PHARMACOGENETIC EVALUATION OF AURORA A KINASE IN COLORECTAL CANCERS

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Background. Aurora kinase A (AurA) is a member of a serine-threonine kinase family which has been implicated in tumorigenesis due to its pivotal role as important regulator of diverse cell cycle events; several studies, performed in human tumours, have described both the frequent gene amplification (1) and the high mRNA levels (2) of AurA. Noteworthy, two functional, non-synonymous, single nucleotide polymorphisms (SNPs) in the AurA gene, namely T91A and G169A, lead to a kinase activity reduction (3). Overall, it may be argued that human tumours are often characterized by overexpression of AurA, while the presence of SNPs is associated to an increased genome instability and the following carcinogenetic process. The aims of this study were: 1) the evaluation of AurA gene expression and polymorphisms in colorectal cancers and in the corresponding healthy mucosa; 2) the evaluation of possible correlation between pathological characteristics of neoplasms and AurA pharmacogenetics in surgical samples. **Methods**. Frozen surgical samples (neoplastic tissue and the corresponding healthy mucosa) were processed to extract nucleic acids (DNA and RNA) by specific kits (QIAGEN). Genomic DNA was amplified to evaluate sample genotype by using a real time-PCR technique (Applied Biosystems), which employed distinct fluorescent probes to discriminate the two alleles of each polymorphism. For gene expression analysis, first strand cDNA synthesis was obtained by reverse transcription of 0.4 µg of total RNA. Quantification was performed by real-time PCR using the $2^{-\Delta\Delta Ct}$ method (Applied Biosystems), and the relative gene expression value was obtained as the ratio between the target gene and glyceraldehyde-3-phosphate dehydrogenase (GAPDH, reference gene). Results of the present study were expressed as mean ± standard error and median values. All statistical calculations were performed by GraphPad Software version 4.0, and the level of significance was set at $p<0.05$. **Results**. Samples from 61 patients were analysed for gene expression. We found a statistically significant difference ($p<0.0001$) between neoplastic tissue (0.16±0.03 and 0.07) and the corresponding healthy mucosa (0.79±0.10 and 0.61). Higher histological grade neoplasms displayed greater, but not significantly, AurA mRNA levels (0.18±0.04 and 0.07) than lower histological grade tumours (0.10±0.03 and 0.06). Stage 3 cancers exhibited higher gene expression values (0.25±0.13 and 0.05) than stage 1 and 2 neoplasms (0.11±0.03 and 0.06), but this difference was not significant. **Conclusions**. These preliminary results indicate that the neoplastic tissue may be characterized by significant lower expression of AurA gene than the corresponding healthy mucosa. Pathological characteristics of neoplasms do not influence significantly AurA mRNA levels, even if the more aggressive malignant phenotype of tumours was associated with greater AurA gene expression.

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