Editorial

Genomics and Epigenomics of Tumor and Aging Cells

It is well established that aberrant DNA methylation, as well as genetic heterogeneity are the hallmarks of malignancies. More recently, it was shown that similar features are accompanying many degenerative processes and in particular aging. However, distinct specific processes of malignant transformation or aging may be characterized by the different changes within particular cell genomics and/or epigenomics. Therefore, in the proposed special issue of Current Genomics entitled “Genomics and epigenomics of tumor and aging cells” we have collected recent research and review papers especially on the genomics and epigenomics of aging and/or malignantly transformed cells in the field of the degenerative diseases, including neurodegeneration, dementia, and tumors.

Since the first fusion gene was discovered decades ago, a considerable number of fusion genes have been detected in leukemia. The majority of them are generated through chromosomal rearrangement or abnormal transcription. With the development of techniques, high-throughput sequencing method makes it possible to detect fusion genes systematically in multiple human cancers. Owing to their biological significance and tumor-specific expression, some of the fusion genes are attractive diagnostic tools and therapeutic targets. Yuhui Wang groups presented a review on the history of fusion genes, mechanisms of formation, and treatments against specific fusion genes in leukemia. Recent reports demonstrated an implication of the recurrent fusion genes in leukemia as an attractive target for diagnosis and treatment strategies. This group showed that Tyrosine Kinase Inhibitors (TKI) targeting BCR-ABL1 fusions, which have been widely used to treat CML, are able to provide only partial information. Therefore, the combination of ATRA and ATO targeting PML-RARA fusions has proved to be effective in Acute Promyelocytic Leukemia (APL). Moreover, therapy with high dose of cytarabine (HDAC) has significantly improved the prognosis of Core Binding Factor (CBF) Acute Myeloid Leukemia (AML) in patients. These studies on fusion genes may benefit patients with leukemia by providing more diagnostic markers and therapies in the future.

Vasily V. Ashapkin and coworkers studied a direct relationship on how aging affects the epigenetic phenomenon. It has been established that hypermethylation of genes associated with promoter CpG islands, and hypomethylation of CpG poor genes, repeat sequences, transposable elements and intergenic genome sections occur during aging in mammals. Moreover, the methylation levels of certain CpG sites display strict correlation with age and can be used as “*epigenetic clock*” to predict biological age. Multi-substrate deacetylases SIRT1 and SIRT6 affect aging *via* locus-specific modulations of chromatin structure and activity of multiple regulatory proteins involved in aging. In addition, the random changes in DNA methylation or chromatin remodeling on aging lead to gradual increase in transcriptional noise introducing phenotypic variation among cells. Therefore, most likely based on the author’s interpretation, such variation could become detrimental to tissue functioning, leading to highly variable progressive decline in organ functions during aging. Multiple data of age-dependent induction of NF- κ B regulated gene sets in various tissues suggest NF- κ B to be a master regulator of gene expression programs in mammalian aging. Vasily V. Ashapkin and coworkers summarized how the upregulation of multiple miRNAs occurs at mid age leading to down-regulation of genes functionally involved in the control of intermediate metabolism, apoptosis, DNA repair, oxidative defense, and mitochondrial oxidative phosphorylation. Strong evidence shows that all epigenetic systems contribute to the life span control in various organisms. Similar to other cell systems, epigenome is prone to gradual degradation due to the genome damage, stressful agents and other aging factors. Critical analysis by Vasily V. Ashapkin *et al.*, demonstrated that unlike mutations and other kinds of the genome damage, age-related epigenetic changes could be fully or partially reversed to a “young” aged state and requires more detailed analysis in the context of the aged associated genetic modification especially during the courses of the development and maturation of human diseases.

