ANTIANGIOGENIC PROPERTIES OF PEPTIDES DERIVED FROM HUMAN ENDOSTATIN

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The neovascularization of a malignant tumour is a critical step for its growth and spreading in the organism. The pharmacological control of this angiogenic process is today considered one of the most promising approaches for the treatment of neoplastic diseases. Endostatin, a 20 kD fragment of Collagen XVIII, and angiostatin, a product of the proteolityc cleavage of plasminogen, have been the first endogeneous antiangiogenic factors discovered only few years ago. They are generally produced by the malignant tumours themselves possibly to suppress the growth of their metastasis. Both these factors have been shown to reduce the vascularization and the growth of experimental tumours in animal model. The great advantage of these substances resides in their lack of toxicity and of acquired drug resistance development which is often seen with the chemotherapy normally used. However, the production in reasonable amount of recombinant endostatin has been difficult and also its solubility in aqueous solution is very poor. For these reasons it would be extremely interesting to identify smaller fragments of the parent protein which still retain antiangiogenic properties and yet they might be more easily produced and administered.
Four peptides have been synthesized, by solid phase method, corresponding to the sequence 6-49(I), 50-92(II), 93-133(III) and 134-178(IV) of human endostatin and tested for their ability to inhibit endothelial cell proliferation, migration and both *in vitro* and *in vivo* angiogenesis. Fragment I and IV have been found fully biologically active in all the angiogenesis assays performed, displaying a potency and efficacy even higher than full-length human endostatin itself. The availability of these peptides can be useful for the identification of the endostatin mechanism(s) of action, still unknown. Our data suggest also a possible development of these peptides as antiangiogenic agents.