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Fundamental Differences Between the Traditional Normal Immune System and the Cancer Immune System

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Abstract

Defects in DNA damage-response and in DNA repair often cause an increase in cancer incidence. Roles of the DNA repair are associated with modulation of hormone signaling pathway. Molecular basis for the progression of prostate cancer which is the most common neoplasm in male population remains an important subject in management of the male cancer. In addition, the molecular mechanisms by which pathogenesis may affect the prostate cancer are poorly elucidated.

Keywords: Prostate Cancer; DNA repair; estrogen; ATM; p53; BRCA1

Introduction

Prostate cancer is the most common malignancy in men worldwide [1,2], which is also known to be a hormone responsive cancer [3]. There are evidences supporting a role for several hormones in stimulating the cancer cell growth [3]. Accordingly, the risk factors of prostate cancer may act at least through hormonal mechanisms [1,2]. Various environmental endocrine disruptors such as Bisphenol A (BPA), which is widely used in the production of plastic polycarbonate, have been shown to make disorders in sexual organs including the prostate gland [4]. Such environmental hormones may play a critical role in influencing for triggering prostate disease [5]. While numerous factors are involved in prostate carcinogenesis [6,7], epidemiological studies have reported a relationship between elevated circulating estrogen levels and prostate diseases [8]. A seminent levels of estrogen are strongly involved in DNA repair system, the signaling pathway of DNA repair may also play a key role in the progression of prostate diseases. Generally, prostate cancer is classified into three risk groups based on the Gleason score, Prostate-Specific Antigen (PSA) level, and clinical staging. Because the drug which blocks androgenic hormone activation significantly reduces the prostate cancer risk, those risk factors may act through androgenic hormonal mechanisms.

Estrogens Involved in Prostate Cancer Development

Sex hormones, such as estrogen, androgen, and progesterone frequently contribute to the initiation and promotion of various type of cancer-development through the specific hormone receptors. Therefore, not only androgens but also estrogens may promote prostate cancer. In fact, prolonged exposure to an elevated level of estrogens plays a role in the development of prostate cancer. Furthermore, fetal exposure to BPA increases the hypertrophic mass of prostate on mature ages in mice. Exposure to 17β-estradiol in neonates brings increased incidence of prostate intra-epithelial hyperplasia. In addition, exposure to high level of estrogens during early developmental stage induces prostate cancer development in the life later. Variation in Estrogen Receptor (ER) activities with the specific ligands and/or with genetic alterations may also modulate the prostate cancer risk. However, increased consumption of phytoestrogens such as genistein, a well-known phytoestrogen as well as a tyrosine-kinase inhibitor, has been associated with a decreased risk of prostate cancer. A combination of selenium and the genistein may offer better efficacy in prostate cancer prevention. In addition, the phytoestrogens protect cells from Reactive Oxygen Species (ROS) by scavenging radicals, up-regulate the expression of GSK-3β, enhance GSK-3β binding to β-catenin, and induce apoptotic cell death, which suggests that phytoestrogens could induce cancer cell apoptosis and then block cancer cell proliferation. The phytoestrogens have also been found to inhibit the molecules in Mitogen Activated Protein Kinase (MAPK) [26], and in p38-MAPK by TGF-β pathway, inhibiting cell invasion and cell metastasis of the prostate cancer. Downregulation of the p38-MAPK signal decreases MutS Homolog 2 (MSH2) expressions, and then enhances the cytotoxic effect. The MSH2 plays a central role in promoting genetic stability by correcting DNA replication-errors.

Suppression of DNA repair pathway seems to obstruct the mechanisms that are essential for cell survival, especially when in a presence of oncogenic mutations. Hence, DNA damaging agents work well in cancer cells with DNA repair defects for therapeutic sense. Epigenetic mechanisms such as histone modifications and/or DNA methylation have also been evaluated with an understanding for improving cancer therapy via the regulation of genes-expression involved in DNA repair. Several reports suggest that estrogen causes the epigenetic changes with histone modifications and DNA methylations in prostate as well as in other estrogen target organs. In addition, aberrant genomic DNA methylation can be observed in human prostate epithelial cells during environmental inorganic arsenic exposure. Estrogen induced malignancy in human prostate epithelial cells may be associated with genomic DNA hypo-methylation. Actually, aberrant hypo-methylation of DNA is apparent in a variety of human diseases including cancer and diabetes.

Eukaryotic cells generally respond to the DNA damage by stopping the cell cycle to initiate DNA repair. Cancer cells due to the disruption in the p53-dependent pathway are mainly dependent on G2/M and S-phase checkpoints to keep the genomic integrity in response to the DNA damage. ERβ may inhibit prostate cell proliferation by regulating components of the cell cycle machinery in those cellular systems. It has been reported that induction of ERβ expression causes abolition of S-phase and Chk1-mediated checkpoints after cisplatin and doxorubicin exposure in p53-defective prostate cancer cells, but not in wildtype-p53cells. Therefore, in cancers where p53 is defective, the presence of ERβ may contribute to an effective response to cisplatin and doxorubicin chemotherapy.

Overview

Since the hormone signaling pathways may play an essential role in the development of prostate cancer, hormonal therapy (such as androgen-deprivation) is the standard systemic treatment for advanced prostate cancer. However, it is obscure whether estrogens have beneficial effects on prostate cancer therapy, or not. Advances of molecular biology in a field of DNA repair have led to a better understanding of the events important in the molecular pathogenesis of hormonal cancers including prostate cancer. Different molecular bio-mechanisms of the action could be also favorable, suggesting a real application in prevention of prostate cancer. Estrogen signaling pathway

has a complex network, and further comprehensive research in this area is obligatory. Discrepancy between the cell proliferation and DNA repair actions may be plausible for the accumulation of DNA errors, susceptible to prostate carcinogenesis, and the exacerbation of the cancer development. Precise understanding of the underlying molecular mechanisms involved in the transition to hormone refractory disease is also necessary for the improvement of effective therapeutic strategies. Mechanistic studies are mandatory in order to recognize these molecular mechanisms of hormonal carcinogenesis, cancer development, and the DNA repair system for the effective therapeutic interventions.

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