During the last several years, many studies were attempted to use genetic biomarkers for the primary as well as differential diagnosis of the gastrointestinal cancer. Marina V. Nemtsova and coworkers attempted to use gastric cancer molecular genetic markers in biopsy and postsurgical samples. Reports based on this study demonstrated aberrant methylation of genes CDH1, RASSF1A, MLH1, N33, DAPK, expression of genes hTERT, MMP7, MMP9, BIRC5 (survivin), PTGS2, and activity of telomerase of 106 gastric tumor samples were obtained post-operatively, and 53 gastric tumor samples from the same group of patients obtained endoscopically before surgical procedures. Biopsy specimens obtained from 50 patients with chronic calculous cholecystitis were used as a control group. Together with tissue samples obtained from different sites remote to tumors, a total of 727 samples was analyzed. The selected parameters comprise a system of molecular markers that can be used in both diagnostics of gastric cancer and in dynamic monitoring of patients after surgery. Special attention was paid to the use of molecular markers for the diagnosis of malignant process in the material obtained endoscopically since the efficacy of morphological diagnostics in biopsies is compromised by intratumor heterogeneity, which may prevent reliable identification of tumor cells in the sampling. This report indicated that certain molecular genetic events provided more sensitive yet specific markers of the tumor, and the molecular profiles detected in preoperative biopsies were confirmed by the material obtained intra-operatively. Therefore, the use of endoscopic material facilitates gastric tumors pre-operative diagnostics, improving early detection of gastric cancer and potential effective treatment strategies.

The study of variations in genes involved in the different events that trigger the atherogenic process, such as lipid metabolism (modification of LDL-cholesterol), endothelial function and hypertension, immune response (recruitment of macrophages and foam cell formation) and stability of atherosclerotic plaques (thrombosis), establishes the susceptibility, risk or probability of an individual for suffering arteriopathy and vascular disorders. Juan C. Carril and Ramón Cacabelos determined genetic risk factors in cerebrovascular disorders and cognitive deterioration. A total of 2455 cases over 50 years of age was genotyped for a panel of 19 SNPs in 15 genes encoding for proteins involved in the atherogenic process. This study shows the relevance of polymorphisms in APOB (odds ratio (OR), 1.17; 95% confidence interval (95% CI), 0.74-1.85), APOC3 (OR, 1.33; 95% 95% CI, 0.82-2.17) and APOE (OR, 1.75; 95% CI, 1.09-2.80) as genetic risk markers for hypercholesterolemia; polymorphisms in ACE (OR, 1.68; 95% CI, 0.32-8.77) and AGT (OR, 1.74; 95% CI, 0.97-3.14) for hypertension; and in APOE*3/*4 (OR, 2.06; 95% CI, 1.70-2.51) and APOE*4/*4 (OR, 3.08; 95% CI, 1.85-5.12) as unambiguous markers of dementia. In addition, these results also show the transversal importance of proinflammatory cytokines in different stages of atherogenesis, with special relevance of IL6 (OR, 1.39; 95% CI, 0.56-3.49) and TNF (OR, 1.40; 95% CI, 0.92-2.15) related to hypercholesterolemia and hypertension. The set of markers involved in this genetic risk panel makes it a powerful tool in the management of patients with different cerebrovascular disorders and their complications such as cognitive deterioration and requires much more studies in the near future.

Cardiovascular and neurodegenerative disorders are among the major causes of mortality in developed countries. Population studies evaluated the genetic risk, *i.e.* the probability of an individual carrying a specific disease-associated polymorphism. Identification of risk polymorphisms is essential for an accurate diagnosis or prognosis of a number of pathologies. Óscar Teijido and coauthors reported the characteristics and the influence of risk polymorphisms associated with lipid metabolism, hypertension, thrombosis, and dementia, in a large population of Spanish individuals affected by a variety of brain and vascular disorders as well as metabolic syndrome. The cross-sectional study included 4415 individuals from a widespread regional distribution in Spain (48.15% males and 51.85% females), with mental, neurodegenerative, cerebrovascular, and metabolic disorders. Results from this study were able to demonstrate polymorphisms in 20 genes involved in obesity, vascular and cardiovascular risk, and dementia in these populations and were compared with representative Spanish and European populations. Risk polymorphisms in ACE, AGT (235), IL6 (573), PSEN1, and APOE (specially the APOE- ϵ 4 allele) are representative of this population as compared to the reference data of Spanish and European individuals. The significantly higher distribution of risk polymorphisms in PSEN1 and APOE- ϵ 4 is characteristic of a representative number of patients with Alzheimer's disease; whereas polymorphisms in ACE, AGT (235), and IL6 (573) are the most probably related with the high number of patients with metabolic syndrome or cerebrovascular damage.

