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Abstract: EP-444

The targeting of eEF1A1-actin complex by GT75 DNA-aptamer fight androgen-independent human prostate adenocarcinoma cells.

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Introduction
Castration-resistant prostate cancer (CRPC) is responsible in men for high cancer-related death worldwide. Treatments are limited and often the resistance towards the second and third lines of treatment occurs. The identification of novel therapeutic strategies/targets remains an urgent need for CRPC. The eukaryotic elongation factor 1A1 (eEF1A1) can play a role in different tumors and we found that it was overexpressed in high Gleason score (7-8) tumor tissues. DNA aptamers can recognize targets with high specificity. Our group has demonstrated that a DNA-aptamer, named GT75, can target eEF1A1 in hepatocarcinoma and chronic lymphocytic leukemia cells.
Material and Methods
PC-3 cell line (resembling the CRCP phenotype) and PZHPV-7 cells (control non-tumorigenic prostate cells), were transfected with GT75 or control CT75 by lipofectamine 3000; cell growth was measured by MTT or MTS at different days after transfection. Autophagy was assessed by a consecutive cell staining with neutral red (NR), and crystal violet (CV), and by an independent MTS assay. In Cell Western assay (ICW) was used to measure eEF1A1 protein level and autophagy LC3B marker; cell adhesion/spreading was measured by methylene blue assay. Confocal immunofluorescence microscopy was performed with FITC-conjugated GT75 or CT75 or with fluorescent-labeled IgG anti-eEF1A1 antibody.
Results and Discussions
In a panel of cancer cells, a single dose of 125 nM of GT75 was able to reduce the cell growth compared to CT75 control, but the highest effect was measured in the PC-3 cells (-59%). Notably, in the non-tumorigenic PZHPV-7 cells, GT75 did not alter cell growth, demonstrating the tumor-specific effect of GT75. Besides, in PC-3 cells the GT75 reduced eEF1A1 protein levels ($p<0.05$). The confocal microscopy analysis in PC3 showed that GT75 targeted the eEF1A1-actin complexes bound to the cytoskeleton. On the contrary, nonspecific co-localization of eEF1A1/actin was found in non-tumorigenic PZHPV-7 cells ($p<0.05$). Finally, in GT75-treated PC-3 cells, a higher rate of autophagy, a lower rate of cell adhesion and spreading compared to CT75 control were observed.
Conclusion
Our data indicate the targeting of GT75 to the eEF1A1-actin complex bound to the cytoskeleton in androgen-independent prostate cancer cells. This was paralleled by the reduction of cell viability, the activation of cell autophagy, the impairment of cell adhesion and spreading. Together our observations open new perspectives for the development of targeted therapies for CRPC.