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Review Article

Epigenetics in the Development of Prostate Cancer Precursors

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Abstract

Prostate cancer development is a very intricate step-wise process that includes different early transformations of specific areas in benign prostatic tissues, followed by the envelopment of its premalignant lesions and if left untreated, progresses to a clinically aggressive form with metastases. Although age, race and family history are well-established risk factors, their molecular basis is not well-understood. Epigenetic were found also to influence significantly the prostate cancer initiation and development. DNA methylation of CpG islands plays an important role in the regulation of gene expression and influencing gene function, contributes to disease development.

Keywords: Prostate Carcinogenesis; Precursors; Epigenetic; Field Effect; Age, SEREPINB5

Introduction and Discussion

Prostate cancer (PCa) is one of the major contributors to malignancy related mortality among men in the Western world and also is a significant social and finance burden for each healthcare system worldwide [1,2]. In 2012, over 1,111,000 new cases of prostate cancer (PCa) were diagnosed worldwide, and estimated 307,000 men died of this disease [3]. Significant efforts are made to understand the development of the prostate cancer but questions about the causes and earliest events, preceding by decades its initiation are not yet fully understood.

Up to now, a myriad of studies convincingly have shown that PCa initiation and progression is an intricate multistep process, starting from*field effect*, which involves large number of cellular, biochemical, histological, genetic, and epigenetic factors and that was suggested to lie at the basis in progressive accumulation of the aforementioned accumulations through progression from normal epithelial cells to invasive PCa [3-5]. These events occur during malignant transformation and include a loss of tumor suppressor genes, activation of oncogenes, promotion and activation of cell proliferation and dies regulation of apoptosis – hallmarks of tumor genesis.

Precursors and early changes in prostate malignant transformation

Prostate cancer initiates from specific lesions, termed as premalignant precursors. Among several suggested plausible precursors, to date only the high-grade prostatic intraepithelial neoplasia (HGPIN) is believed to be the most likely precursor due to epidemiological, morphological, and molecular evidence close to prostatic carcinoma. Prostatic intraepithelial neoplasia (PIN) was first described in the 1960s by McNeal under the name of 'intraductal dysplasia', and was more precisely characterized in 1986 by McNeal and Boost wick [6,7]. Although significant progress was made in the understanding of prostate malignant development, it is still not clear if a direct conversion exists between benign and precancerous lesions (i.e. HGPIN) or rather, an intermediate step as a tissue lesion, intercellular interactions, or signaling pathways may exist between the benign tissue and HGPIN lesions.

In 1999 De Marzo et al. have proposed a new plausible precursor – the proliferative inflammatory atrophy (PIA), which could be a continuum between benign tissue with HGPIN and a possible PCa forerunner. PIA is frequently observed in prostate biopsies and possesses several genetic alterations, common to both HGPIN and PCa lesions. Despite multiple discussions pros and cons of the eventual PIA role as malignant PCa precursor, to date no convincing data are presented in favor of PIA as plausible PCa forerunner [8].

It is important to understand whether the early transformations can be manifested mostly by several distinct morphological and genetic alterations or other manifestations in the altered cell

machinery mirror the onset of malignant reprogramming, months or even years before the precursor lesion will be microscopically detected. On can suppose that the origin of these events can occur at a particular point of human life span. To support these speculations, studies demonstrated that: 1/ presence of PIN lesions are as early as the thirty and fifth decade of life, whereas its incidence and extent tend to increase with age; 2/lesions such post-atrophic hyperplasia (PAH), atypical adenomatous hyperplasia, proliferative inflammatory atrophy (PIA) and PIN, have been designated as *atypical* or *suspicious* due to some morphological characteristics, resembling malignant rather than benign lesions. It is well-known that HGPIN possess morphological features, closer to the prostatic carcinoma -prominent nucleoli, nuclear enlargement, nuclear hyper chromasia, and nuclear crowding. In addition, most of these lesions specifically express antibodies that help to discriminate malignant their benign counterparts. However, how to judge an abnormal gene expression in seemingly *benign* prostatic lesions, without convincing evidence of cellular atypia? Can we consider this phenomenon as an earliest event in the prostate malignant transformation and also, what are the triggering mechanisms for the onset of these events?

