Potential New Tumor Markers in Early Detection and Surveillance of Cancer Bladder

Essay

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By

Ehab Nagy Mohamed Abd El Aziz Serag El-Din
M.B.,B.CH. Ain Shams University

Supervised by

Ass. Prof. Dr. Khaled El Husseiny Nasr
Associate Professor of Clinical Oncology & Nuclear Medicine
Faculty of Medicine, Ain Shams University.

Ass. Prof. Dr. Nagy Sami Gobran
Associate Professor of Clinical Oncology & Nuclear Medicine
Faculty of Medicine, Ain Shams University.

Dr. Mohamed Yassin Mostafa
Lecturer of Clinical Oncology & Nuclear Medicine
Faculty of Medicine, Ain Shams University.

Faculty of Medicine
Ain Shams University
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Ehab Nagy Serag El-Din

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List of Abbreviations

Abb.	Meaning
TCC	Transitional cell carcinoma
SCC	Squamous cell carcinoma
WHO	World health organization
2-DE	2-dimensional gel electrophoresis
MS	Mass spectrometry
ELISA	Enzyme-linked immunosorbent assay
PENK	Proenkephalin
FDA	Food and drug administration
GAG	Glycosaminoglycan layer
CIS	Carcinoma in situ
THMs	Trihalomethanes
IARC	International agency for research on cancer
IVP	Intravenous pyelography
UCB	Urothelial carcinoma of the bladder
BTA stat	Bladder tumor-associated analytes stat
BTA TRAK	Bladder tumor-associated analytes TRAK.
NMP22	Nuclear matrix protein 22
Urinary UBC	Urinary bladder cancer antigen
BLCA-1	Bladder cancer protein 1
BLCA-4	Bladder cancer protein 4
CYP1A2	Cytochrome p450 1A2.
NAT2	N-acetyltransferase 2
GSTM1	Glutathione S-transferase M1
NNCs	N-nitroso compounds
Rb	Retinoblastoma
CDKN2	Cyclin-dependent kinase inhibitor 2A
c-erb-B2	Proto-oncogene c-*erb*-B2
EGFR	Epidermal growth factor receptor
FGFR3	Fibroblast growth factor receptor 3

Abb.	Meaning
HRAS	Harvey rat sarcoma viral oncogene homolog.
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
p16	Biomineralization protein SpP16
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
CPG	Cytosine guanine bonds in DNA
RUNX3	Runt-related transcription factor 3
RASSF1A	Ras association(RalGDS/AF-6)domain family member 1
DAPK	Death-associated protein kinase
RARß	Retinoic Acid Receptor beta
MYO3A	Myosin IIIA
CA10	Carbonic anhydrase 10 protien coding gene
NKX6-2	NK6 homeobox 2
DBC1	Deleted in bladder cancer 1
SOX11	SRY-box containing gene 11
CDH1	Cadherin-1 gene\ E-cadherin gene
CDH13	Cadherin 13 gene
FHIT	Fragile histidine triad gene
APC	Adenomatous polyposis coli gene
P14	Alternating reading frame tumor suppressor gene
BCL2	B-cell lymphocyte gene
TERT	Telomerase reverse transcriptase gene
CDKN2A	Cyclin dependant kinas inhibitor 2A gene
MGMT	o-6-methyl guanine DNA methyl transferase gene
GSTP1	Glutathione s-transferase pi-1 gene
CGH1	Caenorhabditis elegans gene

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Introduction

Bladder cancer is diagnosed in approximately 275,000 people each year all over the world, and about 108,000 die of this disease. In industrialized countries, 90% of bladder cancers are transitional cell carcinoma (TCC). In developing countries particularly in the Middle East and Africa the majority of bladder cancers are squamous cell carcinoma (SCC)**,** but now days in developing countries most of the patients are transitional cell carcinoma because of the industrial revolution ***(American Cancer Society, 2012).***

The world health organization (WHO) classifies bladder cancers as low grade (grades 1 and 2) or high grade (grade 3). Tumors are also classified by growth patterns: papillary (70%), sessile or mixed (20%), and nodular (10%). And also pathology classification: transitional cell carcinoma, squamous cell carcinoma, and adenocarcinoma ***(National Comprehensive Cancer Network, 2012).***

Approximately 80-90% of patients with bladder cancer present with painless gross hematuria. Irritative bladder symptoms such as dysuria, urgency, or frequency of urination occur in 20-30% of patients with bladder cancer. Patients presenting with unexplained or refractory

irritative symptoms should be considered for cystoscopy and urine cytology ***(Bladder Estimated incidence, all ages: both sexes". GLOBOCAN 2010).***

