in tumorigenesis [2].

Being the most abundant human serum protease inhibitor, AAT is encoded by a single gene of 12.2 kb in length, which is located on the long arm of chromosome 14 (14q31-32.2). The protein is highly polymorphic and a number of alleles have so far been identified for it. These alleles are classified into the following four groups; group 1 or normal allele, whose product is AAT with normal function and serum level ranging from 150 up to 350 mg/dL<sup>-1</sup>. Group 2 or the deficient alleles is associated with serum AAT level less than 35% of normal subjects. In addition group 2 alleles may also not function normally. Group 3 includes the null allele as this group display no detectable serum AAT; and finally group 4 which includes dysfunctional alleles. The last group encodes AAT present at normal level; however, the AAT produced by this group is a non-functional AAT [5, 6]. Mutations in the AAT gene has shown to be associated with a number of diseases including Cirrhosis, COPD, pneumothorax, asthma,

wegener's granulomatosis, pancreatitis, gallstones, bronchiectasis, pelvic organ prolapse, primary sclerosing cholangitis, autoimmune hepatitis, emphysema (predominantly involving the lower lobes and causing bullae), renal, and arthritis. In addition in other malignancies such as Hepatocellular carcinoma, Bladder carcinoma, Gallbladder cancer, Lymphoma, and lung cancer defects and mutations of AAT have also been reported [7, 8].

## 2. Alpha-1 antitrypsin deficiency (AATD), conformational disease

Alpha-1 antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder caused by defective production of AAT, which leads to the decreased AAT activity in blood and lungs, and deposition of excessive abnormal AAT protein in liver cells. Severe AAT deficiency causes panacinar emphysema or COPD in adults with complications, especially if they were exposed to cigarette smoke. It also include subjects with various liver diseases in a minority of children and adults [9].

Symptoms of AATD include short dyspnea, wheezing, rhonchi, and rales (Crackles). The patient's symptoms may resemble recurrent respiratory infections or asthma that doesn't respond to treatment. Individuals with AATD may develop emphysema during their thirties or forties even without a history of significant smoking, though smoking greatly increases the risk for emphysema. AATD also causes impaired liver function in some patients and may lead to cirrhosis and liver failure (15%). It is a leading cause of liver transplantation in newborns.

The conformational diseases [10], which include diverse disorders such as Alzheimer's and Parkinson's, amyloidoses, AAT deficiency and the prion encephalopathies, take place due to conformational rearrangements of a specific protein that endows a tendency to aggregate formation and deposition within tissues or cellular compartments [11]. AAT deficiency serves as an excellent model for conformational disease because it is one of the few members of this class for which detailed structural data are available on both the wild type and mutant proteins [11]. Indeed, familial conformational diseases occur when a mutation alters specific conformation of protein resulting in abnormal intermolecular interactions, protein aggregation, and consequent tissue damage. The molecular mechanisms of conformational disease are best understood for the serine protease inhibitor (serpin) superfamily of proteins. The serpinopathies include alpha-1 antitrypsin (SERPINA1) deficiency and the newly characterized familial encephalopathy with neuroserpin inclusion bodies (FENIB) resulting from mutations in the neuroserpin (SERPINI1) gene [12].

Robin Carrell and Lomas [11] have described structural rearrangements that take place when AAT meets and inactivates its target, the serine proteases. In the case of AAT, this inherent instability allows the proteins to undergo loop-sheet polymerization, creating an abnormal structure in which the loop from the active site of one AAT molecule inserts itself as another  $\beta$ -strand into a pre-existing  $\beta$ -sheet of an adjacent molecule [11], [13, 14]. In the figure 1, the mechanism of inhibition of proteases by serpins and mutations resulting in disease has been shown [14]. This intrinsic tendency of wild-type AAT to undergo structural transformation is markedly enhanced in mutant forms. As such forms are more prone to accommodate the extraneous strand from an adjacent molecule since mutations destabilize the sheet, allowing an increased mobility of its constituent strands. This loop-sheet insertion is an example of conversion of a loop to a beta- strand through interactions

