BASICS OF CANCER AND THEIR GENES

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ABSTRACT

PTEN genetic alterations occur in multiple types of cancer, such as brain, prostate, breast, thyroid and endometrial tumors. Thus, PTEN inactivation may play an important role in the pathogenesis of a variety of human malignancies. The present study found PTEN protein significantly diminished in their expression in cervical cancer cell. This suggests that the loss of PTEN expression plays a role in cervical carcinogenesis. Previous reports have also demonstrated that PTEN expression is progressively reduced along a continuum from normal epithelium to squamous cell carcinoma. PTEN, a tumor-suppressing gene, is involved in cellular differentiation, reproduction and apoptosis, as well as cellular adhesion and mobility. The loss or down regulation of PTEN plays an important role in the multiple steps of tumorigenesis and progression of malignancies, and mutations and deletions of this gene have been described in a wide range of human cancers.

Keywords- *cervical cancer, PTEN, Down regulation, Glioblastomas*

INTRODUCTION

Uterine cervical cancer accounted for an estimated 274,000 deaths world-wide in 2002. With nearly 500,000 new cases per year, it is the second most common cancer in women world-wide. It is one of the leading causes of cancer-related deaths in young women (2). The disease incidence shows marked geographical variation. An estimated 83% of new cases now occur in the developing countries, where it represents 15% of new cancers in women. In contrast, cervical neoplasia accounts for only 3.6% of new female cancers in the developed world. The low incidence rate in developed countries is a rather new phenomenon, as the incidenc. In most of Europe, North America, Australia and New Zealand before the introduction of cytological screening in the 1960s and '70s, was similar to that in the developing countries today(1,3). In Norway, 270 women were diagnosed with cervical cancer in 2004 and there are about 100 deaths every year. The age specific incidence maximum was 21 per 100,000 women at age 45-49 years (4,5).

CANCER AND ITS ASPECT

Cancer refers to any one of a large number of diseases characterized by the development of abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue. Cancer often has the ability to spread throughout your body.

1. **Cause of Cancer:** Cancers are a broad group of diseases and accordingly have a wide range of causes. Each cancer is different according to its biology and pathophysiology. All animals and even plants are susceptible to cancers (6).

1.1. Cancer at the molecular level: The body is made up of trillions of living cells. These cells grow, divide, and die in an orderly fashion (1, 5). This process is tightly regulated and is controlled by the DNA machinery within the cell. In a baby or a child normal cells divide rapidly to allow for growth. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries (7,8).When cells of the body at a particular site start to grow out of control, they may become cancerous. Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. In addition, these cells can also invade other tissues. This is a property that normal cells do not possess (9,10). Cancer cells originate from normal cells when their DNA (deoxyribonucleic acid) or blue prints within the cell nucleus is damaged. DNA is in every cell and it directs all the cell's actions, growth, death, protein synthesis etc. when DNA is damaged in a normal cell the cell either repairs the damage or the cell dies.

1.2. Cancer-causing agents: Agents that may cause cancer include:

1.2.1. Chemical carcinogens:

Several chemicals and environmental toxins are responsible for changes in normal cellular DNA (11,12). Substances that cause DNA mutations are known as mutagens, and mutagens that cause cancers are known as carcinogens. Particular substances have been linked to specific types of cancer (13). Tobacco smoking is associated with many forms of cancer, and causes 90% of lung cancer. Similarly, prolonged exposure to asbestos fibres is associated with mesothelioma. Tobacco is also related to other cancers such as lung, larynx, head, neck, stomach, bladder, kidney, oesophagus and pancreas as it contains other known carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons.

1.2.2 Ionizing radiations:

Radiations due to radon gas and prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies. Radiation therapy given for one type of cancer may also cause another type of cancer. For example, those who receive chest radiation therapy for lymphomas may later develop breast cancer (14,15).

1.2.3. Viral and bacterial infections:

Some cancers can be caused by infections with pathogens. Notable among these include liver cancers due to Hepatitis B and C infections; cervical cancer due to infections with Human Papilloma virus (HPV); Epstein Barr virus causing Burkitt's lymphoma and gastric or stomach cancer due to Helicobacter pylori infection (16,17).

