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NARRATIVE PAPER

Prostate cancer as a multifactorial disorder; an overview of different sides of disease

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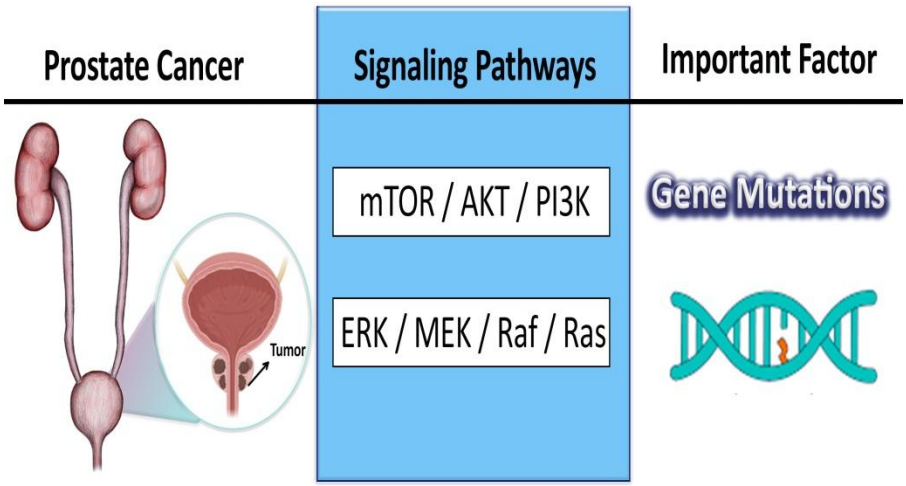
Highlights

- Prostate cancer is the most common malignancy affecting men and is the second-leading cause of cancer death.
- Prostate cancer can be affected by both environmental and genetic factors.
- Two main cellular signalling pathways called to have a chief role in regulating the growth of cancer cells.

Graphical Abstract



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Abstract

Prostate cancer is the most common cancer in males and the second leading cause of death after lung cancer. Prostate tumors are sometimes benign, but malignant ones are clinically divided into two categories. The first group, which appears as a mass with no invasion to other tissues, is known as non-invasive tumors. The second group which causes the majority of mortality is known as invasive tumors. If normal cells are not needed, the process of apoptosis occurs. Two critical signalling pathways called mTOR / AKT / PI3K and ERK / MEK / Raf / Ras play a key role in regulating the growth of cancer cells. Typically, the Phosphatase and tensin homologue (PTEN) protein blocks the PI3K / AKT / MTOR pathway when the cell is ready for apoptosis. In some prostate cancers, the gene makes the PTEN protein mutate, so the PI3K / AKT / MTOR pathway remains active, and the cancer cells lose their apoptotic ability. Thus, gene mutations can be an essential factor in the development of prostate cancer. In this review, different aspects of prostate cancer are evaluated as a multifactorial disorder.

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Introduction

Cancer refers to a group of diseases in which cells in the body grow uncontrollably due to defects in the natural regulatory mechanisms of cell growth and proliferation. The exact cause of this phenomenon is not yet clear, but it may be that genetic factors or other reasons that interfere with cell function lead to changes in the nucleus. Substances such as radioactive chemicals and toxins or excessive radiation such as sunlight can cause these cellular disorders (1, 2). In most cancers, solid glands appear in certain parts of the body, commonly in the skin, breast, lungs, intestines or prostate. Cancer may penetrate other parts of the body through the blood and lymphatic system. Malignant glandular cells can spread from one part of the body to another (3). Cancer cells are isolated from the primary tumor and enter the bloodstream or lymphatic system; these cells can attack other organs and form new tumors that can damage those organs. The spread of cancer is called metastasis. Most cancers are named after the organ in which cancer occurs (4).