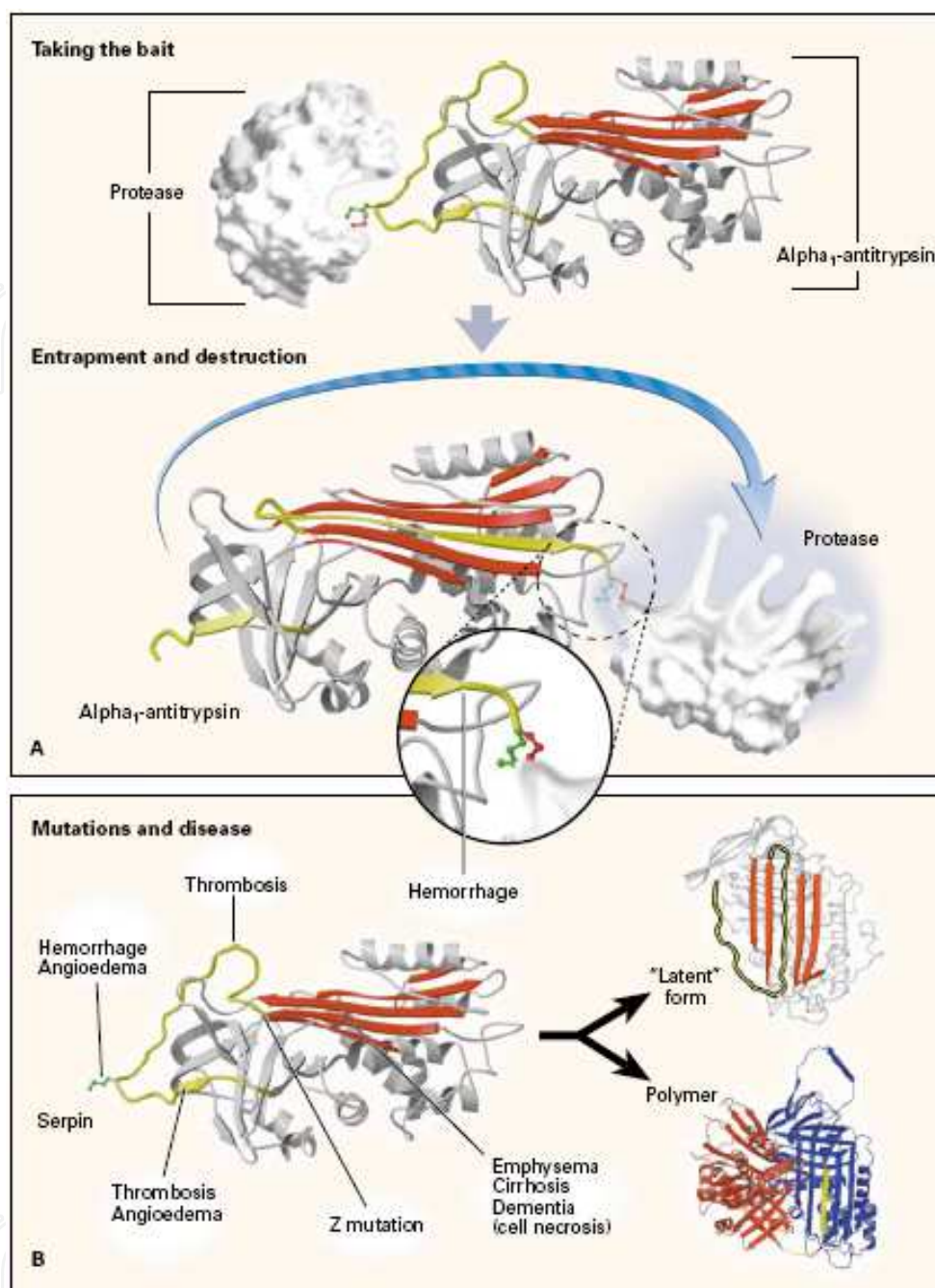


Fig. 1. Mechanism of inhibition of proteases by serpins and mutations resulting in disease.

The mechanism of inhibition of the serpins, represented in Panel A by AAT, is like that of a mousetrap, with a springlike shift from a metastable to a hyperstable state. The protease attacks the reactive center loop (yellow) of alpha1-antitrypsin, with the active serine of the protease (small red side chain) forming a link to the amino acid at the base of the reactive center (small green side chain) of alpha 1-antitrypsin. The resulting cleavage of the reactive loop allows it to snap back into the main *b* sheet (red ribbons with arrows) of the alpha 1 -antitrypsin. This spring-like movement flings the tethered protease to the opposite end of the alpha1 -antitrypsin molecule, distorting its active site (inset) and altering its structure so that it can be destroyed.