1.2.4. Genetic or inherited cancers:

Common examples are inherited breast cancer and ovarian cancer genes including BRCA1 and 2. Li-Fraumeni syndrome includes defects in the p53 gene that leads to bone cancers, breast cancers, soft tissue sarcomas, brain cancers etc. Those with Down's syndrome are known to develop malignancies such as leukemia and testicular cancer (18,19).

1.2.5. Hormonal changes:

Notable among these are changes in the female hormone levels estrogens. Excess estrogens promotes uterine cancer.

1.2.6. Immune system dysfunction

Impaired immunity including HIV infection leads to several cancers including Kaposi's sarcoma, non-Hodgkin's lymphoma, and HPV-associated malignancies such as anal cancer and cervical cancer.

1.2.7. Mutations:

Mutations may be (a) Those in the error-correcting machinery of a cell. This may cause accumulation of errors rapidly in the cell and its progeny. (b) Those in signalling (endocrine) machinery of the cell. This leads transmission of the error signals to nearby healthy cells as well.(c)Those that allow the cells to migrate and disrupt more healthy cells away from the primary site of origin.(d)Those that make the cell immortal so that the abnormal cell refuses to die.

1.2.8. Classification by tissue types: The international standard for the classification and nomenclature of histology is the International Classification of Diseases for Oncology, Third Edition (ICD-O 3). This classification is based on the ICD-O-3(18).

2. TYPES OF CANCER

Based on tissue types cancers may be classified into six major categories:

(A)Carcinoma:

This type of cancer originates from the epithelial layer of cells that form the lining of external parts of the body or the internal linings of organs within the body.

Carcinomas, malignancies of epithelial tissue, account for 80 to 90 percent of all cancer cases since epithelial tissues are most abundantly found in the body from being present in the skin to the covering and lining of organs and internal passageways, such as the gastrointestinal tract. Carcinomas usually affect organs or glands capable of secretion including breast, lungs, bladder, colon and prostate (20, 21). Carcinomas are of two types – adenocarcinoma and squamous cell carcinoma. Adenocarcinoma develops in an organ or gland and squamous cell carcinoma originates in squamous epithelium. Adenocarcinomas may affect mucus membranes and are first seen as a thickened plaque-like white mucosa. These are rapidly spreading cancers.

(B)Sarcoma: These cancers originate in connective and supportive tissues including muscles, bones, cartilage and fat. Bone cancer is one of the sarcomas termed osteosarcoma. It affects the young most

commonly. Sarcomas appear like the tissue in which they grow. Other examples include chondrosarcoma (of the cartilage), leiomyosarcoma (smooth muscles), rhabdomyosarcoma (skeletal muscles), Mesothelial sarcoma or mesothelioma (membranous lining of body cavities), Fibrosarcoma (fibrous tissue), Angiosarcoma or haemangioendothelioma (blood vessels), Liposarcoma (adipose or fatty tissue), Glioma or astrocytoma (neurogenic connective tissue found in the brain), Myxosarcoma (primitive embryonic connective tissue) and Mesenchymous or mixed mesodermal tumor (mixed connective tissue types)(22,23).

(C) Myeloma:

These originate in the plasma cells of bone marrow. Plasma cells are capable of producing various antibodies in response to infections. Myeloma is a type of blood cancer.

(D***)*** **Leukemia:**

This a group of cancers that are grouped within blood cancers. These cancers affect the bone marrow which is the site for blood cell production. When cancerous, the bone marrow begins to produce excessive immature white blood cells that fail to perform their usual actions and the patient is often prone to infection.

(E) Lymphoma:

These are cancers of the lymphatic system. Unlike the leukemias, which affect the blood and are called “liquid cancers”, lymphomas are “solid cancers”. These may affect lymph nodes at specific sites like stomach, brain, intestines These lymphomas are referred to as extranodal lymphomas.Lymphomas may be of two types – Hodgkin’s lymphoma and Non-Hodgkin’s lymphomas. In Hodgkin lymphoma there is characteristic presence of Reed-Sternberg cells in the tissue samples which are not present in Non-Hodgkin lymphoma(24,25).