One of the causes of cancer is a gene mutation, and carcinogens usually work by causing mutations. Sequential processes that occur in several genes increase the risk of cancer (5). Oncogenes, or tumor genes, are altered genes that normally express proteins involved in controlling cell growth and proliferation. These genes are typically called proto-oncogenes, but when they mutate, they become oncogenes. Oncogenes cause cancer. Mutations that convert proto-oncogenes to oncogenes often lead to overexpression of control factors. Oncogenes were first discovered in viruses called viral oncogenes. Due to mutations in the promoter of proto-oncogenes, they are converted to active oncogenes, and their expression is increased, resulting in increased cell proliferation and tumor formation. These genes control the processes by which disruption can lead to cancer. Many tumor suppressor genes control the cell cycle. Some of them affect the message pathways that regulate apoptosis, and some encode anti-proliferative proteins that suppress mitosis and cell growth (6).

If DNA is damaged, cell division must stop. Therefore, the pathways and enzymes that lead to the activation of tumor suppressor genes are activated. In this situation, the role of tumor suppressors includes stopping the cell cycle and activating the repair pathways. However, if DNA repair is not possible, the cell is transferred to the apoptotic phase, preventing the transition of damage or DNA mutations to the daughter cells (7). One of the most critical tumor suppressor genes is P53. The P53 gene is a transcription factor that is activated by many cellular stimulators, including hypoxia or radiation damage, which finally leads the cell to repair or apoptosis by cell cycle stopping (8).

Unlike other cancer genes, microRNA genes do not encode proteins. These gene products are a single RNA strand, about 21-23 nucleotides, whose function is to regulate gene expression. A micro-RNA molecule can bind to an mRNA that has a nucleotide sequence complementary to the micro-RNA sequence. In this way, micro-RNA prevents the translation of the protein or destroys the mRNA (9). Micro-RNA genes can increase or decrease expression in cancer cells. Genes that increase expression act as oncogenes, and those that decrease oncogene expression act as tumor suppressor genes. Also, reduced micro-RNA expression, depending on the type of genes under its control, can act as oncogenes or tumor suppressors (10). Members of the LET7 micro-RNA family, which are deleted or reduced in lung cancer, target the RAS oncogene. Deletion of LET7 leads to increased RAS expression (11).

Prostate cancer is the most common cancer in men and the second leading cause of death in men after lung cancer. Prostate cancer, in fact, the presence of cancer cells in this organ, is due to an increase in androgens that obstruct the urinary tract. Most prostate tumors are adenocarcinomas, which have many same features as common epithelial cancers, such as breast and colon cancers (12). About 10% of prostate cancers are inherited. Men with a family history are at higher risk for prostate cancer. For example, a man whose father has prostate cancer has a lower age of onset than a man who has no family history of the disease. Some review papers are describing the molecular pathways involved in prostate cancer (13, 14), and we decided to narrate this topic differently. This study aimed to evaluate prostate cancer as a multifactorial disorder that detects different aspects of this disease.

Prostate gland

The word prostate is derived from the Greek word Prohistani, which means to stand in front of. The term was first used by Herophilus, 335 BC, to describe the organ's position in front of the bladder (15). The prostate is the largest appendage gland of the male reproductive system surrounding the urethra the bladder neck (15). Behind the prostate gland are seminal vesicles. This gland weight is only a few grams at birth and about 20 grams at the age of twenty. Prostate secretion is a uniform and slightly acidic fluid (pH = 6.6) with low protein content.

The prostate is located in a capsule of a thin layer of fibro-elastic tissue. Walls of the capsule extend inward, dividing the prostate into five lobes: anterior, posterior, middle, and two lateral lobes (15). The prostate gland consisted of four regions: transitional, central, peripheral, and fibrous muscle stroma. The transition region, in young adults, makes up about 5-10% of the prostate gland mass; The central region makes up about 25-20% of the normal prostate gland mass; The peripheral region makes up 75-70% of the normal glandular structure of the prostate, and the fibrous stromal region is not the anterior glandular muscle and forms about one-third of the prostate capsule (16).

Prostate function and growth

Due to the volume and muscle structure of the prostate gland, this gland is involved in controlling the outflow of urine from the bladder. By reducing the acidity of the urethra, prostate fluid maintains the viability of sperm and facilitates and increases sperm motility by introducing a specific factor (albumin) into the seminal plasma. Prostate acid phosphatase is directly involved in spermatozoon nutrition through hydrolysis of phosphorylcholine to choline (15). Reports also show that high zinc levels in seminal human plasma are mainly derived from prostate gland secretion, an antibacterial agent (17).