A sum 200 different mutations in serpins are known to result in disease (Panel B). In particular, mutations affecting antithrombin confer a predisposition to thrombosis, those affecting C1 inhibitor confer a predisposition to angioedema, and those affecting antiplasmin confer a predisposition to hemorrhage. Mutations at the reactive center result in a loss of function (e.g., causing familial angioedema) or more rarely result in a change in function (e.g., causing hemorrhagic disease). The insertion of an amino acid into the peptide loop containing the reactive center of another serpin, alpha2-antiplasmin, reduces the distortion of the catalytic site (inset) of plasmin, allowing its release, with consequent fibrinolysis and hemorrhage. The most common cause of loss of function of serpin molecules are mutations affecting the critical mobile hinges of the molecule. These lead to spontaneous changes in conformation that allow either the insertion of the intact reactive loop into the main *b* sheet, resulting in the formation of an inactive "latent" form, or the insertion of the loop of one molecule into the *b* sheet of the next, resulting in the formation of polymers. Polymerization occurs in AAT with the common Z variant and with mutations at the opening of the sheet, leading to emphysema and cirrhosis. Mutations at the same site in a neuron-specific serpin result in neurodegeneration and dementia (Carrell R.W. and Lomas D.A. 2002 ) with pre-existing  $\beta$ -sheet leading to pathological consequence. The tendency to undergo loop-sheet polymerization is not restricted to AAT as other serpins undergo the same transformation. In a rare form of familial encephalopathy where neuronal inclusion bodies (FENIB) form, it was found that inclusion body formation to be the result of a mutant neuroserpin which undergoes loop-sheet polymerization. Structural modeling of the neuroserpin mutants indicate that it may lead to the instability of  $\beta$ -sheet structure, increasing its propensity to gain an extraneous strand. Robin and Carrell [10] have suggested that such  $\beta$ -promiscuity may account not only for the pathologic properties of serpins, but also could explain the 'pathologic property of  $\beta$ -sheets in prion disorder that seems to be caused by the induced transition from  $\alpha$ -helix to  $\beta$ -strand [11].

### 3. AAT, a response to malignancy and inflammation

AAT augments in the serum of gastrointestinal [15], prostate [16], brain [17] as well as biliary tract cancer [18] patients. Also reports indicate increased serum AAT in pancreatic adenocarcinoma [19], breast tumors [20], and esophageal cancer [21]. A significant correlation between serum AAT level and stage of cancer have also been proposed [22, 23]. Several means by which AAT plays role in malignancy and inflammations have been proposed so far as described in the following paragraphs:

- a. Equilibrium hypothesis; it is assumed that changes in the ratio of a particular protease to its cognate inhibitor account for the increased potential of tumor formation [23]. Neutrophil elastase and AAT constitute a pair including protease and protease inhibitor counterpart which are in equilibration. Perturbation of this equilibration causes tissue damage and provides a favorable environment for carcinogenesis and tumor progression. Laboratory and clinical findings have indicated that deficiency in AAT is associated with the increased risk of cancers such as liver, bladder, gall bladder, malignant lymphoma, and lung cancer. Conversely elevated concentration of neutrophil elastase may promote development; invasion and metastasis of many types of cancers as a result of tissue damage and air trap which foster longer exposure to the carcinogens and hence promotion of cancer by degradation of extracellular matrix. In this regard tumor-necrosis-factor signaling pathway plays a role [24].

- b. The other hypothesis suggests the roles that are played by a protease inhibitor *per se*. While imbalanced equilibration between protease to its cognate inhibitor would affect malignancy (as described above), however the inhibitor by itself seems to play more complicated function. The finding of a high serum concentrations of protease inhibitor even in the advanced stage of cancer at first glance was paradoxical, since inhibitors such as AAT are supposed to counteract the destructive activity of proteolytic enzymes (e.g. trypsin). However, it became clear that the role of protease inhibitors is rather complex and that, in most types of cancers, they play important role in modulating the dynamics of the proteolysis, in which proteases, inhibitors, regulators, cytokines and growth factors interact with each other through unknown mechanisms that have yet to be explored [25]. Tissue dependency of protease inhibitor activity is another phenomenon observed in malignancies. Cancers originated from several tissues often produce tumor associated trypsin inhibitor (TATI), however the strongest expression of which could be seen in mucinous ovarian tumors, both in benign and malignant type of tumors. Thus it appears that expression of TATI is regulated by different mechanisms in different tissues. In the other word expression of TATI is tissue dependent. TATI is a 6 kDa peptide, which is synthesized by several tumors and cell lines and produced by the mucosa of the gastrointestinal tract, where it is thought to protect the mucosal cells from proteolysis. Elevated serum and urine level of TATI occurs in connection with many types of cancer, especially mucinous ovarian cancer, pancreatitis, severe infections and tissue destruction. Thus TATI may behave as an acute phase reactant. While elevation of TATI in cancer and pancreatic disease is associated with expression of trypsin, but such a relationship has not been observed for the inflammatory disease. TATI inhibits trypsin-mediated degradation of extracellular matrix by tumor cells. Therefore it might control activation of tumor-associated trypsinogen [26].