The response rate in the pharmacological treatment of depression has been estimated to be around 50%, achieving a remission in symptomatology in only one third of the patients. Suboptimal prescription of antidepressants has been proposed as a significant explanatory factor for this therapeutic inefficacy. The use of pharmacogenetic testing might favor the optimization of pharmacotherapy in emotional disorders. However, its implementation in the clinical routine requires studies which prove its efficacy. To explore the clinical effects obtained by means of the personalization of antidepressant treatment derived from the pharmacogenetic profile of the individual, Clara Torrellas and coworkers determined optimization of antidepressant use with pharmacogenetic strategies. This group used a sample of 291 patients under antidepressant treatment, and these patients were genotyped for the most common polymorphisms of the CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5 genes using RT-PCR and TaqMan[®] technology. 30 of them were subjected to psycho-affective assessment using the HDRS scale before and after a process of individualization of their psychopharmacological treatment in accordance with the genotype obtained. Results based on this study showed that the 70% of the individuals treated using the traditional criterion of trial-and-error were not taking the active ingredient most suited to their pharmacogenetic profile. The inclusion of this genetic information in the choice of drug and its dosage entailed a significant, progressive reduction in depressive symptomatology, with an efficacy ratio of 80% and a remission of the pathology in almost 30% of the cases. Authors' conclusion based on these results suggests that the prescription of pharmacogenetic profile-based strategies has a positive effect on the therapeutic response to antidepressants.

It has been widely accepted that *helicobacter pylori* is associated with inflammation of different areas of the gastrointestinal system, such as the duodenum and stomach, causing gastritis and gastric ulcers leading to lymphoma and cancer. Pathogenic islands are a type of clustered mobile elements ranging from 10-200 Kb contributing to the virulence of the respective pathogen coding for one or more virulence factors. Virulence factors are molecules expressed and secreted by pathogen and are responsible for causing disease in the host. Deepthi Nammi and colleagues employed the *in silico* analysis of pathogenic islands for identification of drug targets in *helicobacter pylori*, which can be used as a new and successful target for the therapeutic intervention for gastric cancer, suggesting that bacterial genes/virulence factors of the pathogenic islands may represent a promising source for identifying novel drug targets. Screening genome of 23 *H. pylori* strains revealed 642 bacterial genes/virulence factors in 31 pathogenic islands. The analysis identified 101 genes, which were non-homologous to human and essential for the survival of the pathogen; among them, 31 are potential drug targets. Protein-protein interactions for 31 drug targets predicted 609 interacting partners. Predicted interacting partners were further subjected to host-pathogen interactions leading to the identification of important molecules like TNF receptor associated factor 6, (TRAF6) and MAPKKK7, which are closely associated

with gastric cancer. These provocative studies enabled to Deepthi Nammi and colleagues identify important molecules in *H. pylori* and their counter interacting molecules in the host leading to gastric cancer and also a pool of novel drug targets for therapeutic intervention of gastric cancer.

In summary, the contributors of this special issue highlighted various **genomics and epigenomics of tumor and aging cells**, especially the role of genetic and epigenomics in the context of the different tumor and aged associated diseases including dementia, and the development of pharmacogenomics, genetics and proper pharmaceuticals for these chronic pathologies. We hope that this special issue will serve as a resource of recent progress in this area and also provide inspiration to a broad-spectrum of scientists involved.

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