The prostate begins to grow before birth, and it continues to grow until it reaches puberty. Male hormones in the body stimulate this growth. Testosterone is produced in testicles (4). Testosterone is converted to its active form, alpha dihydrotestosterone, by the enzyme 5 alpha-reductase in the prostate stroma. Epithelial secretory cells and stromal cells have intracellular androgen receptors. Dihydrotestosterone signals the prostate to grow. In adults, the prostate remains the mature size as long as male hormones are present. In older men, the inner part of the prostate often continues to grow, leading to a condition called benign prostatic hyperplasia (BPH). In BPH, prostate tissue puts pressure on the urethra, leading to problems passing urine (4).

Types of prostate epithelial cells and their association with prostate cancer

At least three distinct cell types can be identified in prostate epithelial tissue based on morphological features. Among these, luminal secretory cells often make up cells, which are androgen-dependent and produce prostate-secreting proteins. Molecularly, luminal cells are characterized by androgen receptor expression and cytokeratins 8 and 18 and cell surface markers (18). The second group of cells in the cells of the prostate basement membrane. These cells express cytokeratins 5, 14 and CD57 and, to a lesser extent, androgen receptors. Base membrane cells make agents that protect DNA from damage (19). Neuroendocrine cells are the third type of prostate epithelial cells. These cells provide signals for the growth of luminal cells. Neuroendocrine cells are androgen-independent cells spread throughout the basement membrane and produce serotonin, chromogranin A, and some other neuropeptides. In the normal prostate, neuroendocrine cells make up a small population of cells, but the accumulation of neuroendocrine cells is an essential sign of invasive forms of prostate cancer (20).

Benign prostate cancers

Benign prostatic hyperplasia (BPH), is the most common cause of urinary obstruction in men. This condition is also called benign prostatic hypertrophy. Of course, because the term hyperplasia describes an increase in the number of epithelial cells seen on microscopic examination, the term benign prostatic hypertrophy is better

used. During the early phase of BPH, prostate tissue begins to hypertrophy. This may put pressure on the urethra, thus reducing the mechanical obstruction of the urethral lumen (20). As the pressure increases, patients may experience difficulty starting to urinate or weaken the flow of urine. Some patients may even put pressure on the bladder to start urinating. As the symptoms get worse, the bladder becomes irritated. Bladder stimulation is the last phase of BPH. Leaving urine in the bladder may increase the sensitivity of this organ. Even a small amount of urine left in the bladder with pressure from an enlarged prostate can cause polyuria. Of course, these symptoms may also indicate other diseases such as prostatitis, prostate cancer and urinary tract infections. Digital rectal examination (DRE) and prostate-specific antigen test (PSA) help rule out other diseases (21). Prostate infarction is a relatively common complication of a bladder neck adenoma. However, its importance compared to infarction of vital organs such as the brain, heart, lungs, or kidneys is minimal (22).

Malignant prostate cancers

Malignant cancers are clinically divided into two categories. Those present as a mass and do not invade other tissues are known as non-proliferative or non-invasive tumors. The second group that causes the majority of deaths is called proliferative or invasive tumors (23). Many men with prostate cancer have a non-invasive form of the disease. A person with a tumor that grows very slowly can live the rest of his life without the complications of cancer (24).

A small percentage of men experience an invasive form of prostate cancer. The onset of metastasis requires a particular stage called invasion, in which the primary tumor cells break down barriers one by one to enter the later stages. Tumor cells must first cross the extracellular matrix protein (ECM) barrier and attack parenchymal tissue. This barrier protein, specifically called the basement membrane (BM) in epithelial cells, comprises different proteins, including cell-binding proteins (25). Specialized extracellular matrix plays a vital role in maintaining epithelial tissue integrity and separates cells from adjacent stromal tissue. In addition to their important role in isolating epithelial tissue from adjacent tissue, important proteins in this area play a growth factor's role and can be released by proteases secreted from tumor cells during the cancer process. Binding proteins such as integrins can play a role in transmitting messages in the presence of adenocarcinomas and alter the polarity, proliferation, and invasiveness of cancer cells (26).