Regarding malignant diseases; increased level of TATI has been observed both in serum and urine. In most cancers the increased secretion is caused by tumors, however in acute-phase reaction which is induced by tissue destruction and advanced disease TATI secretion is associated with cancer invasion. The concentration of TATI in serum and urine correlates strongly with tumor invasion. However there is more variation in urine concentrations of TATI; therefore the serum concentration of TATI is preferred if it is going to be used as an indicator of the degree of invasion [27].

### 3.1 AAT as an acute phase response

AAT is secreted into circulation and increased level of which is the result of at least three mechanisms: production by tumors, leakage from a diseased pancreas and as a reaction against tissue damage and by impaired renal function [28]. For supporting this proposal, Solakidi, *et al*, have shown that elevated serum tumor associated trypsin inhibitor (TATI) could be due to production of TATI by tumors [28]. They reached to this conclusion because none of patients had any signs or previous history of pancreatic disorders or impaired renal function. Moreover gastric and colorectal neoplasms of patients under study were positive for TATI immunopositivity which could explain the elevated TATI in serum as a result of tumor secretion. To find whether elevation of TATI could be explained in terms of acute-phase reaction, measurement of TATI and CRP (C-reactive protein), a prototype of acute-phase reactant proteins was done; the result of which indicated statistically significant correlation between serum TATI and acute-phase reactant protein level. This finding has

indicated regulation of TATI synthesis as an acute-phase reaction. In supporting this notion, Peracaula, *et al*, [29] have suggested that acute-phase proteins might play important role as sensor of diseases. Both level of acute-phase protein and glycosylation have reported to be altered in the inflammation and other diseases including cancer. Factors that promote acute-phase protein synthesis and enhance the expression of specific glycosyltransferases, such as sialyltransferases and fucosyltransferases, may be up-regulated in some tumors which could explain the changes in acute-phase proteins level and specific *N*-glycosylation modifications of some acute-phase proteins in cancer.

#### 4. AAT as a tumor marker and its clinical applicability

Elevation of serum AAT, assessment and association of its phenotype and genotype with regard to specific type of cancer has been subject of many studies on different types of cancers such as gastrointestinal cancers, brain tumors, biliary tract cancer, pancreatic adenocarcinoma, cancers of the prostate, breast, lung and liver [22, 23, 30-32]. Regarding esophageal cancer, there are limited reports available from Japan and Korea as well as our recent report [21, 33]. These reports have suggested that serum AAT level could be considered as tumor marker. Our results show that the mean range of trypsin inhibitor capacity (TIC) and AAT level are significantly higher in patients than in healthy controls [34]. Hong and colleagues have observed significant increase in serum AAT in malignant esophageal cancer patients compared to benign tumors and healthy controls [35].

Recently Hsu and colleagues identified AAT as a potential biomarker of gastric cancer in gastric juice. They showed gastric juice AAT concentration is markedly higher in gastric cancer patients than in healthy subjects, gastric ulcer patients, and duodenal ulcer patients [2].

Investigating the histological pattern and tumor location of patients, Schena and colleagues [36] showed that AAT represents a diagnostic index of neoplastic diseases, highly sensitive but less specific. Saito and colleagues [37] have investigated severe septic complications as the major cause of post-surgery mortality in esophageal cancer patients. They assessed acute phase proteins in the infection related complications post-surgery in a large number of patients with esophageal cancer and have compared this group of patients with a group of gastric cancer patients and the healthy controls. Elevation of AAT, alpha-1 acidglycoprotein, haptoglobin, and ceruloplasmin was more prominent in patients with esophageal cancer. Stenman and colleagues [27] showed that the TATI level increased in serum of patients with pancreatic, gastric, hepatocellular, biliary tract, and colorectal cancer. They concluded that TATI is a sensitive marker. It increased in 75–95% of pancreatic patients, 40–65% of gastric patients, 60–80% of hepatocellular patients, 75–100% of those with biliary tract, and 34–74% of patients with colorectal cancers [27].