According to the accepted criteria, to consider a prostatic lesion as premalignant, this lesion should be: 1/ present at an earlier stage than cancer, 2/to demonstrate morphological similarities with cancer (cellular, histological and architectural) and also, 3/ an epidemiological relationship must be revealed [9]. Hence, it is essential to identify an*Achilles' heel* or in other words, a specific field where specific changes occur, leading to formation of pre-precursors by triggering the onset of domino effect in malignant reorganizations in otherwise benign cell genome. Of importance is also to verify when these early alterations in non-cancerous tissues occur, harboring hitherto unrecognized premalignant transformations. Due to the fact that development of invasive prostatic carcinoma begins from its benign epithelial glands, one can ask if the early, still invisible cellular changes, demonstrated only by their specific gene expression, could be regarded as a separate diagnostic entity. Available data suggest that the prostate is a vulnerable organ and variety of events give rise to several discrete genetic and cellular alterations, leading to developing of prostate cancer. Some authors have demonstrated that prostate carcinogenesis has a predilection sites that include zonal variation in cell morphology and phenotype. In support of this observation, several studies have demonstrated differences and zonal specificity of basal cells in the peripheral zone (PZ), compared with those in transition zone (TZ) [10]. Based on fact that PZ is a predominant site for prostatic carcinoma development (85%), versus TZ (31 %) [11], it was proposed that in contrast to TZ, PZ can have different biological properties and unique epigenetic signatures.

Aging, Inflammation, DNA Methylation and Prostate Cancer

During its developing and growth, the prostate is constantly exposed to a large number of different factors, altering the prostate cell homeostasis. Among the established risk factors (i.e. age, race and family history), aging essentially contributes the prostate cancer initiation. Along with the cell senescence, epigenetic factors such as aging play an essential role. Strong relationship between the advanced age and DNA methylation has been demonstrated in many studies. Ageing has been described as a slow, time-dependent decline of a set of multiple biological functions. PCa is a primarily disease in elderly and its age dependence was demonstrated as well [12]. This malignancy is extremely rare in men younger than 50 years; in the same time about 80% of diagnosed men are 65 years old with an average patient age is 70 years [13-15]. In-between several suggested PCa precursors, only HGPIN is the most plausible forerunner, harboring methylation of PCa markers such as APC, RARB and, to a lesser extent-GSTP1 [7]. The role of epigenetic in the onset and progression of prostate cancer has been established. Studies about the epigenetic events in the prostate cancer demonstrated that aberrant promoter hyper methylation occurs due to ageing in normal tissues [12,15]. DNA methylation is an epigenetic event, which affects the gene expression by addition of methyl group, catalyzed by DNA methyltransferase (DNMT) to the 5-carbon of cytosine in a CpG island, resulting in dene silencing and inactivation. Prostatic cell is constantly exposed to various damaging agents but is still able to activate its own repair. Later, the rate and number of cellular alterations exceeds significantly the ability of the cell's self-repair, which in turn triggers the onset of a cascade of different cellular alterations that predispose the non-neo plastic prostate tissues to their malignant conversion [15,16].

Epigenetic alterations have been first described in 1983 [17] and since then a growing number of studies have demonstrated the role of promoter methylation of CpG islands in many malignant diseases, including prostate cancer. DNA methylation is one of the most common epigenetic mechanisms that affect gene expression and its clinical relevance in human cancers is extensively investigated since its discovery. Addition of a methyl group to the gene promoter regions that are rich in CpG dinucleotidesalters the chromatin structure, recruits methylated DNA-binding proteins and prevents transcription factor binding, leading to a gene silencing, which leads to cancer developing. Studies have shown that DNA methylation also occurs in benign tissues. Thus, in 1993 Ono et al. have reported an association between the increased methylation and inactivation of collagen a1 gene with its inactivation. Likewise, in several studies Issa et al., [18,19] have shown a relation-

ship between CpG methylation of human estrogen receptor with the advanced age. Recently, another study reported the silencing of 5-alpha reeducates 2 gene due to increased 5AR2 gene promoter methylation in men with symptomatic BPH [20], where the advanced age plays a role of independent prognostic epigenetic factor, leading to gene silencing.