(F)***. Mixed types:***

These have two or more components of the cancer. Some of the examples include mixed mesodermal tumor, carcinosarcoma, adenosquamous carcinoma and teratocarcinoma. Blastomas are another type that involves embryonic tissues.

3. CLASSIFICATION BY GRADE:

Cancers can also be classified according to grade. The abnormality of the cells with respect to surrounding normal tissues determines the grade of the cancer. Increasing abnormality increases the grade, from 1–4. Cells that are well differentiated closely resemble normal specialized cells and belong to low grade tumors. Cells that are undifferentiated are highly abnormal with respect to surrounding tissues. These are high grade tumors. Grade 1 – well differentiated cells with slight abnormality, Grade 2 – cells are moderately differentiated and slightly more abnormal, Grade 3 – cells are poorly differentiated and very abnormal, Grade 4 – cells are immature and primitive and undifferentiated.

4. GENES THAT PLAY IMPORTANT ROLE IN CANCER

(a)Tumor suppressor genes:

Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or tell cells when to die (a process known as *apoptosis* or *programmed cell death*). When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer. A tumor suppressor gene is like the brake pedal on a car. It normally keeps the cell from dividing too quickly, just as a brake keeps a car from going too fast. When something goes wrong with the gene, such as a mutation, cell division can get out of control.An important difference between oncogenes and tumor suppressor genes is that oncogenes result from the *activation* (turning on) of proto-oncogenes, but tumor suppressor genes cause cancer when they are *inactivated* (turned off).Inherited abnormalities of tumor suppressor genes have been found in some family cancer syndromes. They cause certain types of cancer to run in families. But most tumor suppressor gene mutations are acquired, not inherited.For example, abnormalities of the *TP53* gene (which codes for the p53 protein) have been found in more than half of human cancers. Acquired mutations of this gene appear in a wide range of cancers.

(b). RB Gene:

The Rb gene is an archetypal tumor suppressor gene that was first identified in a malignant tumor of the retina known as retinoblastoma. Retinoblastoma is a sporadic or hereditary paediatric neoplasm arising from retinal cells, and Knudson (1971) hypothesized that the tumor phenotype is not apparent unless both copies of the gene are damaged. The cloning of the retinoblastoma Rb gene and the identification of biallelic Rb mutations in retinoblastoma tumors confirm the hypothesis that such gene product exerts the action of a tumor suppressor. Several human tumors show mutations and deletions of the Rb gene, and inherited allelic loss of Rb confers increased susceptibility to cancer formation (Dunn *et al.*, 1988).

(c) P^{53} Gene:

The p53 gene like the Rb gene, is a tumor suppressor gene, i.e., its activity stops the formation of tumors. If a person inherits only one functional copy of the p53 gene from their parents, they are predisposed to cancer and usually develop several independent tumors in a variety of tissues in early adulthood. This condition is rare, and is known as Li-Fraumeni syndrome. p53 and RB are at the heart of the two main tumour-suppressor pathways that control cellular responses to potentially oncogenic stimuli.

5. PTEN STRUCTURE AND FUNCTION:

PTEN protein function:

In 1997 three groups independently identified a novel tumor suppressor gene at 10q23.3, denoted PTEN, MMAC1 (Mutated in Multiple Advanced Cancers), or TEP1 (TGFβ regulated and Epithelial cell-enriched Phosphatase). The *PTEN* gene encodes a protein of 403 amino acids that shares sequence homology with the family of protein tyrosine phosphatases (PTP), as well as with the cytoskeletal protein tensin (27). The protein contains the HCXXGXXR catalytic signature motif