The gold standard for diagnosing bladder cancer is biopsy obtained during cystoscopy. Sometimes it is an incidental finding during cystoscopy. Urine cytology can be obtained in voided urine or at the time of the cystoscopy ("bladder washing"). Cytology is very sensitive (a positive result is highly indicative of bladder cancer) but suffers from low specificity (inability of a negative result to reliably exclude bladder cancer) ***(Walid et al., 2010).***

Understanding of the molecular mechanisms involved in carcinogenesis and cancer progression has identified a large number of molecular markers of bladder cancer, each of which has a potential diagnostic and prognostic value. Cystoscopy is the mainstay for diagnosing bladder cancer, but it is associated with a high cost and patient discomfort. Cytology and many urine-based tumor markers give us marginal information for detecting and predicting the prognosis of bladder cancer. Numerous factors, including chromosomal markers, genetic polymorphisms, and genetic and epigenetic alterations may be involved in tumorigenesis, progression and the patient's survival ***(Dyrskjot, 2011).***

Bladder cancer tumor markers remain a rapidly evolving field. Newer technologies including proteomic markers, gene-expression profiling and epigenetic markers are now in the field evolving and can be used in early detection of cancer bladder and surveillance of recurrences ***(Choi et al., 2010).***

Proteomics refers to the study of proteins, including structure and function using technologies such as, high resolution 2-dimensional gel electrophoresis (2-DE) and mass spectrometry (MS) in urine specimen. nuclear matrix protein 22(NMP22) are the best example that bladder cancer markers can be identified initially through 2-DE and then developed into conventional Enzyme-linked immunosorbent assay (ELISA) tests, other proteomics which is Food and Drug Administration (FDA) approved like bladder tumor-associated analytes stat (BTA stat), bladder tumor-associated analytes TRAK (BTA TRAK), ImmunoCyt, nuclear matrix protein-BladderChek (NMP BladderChek), UroVysion, others under investigations like Telomerase, Survivin ***(Guo et al., 2011).***

Genomic refers to the study of DNA or RNA sequences and gene expression differences between tissues resulting in signature expressions for specific cancer types Using technologies such as gene microarray technology,

tissue microarrays, microRNA profiling, In urothelial tumors somatic mutations in the Fibroblast growth factor receptor 3 (FGFR3), Harvey rat sarcoma viral oncogene homolog (HRAS), Neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS), and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) genes may be of use for early detection of primary and recurrent tumors,for prognosis prediction, and as a companion diagnostic for targeted therapies ***(Hurst et al., 2009).***

Epigenetics is a field that has co-evolved with genomics and proteomics and refers to reversible changes in gene function that occur without any change in genetic sequence. The most common epigenetic changes investigated in bladder tumor markers relate to DNA methylation such as: E-cadherin, p16, p14, Ras association (RalGDS/AF-6) domain family member 1 (RASSF1A), myosin IIIA (MYO3A), Transcription factor SOX11 (SOX11), NK6 homeobox 2 (NKX6-2), proenkephalin (PENK), and deleted in bladder cancer 1(DBC1) ***(Lokeshwar et al., 2011).***

Bladder cancer is a major problem all over the world, many people die yearly from this disease, so it's a large health issues must solved, early diagnosis in high risk patients, will increase the survival and help in success of

the treatment plan, the new era in diagnosis of bladder cancer and surveillance of recurrences is not the invasive maneuvers ***(Bladder Cancer Clinical Guideline Update Panel, 2012).***

Aim of the Work

Routine cystoscopy and biopsy is the gold standard for diagnosis but it's expensive, and sometimes patient discomfort is found. New available urine based biomarkers which is FDA approved is available today that help in early diagnosis, surveillance, and early detection of recurrence, in near future will help to find a target therapy in bladder cancer, also these biomarkers is not expensive, and get patient compliance.

Anatomy, Histology and Pathology of the Bladder

Anatomy of the bladder:

The anatomy of the bladder forms an extraperitoneal muscular urine reservoir that lies behind the pubic symphysis in the pelvis. A normal bladder functions through a complex coordination of musculoskeletal, neurologic, and psychological functions that allow filling and emptying of the bladder contents. The prime effector of continence is the synergic relaxation of detrusor muscles and contraction of the bladder neck and pelvic floor muscles. The normal adult bladder accommodates 300-600 mL of urine; a central nervous system (CNS) response is usually triggered when the volume reaches 400 mL. However, urination can be prevented by cortical suppression of the peripheral nervous system or by voluntary contraction of the external urethral sphincter ***(Kingsnorth et al., 2000).***

Compounds of the bladder:

Bladder wall and bladder neck:

The bladder wall is made up of muscle fibers extending in all directions. This configuration is well suited