Review Article

Epigenetic events in male common urogenital organs cancer

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ABSTRACT

Cancer is a disease initiated and propelled forward by the accumulation and interaction of genetic and epigenetic mutations of genes involved in the regulation of cell signaling and growth. Epigenetics refers to the heritable alterations in gene expression, not attributable to changes in DNA sequence. The two predominant epigenetic mechanisms are DNA methylation and histone modification. The role of epigenetics in the regulation of gene expression has been considered as a basic pathway in the progression and pathogenesis of various malignancies, such as cancers of the urogenital organs. Recently, several studies have focused on the epigenetics of male urogenital system cancers. Epigenetic modifications in the DNA of cancer patients and precancerous lesions provide the promise of novel biomarkers for early cancer prediction, diagnosis, prognosis, and treatment response. In addition, numerous epigenetic modifications represent a potential goal of novel therapeutic strategies and treatment design. Ultimately, pioneering diagnostic methods and treatment regimens probably will be based on epigenetic mechanisms and included into medical practices that address the needs of patients with male urogenital organ cancers.

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1. Introduction

Previously, cancer had been viewed primarily as a genetic disorder. However, it has recently become generally accepted that cancer is not only influenced by genetic factors but also by the consequences of abnormal epigenetic events. Genetic alterations and aneuploidy are linked to changes in the DNA sequence, and are true hallmarks of malignant pathogenesis. Epigenetic changes commonly exist in human cancers as a consequence of heritable alterations in gene expression and chromatin structure, which are transmitted to several cell generations without alterations in DNA sequence. This results in functional costs which correspond to those induced by genetic changes. Significantly, intriguing evidence has emerged indicating that epigenetic modifications may lead and actually provoke genetic alterations. In this scenario, the epigenetic events are main events while genetic changes (for example mutations) are basically a consequence of the epigenetic disruption. This information may clarify why numerous genetic screens proved to be imperfect with regard to cancer pathogenesis and causality. Aberrant epigenetic events influence cellular pathways and multiple genes in a non-random fashion, and thus can predispose the beginning and accumulation of genetic alterations in the course of tumor initiation and development. These considerations are crucial for a better understanding of tumor pathogenesis, cellular and molecular processes underlying the acquisition of drug resistance, in addition to the development of cancer therapy and prevention strategies.

1.1. DNA methylation and carcinogenesis

DNA methylation is defined as the subtraction or addition of a methyl group to a cytosine residue in DNA sequence. The methylation of DNA is controlled by DNA methyltransferase enzymes. In genome-wide association studies, global decreases in DNA methylation (hypomethylation) are functionally related when they occur in transcriptional regions of genes resulting in alternative translations or mRNA levels. It is believed that
Hypomethylation plays a critical role in carcinogenesis by facilitating mitotic recombination, leading to translocations, deletions, and chromosomal rearrangements. The addition of methyl groups (hypermethylation) is much more gene precise. The DNA sequences rich in residues of a cytosine preceding a guanine (CpG dinucleotide) are called CpG islands. In particular, CpG islands occur in the promoter of about half of all genes. The hypermethylation of promoter (CpG islands) results in their transcriptional silencing of protein expression (Fig. 1). Therefore, hypermethylation of tumor suppressor genes is currently recognized to be a means of providing a silencing alternative to mutation or allelic loss in cancer development.

Hypermethylation of genes is also involved in the DNA repair, cell cycle, carcinogens metabolism, apoptosis, and cell–cell interaction which have been implicated in carcinogenesis. Furthermore, hypermethylation can also inhibit the transcription of microRNA leading to carcinogenesis. However, it should be taken into account that hypermethylation also occurs in normal physiological process, for instance during inactivation of the second X chromosome in females. The question is posed as to why aberrant DNA methylation occurs, yet remains incompletely understood. It is known that some genes are methylated in an age-related style, whereas others are methylated in a cancer-specific manner. Definitely, one carcinogenetic pathway of particular relevance to the reproductive system is the CpG regions methylator phenotype (CIMP). CIMP+ cancers have different genetic, pathologic and clinical features. Whether environmental factors such as carcinogens, diet (e.g., folic acid), or other unknown causative agents contribute to DNA methylation remains to be elucidated and continue to be areas of research interest.