An outstanding study carried out by Varela, and López Sáez [38] indicates that plasma level of A1AP (alpha-1 antiprotease); a member of serpins superfamily increases in clinically active cancer compared to the normal controls and normal range values for clinically defined complete remission. The mean value of A1AP was lower in healthy individuals than individuals with chronic non-malignant diseases. Notably A1AP in both groups was lower than individuals with malignant tumors. They also defined a correlation between plasma A1AP level and the type of malignancy such that increased plasma A1AP follows the following scheme; breast, gastrointestinal, head and neck, and lung cancers. Also the mean

range of A1AP has shown to increase in the following clinical order: complete remission, local disease, local-regional disease and metastatic disease. Thus it was concluded that A1AP could be considered as a cancer marker that discriminates cancer from chronic non-tumoral diseases as well as complete clinical remission from relapses[38]. Furthermore Solakidi and colleagues [28] have assessed level of tumor associated trypsin inhibitor (TATI) as well as the carcinoembryonic antigen (CEA), C-reactive protein (CRP), and AAT in association with malignancy or inflammation to demonstrate the role of TATI in gastric and colorectal cancers. Their results showed elevated level of TATI in 50% of patients with gastric cancer and in 41.7% of colorectal cancer patients. Interestingly, elevated level of TATI was observed in only 8% of patients with benign gastrointestinal malignancies. Thus, TATI can be used as a complementary tumor marker in addition to CEA for gastrointestinal cancers. This finding supports our [34] and other reports that elevation of protease inhibitors was observed in the advanced tumor stages. Whether such elevated protease inhibitors, such as TATI and AAT, are functionally effective in the inhibition of proteases or not could be the subject of further investigations. Summarizing our [34] and other reports, it could be concluded that AAT plays role as a biomarker for malignancies including esophageal cancer.

## 5. AAT and esophageal cancer

Esophageal cancer ranks among the top 10 most frequent cancers, characterized by poor prognosis and 5-years survival rate less than 10%. Despite many efforts and investigations, the mechanism underlying development of esophageal cancer is not well understood [39]. Iran is located in the so-called Asian esophageal cancer belt where reports indicate the highest incidence rate of squamous cell carcinoma of esophagus (SCCE) of the world from certain parts of this country. Although recent reports [40-43] indicate attempts for identifying the molecular etiology of SCCE in addition to achievement of suitable tumor markers for this cancer, such efforts have so far been unconvincing and further efforts are therefore required [34]. Delayed diagnosis is a major problem associated with SCCE that most often results in diagnosis of the disease in the advanced stages of tumorigenesis. In addition, the high invasive phenotype of SCCE together with metastatic potential leads to low curative resection and high frequency of relapses. For developing effective approaches of diagnosis, treatment, and follow-up of SCCE availability of appropriate molecular markers is an asset. In this regard assessing proteases and their inhibitors such as AAT level could be helpful [21, 36, 37].

In a recent study, we investigated the level of AAT in serum of SCCE patients, its trypsin inhibitory capacity (TIC), and association of its phenotype with genotype [21, 36, 37]. AAT deficiency is an inherited disease as it is characterized by the reduced level of AAT in the serum. The two common genotypes of AAT deficiency are type Z (PiZ) and type S (PiS), which are associated with several malignancies. We assessed the AAT phenotype as well as genotypes Z and S in SCCE and their association with malignancy in Azeri patients. Azerbaijan is a region in the north west of Iran composed of at least three provinces where epidemiological studies have indicated a high rate of esophageal cancer from this region in addition to the north eastern region of the country where the highest incidence rate of esophageal cancer in the world has reported from there. AAT phenotype identification was done using isoelectric focusing (IEF) and its genotype was determined by restriction fragment length polymorphism (RFLP). Results indicate that the mean range of trypsin inhibitory capacity (TIC) and AAT nephelometry are significantly different in patients than that of healthy



controls. Measurement of AAT indicated higher level of AAT in patients' serum that was in accordance to what previously reported with regard to patho-physiological status and malignancies (as described in detail above). However, and as a significant finding we found that the augmented AAT is non-functional which accounts for further dysfunction as well as reduction of AAT proper protease inhibitor activity in SCCE patients. Moreover, 97.3% of SCCE patients were homozygote for MM (PiMM) (normal genotype), and only 2.7% were MS heterozygous. Neither of the PiZ and PiS genotypes were identified in the patients ( $P < 0.05$ ). Thus AAT is among those tumor suppressors whose augmentation doesn't correlate with proper function, though it might be dysfunctional in tumors.

