PHARMACOLOGICAL CHARACTERIZATION OF NEW ANTAGONIST OF THE EPH RECEPTORS ENDOWED WITH ANTI-ANGIOGENIC ACTIVITY

1)Corrado M. 2)Giorgio C. 3)Incerti M. 4)Russo S. 5)Ballabeni V. 6)Barocelli E. 7)Lodola A. 8)Tognolini M.

University of Parma

Eph receptors and ephrin ligands are overexpressed in a large number of cancer types, such as ovarian and breast cancer [1-2] where they promote metastasis, invasion and tumor angiogenesis [3]. For this reason, targeting the Eph-ephrin system could be a new approach in cancer therapy.

The activity of the Eph receptors can be inhibited by means of intracellular kinase inhibitors or by using protein-protein inhibitors, targeting the extracellular ligand-binding domain of Eph receptor which include antibodies, chimeric proteins and small molecules [4].

Our research group focused its attention on the development of protein-protein inhibitors and we recently obtained UniPR129 [5], (the conjugate of lithocholic acid with L-homo-Tryptophan). It was a competitive and reversible antagonist of EphA2 receptor, endowed with high potency in in vitro anti-angiogenic assays but endowed with unfavourable physicochemical properties which limited its use in vivo.

To overcome this issue, metadynamics was employed to design new derivatives [6] and UniPR139 and UniPR502 emerged as a couple of the most promising compounds.

They showed a Ki of 950 nM and 750 nM respectively blocking the Eph-ephrin interaction in a competitive and reversible manner. They did not discriminate Eph receptor subclasses and they reduced ephrin-A1-induced EphA2 receptor phosphorylation in the low micromolar range without exerting non specific cytotoxic effects. The compounds showed an in vitro and in vivo anti-angiogenic activity, when tested in tube formation assay on HUVEC and in CAM assay, at 3-10 µM concentrations.

The anti-angiogenic activity was related to a reduction of cell proliferation and VEGF-induced VEGFR2 activation, in fact at 30uM UniPR139 and UniPR502 partially interfere with the VEGFR phosphorylation and internalization

IN conclusion UniPR139 and UniPR502 are promising pharmacological for further in vivo characterization.

References:

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