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Identification of genetic and epigenetic abnormalities of chromosome 3 and gene expression changes in ovarian cancer

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Background: In ovarian cancer occupies the third place among gynecological tumors while having the highest death rate. Therefore, the establishment of genetic and epigenetic alterations in this type of cancer with the purpose of improving diagnostics, technique of treatment, and prognosis is of great importance.

Materials and methods: Human chromosome 3 is one of the most common sites of chromosomal abnormalities in human cancer. To perform the global search for genetic and epigenetic alterations (deletion, methylation of promoter, and amplification) in genes/loci from human chromosome 3 in ovarian cancer we have used a novel approach of NotI-microarrays. Then changes in selected genes have been investigated by methyl-specific PCR. Expression changes of some genes have been detected by Northern blot analysis on total RNA.

Results: Analysis of malignant and benign tumor samples from 22 patients has revealed alterations in 92 out of 181 NotI clones. The most frequent changes are hemizygous deletions/methylations. For 32 genes/loci these changes have been shown in more than 30% of tumor samples which proves high probability of involvement of these genes in ovarian cancer development. High frequency of changes in some genes with potential tumor suppressor genes among them (NKIRAS1, RARbeta1, ZIC4, etc) has been detected in other types of epithelial tumors investigated earlier. The results of NotI-microarrays for selected genes have been confirmed by methyl-specific PCR. Northern blot analysis revealed the decreased level of expression for some investigated genes (GORASP1, GNAI2) in ovarian adenocarcinomas.

Conclusions: We have detected the aberrations (hemizygous deletions/methylations) of previously unknown 16 genes/loci in the development of ovarian cancer. The further investigation will be focused on the characterization of selected genes as diagnostic and prognostic markers of ovarian tumors.

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Major risk factors for the development of muscle invasive baldder cancer in Upper Egypt

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Introduction: Globally, bladder cancer is the 4th commonest cancer in men and the 12th in women. In Egypt, where bilharziasis is endemic, it is the commonest cancer in males and the 2nd in females; the squamous cell carcinoma is the commonest type found, with a peculiar mode of presentation. The aim of this study is to identify and rank the risk factors of muscle invasive bladder cancer (MIBC) in Upper Egypt and describe its specific criteria of presentation and histopathology.

Methods: This is an analytical, hospital based, case controlled study through comparing MIBC cases (n=130) with age, sex and residence matched control group (n=260) for the presence of risk factors of MIBC. Data was collected by personal interview using a well designed questionnaire. The files of the patients were studied for histopathology and Radiologic findings.

Results: The risk factors of MIBC in Upper Egypt are positive family history [Adjusted odds ratio (AOR) =7.705], exposure to pesticides [AOR=6.244], bladder stones [AOR=4.954], consanguinity [AOR=3.855], recurrent cystitis [AOR=3.065], bilharziasis [odds ratio (OR) =5.830] and smoking [OR=5.286]. Squamous cell carcinoma represented 67.6% of cases with burning micturition being the presenting symptom in 73.8%.

Conclusion: Unlike what was commonly believed, the most important risk factors of MIBC in Upper Egypt in a descending manner are positive family history, exposure to pesticides and fertilizers, bladder stones, consanguinity, and recurrent bladder inflammation, while bilharziasis and smoking came last. Squamous cell carcinoma is still the commonest histopathologic type of MIBC in Upper Egypt, although its percentage is decreasing.

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Genomic and gene expression characterization of a novel trastuzumab-resistant breast cancer cell line

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Background: HER2-positive breast cancers are more aggressive than HER2-negative tumors and unfortunately become resistant to therapy in several cases. There are only a few experimental models that allow studying the molecular mechanism of the resistance. The aim of this study was to characterize a trastuzumab (Herceptin®) resistant human breast cancer cell line (B585) that was established from an invasive ductal breast carcinoma of a 63 year old patient. Materials and methods: The characteristic behavior of the B585 cell line is that it grows only in immunodeficient mice as a human breast cancer xenograft. Comparative genomic- and fluorescence in situ hybridizations (CGH and FISH) were used to define cytogenetic alterations, whereas gene expression analysis and immunhistochemistry were applied to detect RNA and protein expression. Results: Chromosomal CGH of the original tumor and xenograft revealed several common chromosome alterations. Using array CGH high level amplifications were detected on 50 BAC clones. Focused gene amplifications were identified on loci covering the C-MYC, EGFR, ErbBB2, CCND1 and TOP2-A oncogenes. Amplification of ErbBB2 was heterogeneous by FISH, gene copies varied between 3 - ≥10 signals/cell, chromosome 17 was mainly triploid. TOP2-A gene was co-amplified with ERBB2. Deletions were seen on 60 clones. The average centromeric copy number by FISH varied between 3 and 5 (chromosome index: 3.35). mRNA overexpression was detect ed for almost all amplified genes. Overexpression of the HER2 protein was identified on the cell surface, heterogeneous distribution of the protein expression was observed. Conclusions: In summary, molecular cytogenetic analysis as well as expression profiling of the B585 xenograft revealed several new alterations. Based on the experiments performed in SCID mice and the genotypic and phenotypic characteristics, this new in vivo trastuzumab resistant breast cancer xenograft is a valuable model to investigate molecular mechanism of trastuzumab resistance of breast cancer.

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EDUCATIONAL LECTURE

DNA repair as target for drugs

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Targeting the DNA-damage response as a therapeutic strategy

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Over the past twenty years, it has become increasingly clear that inherited or acquired defects in the detection, signalling and/or repair of DNA damage are associated with a range of human pathologies, the most notable being neurodegenerative disease, immune deficiency and cancer. Our increasing knowledge of the DNA-damage response is therefore providing new insights into the aetiology of such diseases and, moreover, is presenting opportunities for novel therapeutic strategies.

In this seminar, I will first provide an overview of how cells respond to DNA damage and how defects in such events can lead to cancer. I will then explain how our recent work has provided new molecular insights into how cells detect the most cytotoxic form of DNA damage: the DNA double-strand break (DSB). Finally, I will outline how an increasing knowledge of the DNA-damage response is providing exciting opportunities for the development of novel classes of drugs that exhibit selective cytotoxicity towards cancer cells, both in model systems and in the clinic.