Finding a cogent relationship between stages of SCCE at the time of diagnosis and change in marker serum level is important since it affects survival rate following to surgery as well as helping in choosing proper method of treatment. Assessing the pathology records of patients, we found that most diagnosis were done in the late stages of tumorigenesis when tumors were fully grown and developed into highly invasive and metastatic phenotype. This was unfortunately a shortcoming in some studies [21, 36, 37]. Due to nature of SCCE, disease related complications appear late. As a result, diagnosis by clinical examinations becomes only possible in the advanced stages of tumor development. This has been true for 70.3% of cases in our study. Thus low rates of curative resection and high frequency of relapses was observed post-surgery (67.56% of mortality). This finding is in accordance with Yunping and colleagues[39] who found poor prognosis of esophageal cancer with an overall 5 years survival rate less than 10% [39]. Thus measurement of AAT in the late stages of SCCE raises further challenges for the applicability of which as a tumor marker in order to be applied for early stage diagnosis. We propose that further studies are required regarding to the change in the level of AAT as a marker along with analysis its defective functionality in a large sample size to achieve a definite correlation between serum AAT, tumorigenesis, and stages of tumors. Further study is also required to establish a rational relationship between increased level of AAT as a response to defect in its function or as a response to malignancy and inflammation as suggested by other researchers (above) at cellular and molecular level. It should also be kept in mind that most SCCE are diagnosed in the late stages of tumorigenesis due to late referral of patients to clinics. Thus determining augmented AAT level in the early stages remains to be investigated in future studies. One way for elucidation AAT level in early stages of malignancies would be establishing definite relationship between inflammatory diseases and cancers, though the level of AAT increases in inflammation. In addition most malignancies exhibit increased production of inflammatory cytokines. This is also true for SCCE in which increased cyclooxygenase has been well documented [2, 5, 15, 21, 22, 34, 36, 37, 44].

## 6. Conclusion

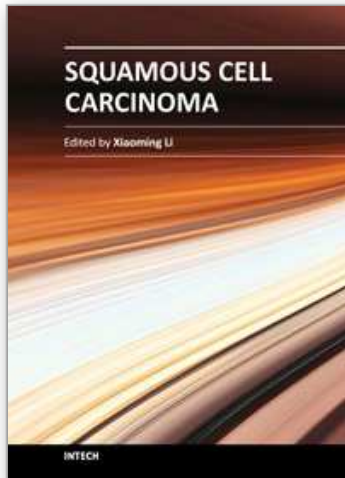
The poor prognosis of malignancies including SCCE in addition to late diagnosis in the advanced stages of tumorigenesis for most cancers demand further efforts for achieving specific and appropriate tumor markers for early stage cancer detection. While we did not have access to the patients at the early stage of SCCE, combining our results with other investigations indicate that AAT is a suitable prognostic rather than early stage diagnostic tumor marker as both we and others found its correlation with the advanced stages of tumors. As a tumor marker, AAT is highly sensitive, however, like most other tumor markers; it lacks tissue specificity which in fact is a drawback for its organ or tissue specific

applicability. Increasing the size of the population under study, establishing a rational correlation between malignancies and inflammatory diseases as well as combining AAT with other tumor markers might be helpful for achieving a better picture of AAT applicability for early stage SCCE and other tumors detection as well as specificity for prediction and evaluation of curative treatment.

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## **Squamous Cell Carcinoma**

Edited by Prof. Xiaoming Li

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This book points to some new areas for investigation on squamous cell carcinoma (SCC). Firstly, the features and management of some specific SCC is discussed to give the readers the general principles in dealing with these uncommon and sophisticated conditions. Some new concepts in adjuvant therapy including neoadjuvant therapy and gold nanoparticle-based photo dynamic therapy are introduced. Secondly, a detailed discussion of molecular aspects of tumor invasion and progression in SCC is provided with the emphasis on the roles of some important factors. The role of tumor microenvironment in head and neck SCC is specifically discussed. Thirdly, the roles of cancer stem cells (CSC) in cancer therapy of SCC are described. Molecular mechanisms involving therapeutic resistance and new therapeutic strategies targeting CSC are discussed in detail. Finally, other aspects concerning SCC are included, which involve the assessment, genetic manipulation and its possible clinical implications for the treatment of SCC.

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