### 1.2. Histone modifications and cancer

Histones are protein molecules of the chromatin, the structure around which DNA is wound (Fig. 2). Histones may undergo a number of types of post-translational modifications, such as methylation, acetylation, phosphorylation, and ubiquitination. These modifications can influence interactions between DNA and histones, resulting in the alteration of gene transcription, DNA repair, DNA replication, in addition to organization of chromosomes. Universally, histone acetylation is associated with transcriptional activation. Consequently, deacetylation is involved in tumor suppressor gene silencing during carcinogenesis. Indeed, inhibitors of histone deacetylase are in early phase clinical trials for medications targeting a number of cancers, with promising results.

Histone methylation occurs mostly at arginines (R) and lysines (K). Methylation by histone post-translational modifications (PTM) have a number of substantial differences compared to the above-described acetylation. Lysines can be monomethylated, dimethylated, or trimethylated, while arginines can be only monomethylated or dimethylated. In arginine methylation, asymmetric or symmetric dimethylation should be distinguished because accurate methyl designation are important for functional outcomes. As opposed to acetylation, the addition of a single methyl group on the side chain does not change its charge, and consequently it is unlikely that methylation can directly alter nucleosomal interactions which are essential for chromatin folding. Another diverse characteristic of histone methylation is that it has been involved in both transcriptional repression and activation. For instance, trimethylation of H3K9, H4K20 (H4K20me3), and H3K27 was found to be implicated in transcriptional silencing, while trimethylation at H3K36 and H3K4 (H3K4me3) serve as active marks. Methylation of arginine, catalyzed by arginine methyltransferases, can serve as a transcriptional repressor or activator. Lysine methylation has been described on all 4 cores of histone types, in addition to histone H1. Additionally, H1K26 was found to be the first methylation site studied in H1.

Methylation of histones is considered to be a critical step involved in many cell fate determinations, including cell differentiation and development processes, pluripotency, and maintenance of genome integrity. Methylation of histones has also been associated with malignancy and other disorders (about 50% of the histone methyltransferase encoded by the human genome are highly associated with diseases and in particular tumorigenesis).

### 1.3. CpG island methylator phenotype criteria (CIMP)

In 1999, two different types of colorectal cancers were identified, and found to display low and high levels of tumor-specific methylation, correspondingly. The latter type of cancer was found to exhibit a “CpG island methylator phenotype” (CIMP). CIMP is negatively linked with genetic aberrations in colorectal cancer, which implies that it can offer an alternative pathway for carcinogenesis. Other cancers that show frequent and concomitant deactivation of several genes via hypermethylation also have been designated as CIMP. These cancers include liver, gastric, leukaemia, and ovarian cancers. Differential expression of the DNA methyltransferase (DNMT) genes in some ovarian...
cancer cell lines has been revealed and changes in DNMT expression might contribute to develop CIMP phenotype in ovarian cancer. Yet, the basic mechanisms that contribute to increases of methylation abnormalities in ovarian cancer cells remain unclear.

Numerous studies have demonstrated that patients with CIMP-positive tumors generally have a poor prognosis possibly due to increases of their epigenetic plasticity. Therefore, it will be important to determine the molecular basis of CIMP, but also to test the present set of methylation biomarkers for detection of CIMP. However, CIMP-positive tumors are easier to diagnose at an early stage because aberrant DNA methylation can be detected with a high level of sensitivity. Also, this phenotype may be able to predict treatment outcomes in ovarian cancer patients. Generally, the compactness of methylated CpG sites within a locus in addition to the number of methylated loci were found to be increased in the late stages of cancer. While the duration of progression-free survival after chemotherapy was found to be considerably shorter for patients with high levels of methylation compared to those with lower methylation levels, enhanced detection of CIMP tumors may aid in treatment planning and outcome.

