The importance of clinical application of molecular biomarkers in bladder cancer detection

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ABSTRACT
It is known that high throughput technologies facilitate the identification of new molecular targets and biomarkers specific for bladder cancer. The new field of molecular medicine promises that clinical outcomes will be improved by directing therapy toward the molecular mechanisms and targets associated with the growth of the patient’s tumor. The great challenge remains to improve the measurement of these targets and to translate this wealth of discovery into clinical management of bladder cancer.

Key words: bladder cancer, biomarkers, tumor suppressor genes, DNA methylation

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INTRODUCTION

Research made over the last decade including the descriptive and mechanistic molecular studies of bladder cancer has brought great insights into the biology of this type of cancer and is starting to shape clinical practice. This fact has been possible because of the technologies such as high-throughput transcript profiling, microarrays, and proteomics that have facilitated the identification and understanding of the molecular pathways and targets that are active in bladder cancer.

Bladder cancer is the most expensive cancer to manage one of diagnosis to death from any cause (1), mainly because bladder cancer also is one of the most recurrent cancers, with some studies showing over half of patients will recur within 5 years (2). The most widely held etiologic hypothesis is that superficial bladder cancer arises from mutations in fibroblastic growth factor 2 receptor and Ras signaling, whereas the aggressive track has been thought to arise from mutations in the p53 and Rb signaling system. Even though over 75% of bladder cancers are superficial at initial diagnosis, the problem of recurrence is particularly insidious because some 15 to 25% of patients progress to aggressive invasive disease (3) that may be responsible for half the deaths from bladder cancer. Poor patient compliance with cystoscopic monitoring begs for noninvasive biomarkers with sensitivity near 95%. Anything less than 95% sensitivity is asking patients to bet their lives on a test with worse sensitivity than the routine “gold standard” of cystoscopy.

Bladder cancer is the fourth most common male cancer in the Western world. The most common symptom of bladder cancer is hematuria. However, hematuria often appears late in individuals with bladder cancer, and the majority of individuals with hematuria do not have bladder cancer. Tumor suppressor genes encode proteins with a protective role against malignant phenotypes. Their inactivation, due to chromosomal alterations, can lead to initiation and progres-
sion of carcinogenesis. With the help of new investigational techniques such as microsatellite analysis and fluorescent in situ hybridization (FISH), chromosomal alterations have been identified, mainly deletions of chromosome 9, 13, 17 in patients with bladder cancer. Tumor suppressor genes that have been found inactivated in bladder carcinomas include p53 (9), Rb (10) and MTS1 (11).

2. Cell-cycle regulatory proteins

It is well known that cell cycle is a strictly controlled process regulated by protein complexes composed of cyclins and cyclin-dependent kinases (cdks) and also by several tumor suppressor gene protein products acting at the Go/G1 checkpoint of the cell-cycle (12). Some of these protein products are p53, pRb, p16, and p14. Their role is the regulation of normal cell growth and consequentially normal cell death (apoptosis). Inactivation of one or more tumor-suppressor genes and/or loss of cell cycle control lead to inadequate phosphorylation of key proteins, which represents the first step of carcinogenesis. The inactivation of a gene occurs by different mechanisms such as mutation, deletion or methylation (13, 14).

3. Telomerase

Telomeres are structures with short repetitive sequences at the ends of a chromosome, and once reattached from the chromosome, they cannot broken. The telomeric sequence can be reattached via an enzyme named telomerase. Although cells from normal tissue show almost no activity of this enzyme, cancer cells show high activity leading to the consequence of maintaining the telomere length and furthering cell immortality (15). In every division chromosomes lose 50-200 nucleotides from their telomeric structure until they acquire a standard length and continue to lead the cells to apoptosis.

4. Cell adhesion molecules

It is known that cells interact with neighbouring cells and the extracellular environment. All these interactions are mediated through adhesion molecules. The most important representatives of the adhesion molecule family are: cadherins, integrins, members of immunoglobulin superfamily, and selectins. These transmembrane glycoproteins have the role to mediate the intercellular matrix adhesion cell-cell adhesion molecules. These adhesion molecules are closely involved in the control of several cellular processes such as: differentiation, proliferation, invasion and colonization of distant organs (16). Cadherins are the most important adhesion molecules.

5. DNA methylation

Loss of tumor suppressor gene expression through methylation silencing appears to be an important malignant characteristic and has been demonstrated to be involved in more than one molecular cancer pathway (17). The cause of altered methylation is unknown but it has been demonstrated that tumors with frequent hypermethylation appear to have specific pathological and clinical phenotypes, in comparison with tumors with low levels of methylation (18).

The methylation index, which represents the number of loci affected, increases as the lesion progresses from normal to dysplastic urothelium and finally to invasive carcinoma. Recent data suggested that this fact indicates the sequential inactivation of the tumor suppressor gene and suggests a molecular mechanism for the progression of the disease.

**COMBINATION OF MOLECULAR BIOMARKERS**

Because the complexity of the molecular abnormalities associated with bladder cancer it is improbable that a single biomarker can accurately segregate tumors of similar clinico-pathologic phenotypes into distinct prognostic categories. Therefore, combinations of independent, complementary biomarkers may provide a more accurate prediction of outcome compared to a single biomarker (19, 20).

**CONCLUSION**

New molecular biology technology is being used to examine DNA (single nucleotide polymorphisms, mutation, amplification and deletions), RNA expression, and of course, proteomics. Biomarkers that are able to distinguish among urinary bladder cancer, normal urothelium and benign urothelial conditions can be used for their potential diagnostic, prognostic and therapeutic value.
REFERENCES