present in all PTPs and in dual specificity phosphatases, which catalyze the hydrolysis of phospho-seryl, -threonyl, and -tyrosyl residues. In addition, this phosphatase signature motif is very well conserved across evolution indicating its functional significance (28). Recombinant PTEN has been shown to dephosphorylate protein substrates *in vitro* on serine, threonine, and tyrosine residues indicating that PTEN can indeed function as a dual specificity protein phosphatase. The best known protein substrate of PTEN is Focal Adhesion Kinase (FAK). In addition PTEN might possess protein phosphatase activity towards itself and the Plateled Derived Growth Factor Receptor (PDGFR). Recombinant PTEN, however, exhibited a high activity towards a highly negatively charged, and multiple phosphorylated substrate like the $(Glu\text{-}Tyr)_n$ polymer, suggesting a preference for highly acidic substrates. Maehama and Dixon (1998) were the first to show that PTEN can also dephosphorylate phosphatidylinositol lipids both *in vitro* and *in vivo*, with a preference for the phosphate group at the D3 position of the inositol ring (Figure 1A).

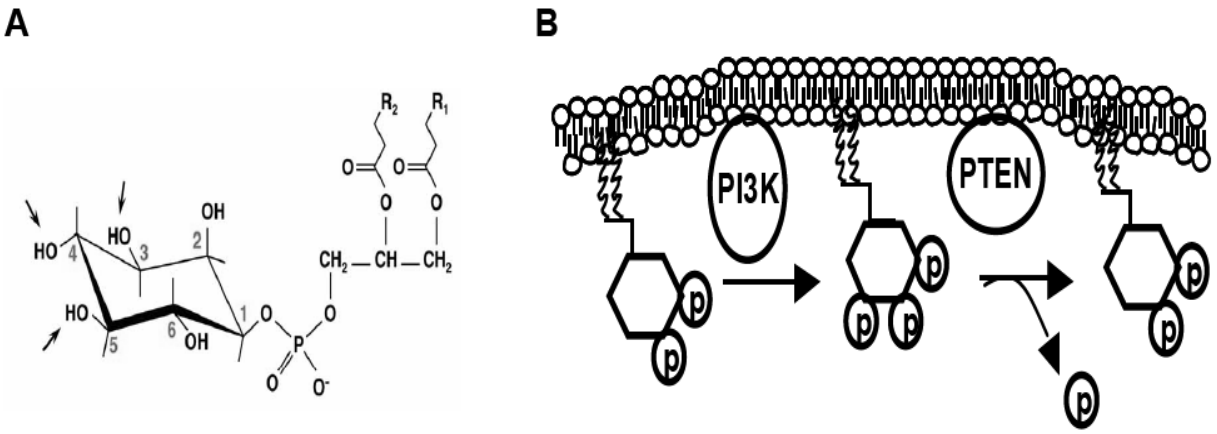

Figure 1. (A) Structure of phosphatidylinositol. Candidate phosphorylation sites are indicated by arrows. PTEN preferentially dephosphorylates PtdIns at the D3 position. (B) PTEN antagonizes the function of PI3K, thereby negatively regulating PI3K dependent signal transduction pathways.

DISCCUSSION

PTEN genetic alterations occur in multiple types of cancer, such as brain, prostate, breast, thyroid and endometrial tumors. Thus, PTEN inactivation may play an important role in the pathogenesis of a variety of human malignancies. The present study found PTEN protein significantly diminished in their expression in cervical cancer cell. This suggests that the loss of PTEN expression plays a role in cervical carcinogenesis. Previous reports have also demonstrated that PTEN expression is progressively reduced along a continuum from normal epithelium to squamous cell carcinoma.

PTEN, a tumor-suppressing gene, is involved in cellular differentiation, reproduction and apoptosis, as well as cellular adhesion and mobility. The loss or downregulation of PTEN plays an important role in the multiple steps of tumorigenesis and progression of malignancies,

and mutations and deletions of this gene have been described in a wide range of human cancers. The incidence is 30–50% in endometrial cancers, 25% in glioblastomas, 21% in ovarian cancer, 13% in prostate cancer and <5% in breast and thyroid cancer. The mutation of PTEN in cervical carcinoma does not appear to be frequent. Yaginuma *et al* reported that one in 43 cervical cancers (2%) had a PTEN mutation in a Japanese population. Rizvi *et al* reported that three of 135 cervical cancers (2%) had a PTEN mutation in an Indian population. However, in a Chinese population, Cheung *et al* reported 0 of 60 cervical cancers had a PTEN mutation.

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