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Abstracts

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C26T polymorphism of LIG4 gene revealed a statistically higher frequency of the variant genotypes in patients compared to controls (C/T: 50.6% vs 30.8%, T/T: 10.8% vs 6.6%, respectively, p=0.006). Allele frequency distribution analysis for LIG4 gene, showed that patients exhibited an almost 2-fold increased risk of carrying at least one mutant allele (T) compared to controls (p=0.004). No statistically significant associations were found for both polymorphisms after stratification of patients according to karyotypic findings. However, an increased frequency of variant genotypes of C26T polymorphism of LIG4 gene was observed in patients with -7/del(7q), -5/del(5q) and +8, compared to controls. Our results showed that the AML risk was not associated with RAD51 gene polymorphism; however, our data provide evidence for an important role of the C26T polymorphic site of the LIG4 gene in AML development.

PM12.004

Principal clinical features of acute myeloid leukemia with mutations DNMT3A R882

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The aim of the research was to analyse frequency of DNMT3A mutations in AML patients, their association with clinico-hematologic parameters and prognostic significance. The investigation group included 143 AML patients. Mutations DNMT3A R882 were identified in 23 (16,1%) patients: R882H - 16, R882C - 6, R882S - 1.
Patients with DNMT3A R882 had higher WBC (p=0,001) and platelets (p=0,020) count at diagnosis and more frequently belonged to FAB groups M5 (p=0,003) and M4 (p=0,012), as compared with DNMT3Awt. Of 23 patients who had AML with DNMT3A mutations, 17 (24,3%) had tumors with normal cytogenetic profiles (of a total of 70 cytogenetically normal samples) (p=0,009). Patients with isolated DNMT3A mutations were seen in 4 cases, whereas in the rest of patients they were detected simultaneously with mutations in genes FLT3, NPM1, NRAS and CKIT. DNTM3A mutations were significantly more prevalent in NPM1mut (p=0,005) and FLT3-ITD (p=0,005) positive cases than wild type. DNMT3A mutations associated with negative influence on patients overall survival (OS) and risk of relapse, compared with DNMT3Awt (Me of OS and RFS: 5,2 and 13,0; 4,8 and 10,0 months; p = 0,031 and p = 0,045, respectively).
Summary. AML with DNMT3A mutations represent the group, homogeneous on a number of clinical and laboratory parameters. DNMT3A mutations are highly recurrent in patients with de novo AML with an intermediate-risk cytogenetic profile. The presence of DNMT3A mutations can be considered as an independent adverse prognostic factor for survival, suggesting that testing of DNMT3A mutations can help further improve risk stratification in AML patients.

PS12.005

Bioinformatics analysis of mature mi-RNA motifs distribution in tumor suppressor genes surroundings

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Every human tumor type has its own unique mi-RNA expression profile. Mi-RNA can be located in intergenic spaces, in antisense strain, in introns and exons. Such genome organization can determine the mechanism of coordination between RNA and protein expression, but also represents the value of mi-RNA motifs in human evolution. Based on the findings that genome functioning is connected with its structure we have conducted the bioinformatics analysis of mature mi-RNA motifs distribution in tumor suppressor genes surroundings.
We analyzed the intergene spaces located in surroundings of the tumor suppressor genes (APC; BRCA1; BRCA2; CDKN2A; DCC; MEN1; NF1; NF2; PTEN; RB1; TP53; VHL; WT1). Sequences were obtained from NCBI data base and miRBase release 21 using E-utilities API. Motif search was carried out with MEME Suite program package. The results were filtered to yield only those matches with 85% identical nucleotides.
The entire set of non-coding DNA sequences contained 755 motifs of 19-23 nucleotides, homologous to 261 mature mi-RNA sequences. About 60% of all motifs were homologous to miR-5585, miR-1273g, miR-619, miR-5196, miR-5095, miR-709 and miR-1285. These motifs can be considered as non-specific and widely spread in human genome. We have found that tumor suppressor genes have specific patterns of mi-RNA homologous motifs distribution. Prevalent motif type and the density of motif distribution varied from gene to gene. Results can be discussed as a background to the search of new targets for tumor diagnostics and therapy.

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PM12.006

Polyposis coli due to low APC somatic mosaicism

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PURPOSE: To present a patient with familial adenomatous polyposis (FAP) caused by adenomatous polyposis coli (APC) somatic mosaicism; Description: we report of a twenty-one year old female presented with rectal bleeding and abdominal pain. Colonoscopy and esophagogastroduodenoscopy revealed extensive polyposis of the recto-sigmoid junction, distal sigmoid, proximal right colon and cecum. The rectum was essentially spared aside from two small pedunculated polyps. The stomach and duodenum, including the papilla, were normal. In preparation for recto-sigmoid sparing surgery, more than sixty polyps were removed. The patient had no extra-colonic signs of FAP. Her maternal grandmother was diagnosed with colon cancer at age seventy-six, but there was no other family history of polyps or colon cancer. Methodology: Next-generation sequencing (NGS) analysis was performed using the ColoSeq™ panel* on DNA extracted from both peripheral blood lymphocytes and colonic polyps. RESULTS: Molecular analysis detected the p.E1408X deleterious mutation in the APC gene in 12 of 276 (4%) reads of the DNA in the peripheral blood and in 30% of the DNA from colonic polyps. CONCLUSIONS: In this patient, 4% APC mosaicism of the peripheral blood lead to florid polyposis. Somatic mosaicism has been reported to cause cancer syndromes in a few cases, but has been underestimated. This case should reinforce the need for NGS analysis in all patients with a personal history of polyposis, no family history of colon polyps/cancer, and no identified germline mutation by traditional less sensitive approaches.

PS12.007

Analysis of BCR-ABL mutations in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors

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Mutations in the BCR-ABL tirozin-kinase (TK) domain represent the most common mechanism of resistance to personalized therapy with TK inhibitors (TKI) in patients with chronic myeloid leukemia (CML).
Mutational status of the BCR-ABL gene corresponding to the TK domain was analyzed by capillary sequencing in 45 CML patients with suboptimal response/failure to TKI, in order to tailor their therapy. The response of the patients to TKI therapy was monitored at molecular and cytogenetic level.
Mutations in the BCR-ABL gene were identified in 18 (40%) patients: a single mutation in 15 patients and 2 mutations in 3 patients. Mutations identified corresponded to several regions of the BCR-ABL oncoprotein, such as: the P-loop (M244V, G250E, Q252H), the ATP-binding region (L298V, V299L, T315I, F317L), the SH2-contact region (M351T) and the substrate-binding region (F359V). The T315I mutation, conferring resistance to almost all known TKI, was detected both as single mutation (in 7 patients) and in combination with M351T (1 patient).
The 2 mutations detected in the BCR-ABL TK domain in case of 2 patients represented different clones; during dasatinib therapy, the resistant clones were selected (M351T and T315 respective), while the clones sensitive to this drug have disappeared.
Different chromosomal abnormalities associated with clonal evolution were identified in 3 patients, which may be the major cause of secondary resistance to TKI.
Conclusions:
- Mutational status of the BCR-ABL TK domain is valuable information for the best therapeutic decision and management of patients with CML;
- Additional TKI resistance mechanisms can be detected by a combined molecular and cytogenetic monitoring of the CML patients.

PM12.008

Changes in the gene expression and copy number aberrations in non-invasive and muscle-invasive bladder tumors

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