Review of Hallmarks of Prostate Cancer (PCa)

Nilgoon Zarei*

Abstract: Prostate cancer (PCa) is the most frequently diagnosed non-cutaneous malignancy in men and is the second and third leading cause of cancer mortality for American and Canadian men, respectively\(^1\),\(^2\). PCa is a disease of disrupted prostate cell genomes and corresponding proteins. Cancer progression starting from normal prostate epithelium to androgen-dependent and eventually hormone-refractory carcinoma is very complex and involves multiple processes associated with up/down regulation (malfunction) of different pathways (cell regulatory circuits)\(^3\). PCa, like any other cancer, has stages from I to IV (I corresponds with low-grade benign cancer and IV is an advanced malignant tumor). To determine the PCa stages, the Gleason system is being used, which is solely based on cancer architectural pattern\(^4\). In this study, the ten hallmarks of PCa have been reviewed. It is important to highlight that PCas with low grade Gleason degree usually do not express all the hallmarks presented herein and there is debate regarding considering them cancer or not\(^4\).

Keywords: Prostate Cancer (PCa), Hallmarks of Cancer

Introduction

The mechanisms and proteins involved in cancer development are complex, and multiple of protein signaling pathways should disrupt so that a normal cell develop into cancer. Despite the complexity, these pathways are categorized into ten hallmarks, each representing a different type of breach in a cell’s anti-cancer mechanism\(^5\)\(^-\)\(^6\). Although there are numerous studies on each hallmark involved with PCa, there is no well-organized literature summarizing all PCa hallmarks. In this paper, a short review on PCa hallmarks is presented.

1. Self-sufficiency in growth signals

Cancer cells generate their own growth signals to stimulate mitosis\(^5\)\(^-\)\(^6\)

The Epidermal Growth Factor Receptor (EGFR) is a cell surface receptor which involves with cell growth regulation, differentiation, motility, and adhesion through interaction with different ligands such as EGF. As a result of these interactions, different downstream signaling pathways will be activated, as shown in Figure 1. RAS-MAPK-MEK-ERK\(^*\) and PI3K-AKT\(^*\) pathways are activated through EGFR, which both are responsible for tumor-progression. Impaired endocytic down-regulation of

* Interdisciplinary Oncology, Faculty of Medicine, UBC, Canada (nilgoon.zarei@gmail.com)
EGFR will result in uncontrolled signaling and eventually development into cancer.\textsuperscript{7} The EGF binding onto the androgen-independent prostatic carcinoma cell line PC3 is analyzed with Scatchard plot, as shown in Fig.2. The steep slope of the line in bound/free plot of Fig.2 shows very high affinity between the ligand and receptor (EGF and EGFR). The PC3 solution was being used for two less aggressive PCa cell lines (human prostate carcinoma, LnCap, and classical prostate cancer cell lines, DU 145). This solution increased cell proliferation for both cell lines, as shown in Fig 3.

**Fig 1.** Different signaling pathways, ERk and Akt two important ones in PCa\textsuperscript{4}

**Fig 2.** Scatchard Plot of EGF binding onto PC3 cells, $K_d=5.38\text{ nM}$ (very high affinity), Bound/Free(B/F)\textsuperscript{8}.

**Fig 3.** Effect of PC3 condition medium on DU145 and LNCaP\textsuperscript{8}.

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RAS: Rat sarcoma  
MAPK: Mitogen-Activated Protein Kinases  
MEK: Mitogen-Activated Protein Kinase Kinase  
ERK: Extracellular-Signal-Regulated Kinases  
PI3K: Phosphoinositide 3-Kinase

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**2. Insensitivity to anti-growth signals**  
*Cancer cells become insensitive to the signals that tell them to stop growing*\textsuperscript{5,6}

Cyclin-Dependent Kinase, Cdk$s$, governs progression through the cell cycle. In cell cycle the transition from G1 to S is governed by the D-type cyclins\textsuperscript{9}. In response to anti-growth signals; cell might enter a post-mitotic state where they stop going through all the processes of cell division and can no longer proliferate.

Cyclin D2, is a cell cycle-regulatory gene whose abnormal expression will force the cells to go through unnecessary replication cycles. This gene is shown to be silent in PCa cells. Analysis of 101 PCa samples showed methylation frequency of Cyclin D2 promoter is significantly high in PCas (32% for PCa vs 6% for nonmalignant prostate tissue)\textsuperscript{9}, Fig.4.
Evading Immune Destruction
Eliminating the monitoring capability of immune system

Cells and tissues are constantly under the control of immune system. This supervision and observation system will aggressively target cancer cells and eliminate them at early stages, however, few of cancer bodies manage to either win this battle or hide from the immune system, in other words evading eradication. One way of doing so is by turning off the T cell switch. Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4), is a protein on the surface of T cells and acts as an off switch for T cells. In PCa, it is shown that blocking CTLA-4 will significantly help to shrink tumors.