Metastatic features of prostate cancer

In cancer metastasize, cells must cross the basement membrane and enter the circulatory or lymphatic system. There are particular genes that command the production of adhesive proteins. If these genes mutate, they produce proteins that do not work usually. Thus, the cells lose their natural adhesion to each other and the basement membrane and go beyond their natural boundaries (25). The normal function of these adhesive molecules in advanced tumors is increasingly reduced and results in metastasis which is one of the most dangerous stages in cancer development. Removing a cancerous mass before it enters this deadly stage will significantly reduce patient mortality. The two most well-known of these adhesive proteins are cadherin and integrin, which have been the subject of much biological research on prostate cancer (27). The ability to metastasize varies in prostate cancer cells; cancer cells separate from the tumor site and reach secondary tissues. Nevertheless, these cells can only grow in these tissues if they have special abilities, including producing new blood vessels. The mechanism of metastasis is complex, and its ability varies according to the target tissue. For example, bones are one of the most common prostate cancer metastasis sites, with up to 75% of prostate cancer patients with metastatic cancer having bone involvement.

Pathophysiology of prostate cancer

Like other cancers, prostate cancer is caused by an interaction between an environment and a defective gene. Normal cells divide as many as needed and then stop, then they attach to other cells and settle in their tissues. Cells become cancerous when a mutation destroys their ability to stop dividing. These cells are unable to attach

to other cells and cannot stabilize where they belong. Normal cells are doomed to apoptosis when they are no longer needed, and until then, these cells are protected from cell death by several proteins and several pathways (28). One of these pathways is the mTOR / AKT / PI3K pathway (the intracellular signalling pathway that is important in regulating the cell cycle), and the other is the ERK / MEK / Raf / Ras pathway (a set of intracellular proteins that are involved in conducting signals from the cell surface receptor into the nucleus). Sometimes some of the genes involved in these protective pathways mutate, turning them into permanent and stable genes. As a result, the cell is no longer capable of apoptosis. This type of mutation, along with other mutations, causes cancer (29, 30) Normally, the homologous protein phosphatase and tensin (PTEN) block the PI3K / AKT / MTOR pathway when the cell is ready for apoptosis. In some prostate cancers, the gene that makes the PTEN protein mutates, so the PI3K/AKT /MTOR pathway remains active, and cancer cells will not be able to apoptosis. Defects in the immune monitoring system that naturally kill malignant cells and abnormal signalling of growth factors in the interaction between stromal cells and epithelial cells can facilitate the growth of malignancy (31, 32, 33). The function of PTEN in cells is demonstrated in Figure 1.

