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Development of biotechnological drug candidates on angiogenesis model in Turkey

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Statement of the Problem: Even though cancer cells are abnormal, they still require oxygen and nutrients. Angiogenesis, the development of blood vessels, is an essential step in the growth of a tumor. Without vessels, tumors cannot grow to be larger than a small fraction of an inch. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR2/KDR) are major mediators of angiogenesis associated with tumors and other pathological conditons, including age-related macular degeneration and proliferative diabetic retinopathy. It is well known that inhibition of VEGF induced angiogenesis is a valid strategy for the treatment of solid tumors and other disorders in humans. In this context, two peptides and two recombinant antibodies able to inhibit angiogenesis have been developed in MRC.

Methodology: In this study, we identified two single chain variable fragments (scFvs) that directly bind VEGFR-2 and inhibit VEGF-dependent cell proliferation and quantified their receptor-binding affinities. Phage display method was used to construct recombinant single-chain antibodies, which are smaller in molecular size, but still retain the VEGF-blocking property of larger antibodies. Two specific single-chain antibodies (KDR1.3 and KDR2.6 scFvs) recognizing the extracellular immunoglobulin-like domains 1–7 of VEGFR-2 were selected from a V-gene phage display library constructed from mice immunized with the commercially available soluble extracellular domains 1–7 of VEGFR-2.

Findings: KDR1.3 and KDR2.6 scFvs were characterized at the DNA and protein levels by ELISA, DNA sequencing, and surface plasmon resonance (SPR) spectroscopy. Both anti-KDR scFvs bind to sKDR D1–7, block VEGF binding to sKDR D1–7, and show potent inhibition of VEGF-induced cell proliferation in human umbilical vein endothelial cells (HUVECs) by a rat cornea angiogenesis assay (CAA).

Conclusion: Our results demonstrated that KDR1.3 and KDR2.6 antibodies could inhibit angiogenesis via. interaction with the VEGFR-2 extracellular domain. Thus the identified recombinant antibodies may have potential to be used as angiogenesis inhibitors.

Figure 1: Blocking effects of peptide and Recombinant antibodies on the VEGF/VEGFR2 signaling

Biography

Berrin Erdag has expertise on Antibody Engineering, Phage Display Technology, Molecular Biology and has successfully completed projects in different field of applications such as Cancer Therapy, Biosensor, in-vitro monitoring. She has a national patent entitled, "Peptide Structures that Bind and Block the Activity of Vascular Endothelial Growth Factor (VEGF)", where an anti-angiogenic peptide is protected. She has also an international patent entitled, "Recombinant antibody structures binding to and blocking the activity of vascular endothelial growth factor-2 (VEGFR-2/KDR)" US patent No: 9193792, 24/11/2015, China patent No: ZL 2010800690064, 29/06/2016, where two anti-angiogenic recombinant antibodies with a potential anti-cancer properties are expected to be protected. She is the co-leader of a Biosimilar development Landmark project which is the first nationally funded biosimilar project in Turkey. The project consists on the development and production of an anti-cancer biosimilar antibody. Right after the support of the biosimilar project, she has been granted by the Ministry of Development for the development of a Centre of Excellence for Medical Biotechnology. She is still working hard for the development of a biotechnological drug development ecosystem in Turkey.

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