Functional evaluation of the new anti-cancer agent NRP-a308 on clear cell Renal Cell Carcinoma model expressing the different Neuropilin isoforms

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Introduction

Clear cell Renal Cell Carcinoma (ccRCC) are among the most vascularized tumors. They represent a paradigm of tumor angiogenesis but also an excellent model to evaluate the efficacy of new anti-angiogenic agents. Sunitinib (Sutent®), the anti-angiogenic ccRCC reference treatment, induces a transient effect with resistance of most of the patients after a few months of treatment. Tumor cell dissemination via the lymphatic network observed in patients treated by sunitinib may be one cause of progression. In this context, Neuropilins (NRPs), co-receptors of VEGF receptors, have emerged as new relevant targets in oncology. Indeed, NRPs overexpression in patient tumors is correlated with a poor prognosis. NRPs downregulation by shRNA in ccRCC model cell lines results in decreasing cancer cells migration, invasion and tumor cells extravasation in the lymphatic network. Compound NRPa-308, a new NRP-1 antagonist, has recently been reported which exerts in vitro anti-angiogenic and anti-proliferative effects, and in vivo anti-cancer effects in mice xenografted with human aggressive breast cancer cells (MDA-MB-231). The work presented aims to demonstrate that NRP-a308 is an anti-cancer molecule able to target ccRCC cells expressing either NRP-1 or NRP-2, or both at the same time.

Methods and Results

Cell Proliferation

NRPa-308 reduces cell proliferation at 0.2µM after 48h, while sunitinib shows an efficient effect at higher concentrations (>2µM) (figure 1A). NRPa-308 IC50 after 48h for 786-O shNRPs cell lines are 10 times bellow those of sunitinib (figure 1B).

Cytotoxicity/Cytostaticity

After one week of treatment by NRPa-308 on 786-O shNRPs colonies, cytotoxic effects are observed at 0.2µM with less and smaller colonies. This cytotoxic effect is less important for sunitinib at 0.2µM (figure 2).

Protein expression

NRPa-308 inhibits two proliferative and survival signalling pathways (ERK and AKT) in a more efficient manner than sunitinib. (figure 6).

CONCLUSION

These experiments have shown that NRPa-308 is a relevant compound to target ccRCC showing good efficiency in reducing 786-O shNRPs cell viability, proliferation and migration. Furthermore, NRPa-308 is more efficient than sunitinib, ccRCC reference treatment, with IC50 more than 10 times lower. NRPa-308, initially described as a NRP-1 inhibitor, still has an effect on ccRCC even if NRP-1 expression is decreased. NRPa-308 is a promising inhibitor for ccRCC treatment but further investigation are needed to determine which others receptors are targeted.