Peptides in angiogenesis. Development of peptidomimetic inhibitors of VEGF co-receptor NRP-1

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Angiogenesis, the growth of new capillary blood vessels from existing ones, is an important physiological process in embryogenesis, wound healing and reproduction. In cancer, angiogenesis permits to develop a network of intra tumour blood vessels supplying oxygen and nutrients thus enhancing tumour growth. Therefore, compounds blocking angiogenesis could be prospective antitumour drugs, but so far only a few angiogenesis inhibitors are used in the clinic for the treatment of cancer.

One of the most important growth factors involved in angiogenesis process is vascular endothelial growth factor-165 ($VEGF_{165}$). $VEGF_{165}$ signal is transduced via VEGF receptors and significantly enhanced by association with co-receptor NRP-1. Moreover, overexpression of NRP-1 was found in different malignant cancer tissues. All these findings suggest that NRP-1 could be involved in pathological angiogenesis and inhibitors of NRP-1 have considerable potential as novel antiangiogenetic and cancer therapeutics.

As a starting point for our study of searching for antiangiogenic peptidomimetics we utilized a heptapeptide ATWLPPR (A7R). It was shown that A7R binds to NRP-1 and selectively inhibits $VEGF_{165}$ binding to NRP-1, and *in vivo* treatment with A7R resulted in decreasing breast cancer angiogenesis and growth [3]. The detailed studies have shown the importance of C-terminal arginine and that its shortest sequence preserving inhibitory activity is the C-terminal tetrapeptide LPPR [2].

This presentation reports structure-activity relationship studies of the tetrapeptide LPPR in order to understand the structural determinants for inhibition of binding $VEGF_{165}$ to NRP-1 by this tetrapeptide and to develop more resistant to enzymatic degradation peptidomimetic NRP-1inhibitors. These compounds may serve as tools for the study of NRP-1 biology and provide a point of departure for development of more potent anti-NRP-1 drugs in the future [1].

References:

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Acknowledgements:

This work was supported by NCN grant no N 204 350940. Project was carried out with the use of CePT infrastructure cofinanced by the European Union – the European Regional Development Fund within the Operational Programme "Innovative economy" for 2007-2013.