1.4. MicroRNAs and cancer

MicroRNAs (miRNAs) are known as small non-coding regulatory RNAs typically found in sizes ranging from 17 to 25 nucleotides. This definition of miRNAs is based on their production via the action of the enzyme Dicer, an RNase that processes hairpin structured precursors into mature miRNAs. MiRNAs post-transcriptionally repress gene expression via recognition of complementary target sites in the 3' untranslated region (UTR) of target mRNAs. MicroRNAs play vital roles in a variety of functions in the cell such as cell development, differentiation, cell cycle involvement and apoptosis. The expression of miRNA is deregulated in malignancy by a variety of mechanisms including amplification, mutation, deletion, and epigenetic silencing. Several reports have indicated the involvement of miRNAs in cancer initiation and progression. Importantly, there are three different epigenetic modifications i.e., DNA methylation, histone modification and miRNAs interaction and their influence with each other. For example, miRNA expression can be regulated via DNA methylation in the respective regions of their promoters. Likewise, miRNAs can target chromatin remodeling enzymes and DNA methyltransferases (DNMTs) and, therefore, modulate the downstream effects. Genes or miRNAs that are epigenetically silenced or regulated in male urogenital organs cancer are summarized in Table 1.

1.5. Prostate cancer

Prostate cancer is one of the most widespread cancers affecting men, with more than 1,100,000 new cases and 300,000 annual deaths globally. The disease occurs more frequently among older men, with a middle age at diagnosis of somewhat above 60 years. Prostate cancer is predominantly a medical problem that requires urgent attention as the disease is indolent, shows prolonged latency and is associated with high morbidity and mortality. Epigenetic modifications have been found to play critical roles in prostate cancer development and metastasis.

1.6. Epigenetic modifications in prostate cancer

Prostate cancer is one of the most frequent human malignancies and is driven by genetic and epigenetic modifications. Such
epigenetic modifications include DNA methylation, histone modifications, and microRNAs (miRNA) which produce heritable alterations in gene expression without changing the DNA sequence. Aberrant DNA methylation (hypermethylation and hypomethylation) is the most extensively characterized alteration in prostate cancer and leads to instability of genome and improper gene expression. Global and locus-specific alterations in chromatin rearrangement are associated with prostate cancer, suggesting a causative malfunction of histone-modifying enzymes. In addition, microRNA deregulation contributes to the carcinogenesis of prostate cancer, including interference with apoptosis and androgen receptor signaling pathways. There are significant relations between common genetic alterations and changes in the epigenetic landscape.

1.7. The role of hypomethylation in prostate cancer

Hypomethylation is the most commonly observed methylation problem seen in a wide variety of cancers including prostate cancer. Hypermethylation alterations seem to precede hypomethylation alterations, which are usually detected in late stage cancers, and occur heterogeneously during prostate cancer development and metastatic dissemination. Hypermethylation has been proposed to contribute to oncogenesis via several mechanisms including: activation of oncogenes for instance H-RAS and c-MYC, activation of latent retrotransposons, and through contributing to chromosome unstainability. Recent reports have confirmed a strong association between MYC upregulation in prostate cancer cell and clinical progression. MYC plays a crucial role in androgen-dependent growth, and subsequent to its ectopic expression can stimulate androgen-independent growth in prostate cancer tissue.

1.8. The role of hypermethylation in prostate cancer

The majority of studies focused on DNA hypermethylation have been done in the epigenetic field of prostate cancer. Certainly, gene silencing is found to be more frequently facilitated by hypermethylation of the promoter region compared to mutations gene silencing is found to be more frequently facilitated by hypermethylation of the promoter region compared to mutations. Many studies focusing on different hypermethylated genes in different types of cancers propose the main part of the carcinogenesis. At present, more than 100 genes have been detected for their deregulations, and how to control their expressions will possibly become novel avenues through which newer therapeutic strategies might be developed for the medication of metastatic castration-resistant prostate cancer. Several types of miRNA play a crucial role in prostate cancer, for example, miRNA-488, miRNA -221 and miRNA-222. Additionally, the role of miRNAs in prostate cancer progression is summarized in Table 2.