Limitless replication potential
Long DNA ends – cancer cells have limitless replication potential

To protect the genome, an enzyme called telomerase adds “extra” base pairs at the ends of the chromosomes and lengthens the DNA. Telomerase is active during embryogenesis and in cells that need to undergo many cell division cycles, such as stem cells in the bone marrow, but is inactive in adult cells. Therefore, chromosomal DNA becomes shorter with each successive cell division cycle, which sets a limit on the number of cell divisions a cell can undergo. The human telomerase (such as HumanTelomerase Reverse Transcriptase, hTERT) is regulated by Androgen Receptor (AR) signaling. LNCaP which expresses a mutant but functional AR, meditates telomerase activity and increase transcription.

Tumor promoting inflammation
Cancer initiation/progression via inflammation

Inflammation has a profound effect on cancer development (initiation to metastasis). It is believed that inflammation stimulates carcinogenesis. Inflammation causes cell/genomic damage, enhances cell replication, and carries many more destructive effects. There is a strong relationship between inflammation and PCas. The level of proinflammaoarty cytokines is shown to be significantly higher in chronic prostatitis sections comparing to normal samples. Moreover, there exists evidence confirming the higher risk of PCa for men with prostatic inflammation history.
6. Tissue invasion and metastasis

Cancer cells invade neighboring cells and spread throughout the body to new sites.

Spread of cancer cells to other distant tissues and starting new colonies is known as cancer invasion or metastasis. Cancer cells release protease enzyme which allows them to dissociate, and migrate independently in the extracellular space and eventually reside in distant locations and form colonies.

Interaction between the stromal cell-derived factor 1 (SDF-1), known as C-X-C motif Chemokine 12 (CXCL12), and C-X-C Chemokine Receptor type 4 (CXCR-4), also known as fusin, plays a critical role in PCa metastasis into the bone. The expression of CXCL4 is shown in both PCa and bone stromal cells. In fact migration and culturing of PC-3 cells in bone depends on CXCL12/CXCR4 signaling and Akt activation through PI3-kinase, as shown in Fig1. Also CXCL12 induces expression of Matrix Metallo Peptidase 9 (MMP-9) in PCa cells, which is associated with tumor progression and metastasis.

7. Sustained angiogenesis

The growth of new blood vessels

Cancerous bodies which reach a size of 1 mm need to initiate angiogenesis, to receive oxygen and nutrients from the vessels. So they turn on the angiogenic switch and start to secrete angiogenesis-inducing factors. One such important factor is Vascular Endothelial Growth Factor (VEGF) which is mediated by hypoxia, cytokines and androgen. VEGF also involves in other pathways such as (Ras, Raf, and Src) activation and inactivation of genes responsible for tumor suppression. VEGF levels, measured by immunohistochemical analysis showed higher level of VEGF in patients with metastatic prostatic cancer than those with localized prostatic cancer.

8. Genome Instability

DNA mutation and repair

Certain genome alteration during mutation can simply enforce the normal cells to outgrow and develop into cancer. Poly (ADP-ribose) Polymerase, PARP, is a protein involved in repairing DNA damage of cancerous cell (the natural damage during fast replication and the artificial damage during cancer treatment).

PCa of patients which lacks the homologous recombination DNA repair (due to loss-of-function BRCA1 or BRCA2 mutations) can be treated with PARP inhibitors. PARP also impacts ERG transcription and androgen signaling which are very important pathways in PCas.

* BRCA1: the official name of this gene is “breast cancer 1, early onset.
* BRCA2: the official name of this gene is “breast cancer 2, early onset.
** RAS: Rat sarcoma, RAF:Rapidly Accelerated Fibrosarcoma, SRC: Steroid Receptor Coactivator,
9. Evading apoptosis

Cancer cells resist apoptosis

All healthy cells will go through natural (programmed) cell death process known as apoptosis. Apoptosis can be triggered from both internal and external signals.

Defender Against Cell Death 1, DAD1, is a downstream target of the NFkB(Nuclear Factor Kappa-Light-Chain-Enhancer of activated B cells) survival pathway and boosts cell resistance to apoptosis. High DAD1 expression is associated with cancerous epithelium and its protein level also exhibited a strong association with microscopic tumor architecture (Gleason pattern).

10. Deregulating cellular energetics

Reprogrammed metabolism to support proliferation

Cancer cells reprogram glucose metabolism, which increases the uptake of glucose into the cell and also favor glycolysis even under aerobic condition. Pyruvate kinase M2 (PKM2) is essential for aerobic glycolysis. By immunohistochemistry the researchers have shown that the expression level of PKM2 is higher in aggressive prostate tumor.

Conclusion

In this survey, ten hallmarks of PCa have been reviewed and summarized. As explained in this paper, interruption in cells’ regulatory mechanisms can eventually result in modified biological capabilities (hallmarks) and cell development into tumor. Any prostate lesion should adopt all the aforementioned hallmarks of cancer in order to be considered cancerous.

References


