Review

The Mechanisms Of Urothelial Carcinogenesis: A Literature Review

A.E.STEPAN[(1)], CORINA MARIA DOCHIȚ[(2)], C. ALBITA[(3)], CRISTIANA SIMIONESCU[(1)]

[(1)] Department of Pathology, University of Medicine and Pharmacy of Craiova; [(2)] PhD candidate, Pathology Laboratory, Craiova Emergency County Hospital; [(3)] PhD candidate, The Department of Legal Medicine, UMP Craiova

ABSTRACT The present direction of research activities in bladder cancer case is that to find practical applications of biomarkers utility. Urothelial carcinogenesis represents a complex process which implicates a lot of abnormal biomechanisms, like proliferation, angiogenesis, lymphangiogenesis, apoptosis, loss of the cellular phenotype, extracellular matrix alteration. Every of them can be investigated starting from histopathological features and finishing with biomolecular analysis.

KEY WORDS *Urothelial carcinogenesis*

Introduction

Urothelial carcinomas of the urinary bladder represent an unique model for study by endoscopic accessibility, concerning their prognostic and reccurence. The concomitant presence of precursor and invasive urothelial lesions reflects a multistage proces deployment, with implication of tumoral genes and oncogenes and having as result phenotypic and genotypic carcinogenesis-associated alterations.

The dual pathogenic way represent a concept which was proposed for urothelial carcinogenesis, recking on the histopathological and biomolecular lesions analysis. This concept postulate that in urinary bladder case the cancer can arise on two different pathogenic ways, having as results papillary and non-papillary (flat) malignant tumors (3, 17).

Histopathological proves for the dual pathogenesis of carcinogenic process

The majority of bladder tumors are superficial, exophytic, papillary tumours that are well differentiated and do not penetrate the epithelial basement membrane at the diagnosis moment. Such tumours are described as stage Ta. Histopathological observation suggests that these arise from the normal urothelium via hyperplasia and the development of a branching vasculature. Also, these tumors are not usually associated with the high-grade lesion carcinoma in situ, which is considedered a high risk lesions (9, 12, 13). These tumors relapse frequently, are often multifocal but progression to muscle invasion is not common and when it appear, it is about old pacients with relapses and initially has papillary growth pattern (9).

Muscle invasive tumours are usually diagnosed in patients with no previous history of papillary tumours. These may penetrate muscle and extend beyond the bladder wall or into adjacent structures. Commonly the tumour epithelium is poorly differentiated

and such tumours are often associated with CIS in peritumoral areas, which is believed to represent the precursor lesion (12). Tumours that have penetrated the basement membrane but are not invading muscle (T1) are considered superficially, but in many cases these are porly differentiated and can have more genetic alterations then the tumors which invaded muscularis propria (11,12).

The actual suppositions are that the two tumoral groups are distinctive and the carcinomas which are diagnosed like non-invasive not evolve ever on invasive ones, or its possible some papillary non-invasive lesions to change their behavior, becoming more aggressive and more invasive.

Between these tumoral groups, with different histopathological features and different prognosis, can find Ta stage, poorly differentiated carcinomas, which arise usually on dysplastic lesions, growing anywhere at bladder urothelium level. The biological behavior of these tumors is usually an aggessive one, presenting a lot of genetic alterations.

Some studies indicated that it is possible that the papillary high-grade urothelial carcinomas to develop on atypical ot dysplastic epithelial lesions, like in carcinoma in situ case, but accompanied by hyperplasia development which finally will give an papillary architecture in lesion (11, 19).

Genetic and biomoleculare proves for the dual pathogenesis of carcinogenic process

Molecular and genetic events which appears in urothelial carcinomas of the urinary bladder development and evolution can be classified in three principal categories, every of them being interconnected with the others:

- chromosomal alterations which initiate cancerous process,
- loss of cell cycle regulation accounting for cellular proliferation and
- progression and metastasis (which included another complex mechanisms like angiogenesis, lymphangiogenesis, apoptosis, loss of the cellular phenotype, extracellular matrix alteration) (18).

Deletions on chromosome 9 are the most common chromosomal abnormalities in urothelial carcinomas and are found in >50% of all grades and stages of these lesions. It is becoming clear that most muscle invasive bladder tumors have supplementary chromosomal alterations while the most superficially ones only show few additionally genetic alterations, being described hypothetis that the chromosomal 9 modifications represent an initial event in the development of urothelial carcinoma (6, 16). The majority of deletions on chromosome 9 have been found on the short arm, in a complex genomic region which encodes three distinct proteins: p16, p14 and p15- all of them acts as negative cell cycle regulators (8).