1.9. The role of histone modification in prostate cancer

Histone modifications play a critical role in both normal and cancer cells, becoming an orchestrating key of physiological and pathological processes. In prostate cell lines, methylation of lysine 9 in histone 3 (H3K9) is associated with histone H3K4 methylation, and repression of androgen receptor (AR) genes is linked to AR gene activation in castration-resistant prostate cancer (CRPC) cell lines and tissues. H3K4 is significantly methylated at the androgen receptor enhancer of the proto-oncogene (ubiquitin-conjugating enzyme E2C) UBE2C gene in CRPC, which cause androgen receptor binding and expression of UBE2C mRNA. Heat shock protein 90 has also been found to play a critical role in androgen-induced and -independent nuclear localization and activation of AR. Histone deacetylase 6 (HDAC6) regulates AR hypersensitivity and nuclear localization, mainly through modulating Tumor Necrosis Factor Receptor-Associated Protein-1 (TRAP1) acetylation.

1.10. The role of MicroRNAs in prostate cancer

The miRNAs are small, noncoding molecules of RNAs consisting of 18–22 nucleotides, and bind to the 3’ untranslated region of mRNAs. They play critical roles in post-transcriptional degradation or inhibition of target mRNA, depending on the level of complementary base pairing. Thus, miRNAs play a vital role in the regulation of many cell and tissue functions, including cell differentiation, development, metabolism and cell cycle. Aberrant expression of miRNAs is found to have critical impact on a variety of biological processes such as infection and cancer development.

The role of miRNAs in cellular differentiation, growth, and apoptosis of cancer cells via their targeting mRNA has been previously reported. MiRNAs may be tumor suppressors or oncogenic molecules. With tumor suppressors being downregulated and oncogenic molecules being upregulated in cancers. Commonly, the roles of miRNAs in the cancer has been emphasized by the fact that approximately 50% of all miRNA genes are located in the so called ‘fragile sites’, the cancer associated genomic regions that are frequently altered in cancer. A bulk of data has already been documented about aberrant expression of miRNAs in the cancers. However, an understanding of the functional consequences of these abnormalities has not been molecularly developed.

The role of miRNAs in prostate cancer is getting clearer by understanding the interactions between miRNAs and their targeted mRNAs and the consequential impact on carcinogenesis of the prostate cancer. It has been found that miRNAs and their targeted mRNA are aberrantly expressed in prostate cancers which, in turn, change the cellular invasion, growth, and metastatic potential of prostate cancer cells. The deregulation of certain miRNAs expressions are now considered crucial biomarkers for the classification, prognosis and diagnosis of prostate cancer. All of the above-mentioned data highlight the significance of the biology of miRNAs in prostate cancer. Their specific deregulations, and how to control their expressions will possibly become novel avenues through which newer therapeutic strategies might be developed for the medication of metastatic castration-resistant prostate cancer. Several types of miRNA play a crucial role in prostate cancer, for example, miRNA-488, miRNA -221 and miRNA-222. Additionally, the role of miRNAs in prostate cancer progression is summarized in Table 2.

1.11. Bladder cancer

Bladder cancer is one of the most widely dispersed cancers and is the seventh most common cancer in the world. Cigarette-smoking, exposure to chemicals (for example aromatic amines), bladder inflammation, genetic factors, and age are risk factors associated with the development of bladder tumor. In the United States, over 90% of bladder cancers are diagnosed as urothelial carcinoma, 2% as adenocarcinomas and 5% as squamous-cell carcinoma. In tropical countries, where chronic urinary infection caused by Schistosoma haematobium is widespread, the majority of bladder cancers are squamous-cell carcinoma.

At present, a number of histone modifications and the aberrant expression of miRNAs have been associated with tumorigenesis and have also been identified as strong biomarkers for cancer of the
Table 2

The role of miRNAs in prostate cancer progression.

