

Anti-Angiogenic Effects of the *Macrovipera lebetina obtusa* Snake Crude Venom and Obtustatin

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Abstract : *Macrovipera lebetina obtusa* (MLO) is a poisonous snake in Armenia. Obtustatin represents the shortest known monomeric disintegrin, isolated from the snake venom of MLO, and is known to specifically inhibit $\alpha 1\beta 1$ integrin. Its oncostatic effect is due to the inhibition of angiogenesis, which likely arises from $\alpha 1\beta 1$ integrin inhibition in the endothelial cells. To explore the therapeutic potential of the MLO snake venom and obtustatin, we studied activity of obtustatin and MLO venom in vitro, by testing their efficacy in human dermal microvascular endothelial cells (HMVEC-D) and in vivo, using chick embryo chorioallantoic membrane assay (CAM assay). Our in vitro results showed that obtustatin in comparison with MLO venom did not exhibit cytotoxic activity in HMVEC-D cells in comparison to MLO venom. But in vivo results have shown that 4 μ g /embryo (90 μ M) of obtustatin inhibited angiogenesis induced by FGF2 by 17% while MLO snake venom induced 22% reduction of the angiogenic index. The concentration of obtustatin in the crude MLO venom was 0.3 nM, which is 300.000 times less than the concentration of the obtustatin itself. Given this enormous difference in concentration, it is likely that some components of the crude venom contribute to the observed anti-angiogenic effect. Hypotheses will be ascertained to justify this action: components in the MLO venom may increase obtustatin efficacy or have independent but synergic anti-angiogenic activities.

Keywords : angiogenesis, $\alpha 1\beta 1$ integrin, *Macrovipera lebetina obtusa*, obtustatin

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