Discovery of VEGF inhibitory peptides directed to extracellular ligand-binding domain of the VEGF receptors

Jussara Michaloski Souza [1], Alexandre Rodrigues Redondo [1], Leila da silva Magalhães [1], Ricardo José Giordano [1]

[1] Instituto de Química Universidade de São Paulo, Bioquímica (São Paulo, Brasil)

INTRODUCTION

Vascular endothelial growth factor (VEGF) is a key molecule that stimulates angiogenesis (formation of new blood vessels from pre-existing ones) by activating tyrosine kinases expressed in the endothelium, the VEGF receptors (VEGFRs). Given the central role of VEGF in angiogenesis, anti-VEGF therapies were among the first approved by FDA for treatment of diseases with an angiogenic component such as colon cancer and retinopathy. However, the development of novel agents directed against VEGF family members is still an important step toward a new generation of safer and more effective anti-angiogenic drugs.

OBJECTIVES

To rationally design anti-angiogenic compounds we search for peptides that bind to the VEGF receptors and prevent neovascularization in vivo.

MATERIALS AND METHODS

We combined phage display technology and the mouse model of oxygen-induced retinopathy to identify peptides with anti-angiogenic activity.

DISCUSSION AND RESULTS

Our results show that two small 6-mer peptides targeting the extracellular ligand-binding domain of the three VEGF receptors are in fact pan-VEGF inhibitors. The peptides prevent ligand binding to all VEGF receptors and one of these inhibits angiogenesis in vivo in the retina using a well-established mouse model.

CONCLUSION

In summary, these peptides define a possible binding site share by all three VEGF receptors. This binding site might be an important domain for drug development for angiogenic dependent disease such as cancer and retinopathy.

Keywords: Angiogenesis, VEGF, Phage Display

Supported by: Fapesp, CNPq, CAPES, Universidade de São Paulo (NAP-NUBIC)