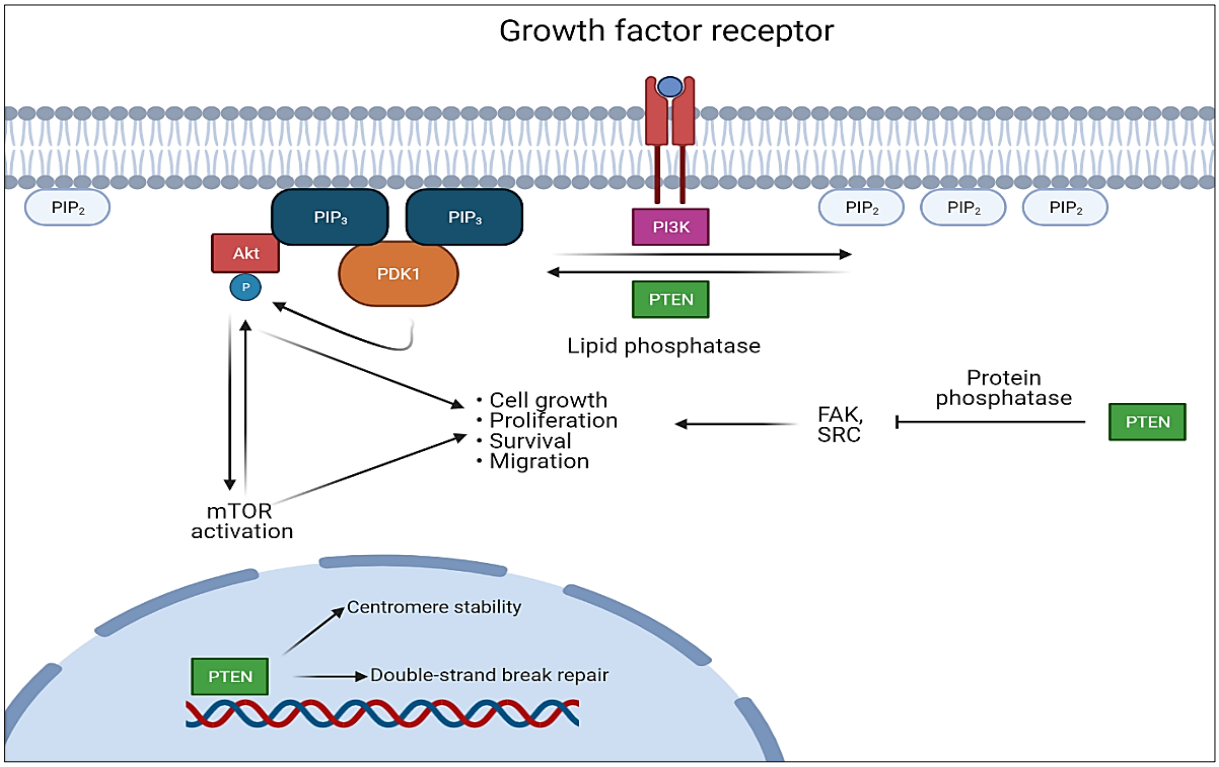

Figure 1. The cellular function of PTEN. Phosphatase and PTEN perform lipid phosphatase activity, converting PIP3 to PIP2.

In this capacity, PTEN plays as an antagonist for the function of PI3K, which changes PIP2 to PIP3. The lipid phosphatase function of PTEN inhibits the activation of AKT and the mTOR signalling pathway. Though PTEN also has numerous other non-established actions, counting frail protein phosphatase function with FAK and SRC. Lastly, PTEN possibly acts in the nucleus in a manner ofPI3K-independent to encourage DNA repair and chromosome stability. The figure was deduced from a report by Jamaspishvili et al., 2018 and was drawn by BioRenderonline software (34).

Epidemiological study of prostate cancer

Prostate cancer is the second most common cancer among men after lung cancer, ranking first in developed countries with 19% of cases. This cancer is one of the most important causes of death for men in European countries, with 145,000 new cases and 56,000 deaths in 1998 (35). In 2002, 679 thousand cases were diagnosed worldwide, with an incidence of 325 cases per 100,000 people, of which 76% were observed in developed

countries (36, 37). According to a 2011 US report, prostate cancer is the most common cancer among men with 29% of cases and is the second most common cancer after lung and bronchial cancer with 11% of deaths (38). The incidence of prostate cancer varies in different parts of the world, with the highest reported in the United States (124.8 cases per 100,000 people) and the lowest in Bangladesh (0.3 cases) (39, 40).

Conclusion

Prostate cancer is the most common malignancy and the second leading cause of cancer death in men, which is a significant health threat to men worldwide. Although the cancer is more common in older men, epidemiological studies have shown that one-third of men in their 30s and 40s have evidence of prostate cancer. In addition to age, the incidence of prostate cancer is associated with other factors, including heredity, diet, lifestyle, and environmental factors. Increased incidence of prostate cancer in men who migrate from areas with low prevalence to high prevalence is evidence that environmental factors also play an essential role in the development of prostate cancer. But genetic mutations can also be another factor in this disease. For example, a mutation in PTEN can divert the cell from the apoptotic pathway and cause it to become cancerous.

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