New biomarkers and therapeutic targets of human cancer

This research line concerns: 1. the characterization of new genes with functional or diagnostic relevance in various types of human neoplasia; 2. the development of new anticancer therapeutic tools through the use of aptamers and pharmacological inhibitors. 1. The research lines dedicated to the factors that regulate gene expression HMGA1/2, PATZ1, and PAX8, of which we have outlined the mechanism of action in tumorigenesis and in the biology of tumor stem cells, are placed in this context. Inactivation of PATZ1 causes papillary thyroid carcinomas (PTCs) to progress to more aggressive subtypes. PATZ1 represents a new diagnostic and prognostic marker of malignant gliomas, where it counteracts the proneural-mesenchymal transdifferentiation. The transcription factor PAX8 is a marker of high grade serous ovarian carcinomas and is a survival gene for ovarian cancer cell proliferation. Our studies are focused on: 1) PAX8 function in the epithelia of the reproductive tract derived from the Mullerian duct; 2) the role of PAX8 in the development of ovarian cancer; 3) the identification of new strategies for PAX8 silencing in vivo in tumor cells. Another line of research concerns non-coding RNA (lncRNA), key molecules of various biological processes. We recently demonstrated that PAR5 lncRNA is downregulated in anaplastic thyroid carcinoma and that it exerts its tumor suppressor function by impairing cell growth and migration rate, interacting with the EZH2 protein and inhibiting its activity. In addition, we observed that MPPED2-AS1 lncRNA (RP5-1024C24.1) is downregulated in papillary thyroid carcinoma, and that the loss of its expression contributes to thyroid carcinogenesis. LncRNAs can also function as competitive endogenous RNAs (ceRNAs) that compete with microRNAs in the regulation of numerous targets. Among them, our research group has characterized two HMGA1 pseudogenes that represent the key regulators of a novel oncogenic ceRNA network. In fact, we have shown that HMGA1P6 and HMGA1P7 are able to induce cell proliferation, migration and invasion by increasing the expression of the HMGA1 protein. 2. In the field of innovative therapies, our institute has developed a specific expertise in the field of aptamers, short single-stranded oligonucleotides which, folding into three-dimensional structures, bind with high affinity to a target molecule and are therefore suitable for applications that include cancer diagnostics and therapy. Aptamers are selected by SELEX (Systematic Evolution of Ligands by EXponentialrichment) technology, for which we have a consolidated experience. To date, we have generated RNA aptamers, which recognize important cancer-related receptors, including EGFR / EGFRvIII, AXL, PDGFRβ, EphA2 and other biomarkers. We have shown that the selected aptamers can: 1) identify new biomarkers of human tumors; 2) discriminate different subtypes of tumors by tissue staining; 3) visualize and inhibit tumor development and progression in new theranostic and in vivo imaging modalities; 4) interfere with the malignant phenotype alone and/or in combination with conventional chemotherapy and immunotherapy with monoclonal antibodies; 5) act as agents for the selective targeting of therapeutic agents of various kinds (siRNA, miRNA, anti-miR and drug-loaded nanoparticles), thus avoiding off-target effects.

Other studies are focused on another therapeutic target, p90RSK, an effector protein of the MAPK pathway, constitutively activated in many human tumors due to oncogenic mutations of its components. The aim of this project is to analyze the role of p90RSK in the regulation of the p53 pathway. We observed that p90RSK binds MDM2 and phosphorylates it on serine 166. The pharmacological inhibitor of RSK BI-D1870, by dephosphorylating MDM2, induces a rapid accumulation of p53; this leads to a strong increase in MDM2 transcription which again induces p53 degradation. The inhibition of p90RSK in tumor cells has growth blocking effects and induction of p53-dependent apoptosis.

References:


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