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UROLOGICAL ONCOLOGY

Genetic polymorphism intermingled with environmental factors substantially contributes to the bladder cancer progression

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Bladder cancer is a common issue in urological practice. The tumor originates in urothelium – an internal epithelial lining of urinary bladder. Hence, the urothelium is exposed to numerous pathogens excreted in urine, natural as well as synthetic compounds such as: bacteria, viruses, hormones, drug metabolites, salts, and xenobiotic toxins (aromatic amines, polycyclic aromatic hydrocarbons, other environmental toxins etc.) – a real waste–pipe of the human body. All compounds may cause DNA structural changes. Intense biochemical processes, cell proliferation and turnover together with escalated tissue repair may increase the risk of DNA transcription errors.

Thus, bladder carcinogenesis is influenced by a medley of genetic and environmental interactions. The distorted expression of different genes and the simultaneous presence of numerous toxins in many cancer tissues has been presented by many authors before.

The current issue of CEJU carries a noteworthy paper from the Medical University of Łódź published on page 14.

The research topic directly touches up the interrelations of gene variants/mutations and environmental/infectious stimuli as causative factors of bladder carcinoma. This problem is attracting a good deal of attention in present–day oncological investigations. It should capture our attention as well.

Doctor Banaszkiewicz and co–workers' study demonstrates a correlation between CHEK2 and CYP1B1 polymorphisms, HPV infestation, tumor grade, and increased risk of progression to bladder carcinoma. This compelling issue deserves some words of comment.

The CHECK2 gene product is a protein kinase that controls cell cycle and regulates BRCA1 and the p53 protein through their phosphorylation in response to DNA structural damage [1,2]. Its correct function induces cell–cycle arrest at G1 and thereby stops proliferation of cells with putative ominous fate. So, it belongs to the tumor suppressor genes. Structural changes of the CHECK2 gene may lead to the creation of malfunctioning/inactive kinases that are unable to block incorrect pathways. Such mutations have been proven in rare hereditary tumors and in an array of widespread cancers: tumors of breast, lung, thyroid gland, and ovary, as well as lymphomas. Some evidence links this phenomenon with prostate carcinoma [1]. Next, cytochrome P450 1B1 (CYP1B1) polymorphisms may have a remarkable deleterious effect on cellular "milieu intérieur". This protein, coded by the CYP1B1 gene is a member of the cytochrome P450 enzyme family and plays a crucial role in manifold biochemical processes, xenobiotic and hormone transformations, and carcinogen biotransformations and detoxifications among other things. In some fatal circumstances, normal CYP1B1 may activate inactive procarcinogens [3]. Even tiny structural changes in the CYP1B1 gene may result in a significantly distorted function of the CYP1B1 protein (as was clearly presented by the authors) [3, 4].

Activated estrogens and other metabolites of sex hormones created by the regular action (hydroxylation) of CYP1B1 may be detrimental to DNA stability and function. The hyper–activated enzyme produces these metabolites in excess, thus such alteration in CYP1B1 plays a role as a "starter" in carcinogenesis. Excessively active polymorphic variants of CYP1B1 were demonstrated in numerous tumors (lungs, prostate, ovary, breast etc.) [3, 5].

Different reactive environmental carcinogens are strongly related to bladder cancer. Particularly tobacco inorganic compounds, synthetic aromatic toxins, and environmental pollutants (pesticides with estrogen–like activity, ubiquitous bisphenol A etc.) are involved with increased risk of development of an array of cancers (lungs, urinary bladder etc.). Insufficient carcinogen deactivation or lack of it in consequence of altered function of CYP1B1 due to CYP1B1 gene modifications (polymorphisms, hypermethylation etc.) have been noted in many cancers [4, 6].

Such changes were found by the authors in bladder cancer tissues (355T/T polymorphism of CYP1B1). Similar observations were published by other researchers (polymorphisms Ala119Ser and Leu-

432Val) [3]. One should note that some previously published papers did not confirm the role of CYP1B1 polymorphisms in bladder cancer development [7].

HPV infestation is another example of the putative role of environmental factors in bladder cancer development. The harmful effect of HPV proteins (E6, E7 oncoproteins) on the cell cycle is presented in the discussed article. Yet, scientific data are inconclusive, even conflicting. Some authors found an association of high–risk HPV's with bladder cancer but others firmly denied such coexistence [8, 9]. However, HPV contamination with so called high–risk HPV types (16 and 18) as a possible risk factor has been suggested for tumors of the cervix, vulva, head and neck, anus, and breast [8]. Doctor Banaszkiewicz and co–workers found that "…oncogenic HPV types are observed with a higher, statistically significant prevalence in neoplastic tissue of urinary bladder carcinoma". Moreover, after analysis of their own material, the authors concluded that CHEK2 mutations, the 355T/T CYP1B1 polymorphism, and the presence of high–risk HPV types significantly correlate with malignancy grade in bladder carcinoma.

The data obtained by the authors and their explanations gracefully illustrate the issue of correlations between impaired gene function, cell cycle disturbance, and superimposing of external, environmental factors. The authors should be congratulated for this.

I would like to draw readers' attention to the fact that this paper has one weakness, in my personal opinion raising a reservation: the authors did not disclose the patients' possible occupational hazards and tobacco addictions. Regardless, this excellent paper is well written and I strongly recommend this study to all colleagues.

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