Two other very important chromosomal alterations that appear in urothelial carcinomas involve 17 chromosome. The inactivation of CDKN2A locus (the inhibitor of cyclin-dependent kinase 2A) play an important role in the development of carcinomas, because the implications of two supresor tumoral genes: p53 and pRb (retinoblastoma gene) (1). The well and moderatly differentiated pTa tumors presents few molecular alterations like EGFR3 mutations (epidermal growth factor receptor 3) which is the most frequent (2).

One of the carcinogenesis proposed models is that the chromosome 9 primary alteration, followed by p53 gene mutations in advanced stages (7). Another studies showed that the p53 mutations in carcinoma in situ cases appear more early (10).

The need to predict which superficial tumors will recur or progress, and which invasive tumors will metastasize has led to a much better understanding of the molecular pathways associated with bladder cancer (18). Some supresor tumoral genes (p53, Rb, p16, p14) plays an important role on G0/G1 checkpoint of the cell cycle and their proteins are essentials for the cell czrcle progression (18).

Inactivation of one or more tumoral supresor genes and loss of cell cycle control appear to be early steps in the development of carcinogenesis and ultimately cancer progression (18). The cellular proliferation represent an important oncogenic biological mechanism being investigated with biomarkers like PCNA (Proliferating Cell Nuclear Antigen) and Ki67 which can offer us a direct relationship with progression, agressivity and prognosis of urothelial bladder carcinomas.

Most tumors in humans persist for a certain period of time without neovascularization until a subset of neoplastic cells acquires an angiogenic phenotype. The switch to the angiogenic phenotype involves overexpression of angiogenic factors by tumor cells (4). Angiogenesis can be quantified by using intra- and peritumoral microvessel density, with neoformation endothelial cells and imature vessels which are immunohistochemical stained.

The neoplastic progression and metastatic moment can been appreciated by lymphangiogenesis investigation. This process can be analysed using vasculo-endothelial growth factors like VEGF-C, VEGF-D, and their receptors (VEGFR3), which are associated with lymph nodes metastasis risc (15).

The tumoral growth rate is based on neoplastic cells proliferation and number of the death apoptotic cells (14). The alteration of biomoleculare mechanisms which controls bladder urothelium apoptosis can induce the survival of genetic abnormal cells, tumorigenesis and resistance to anticancer therapy. Low levels of the apoptotic factors (FAS) and their receptors (FASL) were associated with increase of urinary bladder tumor agresivity (20).

Urothelial carcinomas evolution can determine the loss of cellular fenotype, which is the result of cytokeratins and adhesion molecules alteration. In this cases are investigated CK20, CK7, 35betaE2 and cadherins.

One of the principal condition for metastasis appear is represented by the tumor stromal invasion. Matrix metalloproteinases MMP2 and MMP9 are implicated in extracellular matrix degradation and their expression is associated with tumor agresivity (5).

At this moment are studied the implication in tumoral urothelial carcinogenesis of some biomolecules like p63, p73, uroplakin, which can

become important biomarkers for tumoral progression investigation.

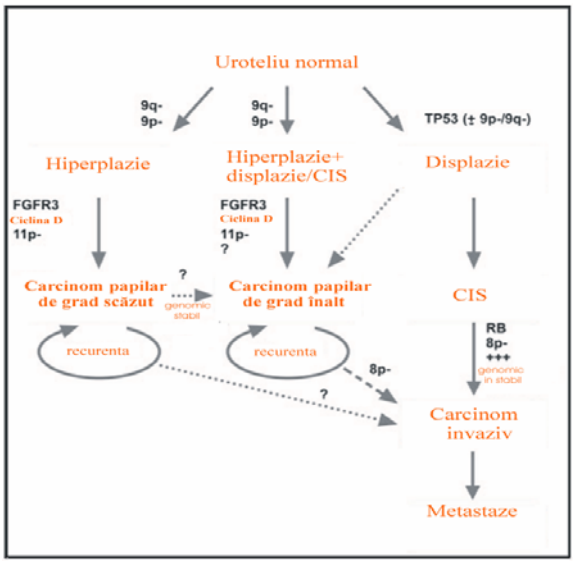

Figure 1: Potential pathways of urothelial tumorigenesis (after Margaret A.Knowles, Molecular subtypes of bladder cancer: Jekyll and Hyde or chalk and cheese?, 2006, Carcinogenesis)

Urothelial carcinogenesis knowledge importance

The information accumulated in the last few years on the molecular changes associated with papillary and invasive bladder tumors allows a more accurate and more practical molecular classification of them. This information may help in the prediction of patient outcome and also in the selection of treatment. Bladder cancer is one of the tumors in which molecular studies may become part of standard clinical practic

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Correspondence Adress: Assist Prof. A.E.Stepan MD, PhD StudentDepartment of Pathology, University of Medicine and Pharmacy of Craiova; Str Petru Rares nr. 4, 200456, Craiova, Dolj, România: mail astepan76@yahoo.com