<table>
<thead>
<tr>
<th>Type of miRNA</th>
<th>Role in prostate cancer</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-15a and miR-16</td>
<td>Tumor suppressors</td>
<td>Inhibit cell proliferation, invasion and angiogenesis via regulation of multiple mRNA targets</td>
</tr>
<tr>
<td>miR-21</td>
<td>Onco-miRNA</td>
<td>Increases tumor growth, invasion and metastasis</td>
</tr>
<tr>
<td>miR-125b</td>
<td>Onco-miRNA</td>
<td>Inhibits apoptosis and increases cell proliferation</td>
</tr>
<tr>
<td>miR-143</td>
<td>Tumor suppressor</td>
<td>Inhibits cell proliferation and migration by regulating KRAS, MAPK pathways and cell cycle. Also inhibits metastasis</td>
</tr>
<tr>
<td>miR-145</td>
<td>Tumor suppressor</td>
<td>Inhibits migration, invasion and metastasis</td>
</tr>
<tr>
<td>miR-200 s</td>
<td>Tumor suppressor</td>
<td>Inhibits cell migration and invasion by reversing EMT</td>
</tr>
<tr>
<td>miR-221</td>
<td>Onco-miRNA</td>
<td>Stimulates cell growth and influences cell cycle progression</td>
</tr>
<tr>
<td>miR-222</td>
<td>Onco miRNA</td>
<td>Increased cell cycle progression</td>
</tr>
<tr>
<td>miR-488</td>
<td>Onco-miRNA</td>
<td>Increased cell cycle progression</td>
</tr>
</tbody>
</table>

Table 3

Hypermethylation of genes with clinical significance in the development and progression of bladder cancer.

<table>
<thead>
<tr>
<th>Full name of gene</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC, ALX4, APBA1, BRCA1, CFC1, CDH13, HPSE, MTTA1, RASSF1A, RPRM and SALL3</td>
<td>[184]</td>
</tr>
<tr>
<td>APC, GSTP1 and RARRES1</td>
<td>[185]</td>
</tr>
<tr>
<td>GDF15, TMEFF2, VIM</td>
<td>[179]</td>
</tr>
<tr>
<td>APC, CDH1, RASSF1A</td>
<td>[186]</td>
</tr>
<tr>
<td>DKK3, SFRP1, SFRP2, SFRP4, SFRP5, WIF1</td>
<td>[187]</td>
</tr>
<tr>
<td>APC, ARF, CDKN2A, CDH1, GSTP1, MGMT, RARB, RASSF1A and TIMP3</td>
<td>[188]</td>
</tr>
<tr>
<td>BCL2, DAPK1 and TERT</td>
<td>[189]</td>
</tr>
<tr>
<td>APC, CDKN2A and RASSF1A</td>
<td>[190]</td>
</tr>
<tr>
<td>CDKN2A, CDH1, DAPK1 and RARB</td>
<td>[191]</td>
</tr>
<tr>
<td>NID2 and TWIST1</td>
<td>[192]</td>
</tr>
<tr>
<td>RARB</td>
<td>[193]</td>
</tr>
<tr>
<td>RUNX3</td>
<td>[194]</td>
</tr>
<tr>
<td>RASSF1A</td>
<td>[195]</td>
</tr>
<tr>
<td>A2B1, C10, DBC1, MYO3A, NPTX2, NKK6-2, and PENK, SOX11</td>
<td>[196]</td>
</tr>
<tr>
<td>APC, CDH1, CDH13, DAPK, FHT, GSTP1, MGMT, SSF1A, RARβ and p16INK4A</td>
<td>[197]</td>
</tr>
<tr>
<td>APC, BCL2, CDKN2A, CDH13, DAPK, OPCML, RASSF1A and TIMP3</td>
<td>[189,197-199]</td>
</tr>
<tr>
<td>DAPK1, H19 and TIMP3</td>
<td>[190]</td>
</tr>
</tbody>
</table>

DNA methylation plays a critical role during germ cell development. These epigenetic modifications rely on DNA methyltransferases (DNMTs); among these enzymes, the expression profiles of DNMT3a and DNMT3b propose that they may function during embryonic germ cell development for the organization of de novo DNA methylation. On the other hand, DNMT1 and DNMT3b are found to apparently increase following the birth in male. Thus, it is assumed that these two enzymes may be implicated in the maintenance of DNA methylation patterns in the proliferation of spermatogonia.

1.14. Epigenetic modification in testicular cancer

The major role of epigenetic modifications has been reported to be in carcinogenesis. Certainly, it has been found that DNA methylation is linked with repression of the expression of the tumor suppressor gene. This epigenetic alteration is one of the most frequently studied in the cancer research field, and has been documented as a major mechanism during testicular cancer progression. The DNA methylation patterns seem to be associated with histological characteristics of the different types of testicular cancer. Dnmt1 was not expressed in seminoma; however, it was over expressed in embryonic carcinoma. In contrast, the expression of Dnmt3a was found to be over expressed in testicular cancer compared to non-tumor testicular tissues. The pattern of Dnmt3b expression has been extensively studied, and demonstrated that it could be used as a prognostic biomarker for relapse of stage I seminomas. Additionally, it was further observed that Dnmt3l was upregulated in the non-seminoma tumors.