Age-specific DNA methylation changes affect the expression of some genes such as SERPINB5 (also maspin), GSTP1, caspase-8, RASSF1A gene, and the estrogen receptor (ESR1) that respond to aberrant changes and maintain the normal cell homeostasis by eliminating the products from oxidative stress, hypoxia and inflammation. It was established that chronic inflammation is age-related and can be associated with DNA hyper methylation. Several authors have reported a strong relationship between DNA hyper methylation and inflammation [21-23]. And indeed, as inflammation increases with the advanced age, the incidence of methylation also increases and the rate of methylation changes accelerates [21]. We can speculate that the described events might represent an initial stage in the PCa development. DNA hyper methylation is best studied in GSTP1 gene in prostatic carcinoma (1071 cases/total 24 studies). The methylation of GSTP1 was found in over 81% of cases and in addition a strong relationship with the advanced age was demonstrated. Hyper methylation of GSTP1 was shown to play a significant role in the early prostatic carcinogenesis, namely in PIA (6.3%) and HGPIN (68.8%), respectively. The mechanism causing the age-dependent changes in DNA methylation is very intricate and can occur at different stages of human life [16]. The potential methylation mechanisms, associated with ageing are not well elucidated but several new studies suggested the role of increased DNMT1 in prostatic tissues [21,24]. The age-related relationship was shown in a study that have reported a specific pattern of expression of DNMT1 in T-lymphocytes during certain stages of human life (i.e. newborns, middle aged and elderly subjects) and its association with age [25]. Lopatina et al., 2002 also reported the relationship between methyltransferase expressions and senescence of cultured fibroblasts [26].In addition GeR et al., 2015havereported evidence of the impact of age-related DNA methylation and inflammatory changes (TNF-a, NF-kB, and IL-6)in prostatic tissues [21]. These studies demonstrated CpG hyper methylation in non-cancerous lesions, thus suggesting that a subset of specific genes can be methylatedin benign tissues as well [27,28]. However, certain genes can be specifically methylated in pre- and malignant prostatic tissues (e.g. AMACR, NKX3.1). Detection of DNA hyper methylation in prostatic precursors represents a very interesting and exciting area of research. It is reasonable to ask if the methylation of these genes mirrors a designated specific event in the stage of malignant conversion or rather is influenced from the adjacent cancerous tissues (GSTP1 hyper methylation in 69% of PIN lesions and 91% of prostate cancer) [29]. Of importance is to note that a DNA methylation tissue-specific predilection can exist, inviting future studies to explore utilization of zone-specific DNA methylation as a gene signature for the early detection and possible prevention of patients at risk to prostate cancer.

An interesting finding from our laboratory (unpublished data) is the over expression of gene SERPINB5 in a subset of basal cell hyperplasia cells. SERPINB5 is a mammary serine protease inhibitor that is epigenetically regulated. SERPINB5 is a tumor protective gene that inhibits urokinase-type plasminogen activator on cell surface and its loss is associated with destruction of basal cell layer membrane with further propagation of tumor cells and cancer progression. Loss of SERPINB5 expression in prostate neoplasms is associated with non-favorable progression of cancer and shortened survival of patients. SERPINB5 expression is down-regulated in breast, prostate, gastric and melanoma cancers but over-expressed in pancreatic, gallbladder and colorectal carcinomas. Although SERPINB5 is also expressed in normal tissues, its highest expression was detected in HGPIN lesions with further gradual decrease in low-grade prostatic cancers reaching a complete loss in high-grade cancer [30]. However, here we detected remarkably elevated SERPINB5immunoreactivity in basal cell hyperplasia and not in HGPIN lesions, as previously reported [30], [our unpublished data]. This finding is intriguing due to the possibly this pattern of expression to be affected by an epigenetic event (age, inflammation, etc.) and perhaps may represent a field effect, in which the early lesions are not yet presented by histological aberrations. It could be interesting to investigate SERPINB5 expression in this type of tissue (i.e. basal cell hyperplasia) to better understand its role in tumor development.

Conclusions

There is a growing body of evidence, supporting the role of DNA methylation in the early events of cancer development. The understanding of mechanisms, driving the specific epigenetic patterns and pathways in the prostatic cancer evolution is important and will contribute to the early detection of premalignant state of PCa, a long before its clinically active form will occur. In addition, the epigenetic alterations could be used as useful biomarkers for stratification of men at risk of PCa and also to represent suitable therapeutic targets for the personalized treatment of patients with prostate cancer.

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