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Relationships between retrogenes and cancer – evolutionary context

ABSTRACT

The process of retroposition, in which mature mRNA is reverse transcribed into cDNA and reintegrated into the genome, results in the creation of an additional copy of an existing gene (parental gene). Such copies, called retrocopies or retrogenes, are often embedded in introns of other genes, called host genes. Retrocopies, previously described as non-functional elements, are now recognized as important in the context of evolution, and their role in shaping genomes, transcriptomes and proteomes is becoming increasingly evident. An increasing amount of data from high-throughput experiments is allowing the identification of new functional retrogenes. Very often, they regulate the expression level of their parental genes by acting as miRNA sponges or antisense transcripts, and may participate in epigenetic regulation, modification of alternative splicing or in the formation of fusion transcripts. The phenomenon of retroposition has been particularly intensified during the evolution of primates. The relationship between the exceptionally high number of human retrocopies, compared to other animal species, and neoplastic transformation in our species is not well understood. Therefore, the main aim of the study was to investigate to what extent the intensive process of retroposition in primates can be linked to increased, compared to other species, processes of human carcinogenesis.

The study material consisted of transcriptomic data from human, dog and chicken. The expression of retrogenes associated with tumors was also experimentally verified in human cell lines, in a panel of cDNA from different organs of the studied species and in fresh-frozen tumor samples and surrounding tissues collected from dogs and rats. The expression of selected retrogenes was silenced in human cell lines to examine the effect on the expression of the parental gene or the host gene.

Based on the results of the differential expression analysis, 135 retrogenes with altered expression in human tumors were identified. Of these, more than three times as many belong to primate-specific retrogenes. The retrogenes *HSPA2, RHOB* and *CALML5* were identified as retrogenes associated with cancers of evolutionarily distant vertebrate species. In addition, we identified cancer-associated retrogenes that are specific to the vertebrate species studied, as well as retrogenes that may act as important non-coding RNAs regulating genes known to play a role in cancer cells. The results of this work allow, for the first time on such a large scale, to consider the expression profile of retrogenes in cancers in an evolutionary context.