

The Urgent Need for New Therapeutical Approaches for Renal and Bladder Cancer: Mitochondrial Non-Coding RNAs as Efficient Targets

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Editorial

According to the American Cancer Society, bladder cancer is the 6th most common cancer in the U.S. When diagnosed and treated early, the 5 year survival rate is 94%. However, patients with invasive cancer have a much worse prognosis, with a 50% 5-year survival rate.

Renal Cell Carcinoma (RCC) is the seventh most common cancer in men and the tenth in women, with the second highest mortality among urogenital cancers. Patients with distant metastasis have a 5 year survival rate of <15%, mainly due to radio- and chemoresistance of metastatic RCC.

The high existing unmet need in treatment of renal and bladder cancer is reflected by the poor prognosis of patients with advanced stage disease.

There are today 216 companies plus partners developing 253 drugs targeting renal cancer. In addition, there are 3 suspended drugs. For bladder cancer there are today 122 companies plus partners developing 149 drugs targeting bladder cancer. All included targets have been cross-referenced for the presence of mutations associated with these cancers.

Long non-coding RNAs (lncRNA) are non-protein coding transcripts longer than 200 nucleotides. The repertoire of lncRNA functions is rapidly expanding with defined roles in development, as mediators of mRNA decay, host genes for miRNAs, etc. Accumulating evidence indicates that aberrant expression of lncRNAs may play an important role in cancer biology.

Human cells express a family of mitochondrial long non-coding RNAs (ncmtRNAs) and the functional role of these molecules outside the mitochondria is suggested by their cytoplasmic and nuclear localization [1]. One of these transcripts, sense ncmtRNA (S-ncmtRNA) is expressed in normal proliferating cells, as well as in tumor cells but not in non-dividing cells, suggesting a role in cell cycle progression [2]. Normal proliferating cells also express two antisense transcripts, named AS-ncmtRNA-1 and -2. Remarkably however, tumor cell lines, as well as tumor cells present in human biopsies, down-regulate the expression of AS-ncmtRNAs [3]. A hallmark of carcinogenesis is down-regulation of tumor suppressor genes, mediated by several mechanisms. Because the AS-ncmtRNAs are down-regulated in tumor cells, we hypothesized that these transcripts might function as unique mitochondrial-encoded tumor suppressor.

In tumor cell lines, we found that knocking down these transcripts *in vitro* with antisense oligonucleotides (ASO) induces a strong inhibition of cell proliferation, induction of caspase activation, DNA fragmentation, and inhibition of stemness, mediated by a drastic reduction in the levels of inhibitor of apoptosis survivin, which is up-regulated in practically all human cancers. An important point is that the same treatments that induce massive cell death in tumor cells do not affect the viability of normal proliferating cells [4].

For *in vivo* evaluation, a preclinical study was performed in a subcutaneous syngeneic model of renal cancer by intraperitoneal injections with an ASO complementary to mouse AS-ncmtRNA (ANDES 1560). The ability to inhibit tumor growth and increase survival in mice treated with the ASO against AS-ncmtRNA, compared to control groups (ODN-NR and physiological saline), was demonstrated. A model of orthotopic syngeneic immunocompetent renal cancer was also established. Treatment effectiveness was evidenced by a response in 80% of mice in the inhibition of tumor growth and lung metastases.

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For bladder cancer, a subcutaneous xenograft model was developed, in which administration of ASO complementary to AS-ncmtRNA (ANDES 1537) induced a strong delay in tumor growth. Immunohistochemistry of tumors from animals treated with ANDES 1230 (renal) or ANDES 1537 (bladder) showed that, compared with the corresponding controls, a strong down-regulation of survivin is observed, accompanied by an important increase in tissue apoptosis, determined by TUNEL assay.

The accumulated experimental evidence shows that ANDES 1537 displays an excellent biosafety profile in mice and monkeys and shows a high anti-tumor efficacy, independent of the tumor type tested. Therefore, after a long evaluation FDA authorized this ASO to be tested in human patients in an open-label, dose escalation and expansion, 2-part study to determine the safety, tolerability, and maximum tolerated dose of Andes-1537 for Injection in patients with advanced unresectable solid tumors that are refractory to standard therapy or for which no standard therapy is available [5].

Therefore, the targeted inhibition of AS-ncmtRNAs mediated by ANDES 1537 will be assessed as a new therapeutic drug and the results obtained of this first trial will be known in September 2016.

From this point on, there will be a long road in which the drug will be evaluated under FDA protocols in order to provide new evidences for therapeutic application of this antisense approach.

References

1. Landerer E, Villegas J, Burzio VA, Oliveira L, Villota C, Lopez C, et al. Nuclear localization of the mitochondrial ncRNAs in normal and cancer cells. See comment in PubMed Commons below *Cell Oncol (Dordr)*. 2011; 34: 297-305.
2. Villegas J, Burzio V, Villota C, Landerer E, Martinez R, Santander M, et al. Expression of a novel non-coding mitochondrial RNA in human proliferating cells. See comment in PubMed Commons below *Nucleic Acids Res*. 2007; 35: 7336-7347.
3. Burzio VA, Villota C, Villegas J, Landerer E, Boccardo E, Villa LL, et al. Expression of a family of noncoding mitochondrial RNAs distinguishes normal from cancer cells. See comment in PubMed Commons below *Proc Natl Acad Sci U S A*. 2009; 106: 9430-9434.
4. Vidaurre S, Fitzpatrick C, Burzio VA, Briones B, Villota C, Villegas J, et al. Down-regulation of the Antisense Mitochondrial ncRNAs is a Unique Vulnerability of Cancer Cells and a Potential Target for Cancer Therapy. *J. Biol. Chem*. 2014; 289: 27182–27198.
5. ClinicalTrials.gov Identifier: NCT02508441. Phase 1 Safety and Tolerability Study of Andes-1537 for Injection in Patients With Advanced Unresectable Solid Tumors.