1.16. Histone modifications

The most important role of histone acetylation during the spermatogenesis is the histone H4 hyperacetylation during spermiogenesis. This process seems to play a critical role for genuine sterility problem which affects men throughout their reproductive period. Interestingly, the development of testicular cancer is associated with urogenital disorders. Testicular cancer development also has been linked to hypospadias, cryptorchidism and low fertility. In fact, epidemiological studies dispute whether there is an increased risk of testicular germ cell tumor in males who experience fertility troubles.
subtraction of histones and their replacement via protamines, which is a fundamental characteristic for nucleus condensation and consequently formation of spermatozoa. There are several members divided in different subfamilies. Interestingly, choriocarcinomas displayed a commonly high expression for all three classes I of HDAC isozymes. In contrast with other types of cancers, no diagnostic or predictive values for HDAC1–3 in testicular cancer could be inferred.

1.17. Imprinting genes in testicular cancer

Genomic imprinting is one of the epigenetic mechanisms that induces functional differences between maternal and paternal genomes, and plays a crucial role in mammalian embryonic development. The differential methylation of CpG islands in critical regions of imprinted genes is the mechanism of the imprinting progression that differentiates maternal and paternal alleles. Maternally expressed H19 is one of the most well-characterized imprinted genes. Expressions of imprinted genes, for instance H19, in the germ line become biallelic at day 11.5 during embryonic development.

The 5′-region of H19 is usually methylated on the paternal allele in human genomes. It has been shown that fetal spermatogonia are mainly unmethylated at the differentially methylated CpG regions of H19, while adult testicular germ cells show significant methylation at the same CpG regions. These phenomena are considered to be “DNA reprogramming”, which are seen in genome-wide survey of germ cells or pre-implantation embryos. It has also been determined that complete epigenetic reprogramming occurs within 1 day of the embryonic developmental period in mouse primordial germ cells after reaching the genital crest. In addition, loss of allele-specific imprinted gene methylation has also been seen in both male and female primordial mouse germ cells. These data support the notion that pre-existing imprints are erased in the germ line by this stage.

2. Conclusion and future directions

Cancer epigenetics offer scientists hope to understand the complexity of interactions from the genetic code to eventual cellular fate. Since the number of known genes that undergo aberrant epigenetic deactivation linked with male urogenital organs cancers is growing, a number of questions need to be answered before we completely understand the biologic implication and outcome of this process. For instance, what is the mechanism deriving selective methylation of genes in male urogenital organs cancers which increases the activity and expression of DNMTs. Why do hypermethylation and hypomethylation occur in male urogenital organs cancer cells? Is there an active demethylating process that can explain hypomethylation, or is it caused by reduced hypermethylation?

Scientific evidence suggests that the detection of DNA methylation can serve as a promising cancer biomarker. In males some genes shows adequate sensitivity and specificity in the detection of cancers to guarantee further testing as a cancer biomarker in patients’ body fluids for example urine, serum, and semen. Further work is required to focus on the identification of novel aberrantly methylated genes via high-throughput screening techniques such as CpG island microarray assays as the gateway toward cancer biomarker confirmation. Moreover, the methylation fingerprint comprises several genes and may be more precise than that of individual genes in the early diagnosis and risk measurement of male urogenital organs cancers and molecular detection of resected specimens.

Before the causes and consequences of global hypomethylation in male urogenital organs cancers have been fully identified, the therapeutics targeting DNMTs in cancer should be used with care and discretion. Ideally, therapeutic treatment would involve selective triggering of a set of methylated genes without unwanted demethylating to the rest of the genome. Given the close relationship between DNA methylation and histone deacetylation in epigenetic deactivation, a combination of both DNMT inhibitors and histone deacetylation inhibitors may be an effective strategy for the treatment of female cancer patients.

Conflict of interest

The authors state there are no conflicts of interests.

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