Association of P53 with Esophageal Carcinoma: Review

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Abstract: P53, also known as tumor suppressor is guard or gatekeeper of the cell and genome. It protects the cells from any type of stress by DNA repair or apoptosis or cell cycle arrest thus maintaining normal homeostasis. But in certain circumstances, there occurs overexpression or mutation of P53, resulting in disruption on normal cellular mechanism and disturbance of homeostasis causing the cells to grow unexpectedly. Overexpression of P53 is mostly encountered in advanced stage of tumors. Among the mutant verities, missense mutation is commonly encountered. Esophageal carcinoma is one of them which results from either overexpression or due to mutation of P53. Serum P53 antibody can be detected from patients with esophageal carcinoma. P53 directed therapy has shown good results in patients with esophageal carcinoma. So P53 represents an important biomarker and thus has clear association with esophageal carcinoma.

Keywords: Esophageal carcinoma, P53, P53 overexpression, P53 mutation.

1. INTRODUCTION

Cancer, as a highly complex disorder involves genomic changes, immunological, hormonal, environmental factors as well as other diseases. It is well known that cancer sera contain antibodies that react with groups of autologous cellular antigens called tumor-associated antigens (TAAs). These antigens may be cellular proteins, such as p53, p62, p90 and p16, whose default regulation and or overexpression can lead to tumorigenesis [1].

Esophageal cancer ranks as the eighth most common cancer in the world. Being a disease of high mortality, it is the sixth most common cause of cancer related death worldwide [2]. Esophageal cancers are of two important histological types: esophageal squamous cell carcinoma and esophageal adenocarcinoma. Esophageal squamous cell carcinoma may occur as a result of achalasia. Achalasia causes food retention as well as stasis and leads to esophagitis. These factors in turn cause esophageal dilatation a term called mega-esophagus, which increases the chance to develop squamous cell carcinoma by 3-8%. Esophageal adenocarcinoma may occur as a result of Barrett’s esophagus in which intestinal metaplasia occurs.

Esophageal squamous cell carcinoma is predominant worldwide but incidence of esophageal adenocarcinoma is increasing now a days. The incidence of esophageal carcinoma varies geographically as well as ethnically [3,5]. The incidence is high in Northern China and also in Northern Iran, moderately high in Japan, South Asia as well as South Africa and low in western Africa [2,3,5]. Esophageal squamous cell carcinoma is the main type in the areas of high incidence [4]. Environmental carcinogens, dietary factors, nutritional deficiencies especially antioxidants, thermal radiation, hot beverages, betel chewing, smoking, alcohol as well as fermented foods are the causes for different histology as well as geographical variation according to the life style [2,3,5]. During the initial stage of the disease patients are usually asymptomatic, so they are usually undetected till the disease becomes difficult to cure. Because of the late detection
P53 is a protein normally found in cells, which is also known as gatekeeper of the cell or genome because it regulates the cellular response in presence of cellular stress. In response to various stimuli like DNA damage, oxidative cellular stress, oncogene activation, heat shock, hypoxia; P53 functions as cellular response by apoptosis, DNA repair, cell cycle arrest or autophagy \[10,11,13\]. It is also known as tumor suppressor gene and is located at chromosome 17q13.1 \[12,15\]. P53 protein is present at low level in normal condition or in the absence of stress because of the balance between its transcription and degradation. This balance is of much importance because excessive P53 can damage the cells but low-level can let the cancers to grow \[13\]. For the stress response pathway to work properly target gene must be transcripted by P53 but P53 can also work independent of transcription \[10,11\].

When, cell damage due to any type of stress is minimal, then P53 stimulates transient cell cycle arrest either in G1 or G2 phase allowing repair of damage and again begins normal cell cycle. But when the damage is excessive or irreparable then P53 triggers apoptosis, which is a primary cause of tumor suppression. These different results are due to activation of different P53 target genes \[11,13\].

P53 and DNA REPAIR:

P53 has the ability to repair DNA after cellular stress. Transcriptional regulation along with direct interaction with mediators occurs in the presence of P53 to help repair damaged DNA. The cells that lack P53, do not have the ability to repair DNA properly, rather they do repair by nucleotide excision \[14\].

P53 and APOPTOSIS:

Apoptosis is an important tumor suppressor mechanism. Apoptosis is triggered by P53 when the damage to the cell is excessive and irreparable \[11\]. These are mediated through two apoptotic pathways. In extrinsic pathway, the expression of APO-1/Fas receptor as well as TRAIL receptor are increased by nuclear P53 where as caspase 8 and 3 are activated by cytoplasmic P53. In intrinsic pathway, the expression of pro-apoptotic proteins PIDD and BH3 only proteins are increased by nuclear P53 resulting in increased MMP, cytochrome C release as well as activation of caspase 9 and 8 whereas cytoplasmic P53 forms a complex with BCL-2/BCL-XL and releases pro-apoptotic proteins BAX an BAK. All these leads to apoptosis \[15,16\].

P53 and CELL CYCLE ARREST:

Cell cycle arrest is an important mechanism by which P53 suppresses tumor growth. After DNA damage, P53 arrests cell at G1/S transition by the expression of cycline dependent kinase (CDK) P21. Like G1 arrest P53 is also involved in G2/M arrest. In G2 arrest P53 is involved in maintenance but not in initiation of the arrest. This is true for cells with wild type P53 but not for mutant P53 \[14\]. So tumor can grow in cells with mutant P53. Cell senescence is another mechanism for cell cycle arrest, preventing tumor growth. In senescence, growth is arrested with a DNA content of G1 phase. After growth arrest, even in the presence of growth conditions, initiation of DNA replication is failed which is caused by cell cycle inhibitors and this is permanent \[17\].

P53 and TUMEROGENESIS:

This important protein P53 is inactivated or mutated in many tumors leading to low or no expression. This inactivation of p53 expression may play a role early in tumor formation and tumor progression \[13,15,18\]. P53 can be inactivated at protein level by binding to viral proteins or by p53 degradation or nuclear exclusion etc. \[12,13\].

Advance stage of tumors may have P53 overexpression. Overexpression of P53 occurs in those tumors, which contains genetically wild type TP53 gene with inert protein \[12,19,20\]. The difference between mutated and overexpressed P53 is that many of the mutant p53 forms lose their tumor suppressive function and have mainly-negative activities. They also gain onco-genic properties that are independent of wild-type p53. The main type of mutations in P53 is missense mutation,
which forms mutant P53 that cannot suppress tumor formation. Frequencies of TP53 mutation ranges from 10% (hematopoietic malignancies) to 50-70% (ovarian, head/neck, gastrointestinal malignancies). P53 mutations can be divided into two classes. First are mutations, which are mainly involved in DNA binding and second are mutations that cause conformational or local changes. The main mutations noted in development of human tumors are of first type [20]. Mutant P53 that leads to tumor progression causes chromosomal instability along with inhibition of DNA repair pathways and also leads to invasiveness of the tumor. It also inhibits the function of other family members of P53 [21].

P53 and ESOPHAGEAL CARCINOMA:

There are many researches regarding P53 with esophageal carcinoma. From those researches it is clear that P53 is an important protein and TP53 an important gene in the context of esophageal carcinoma.

Some researches are based on animal model and some are on human tissues. Researches on mice showed the accumulation of wild type P53 in mice with adenocarcinoma of esophagus but it was negative for squamous cell carcinoma of esophagus. Loss of P53 function resulted in increased cell cycle progression, genetic instability and malignancy [22, 23]. Somatic alteration in exon 6 of P53 gene have been found in more than 50% of cases of esophageal squamous cell carcinoma patients [24]. In one study, immunohistochemistry study demonstrated that P53 was overexpressed in 64% of cases (72% cases with adenocarcinoma and 67% of cases with squamous carcinoma of esophagus). Excessive TP53 mutation was noted in smokers with esophagus squamous cell carcinoma. P53 gene mutation was noted in 36-80% of cases with esophageal cancer [25, 26]. One Japanese study demonstrated P53 gene mutation in 47.4% of patients with esophageal carcinoma. Another study from South America reported Tp53 mutation in 63% of cases of squamous cell carcinoma of esophagus [27-29].

Under normal conditions, P53 are usually very low or undetectable but high staining of P53 is due to increased number or less degradation and is usually due to overexpression or mutation of P53 [29].

One study demonstrated that patients with esophageal carcinoma have more chance of positive serum P53 antibody detection. ELISA can detect P53 antibodies, so P53 antibodies can be a valuable marker for screening esophageal carcinoma as well as to know the response of treatment [6]. Other study shows the detection of P53 antibody in 39.1% of cases of esophageal carcinoma but not in healthy persons. This study also explored significant reduction of P53 antibody after radiotherapy and concluded P53 antibody as a useful marker to evaluate the response of treatment as well as prognosis [30].

One recent study serves that, tumor invasion and growth can be halted by removal of the mutant P53 [31]. Yet another study demonstrated that, intra-tumor administration of adenoviral gene therapy (Ad5CMV-p53) caused esophageal cancer cells to be trans-ducted and downstream genes to be activated. Similar type of another study also explored good efficacy in esophageal squamous cell carcinoma patients with P53 gene therapy medicated by adenovirus [32, 33].

Regarding prognosis, one study demonstrated that, P53 gene alteration in esophageal adenocarcinoma detected by immunohistochemistry has no prognostic value. Another study showed that P53 mutated tumor have worst prognosis and anti P53 antibodies to be independent prognostic marker in esophageal carcinoma due to lack of sensitivity [34,35]. Similar type of another study explored that, high level of serum P53 antibody can be assessed before surgery to evaluate the risk and poor prognosis [36]. Another study also demonstrated that neither of the markers such as: P53, p16, p27 are of prognostic value in esophageal carcinoma [37].

As a biomarker, P53 can be used to measure the efficacy of diagnosis and treatment in esophageal carcinoma [15,38]. To improve the effectiveness of currently available therapies used to suppress cancer cells having P53 mutants, restoration of ATM function and destabilization of P53 mutants is necessary [39].

2. CONCLUSION

From the associations that are discussed above, we can easily conclude that, P53 is an important protein and it must be normally expressed in cells to keep proper homeostasis. Failure to do so results in abnormal repair of DNA or abnormal and unprogrammed growth of cells. Esophageal carcinoma is one example to prove this. Esophageal carcinoma has close relation with P53 in every aspect, such as etiology, diagnosis as well as treatment because many of the researches are convincing to prove this. The only place that it lacks adequate association seems to be of prognosis. So many more studies are underway to correlate its association further.
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